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1 - Nutritional Disorders

Chapter 1. Nutrition: General Considerations

Introduction

Nutrition is the science of food and its relationship to health. Nutrients are chemicals in foods that are used by the body for growth, maintenance, and energy. Nutrients that cannot be synthesized by the body and thus must be derived from the diet are considered essential. They include vitamins, minerals, some amino acids, and some fatty acids. Nutrients that the body can synthesize from other compounds, although they may also be derived from the diet, are considered nonessential. Macronutrients are required by the body in relatively large amounts; micronutrients are needed in minute amounts.

Lack of nutrients can result in deficiency syndromes (eg, kwashiorkor, pellagra) or other disorders (see p. 9). Excess intake of macronutrients can lead to obesity (see p. 56) and related disorders; excess intake of micro-nutrients can be toxic. Also, the balance of various types of nutrients, such as how much usaturated vs saturated fat is consumed, can influence the development of disorders.

Macronutrients

Macronutrients constitute the bulk of the diet and supply energy and many essential nutrients. Carbohydrates, proteins (including essential amino acids), fats (including essential fatty acids), macrominerals, and water are macronutrients. Carbohydrates, fats, and proteins are interchangeable as sources of energy; fats yield 9 kcal/g (37.8 kJ/g); proteins and carbohydrates yield 4 kcal/g (16.8 kJ/g).

Carbohydrates: Dietary carbohydrates are broken down into glucose and other monosaccharides. Carbohydrates increase blood glucose levels, supplying energy. Simple carbohydrates are composed of small molecules, generally monosaccharides or disaccharides, which increase blood glucose levels rapidly. Complex carbohydrates are composed of larger molecules, which are broken down into monosaccharides. Complex carbohydrates increase blood glucose levels more slowly but for a longer time. Glucose and sucrose are simple carbohydrates; starches and fiber are complex carbohydrates.

The glycemic index measures how rapidly consumption of a carbohydrate increases plasma glucose levels. Values range from 1 (the slowest increase) to 100 (the fastest increase, equivalent to pure glucose—see Table 1-1). However, the actual rate of increase also depends on what foods are consumed with the carbohydrate.

Carbohydrates with a high glycemic index may increase plasma glucose to high levels rapidly. It is hypothesized that, as a result, insulin levels increase, inducing hypoglycemia and hunger, which tends to lead to consumption of excess calories and weight gain. Carbohydrates with a low glycemic index increase plasma glucose levels slowly, resulting in lower postprandial insulin levels and less hunger, which probably makes consumption of excess calories less likely. These effects are predicted to result in a more favorable lipid profile and a decreased risk of obesity, diabetes mellitus, and complications of diabetes if present.

Proteins: Dietary proteins are broken down into peptides and amino acids. Proteins are required for tissue maintenance, replacement, function, and growth. However, if the body is not getting enough calories from dietary sources or tissue stores (particularly of fat), protein may be used for energy.

As the body uses dietary protein for tissue production, there is a net gain of protein (positive nitrogen balance). During catabolic

[**Table 1-1.** Glycemic Index of Some Foods]

states (eg, starvation, infections, burns), more protein may be used (because body tissues are broken down) than is absorbed, resulting in a net loss of protein (negative nitrogen balance). Nitrogen balance is best determined by subtracting the amount of nitrogen excreted in urine and feces from the amount of

nitrogen consumed.

Of the 20 amino acids, 9 are essential amino acids (EAAs); they cannot be synthesized and must be obtained from the diet. All people require 8 EAAs; infants also require histidine.

The weight-adjusted requirement for dietary protein correlates with growth rate, which decreases from infancy until adulthood. The daily dietary protein requirement decreases from 2.2 g/kg in 3-mo-old infants to 1.2 g/kg in 5-yr-old children and to 0.8 g/kg in adults. Protein requirements correspond to EAA requirements (see Table 1-2). Adults trying to increase muscle mass need very little extra protein beyond the requirements in the table.

The amino acid composition of protein varies widely. Biological value (BV) reflects the similarity in amino acid composition of protein to that of animal tissues; thus, BV indicates what percentage of a dietary protein provides EAAs for the body. A perfect match is egg protein, with a value of 100. Animal proteins in milk and meat have a high BV (~90); proteins in cereal and vegetables have a lower BV (~40), and some derived proteins (eg, gelatin) have a BV of 0. The extent to which dietary proteins supply each other's missing amino acids (complementarity) determines the overall BV of the diet. The recommended daily allowances (RDA) for protein assumes that the average mixed diet has a BV of 70.

Fats: Fats are broken down into fatty acids and glycerol. Fats are required for tissue growth and hormone production. Saturated fatty acids, common in animal fats, tend to be solid at room temperature. Except for palm and coconut oils, fats derived from plants tend to be liquid at room temperature; these fats contain high levels of monounsaturated fatty acids or polyunsaturated fatty acids (PUFAs).

Partial hydrogenation of unsaturated fatty acids (as occurs during food manufacturing) produces trans fatty acids, which are solid or semisolid at room temperature. In the US, the main dietary source of trans fatty acids is partially hydrogenated vegetable oils, used in manufacturing certain foods (eg, cookies, crackers, chips) to prolong shelf-life. Trans fatty acids may elevate LDL cholesterol and lower HDL; they may also independently increase the risk of coronary artery disease.

Essential fatty acids (EFAs) are linoleic acid, an ω-6 (n-6) fatty acid, and linolenic acid, an ω-3 (n-3) fatty acid. Other ω-6 acids (eg, arachidonic acid) and other ω-3 fatty acids (eg, eicosapentaenoic acid, docosahexaenoic acid) are required by the body but can be synthesized from EFAs.

EFAs (see also p. 19) are needed for the formation of various eicosanoids (biologically active lipids), including prostaglandins, thromboxanes, prostacyclins, and leukotrienes. Consumption of ω-3 fatty acids may decrease the risk of coronary artery disease.

[**Table 1-2.** Essential Amino Acid Requirements in mg/kg Body Weight]

Requirements for EFAs vary by age. Adults require amounts of linoleic acid equal to at least 2% of total caloric needs and linolenic acid equal to at least 0.5%. Vegetable oils provide linoleic acid and linolenic acid. Oils made from safflower, sunflower, corn, soya, primrose, pumpkin, and wheat germ provide large amounts of linoleic acid. Marine fish oils and oils made from flax-seeds, pumpkin, soy, and canola provide large amounts of linolenic acid. Marine fish oils also provide some other ω-3 fatty acids in large amounts.

Macrominerals: Na, Cl, K, Ca, P, and Mg are required in relatively large amounts per day (see Tables 1-3, 1-4, and 5-2).

Water: Water is considered a macronutrient because it is required in amounts of 1 mL/kcal (0.24 mL/kJ) of energy expended, or about 2500 mL/day. Needs vary with fever, physical activity, and changes in climate and humidity.

[**Table 1-3.** Macrominerals]

[**Table 1-4.** Recommended Dietary Reference Intakes* for Some Macronutrients, Food and Nutrition Board, Institute of Medicine of the National Academies]

Micronutrients

Vitamins and minerals required in minute amounts (trace minerals) are micronutrients (see Chs. 4 and 5).

Water-soluble vitamins are vitamin C (ascorbic acid) and 8 members of the vitamin B complex: biotin, folate, niacin, pantothenic acid, riboflavin (vitamin B_2), thiamin (vitamin B_1), vitamin B_6 (pyridoxine), and vitamin B_{12} (cobalamin).

Fat-soluble vitamins are vitamins A (retinol), D (cholecalciferol and ergocalciferol), E (α-tocopherol), and K (phylloquinone and menaquinone).

Only vitamins A, E, and B_{12} are stored to any significant extent in the body; the other vitamins must be consumed regularly to maintain tissue health.

Essential trace minerals include chromium, copper, iodine, iron, manganese, molybdenum, selenium, and zinc. Except for chromium, each of these is incorporated into enzymes or hormones required in metabolism. Except for deficiencies of iron and zinc, micromineral deficiencies are uncommon in developed countries (see Ch. 5).

Other minerals (eg, aluminum, arsenic, boron, cobalt, fluoride, nickel, silicon, vanadium) have not been proved essential for people. Fluoride, although not essential, helps prevent tooth decay by forming a compound with Ca (CaF_2), which stabilizes the mineral matrix in teeth.

All trace minerals are toxic at high levels, and some (arsenic, nickel, and chromium) may cause cancer.

Other Dietary Substances

The daily human diet typically contains as many as 100,000 chemicals (eg, coffee contains 1000). Of these, only 300 are nutrients, only some of which are essential. However, many nonnutrients in foods are useful. For example, food additives (eg, preservatives, emulsifiers, antioxidants, stabilizers) improve the production and stability of foods. Trace components (eg, spices, flavors, odors, colors, phytochemicals, many other natural products) improve appearance and taste.

Fiber: Fiber occurs in various forms (eg, cellulose, hemicellulose, pectin, gums). It increases GI motility, prevents constipation, and helps control diverticular disease. Fiber is thought to accelerate the elimination of cancer-causing substances produced by bacteria in the large intestine. Epidemiologic evidence suggests an association between colon cancer and low fiber intake and a beneficial effect of fiber in patients with functional bowel disorders, Crohn's disease, obesity, and hemorrhoids. Soluble fiber (present in fruits, vegetables, oats, barley, and legumes) reduces the postprandial increase in blood glucose and insulin and can reduce cholesterol levels.

The typical Western diet is low in fiber (about 12 g/day) because of a high intake of highly refined wheat flour and a low intake of fruits and vegetables. Increasing fiber intake to about 30 g/day by consuming more vegetables, fruits, and high-fiber cereals and grains is generally recommended. However, very high fiber intake may reduce absorption of certain minerals.

Nutritional Requirements

Good nutrition aims to achieve and maintain a desirable body composition and high potential for physical and mental work. Balancing energy intake with energy expenditure is necessary for a desirable body weight. Energy expenditure depends on age, sex, weight (see Table 1-4), and metabolic and physical activity. If energy intake exceeds expenditure, weight is gained. Taking in about 100 calories/day more than needed results in a weight gain of about 4 to 5 kg in a year. If energy intake is less than expenditure, weight is lost.

Daily dietary requirements for essential nutrients also depend on age, sex, weight, and metabolic and physical activity. Every 5 yr, the Food and Nutrition Board of the National Academy of Sciences/National Research Council and the US Department of Agriculture (USDA) issues the dietary reference intakes (DRIs) for protein, energy, and some vitamins and minerals (see Tables 1-4, 4-1, and 5-2). For vitamins and minerals about which less is known, safe and adequate daily dietary intakes are estimated.

Pregnant women (see p. 2608) and infants (see p. 2703) have special nutritional needs.

The USDA publishes the Food Guide Pyramid, which specifies the number of recommended daily servings of various food groups. The recommendations are individualized based on age, sex, and physical activity (see Table 1-5). Generally, the recommended intake decreases with aging because physical activity tends to decrease, resulting in less energy expended. The new Food Guide Pyramid emphasizes the following:

• Increasing consumption of whole grains

• Increasing consumption of vegetables and fruits

• Substituting fat-free or low-fat milk products (or equivalents) for whole-fat milk products

• Reducing consumption of saturated fats and trans fatty acids

• Exercising regularly

Adequate fluid intake is also important.

Fats should constitute ≤ 30% of total calories, and saturated and trans fatty acids should constitute < 10%. Excess intake of saturated fats contributes to atherosclerosis. Substituting polyunsaturated fatty acids for saturated fats can decrease the risk of atherosclerosis. Routine use of nutritional supplements is not necessary or beneficial; some supplements can be harmful. For example, excess vitamin A can lead to hypervitaminosis A, with headaches, osteoporosis, and rash.

Nutrition in Clinical Medicine

Nutritional deficiencies can often worsen health outcomes (whether a disorder is present or not), and some disorders (eg, malabsorption) can cause nutritional deficiencies. Also, many patients (eg, elderly patients during acute hospitalization) have unsuspected nutritional deficiencies that require treatment. Many medical centers have multi-disciplinary nutrition support teams of physicians, nurses, dietitians, and pharmacists to help the clinician prevent, diagnose, and treat occult nutritional deficiencies.

Overnutrition may contribute to chronic disorders, such as cancer, hypertension, obesity, diabetes mellitus, and coronary artery disease. Dietary restrictions are necessary in many hereditary metabolic disorders (eg, galactosemia, phenylketonuria).

Evaluation of Nutritional Status

Indications for nutritional evaluation include undesirable body weight or body composition, suspicion of specific deficiencies or toxicities

[**Table 1-5.** Recommended Dietary Intake for 40-yr-Olds with Moderate Physical Activity*]

of essential nutrients, and, in infants and children, insufficient growth or development. Nutritional status should be evaluated routinely as part of the clinical examination for infants and children, the elderly, people taking several drugs, people with psychiatric disorders, and people with systemic disorders that last longer than several days.

Evaluating general nutritional status includes history, physical examination, and sometimes tests. If undernutrition is suspected, laboratory tests (eg, albumin levels) and skin tests for delayed hypersensitivity may be done (see p. 13). Body composition analysis (eg, skinfold measurements, bioelectrical impedance analysis) is used to estimate percentage of body fat and to evaluate obesity (see p. 58).

History includes questions about dietary intake, weight change, and risk factors for nutritional deficiencies and a focused review of systems (see Table 2-1 on p. 11). A dietitian can obtain a more detailed dietary history. It usually includes a list of foods eaten within the previous 24 h and a food questionnaire. A food diary may be used to record all foods eaten. The weighed ad libitum diet, in which the patient weighs and writes down all foods consumed, is the most accurate record.

A complete physical examination, including measurement of height and weight and distribution of body fat, should be done. Body mass index (BMI)—weight(kg)/height(m)^2, which adjusts weight for height (see Table 6-2 on p. 59), is more accurate than height and weight tables. There are standards for growth and weight gain in infants, children, and adolescents (see p. 2756).

Distribution of body fat is important. Disproportionate truncal obesity (ie, waist/hip ratio > 0.8) is associated with cardiovascular and cerebrovascular disorders, hypertension, and diabetes mellitus more often than fat located elsewhere. Measuring waist circumference in patients with a BMI of < 35 helps determine whether they have truncal obesity and helps predict risk of diabetes, hypertension, hypercholesterolemia, and cardiovascular disorders. Risk is increased if waist circumference is > 102 cm (> 40 in) in men or > 88 cm (> 35 in) in women.

Nutrient-Drug Interactions

Nutrition can affect the body's response to drugs; conversely, drugs can affect the body's nutrition.

Foods can enhance, delay, or decrease drug absorption. Foods impair absorption of many antibiotics. They can alter metabolism of drugs; eg, high-protein diets can accelerate metabolism of certain drugs by stimulating cytochrome P-450. Eating grapefruit can inhibit cytochrome P-450 34A, slowing metabolism of some drugs (eg, amiodarone, carbamazepine, cyclosporine, certain Ca channel blockers). Diets that alter the bacterial flora may markedly affect the overall metabolism of certain drugs. Some foods affect the body's response to drugs. For example, tyramine, a component of cheese and a potent vasoconstrictor, can cause hypertensive crisis in some patients who take monoamine oxidase inhibitors and eat cheese.

Nutritional deficiencies can affect drug absorption and metabolism. Severe energy and protein deficiencies reduce enzyme tissue concentrations and may impair the response to drugs by reducing absorption or protein binding and causing liver dysfunction. Changes in the GI tract can impair absorption and affect the response to a drug. Deficiency of Ca, Mg, or zinc may impair drug metabolism. Vitamin C deficiency decreases activity of drug-metabolizing enzymes, especially in the elderly.

Many drugs affect appetite, food absorption, and tissue metabolism (see Table 1-6). Some drugs (eg, metoclopramide) increase GI motility, decreasing food absorption. Other drugs (eg, opioids, anticholinergics) decrease GI motility. Some drugs are better tolerated if taken with food.

Certain drugs affect mineral metabolism. For example, diuretics, especially thiazides, and corticosteroids can deplete body K, increasing susceptibility to digoxin-induced cardiac arrhythmias. Repeated use of laxatives may deplete K. Cortisol, desoxycorticosterone, and aldosterone cause marked Na and water retention, at least temporarily; retention is much less with prednisone, prednisolone, and some other corticosteroid analogs. Sulfonylureas and lithium can impair the uptake or release of iodine by the thyroid. Oral contraceptives can lower blood zinc levels and increase copper levels. Certain antibiotics (eg, tetracyclines) reduce iron absorption, as can certain foods (eg, vegetables, tea, bran).

Certain drugs affect vitamin absorption or metabolism. Ethanol impairs thiamin utilization, and isoniazid interferes with niacin and pyridoxine metabolism. Ethanol and oral contraceptives inhibit folate (folic acid)

absorption. Most patients receiving phenytoin, phenobarbital, primidone, or phenothiazines develop folate deficiency, probably because hepatic microsomal drug-metabolizing enzymes are affected. Folate supplements may

[**Table 1-6.** Effects of Some Drugs on Nutrition]

make phenytoin less effective. Anticonvulsants can cause vitamin D deficiency. Malabsorption of vitamin B_{12} can occur with use of aminosalicylic acid, slow-release K iodide, colchicine, trifluoperazine, ethanol, and oral contraceptives. Oral contraceptives with a high progestin dose can cause depression, probably because of metabolically induced tryptophan deficiency.

Food Additives and Contaminants

Additives: Chemicals are often combined with foods to facilitate their processing and preservation or to enhance their desirability. Only amounts of additives shown to be safe by laboratory tests are permitted in commercially prepared foods.

Weighing the benefits of additives (eg, reduced waste, increased variety of available foods, protection against food-borne illness) against the risks is often complex. For example, nitrite, which is used in cured meats, inhibits the growth of *Clostridium botulinum* and improves flavor. However, nitrite converts to nitrosamines, which are carcinogens in animals. On the other hand, the amount of nitrite added to cured meat is small compared with the amount from naturally occurring food nitrates converted to nitrite by the salivary glands. Dietary vitamin C can reduce nitrite formation in the GI tract. Rarely, some additives (eg, sulfites) cause food hypersensitivity (allergy) reactions. Most of these reactions are caused by ordinary foods (see p. 1118).

Contaminants: Sometimes limited amounts of contaminants are allowed in foods because the contaminants cannot be completely eliminated without damaging the foods. Common contaminants are pesticides, heavy metals (lead, cadmium, mercury), nitrates (in green leafy vegetables), aflatoxins (in nuts and milk), growth-promoting hormones (in dairy products and meat), animal hairs and feces, and insect parts.

FDA-estimated safe levels are levels that have not caused illness or adverse effects in people. However, demonstrating a causal relationship between extremely low level exposures and adverse effects is difficult; long-term adverse effects, although unlikely, are still possible. Safe levels are often determined by consensus rather than by hard evidence.

Chapter 2. Undernutrition

Introduction

Undernutrition is a form of malnutrition. (Malnutrition also includes overnutrition—see Ch. 6). Undernutrition can result from inadequate ingestion of nutrients, malabsorption, impaired metabolism, loss of nutrients due to diarrhea, or increased nutritional requirements (as occurs in cancer or infection). Undernutrition progresses in stages; each stage usually takes considerable time to develop. First, nutrient levels in blood and tissues change, followed by intracellular changes in biochemical functions and structure. Ultimately, symptoms and signs appear.

Risk Factors

Undernutrition is associated with many disorders and circumstances, including poverty and social deprivation. Risk is also greater at certain times (ie, during infancy, early childhood, adolescence, pregnancy, breastfeeding, and old age).

Infancy and childhood: Infants and children are particularly susceptible to undernutrition because of their high demand for energy and essential nutrients. Because vitamin K does not readily cross the placenta, neonates may be deficient, so all are given a single injection of vitamin K within 1 h of birth to prevent hemorrhagic disease of the newborn, a life-threatening disorder (see pp. 46 and 2783). Infants fed only breast milk, which is typically low in vitamin D, are given supplemental vitamin D; they can develop vitamin B_{12} deficiency if the mother is a vegan. Inadequately fed infants and children are at risk of protein-energy undernutrition (PEU—previously called protein-energy malnutrition) and deficiencies of iron, folate (folic acid), vitamins A and C, copper, and zinc. During adolescence, nutritional requirements increase because the growth rate accelerates. Anorexia nervosa (see p. 1535) may affect adolescent girls in particular.

Pregnancy and breastfeeding: Requirements for nutrients increase during pregnancy and breastfeeding. Aberrations of diet, including pica (consumption of nonnutritive substances, such as clay and charcoal), may occur during pregnancy. Anemia due to iron deficiency is common, as is anemia due to folate deficiency, especially among women who have taken oral contraceptives. Vitamin D deficiency is common during late pregnancy, predisposing the child to decreased bone mass.

Old age: Aging—even when disease or dietary deficiency is absent—leads to sarcopenia (progressive loss of lean body mass), starting after age 40 and eventually amounting to a muscle loss of about 10 kg (22 lb) in men and 5 kg (11 lb) in women. Undernutrition contributes to sarcopenia, and sarcopenia accounts for many of the complications of undernutrition (eg, decreased nitrogen balance, increased susceptibility to infections). Causes of sarcopenia include the following:

- Decreased physical activity
- Decreased food intake
- Increased levels of cytokines (particularly interleukin-6)
- Decreased levels of growth hormone and mechano growth factor (insulin-like growth factor-3)
- In men, decreasing androgen levels

Aging decreases basal metabolic rate (due mainly to decreased fat-free mass), total body weight, height, and skeletal mass; aging increases mean body fat (as a percentage of body weight) to about 30% (from 20%) in men and to 40% (from 27%) in women.

From age 20 to 80, food intake decreases, especially in men. Anorexia due to aging itself has many causes, including reduced adaptive relaxation of the stomach's fundus, increased release and activity of

cholecystokinin (which produces satiation), and increased leptin (an anorectic hormone produced by fat cells). Diminished taste and smell can decrease eating pleasure but usually decrease food intake only slightly. Anorexia may have other causes (eg, loneliness, inability to shop or prepare meals, dementia, some chronic disorders, use of certain drugs). Depression is a common cause. Occasionally, anorexia nervosa (sometimes called anorexia tardive in the elderly), paranoia, or mania interferes with eating. Dental problems limit the ability to chew and subsequently to digest foods. Swallowing difficulties (eg, due to strokes, other neurologic disorders, esophageal candidiasis, or xerostomia) are common. Poverty or functional impairment limits access to nutrients.

The institutionalized elderly are at particular risk of PEU. They are often confused and may be unable to express hunger or preferences for foods. They may be physically unable to feed themselves. Chewing or swallowing may be very slow, making it tedious for another person to feed them enough food.

In the elderly, particularly the institutionalized elderly, inadequate intake and often decreased absorption or synthesis of vitamin D, increased demand for vitamin D, and inadequate exposure to sunshine contribute to osteomalacia (see p. 41).

Disorders and medical procedures: Diabetes, some chronic disorders that affect the GI tract, intestinal resection, and certain other GI surgical procedures tend to impair absorption of fat-soluble vitamins, vitamin B_{12}, Ca, and iron. Gluten enteropathy, pancreatic insufficiency, or other disorders can result in malabsorption. Decreased absorption possibly contributes to iron deficiency and osteoporosis. Liver disorders impair storage of vitamins A and B_{12} and interfere with metabolism of protein and energy sources. Renal insufficiency predisposes to protein, iron, and vitamin D deficiencies. Anorexia causes some patients with cancer or depression and many with AIDS to consume inadequate amounts of food. Infections, trauma, hyperthyroidism, extensive burns, and prolonged fever increase metabolic demands. Any condition that increases cytokines may be accompanied by muscle loss, lipolysis, low albumin levels, and anorexia.

Vegetarian diets: Iron deficiency can occur in ovo-lacto vegetarians (although such a diet can be compatible with good health). Vegans may develop vitamin B_{12} deficiency unless they consume yeast extracts or Asian-style fermented foods. Their intake of Ca, iron, and zinc also tends to be low. A fruit-only diet is not recommended because it is deficient in protein, Na, and many micronutrients.

Fad diets: Some fad diets result in vitamin, mineral, and protein deficiencies; cardiac, renal, and metabolic disorders; and sometimes death. Very low calorie diets (< 400 kcal/day) cannot sustain health for long.

Drugs and nutritional supplements: Many drugs (eg, appetite suppressants, digoxin) decrease appetite; others impair nutrient absorption or metabolism. Some drugs (eg, stimulants) have catabolic effects. Certain drugs can impair absorption of many nutrients; eg, anticonvulsants can impair absorption of vitamins.

Alcohol or drug dependency: Patients with alcohol or drug dependency may neglect their nutritional needs. Absorption and metabolism of nutrients may also be impaired. IV drug addicts typically become undernourished, as do

[
Table 2-1. Symptoms and Signs of Nutritional Deficiency]

alcoholics who consume ≥ 1 quart of hard liquor/day. Alcoholism can cause deficiencies of Mg, zinc, and certain vitamins, including thiamin.

Symptoms and Signs

Symptoms vary depending on the cause and type of undernutrition (see p. 15 and Chs. 4 and 5).

Evaluation

Diagnosis is based on results of medical and diet histories, physical examination, body composition analysis (see p. 58), and selected laboratory tests.

History: History should include questions about dietary intake (see Fig. 2-1), recent changes in weight, and risk factors for undernutrition, including drug and alcohol use. Unintentional loss of ≥ 10% of usual body weight during a 3-mo period indicates a high probability of undernutrition. Social history should include questions about whether money is available for food and whether the patient can shop and cook.

Review of systems should focus on symptoms of nutritional deficiencies (see Table 2-1). For example, impaired night vision may indicate vitamin A deficiency.

Physical examination: Physical examination should include measurement of height and weight, inspection of body fat distribution, and anthropometric measurements of lean body mass. Body mass index (BMI = weight(kg)/height(m)^2) adjusts weight for height (see Table 6-2 on p. 59). If weight is < 80% of what is predicted for the patient's height or if BMI is ≤ 18, undernutrition should be suspected. Although these findings are useful in diagnosing undernutrition and are acceptably sensitive, they lack specificity.

[**Fig. 2-1.** Mini nutritional assessment.]

The mid upper arm muscle area estimates lean body mass. This area is derived from the triceps skinfold thickness (TSF) and mid upper arm circumference. Both are measured at the same site, with the patient's right arm in a relaxed position. The average mid upper arm circumference is about 32 ± 5 cm for men and 28 ± 6 cm for women. The formula for calculating the mid upper arm muscle area in cm^2 is as follows:

$$\frac{[\text{midarm circumference (cm)} - (3.14 \times \text{TSF cm})]^2}{4\pi} - 10\,(\text{males}) \text{ or } -6.5\,(\text{females})$$

This formula corrects the upper arm area for fat and bone. Average values for the mid upper arm muscle area are 54 ± 11 cm^2 for men and 30 ± 7 cm^2 for women. A value < 75% of this standard (depending on age) indicates depletion of lean body mass (see Table 2-2). This measurement may be affected by physical activity, genetic factors, and age-related muscle loss.

Physical examination should focus on signs of specific nutritional deficiencies. Signs of PEU (eg, edema, muscle wasting, skin changes) should be sought. Examination should also focus on signs of conditions that could predispose to nutritional deficiencies, such as dental problems. Mental status should be assessed, because depression and cognitive impairment can lead to weight loss.

The widely used Subjective Global Assessment (SGA) uses information from the patient history (eg, weight loss, change in intake, GI symptoms), physical examination findings (eg, loss of muscle and subcutaneous fat, edema, ascites), and the clinician's judgment of the patient's nutritional status. The Mini Nutritional Assessment (MNA) has been validated and is widely used, especially for elderly patients (see Fig. 2-1). The Simplified Nutrition Assessment Questionnaire (SNAQ), a simple, validated method of predicting future weight loss, may be used (see Fig. 2-2).

Testing: The extent of laboratory testing needed is unclear and may depend on the patient's circumstances. If the cause is obvious and correctable (eg, a wilderness survival situation), testing is probably of little benefit. Other patients may require more detailed evaluation.

Serum albumin measurement is the laboratory test most often used. Decreases in albumin and other proteins (eg, prealbumin [transthyretin], transferrin, retinol-binding protein) may indicate protein deficiency or PEU. As undernutrition progresses, albumin decreases slowly; prealbumin, transferrin, and retinol-binding protein decrease rapidly. Albumin measurement is inexpensive and predicts morbidity and

mortality better than measurement of the other proteins. However, the correlation of albumin with morbidity and mortality may be related to nonnutritional as well as nutritional factors. Inflammation produces cytokines that cause albumin and other nutritional protein markers to extravasate, decreasing serum levels. Because prealbumin, transferrin, and retinol-binding protein decrease more rapidly during starvation than does albumin, their measurements are sometimes used to diagnose or assess the severity of acute starvation. However, whether they are more sensitive or specific than albumin is unclear.

Total lymphocyte count, which often decreases as undernutrition progresses, may be determined. Undernutrition causes a marked decline in CD4+ T lymphocytes, so this count may not be useful in patients who have AIDS.

Skin tests using antigens can detect impaired cell-mediated immunity in PEU and in some other disorders of undernutrition (see p. 1098).

Other laboratory tests, such as measuring vitamin and mineral levels, are used selectively to diagnose specific deficiencies.

[**Table 2-2.** Mid Upper Arm Muscle Area in Adults]

[**Figure 2-2.** Simplified Nutrition Assessment Questionnaire (SNAQ).]

Protein-Energy Undernutrition

Protein-energy undernutrition (PEU), previously called protein-energy malnutrition, is an energy deficit due to chronic deficiency of all macronutrients. It commonly includes deficiencies of many micronutrients. PEU can be sudden and total (starvation) or gradual. Severity ranges from subclinical deficiencies to obvious wasting (with edema, hair loss, and skin atrophy) to starvation. Multiple organ systems are often impaired. Diagnosis usually involves laboratory testing, including serum albumin. Treatment consists of correcting fluid and electrolyte deficits with IV solutions, then gradually replenishing nutrients, orally if possible.

In developed countries, PEU is common among the institutionalized elderly (although often not suspected) and among patients with disorders that decrease appetite or impair nutrient digestion, absorption, or metabolism. In developing countries, PEU affects children who do not consume enough calories or protein.

Classification and Etiology

PEU is graded as mild, moderate, or severe. Grade is determined by calculating weight as a percentage of expected weight for length or height using international standards (normal, 90 to 110%; mild PEU, 85 to 90%; moderate, 75 to 85%; severe, <75%).

PEU may be primary or secondary. Primary PEU is caused by inadequate nutrient intake. Secondary PEU results from disorders or drugs that interfere with nutrient use.

Primary PEU: Worldwide, primary PEU occurs mostly in children and the elderly who lack access to nutrients, although a common cause in the elderly is depression. PEU can also result from fasting or anorexia nervosa. Child or elder abuse may be a cause.

In children, chronic primary PEU has 2 common forms: marasmus and kwashiorkor. The form depends on the balance of nonprotein and protein sources of energy. Starvation is an acute severe form of primary PEU.

Marasmus (also called the dry form of PEU) causes weight loss and depletion of fat and muscle. In developing countries, marasmus is the most common form of PEU in children.

Kwashiorkor (also called the wet, swollen, or edematous form) is associated with premature abandonment

of breastfeeding, which typically occurs when a younger sibling is born, displacing the older child from the breast. So children with kwashiorkor tend to be older than those with marasmus. Kwashiorkor may also result from an acute illness, often gastroenteritis or another infection (probably secondary to cytokine release), in a child who already has PEU. A diet that is more deficient in protein than energy may be more likely to cause kwashiorkor than marasmus. Less common than marasmus, kwashiorkor tends to be confined to specific parts of the world, such as rural Africa, the Caribbean, and the Pacific islands. In these areas, staple foods (eg, yams, cassavas, sweet potatoes, green bananas) are low in protein and high in carbohydrates. In kwashiorkor, cell membranes leak, causing extravasation of intravascular fluid and protein, resulting in peripheral edema.

Starvation is a complete lack of nutrients. It occasionally occurs when food is available (as in fasting or anorexia nervosa) but usually occurs because food is unavailable (eg, during famine or wilderness exposure).

Secondary PEU: This type most commonly results from the following:

- Disorders that affect GI function: These disorders can interfere with digestion (eg, pancreatic insufficiency), absorption (eg, enteritis, enteropathy), or lymphatic transport of nutrients (eg, retroperitoneal fibrosis, Milroy's disease).

- Wasting disorders: In wasting disorders (eg, AIDS, cancer) and renal failure, catabolism causes cytokine excess, resulting in undernutrition via anorexia and cachexia (wasting of muscle and fat). End-stage heart failure can cause cardiac cachexia, a severe form of undernutrition; mortality rate is particularly high. Factors contributing to cardiac cachexia may include passive hepatic congestion (causing anorexia), edema of the intestinal tract (impairing absorption), and, in advanced disease, increased O_2 requirement due to anaerobic metabolism. Wasting disorders can decrease appetite or impair metabolism of nutrients.

- Conditions that increase metabolic demands: These conditions include infections, hyperthyroidism, pheochromocytoma, other endocrine disorders, burns, trauma, surgery, and other critical illnesses.

Pathophysiology

The initial metabolic response is decreased metabolic rate. To supply energy, the body first breaks down adipose tissue. However, later when these tissues are depleted, the body may use protein for energy, resulting in a negative nitrogen balance. Visceral organs and muscle are broken down and decrease in weight. Loss of organ weight is greatest in the liver and intestine, intermediate in the heart and kidneys, and least in the nervous system.

Symptoms and Signs

Symptoms of moderate PEU can be constitutional or involve specific organ systems. Apathy and irritability are common. The patient is weak, and work capacity decreases. Cognition and sometimes consciousness are impaired. Temporary lactose deficiency and achlorhydria develop. Diarrhea is common and can be aggravated by deficiency of intestinal disaccharidases, especially lactase (see p. 157). Gonadal tissues atrophy. PEU can cause amenorrhea in women and loss of libido in men and women.

Wasting of fat and muscle is common in all forms of PEU. In adult volunteers who fasted for 30 to 40 days, weight loss was marked (25% of initial weight). If starvation is more prolonged, weight loss may reach 50% in adults and possibly more in children.

In adults, cachexia is most obvious in areas where prominent fat depots normally exist. Muscles shrink and bones protrude. The skin becomes thin, dry, inelastic, pale, and cold. The hair is dry and falls out easily, becoming sparse. Wound healing is impaired. In elderly patients, risk of hip fractures and pressure (decubitus) ulcers increases.

With acute or chronic severe PEU, heart size and cardiac output decrease; pulse slows

[
Table 2-3. Values Commonly Used to Grade the Severity of Protein-Energy Undernutrition]

and BP falls. Respiratory rate and vital capacity decrease. Body temperature falls, sometimes contributing to death. Edema, anemia, jaundice, and petechiae can develop. Liver, kidney, or heart failure may occur.

Cell-mediated immunity is impaired, increasing susceptibility to infections. Bacterial infections (eg, pneumonia, gastroenteritis, otitis media, UTIs, sepsis) are common in both forms of PEU. Infections result in release of cytokines, which cause anorexia, worsen muscle wasting, and cause a marked decrease in serum albumin levels.

Marasmus in infants causes hunger, weight loss, growth retardation, and wasting of subcutaneous fat and muscle. Ribs and facial bones appear prominent. Loose, thin skin hangs in folds.

Kwashiorkor is characterized by peripheral and periorbital edema. The abdomen protrudes because abdominal muscles are weakened, the intestine is distended, the liver enlarges, and ascites is present. The skin is dry, thin, and wrinkled; it can become hyperpigmented and fissured and later hypopigmented, friable, and atrophic. Skin in different areas of the body may be affected at different times. The hair can become thin, reddish brown, or gray. Scalp hair falls out easily, eventually becoming sparse, but eyelash hair may grow excessively. Alternating episodes of undernutrition and adequate nutrition may cause the hair to have a dramatic "striped flag" appearance. Affected children may be apathetic but become irritable when held.

Total starvation is fatal in 8 to 12 wk. Thus, certain symptoms of PEU do not have time to develop.

Diagnosis

• Diagnosis usually based on history

• To determine severity: BMI, serum albumin, total lymphocyte count, CD4+ count, serum transferrin

• To diagnose complications and consequences: CBC, electrolytes, BUN, glucose, Ca, Mg, phosphate

Diagnosis can be based on history when dietary intake is markedly inadequate. The cause of inadequate intake, particularly in children, needs to be identified. In children and adolescents, child abuse and anorexia nervosa should be considered.

Physical examination findings can usually confirm the diagnosis. Laboratory tests are required if dietary history does not clearly indicate inadequate caloric intake. Measurement of serum albumin, total lymphocyte count, CD4+ T lymphocytes, transferrin, and response to skin antigens may help determine the severity of PEU (see Table 2-3) or confirm the diagnosis in borderline cases. Many other test results may be abnormal: eg, decreased levels of hormones, vitamins, lipids, cholesterol, prealbumin, insulin growth factor-1, fibronectin, and retinol-binding protein. Urinary creatine and methylhistidine levels can be used to gauge the degree of muscle wasting. Because protein catabolism slows, urinary urea level also decreases. These findings rarely affect treatment.

Laboratory tests are required to identify causes of suspected secondary PEU. C-reactive protein or soluble interleukin-2 receptor should be measured when the cause of undernutrition is unclear; these measurements can help determine whether there is cytokine excess. Thyroid function tests may also be done.

Other laboratory tests can detect associated abnormalities that may require treatment. Serum electrolytes, BUN, glucose, and possibly levels of Ca, Mg, and phosphate should be measured. Levels of serum glucose, electrolytes (especially K, occasionally Na), phosphate, Ca, and Mg are usually low. BUN is often low unless renal failure is present. Metabolic acidosis may be present. CBC is usually obtained; normocytic anemia (usually due to protein deficiency) or microcytic anemia (due to simultaneous iron deficiency) is usually present.

Stool cultures should be obtained and checked for ova and parasites if diarrhea is severe or does not resolve with treatment. Sometimes urinalysis, urine culture, blood cultures, tuberculin testing, and a chest x-ray are used to diagnose occult infections because people with PEU may have a muted response to infections.

Prognosis

Children: In children, mortality varies from 5 to 40%. Mortality rates are lower in children with mild PEU and those given intensive care. Death in the first days of treatment is usually due to electrolyte deficits, sepsis, hypothermia, or heart failure. Impaired consciousness, jaundice, petechiae, hyponatremia, and persistent diarrhea are ominous signs. Resolution of apathy, edema, and anorexia is a favorable sign. Recovery is more rapid in kwashiorkor than in marasmus.

Long-term effects of PEU in children are not fully documented. Some children develop chronic malabsorption and pancreatic insufficiency. In very young children, mild intellectual disability may develop and persist until at least school age. Permanent cognitive impairment may occur, depending on the duration, severity, and age at onset of PEU.

Adults: In adults, PEU can result in morbidity and mortality (eg, progressive weight loss increases mortality rate for elderly patients in nursing homes). In elderly patients, PEU increases the risk of morbidity and mortality due to surgery, infections, or other disorders. Except when organ failure occurs, treatment is uniformly successful.

Treatment

• Usually, oral feeding

• Possibly avoidance of lactose (eg, if persistent diarrhea suggests lactose intolerance)

• Supportive care (eg, environmental changes, assistance with feeding, orexigenic drugs)

• For children, feeding delayed 24 to 48 h

Worldwide, the most important preventive strategy is to reduce poverty and improve nutritional education and public health measures.

Mild or moderate PEU, including brief starvation, can be treated by providing a balanced diet, preferably orally. Liquid oral food supplements (usually lactose-free) can be used when solid food cannot be adequately ingested. Diarrhea often complicates oral feeding because starvation makes the GI tract more likely to move bacteria into Peyer's patches, facilitating infectious diarrhea. If diarrhea persists (suggesting lactose intolerance), yogurt-based rather than milk-based formulas are given because people with lactose intolerance can tolerate yogurt. Patients should also be given a multivitamin supplement.

Severe PEU or prolonged starvation requires treatment in a hospital with a controlled diet. The first priority is to correct fluid and electrolyte abnormalities (see Ch. 97) and treat infections. Next is to supply macronutrients orally or, if necessary (eg, when swallowing is difficult), through a feeding tube, a nasogastric tube (usually), or a gastrostomy tube. Parenteral nutrition is indicated if malabsorption is severe (see p. 23).

Other treatments may be needed to correct specific deficiencies, which may become evident as weight increases. To avoid deficiencies, patients should take micronutrients at about twice the recommended daily allowance (RDA) until recovery is complete.

Children: Underlying disorders should be treated. For children with diarrhea, feeding may be delayed 24 to 48 h to avoid making the diarrhea worse; during this interval, children require oral or IV rehydration. Feedings are given often (6 to 12 times/day) but, to avoid overwhelming the limited intestinal absorptive capacity, are limited to small amounts (< 100 mL). During the first week, milk-based formulas with supplements added are usually given in progressively increasing amounts; after a week, the full amounts

of 175 kcal/kg and 4 g of protein/kg can be given. Twice the RDA of micronutrients should be given, using commercial multivitamin supplements. After 4 wk, the formula can be replaced with whole milk plus cod liver oil and solid foods, including eggs, fruit, meats, and yeast.

Energy distribution among macronutrients should be about 16% protein, 50% fat, and 34% carbohydrate. An example is a combination of powdered cow's skimmed milk (110 g), sucrose (100 g), vegetable oil (70 g), and water (900 mL). Many other formulas (eg, whole [full-fat] fresh milk plus corn oil and maltodextrin) can be used. Milk powders used in formulas are diluted with water.

Usually, supplements should be added to formulas:

- Mg 0.4 mEq/kg/day IM is given for 7 days.
- B-complex vitamins at twice the RDA are given parenterally for the first 3 days, usually with vitamin A, phosphorus, zinc, manganese, copper, iodine, fluoride, molybdenum, and selenium.
- Because absorption of oral iron is poor in children with PEU, oral or IM iron supplementation may be necessary.

Parents are taught about nutritional requirements.

Adults: Underlying disorders should be treated. For example, if AIDS or cancer results in excess cytokine production, megestrol acetate or medroxyprogesterone may improve food intake. However, because these drugs dramatically decrease testosterone in men (possibly causing muscle loss), testosterone should be replaced. Because these drugs can cause adrenal insufficiency, they should be used only short-term (< 3 mo).

In patients with functional limitations, home delivery of meals and feeding assistance are key.

An orexigenic drug, such as the cannabis extract dronabinol, should be given to patients with anorexia when no cause is obvious or to patients at the end of life when anorexia impairs quality of life. An anabolic steroid (eg, enanthate, nandrolone, testosterone) or growth hormone can benefit patients with cachexia due to renal failure and possibly elderly patients (eg, by increasing lean body mass or possibly by improving function).

Correction of PEU in adults generally resembles that in children; feedings are often limited to small amounts. However, for most adults, feeding does not need to be delayed. A commercial formula for oral feeding can be used. Daily nutrient supply should be given at a rate of 60 kcal/kg and 1.2 to 2 g of protein/kg. If liquid oral supplements are used with solid food, they should be given at least 1 h before meals so that the amount of food eaten at the meal is not reduced.

Treatment of institutionalized elderly patients with PEU requires multiple interventions:

- Environmental measures (eg, making the dining area more attractive)
- Feeding assistance
- Changes in diet (eg, use of food enhancers and caloric supplements between meals)
- Treatment of depression and other underlying disorders
- Use of orexigenics, anabolic steroids, or both

The long-term use of gastrostomy tube feeding is essential for patients with severe dysphagia; its use in patients with dementia is controversial. Increasing evidence supports the avoidance of unpalatable therapeutic diets (eg, low salt, diabetic, low cholesterol) in institutionalized patients because these diets decrease food intake and may cause severe PEU.

Complications of treatment: Treatment of PEU can cause complications (refeeding syndrome), including fluid overload, electrolyte deficits, hyperglycemia, cardiac arrhythmias, and diarrhea. Diarrhea is usually mild and resolves; however, diarrhea in patients with severe PEU occasionally causes severe dehydration or death. Causes of diarrhea (eg, sorbitol used in elixir tube feedings, *Clostridium difficile* if the patient has received an antibiotic) may be correctable. Osmotic diarrhea due to excess calories is rare in adults and should be considered only when other causes have been excluded.

Because PEU can impair cardiac and renal function, hydration can cause intravascular volume overload. Treatment decreases extra-cellular K and Mg. Depletion of K or Mg may cause arrhythmias. Carbohydrate metabolism that occurs during treatment stimulates insulin release, which drives phosphate into cells. Hypophosphatemia can cause muscle weakness, paresthesias, seizures, coma, and arrhythmias. Because phosphate levels can change rapidly during parenteral feeding, levels should be measured regularly.

During treatment, endogenous insulin may become ineffective, leading to hyperglycemia. Dehydration and hyperosmolarity can result. Fatal ventricular arrhythmias can develop, possibly caused by a prolonged QT interval.

Carnitine Deficiency

Carnitine deficiency results from inadequate intake of or inability to metabolize the amino acid carnitine. It can cause a heterogeneous group of disorders. Muscle metabolism is impaired, causing myopathy, hypoglycemia, or cardiomyopathy. Infants typically present with hypoglycemic, hypoketotic encephalopathy. Most often, treatment consists of dietary L-carnitine.

The amino acid carnitine is required for the transport of long-chain fatty acyl coenzyme A (CoA) esters into myocyte mitochondria, where they are oxidized for energy. Carnitine is obtained from foods, particularly animal-based foods, and via endogenous synthesis.

Causes of carnitine deficiency include the following:

- Inadequate intake (eg, due to fad diets, lack of access, or long-term TPN)
- Inability to metabolize carnitine due to enzyme deficiencies (eg, carnitine palmitoyltransferase deficiency, methylmalonicaciduria, propionicacidemia, isovalericacidemia)
- Decreased endogenous synthesis of carnitine due to a severe liver disorder
- Excess loss of carnitine due to diarrhea, diuresis, or hemodialysis
- A hereditary disorder in which carnitine leaks from renal tubules
- Increased requirements for carnitine when ketosis is present or demand for fat oxidation is high (eg, during a critical illness such as sepsis or major burns; after major surgery of the GI tract)
- Decreased muscle carnitine levels due to mitochondrial impairment (eg, due to use of zidovudine)
- Use of valproate

The deficiency may be generalized (systemic) or may affect mainly muscle (myopathic).

Symptoms and Signs

Symptoms and the age at which symptoms appear depend on the cause. Carnitine deficiency may cause muscle necrosis, myoglobinuria, lipid-storage myopathy, hypoglycemia, fatty liver, and hyperammonemia with muscle aches, fatigue, confusion, and cardiomyopathy.

Diagnosis

In neonates, carnitine palmitoyltransferase deficiency is diagnosed using mass spectrometry to screen blood. Prenatal diagnosis may be possible using amniotic villous cells. In adults, the definitive diagnosis is based on acylcarnitine levels in serum, urine, and tissues (muscle and liver for systemic deficiency; muscle only for myopathic deficiency).

Treatment

• Avoidance of fasting and strenuous exercise

• Dietary interventions, based on cause

Carnitine deficiency due to inadequate dietary intake, increased requirements, excess losses, decreased synthesis, or (sometimes) enzyme deficiencies can be treated by giving L-carnitine 25 mg/kg po q 6 h.

All patients must avoid fasting and strenuous exercise. Consuming uncooked cornstarch at bedtime prevents early morning hypoglycemia. Some patients require supplementation with medium-chain triglycerides and essential fatty acids (eg, linoleic acid, linolenic acid). Patients with a fatty acid oxidation disorder require a high-carbohydrate, low-fat diet.

Essential Fatty Acid Deficiency

Essential fatty acid (EFA) deficiency is rare, occurring most often in infants fed diets deficient in EFAs. Signs include scaly dermatitis, alopecia, thrombocytopenia, and, in children, growth retardation. Diagnosis is clinical. Dietary replenishment of EFAs reverses the deficiency.

The EFAs linoleic and linolenic acid are substrates for the endogenous synthesis of other fatty acids that are needed for many physiologic processes, including maintaining the integrity of skin and cell membranes and synthesizing prostaglandins and leukotrienes. For example, eicosapentaenoic acid and docosahexaenoic acid, synthesized from EFAs, are important components of the brain and retina.

For EFA deficiency to develop, dietary intake must be very low. Even small amounts of EFAs can prevent EFA deficiency. Cow's milk has only about 25% of the linoleic acid in human milk, but when ingested in normal amounts, it has enough linoleic acid to prevent EFA deficiency. Total fat intake of people in many developing countries may be very low, but the fat is often vegetable based, with large amounts of linoleic acid and enough linolenic acid to prevent EFA deficiency.

Babies fed a formula low in linoleic acid, such as a skim-milk formula, can develop EFA deficiency. EFA deficiency used to result from long-term TPN if fat was not included. But now, most TPN solutions include fat emulsions to prevent EFA deficiency. In patients with fat malabsorption or increased metabolic needs (eg, because of surgery, multiple trauma, or burns), laboratory evidence of EFA deficiency may be present without clinical signs.

Dermatitis due to EFA deficiency is generalized and scaly; in infants, it can resemble congenital ichthyosis. The dermatitis increases water loss from the skin.

Diagnosis is usually clinical; however, laboratory assays are now available in large research centers.

Treatment consists of dietary EFAs, reversing the deficiency.

Chapter 3. Nutritional Support

Introduction

Many undernourished patients need nutritional support, which aims to increase lean body mass. Oral feeding can be difficult for some patients with anorexia or with eating or absorption problems. Behavioral measures that sometimes enhance oral intake include the following:

• Encouraging patients to eat

• Heating or seasoning foods

• Providing favorite or strongly flavored foods

• Encouraging patients to eat small portions

• Scheduling around meals

• Assisting patients with feeding

If behavioral measures are ineffective, nutritional support—oral, enteral tube, or parenteral nutrition—is indicated, except sometimes for dying or severely demented patients (see p. 25).

Predicting Nutritional Requirements

Nutritional requirements are predicted so that interventions can be planned. Requirements can be estimated by formulas or measured by indirect calorimetry. Indirect calorimetry requires use of a metabolic cart (a closed rebreathing system that determines energy expenditure based on total CO_2 production), which requires special expertise and is not always available. Thus, total energy expenditure (TEE) and protein requirements usually are estimated.

Energy expenditure: TEE varies based on the patient's weight, activity level, and degree of metabolic stress (metabolic demands); TEE ranges from 25 kcal/kg/day for people who are sedentary and not under stress to about 40 kcal/kg/day for people who are critically ill. TEE equals the sum of

• Resting metabolic rate (RMR, or resting energy expenditure rate), which is normally about 70% of TEE

• Energy dissipated by metabolism of food (10% of TEE)

• Energy expended during physical activity (20% of TEE)

Undernutrition can decrease RMR up to 20%. Conditions that increase metabolic stress (eg, critical illness, infection, inflammation, trauma, surgery) can increase RMR but rarely by > 50%.

The Mifflin-St. Jeor equation estimates RMR more precisely and with fewer errors than the commonly used Harris-Benedict equation, usually providing results that are within 20% of those measured by indirect calorimetry. The Mifflin-St. Jeor equation estimates RMR as follows:

Men: kcal / day = 66 + (13.7 × wt[kg]) + (5 × height[cm]) - (6.8 × age)
Women: kcal / day = 665 + (9.6 × wt[kg]) + (1.8 × height[cm]) - (4.7 × age)

TEE can be estimated by adding about 10% (for sedentary people) to about 40% (for people who are critically ill) to RMR.

Protein requirements: For healthy people, protein requirements are estimated at 0.8 g/kg/day. However, for patients with metabolic stress or kidney failure and for elderly patients, requirements may be higher (see

Table 3-1).

Assessing Response to Nutritional Support

There is no gold standard to assess response. Clinicians commonly use indicators of lean body mass such as the following:

• Body mass index (BMI)

• Body composition analysis

• Body fat distribution (see pp. 11 and 58)

Nitrogen balance, response to skin antigens, muscle strength measurement, and indirect calorimetry can also be used.

[**Table 3-1.** Estimated Adult Daily Protein Requirement]

Nitrogen balance, which reflects the balance between protein needs and supplies, is the difference between amount of nitrogen ingested and amount lost. A positive balance (ie, more ingested than lost) implies adequate intake. Precise measurement is impractical, but estimates help assess response to nutritional support. Nitrogen intake is estimated from protein intake: nitrogen (g) equals protein (g)/6.25. Estimated nitrogen losses consist of urinary nitrogen losses (estimated by measuring urea nitrogen content of an accurately obtained 24-h urine collection) plus stool losses (estimated at 1 g/day if stool is produced; negligible if stool is not produced) plus insensible and other unmeasured losses (estimated at 3 g).

Response to skin antigens, a measure of delayed hypersensitivity, often increases to normal as undernourished patients respond to nutritional support. However, other factors can affect response to skin antigens.

Muscle strength indirectly reflects increases in lean body mass. It can be measured quantitatively, by hand-grip dynamometry, or electrophysiologically (typically by stimulating the ulnar nerve with an electrode).

Levels of acute-phase reactant serum proteins (particularly short-lived proteins such as prealbumin [transthyretin], retinol-binding protein, and transferrin) sometimes correlate with improved nutritional status, but these levels correlate better with inflammatory conditions.

Enteral Tube Nutrition

Enteral tube nutrition is indicated for patients who have a functioning GI tract but cannot ingest enough nutrients orally because they are unable or unwilling to take oral feedings. Compared with parenteral nutrition, enteral nutrition has the following advantages:

• Better preservation of the structure and function of the GI tract

• Lower cost

• Probably fewer complications, particularly infections

Specific indications for enteral nutrition include the following:

• Prolonged anorexia

• Severe protein-energy undernutrition

• Coma or depressed sensorium

• Liver failure

• Inability to take oral feedings due to head or neck trauma or neurologic disorders

• Critical illnesses (eg, burns) causing metabolic stress

Other indications may include bowel preparation for surgery in seriously ill or undernourished patients, closure of enterocutaneous fistulas, and small-bowel adaptation after massive intestinal resection or in disorders that may cause malabsorption (eg, Crohn's disease).

Procedure: If tube feeding is needed for ≤ 4 to 6 wk, a small-caliber, soft nasogastric or nasoenteric (eg, nasoduodenal) tube made of silicone or polyurethane is usually used. If a nasal injury or deformity makes nasal placement difficult, an orogastric or other oroenteric tube can be placed.

Tube feeding for > 4 to 6 wk usually requires a gastrostomy or jejunostomy tube, placed endoscopically, surgically, or radiologically. Choice depends on physician capabilities and patient preference.

Jejunostomy tubes are useful for patients with contraindications to gastrostomy (eg, gastrectomy, bowel obstruction proximal to the jejunum). However, these tubes do not pose less risk of tracheobronchial aspiration than gastrostomy tubes, as is often thought. Jejunostomy tubes are easily dislodged and are usually used only for inpatients.

Feeding tubes are surgically placed if endoscopic and radiologic placement is unavailable, technically impossible, or unsafe (eg, because of overlying bowel). Open or laparoscopic techniques can be used.

Formulas: Liquid formulas commonly used include feeding modules and polymeric or other specialized formulas.

Feeding modules are commercially available products that contain a single nutrient, such as proteins, fats, or carbohydrates. Feeding modules may be used individually to treat a specific deficiency or combined with other formulas to completely satisfy nutritional requirements.

Polymeric formulas (including blenderized food and milk-based or lactose-free commercial formulas) are commercially available and generally provide a complete, balanced diet. For oral or tube feedings, they are usually preferred to feeding modules. In hospitalized patients, lactose-free formulas are the most commonly used polymeric formulas. However, milk-based formulas tend to taste better than lactose-free formulas. Patients with lactose intolerance may be able to tolerate milk-based formulas given slowly by continuous infusion.

Specialized formulas include hydrolyzed protein or sometimes amino acid formulas, which are used for patients who have difficulty digesting complex proteins. However, these formulas are expensive and usually unnecessary. Most patients with pancreatic insufficiency, if given enzymes, and most patients with malabsorption can digest complex proteins. Other specialized formulas (eg, calorie- and protein-dense formulas for patients whose fluids are restricted, fiber-enriched formulas for constipated patients) may be helpful.

Administration: Patients should be sitting upright at 30 to 45° during tube feeding and for 1 to 2 h afterward to minimize incidence of nosocomial aspiration pneumonia and to allow gravity to help propel the food. Tube feedings are given in boluses several times a day or by continuous infusion. Bolus feeding is more physiologic and may be preferred for patients with diabetes. Continuous infusion is necessary if boluses cause nausea.

[
Table 3-2. Complications of Enteral Tube Nutrition]

For bolus feeding, total daily volume is divided into 4 to 6 separate feedings, which are injected through

the tube with a syringe or infused by gravity from an elevated bag. After feedings, the tube is flushed with water to prevent clogging.

Nasogastric or nasoduodenal tube feeding often causes diarrhea initially; thus, feedings are usually started with small amounts of dilute preparations and increased as tolerated. Most formulas contain 0.5, 1, or 2 kcal/mL. Formulas with higher caloric concentration (less water per calorie) may cause decreased gastric emptying and thus higher gastric residuals than when more dilute formulas with the same number of calories are used. Initially, a 1-kcal/mL commercially prepared solution may be given undiluted at 50 mL/h or, if patients have not been fed for a while, at 25 mL/h. Usually, these solutions do not supply enough water, particularly if vomiting, diarrhea, sweating, or fever has increased water loss. Extra water is supplied as boluses via the feeding tube or IV. After a few days, the rate or concentration can be increased as needed to meet caloric and water needs.

Jejunostomy tube feeding requires greater dilution and smaller volumes. Feeding usually begins at a concentration of ≤ 0.5 kcal/mL and a rate of 25 mL/h. After a few days, concentrations and volumes can be increased to eventually meet caloric and water needs. Usually, the maximum that can be tolerated is 0.8 kcal/mL at 125 mL/h, providing 2400 kcal/day.

Complications: Complications are common and can be serious (see Table 3-2).

Total Parenteral Nutrition

Parenteral nutrition is by definition given IV.

Partial parenteral nutrition supplies only part of daily nutritional requirements, supplementing oral intake. Many hospitalized patients are given dextrose or amino acid solutions by this method.

Total parenteral nutrition (TPN) supplies all daily nutritional requirements. TPN can be used in the hospital or at home. Because TPN solutions are concentrated and can cause thrombosis of peripheral veins, a central venous catheter is usually required.

Parenteral nutrition should not be used routinely in patients with an intact GI tract. Compared with enteral nutrition, it causes more complications, does not preserve GI tract structure and function as well, and is more expensive.

Indications: TPN may be the only feasible option for patients who do not have a functioning GI tract or who have disorders requiring complete bowel rest, such as the following:

• Some stages of Crohn's disease or ulcerative colitis

• Bowel obstruction

• Certain pediatric GI disorders (eg, congenital GI anomalies, prolonged diarrhea regardless of its cause)

• Short bowel syndrome due to surgery

Nutritional content: TPN requires water (30 to 40 mL/kg/day), energy (30 to 60 kcal/kg/day, depending on energy expenditure), amino acids (1 to 2.0 g/kg/day, depending on the degree of catabolism), essential fatty acids, vitamins, and minerals (see Table 3-3). Children who need TPN may have different fluid requirements and need more energy (up to 120 kcal/kg/day) and amino acids (up to 2.5 or 3.5 g/kg/day).

Basic TPN solutions are prepared using sterile techniques, usually in liter batches according to standard formulas. Normally, 2 L/day of the standard solution is needed. Solutions may be modified based on laboratory results, underlying disorders, hypermetabolism, or other factors.

Most calories are supplied as carbohydrate. Typically, about 4 to 5 mg/kg/day of dextrose is given. Standard solutions contain up to about 25% dextrose, but the amount and concentration depend on other

factors, such as metabolic needs and the proportion of caloric needs that are supplied by lipids. Commercially available lipid emulsions are often added to supply essential fatty acids and triglycerides; 20 to 30% of total calories are usually supplied as lipids. However, withholding lipids and their calories may help obese patients mobilize endogenous fat stores, increasing insulin sensitivity.

Solutions: Many solutions are commonly used. Electrolytes can be added to meet the patient's needs.

Solutions vary depending on other disorders present and patient age, as for the following:

- For renal insufficiency not being treated with dialysis or for liver failure: Reduced protein content and a high percentage of essential amino acids
- For heart or kidney failure: Limited volume (liquid) intake
- For respiratory failure: A lipid emulsion that provides most of nonprotein calories to minimize CO_2 production by carbohydrate metabolism
- For neonates: Lower dextrose concentrations (17 to 18%)

Beginning TPN administration: Because the central venous catheter needs to remain in place for a long time, strict sterile technique must be used during insertion and maintenance. The TPN line should not be used for any other purpose. External tubing should be changed every 24 h with the first bag of the day. In-line filters have not been shown to decrease complications. Dressings should be kept sterile and are usually changed every 48 h using strict sterile techniques. If TPN is given outside the hospital, patients must be taught to recognize symptoms of infection, and qualified home nursing must be arranged.

The solution is started slowly at 50% of the calculated requirements, using 5% dextrose to make up the balance of fluid requirements. Energy and nitrogen should be given simultaneously. The amount of regular insulin given (added directly to the TPN solution) depends on the plasma glucose level; if the level is normal and the final solution contains 25% dextrose, the usual starting dose is 5 to 10 units of regular insulin/L of TPN fluid.

Monitoring: Progress should be followed on a flowchart. An interdisciplinary nutrition team, if available, should monitor patients. Weight, CBC, electrolytes, and BUN should be monitored often (eg, daily for inpatients). Plasma glucose should be monitored every 6 h until patients and glucose levels become stable. Fluid intake and output should be monitored continuously. When patients become stable, blood tests can be done much less often.

Liver function tests should be done. Plasma proteins (eg, serum albumin, possibly transthyretin or retinol-binding protein), PT, plasma and urine osmolality, and Ca, Mg, and phosphate should be measured twice/wk. Changes in transthyretin and retinol-binding protein reflect overall clinical status rather than nutritional status alone. If possible, blood tests should not be done during glucose infusion. Full nutritional assessment (including BMI calculation and anthropometric measurements—see pp. 11 and 58) should be repeated at 2-wk intervals.

Complications: About 5 to 10% of patients have complications related to central venous access.

[**Table 3-3.** Basic Adult Daily Requirements for Total Parenteral Nutrition]

Catheter-related sepsis occurs in about ≥ 50% of patients. Glucose abnormalities (hyperglycemia or hypoglycemia) or liver dysfunction occurs in > 90% of patients.

Glucose abnormalities are common. Hyperglycemia can be avoided by monitoring plasma glucose often, adjusting the insulin dose in the TPN solution and giving subcutaneous insulin as needed. Hypoglycemia can be precipitated by suddenly stopping constant concentrated dextrose infusions. Treatment depends on the degree of hypoglycemia. Short-term hypoglycemia may be reversed with 50% dextrose IV; more prolonged hypoglycemia may require infusion of 5 or 10% dextrose for 24 h before

resuming TPN via the central venous catheter.

Hepatic complications include liver dysfunction, painful hepatomegaly, and hyperammonemia. They can develop at any age but are most common among infants, particularly premature ones (whose liver is immature).

- Liver dysfunction may be transient, evidenced by increased transaminases, bilirubin, and alkaline phosphatase; it commonly occurs when TPN is started. Delayed or persistent elevations may result from excess amino acids. Pathogenesis is unknown, but cholestasis and inflammation may contribute. Progressive fibrosis occasionally develops. Reducing protein delivery may help.

- Painful hepatomegaly suggests fat accumulation; carbohydrate delivery should be reduced.

- Hyperammonemia can develop in infants, causing lethargy, twitching, and generalized seizures. Arginine supplementation at 0.5 to 1.0 mmol/kg/day can correct it.

If infants develop any hepatic complication, limiting amino acids to 1.0 g/kg/day may be necessary.

Abnormalities of serum electrolytes and minerals should be corrected by modifying subsequent infusions or, if correction is urgently required, by beginning appropriate peripheral vein infusions. Vitamin and mineral deficiencies are rare when solutions are given correctly. Elevated BUN may reflect dehydration, which can be corrected by giving free water as 5% dextrose via a peripheral vein.

Volume overload (suggested by > 1 kg/day weight gain) may occur when patients have high daily energy requirements and thus require large fluid volumes.

Metabolic bone disease, or bone demineralization (osteoporosis or osteomalacia), develops in some patients given TPN for > 3 mo. The mechanism is unknown. Advanced disease can cause severe periarticular, lower-extremity, and back pain. Temporarily or permanently stopping TPN is the only known treatment.

Adverse reactions to lipid emulsions (eg, dyspnea, cutaneous allergic reactions, nausea, headache, back pain, sweating, dizziness) are uncommon but may occur early, particularly if lipids are given at > 1.0 kcal/kg/h. Temporary hyperlipidemia may occur, particularly in patients with kidney or liver failure; treatment is usually not required. Delayed adverse reactions to lipid emulsions include hepatomegaly, mild elevation of liver enzymes, splenomegaly, thrombocytopenia, leukopenia, and, especially in premature infants with respiratory distress syndrome, pulmonary function abnormalities. Temporarily or permanently slowing or stopping lipid emulsion infusion may prevent or minimize these adverse reactions.

Gallbladder complications include cholelithiasis, gallbladder sludge, and cholecystitis. These complications can be caused or worsened by prolonged gallbladder stasis. Stimulating contraction by providing about 20 to 30% of calories as fat and stopping glucose infusion several hours a day is helpful. Oral or enteral intake also helps. Treatment with metronidazole, ursodeoxycholic acid, phenobarbital, or cholecystokinin helps some patients with cholestasis.

Nutritional Support for Dying or Severely Demented Patients

Anorexia or loss of appetite is common among dying patients (see p. 3485). Behavioral measures (eg, using flexible feeding schedules, feeding slowly, giving small portions or favorite or strongly flavored foods) can often increase oral intake. A small amount of a favorite alcoholic drink, given 30 min before meals, may also help. Certain antidepressants, megestrol acetate, and dronabinol may stimulate appetite. Metoclopramide enhances gastric emptying, but it may take 1 to 2 wk to reach peak effectiveness.

Advanced dementia eventually leads to inability to eat; sometimes affected patients are given tube feedings. However, there is no convincing evidence that tube feedings prolong life, provide comfort, improve function, or prevent complications (eg, aspiration, pressure ulcers).

Tube feedings and parenteral nutrition cause discomfort and are usually not indicated for patients who

are dying or too demented to eat. Forgoing nutritional support may be difficult for family members to accept, but they should understand that patients are usually more comfortable eating and drinking as they choose. Sips of water and easy-to-swallow foods may be useful. Supportive care, including good oral hygiene (eg, brushing the teeth, moistening the oral cavity with swabs and ice chips as needed, applying lip salve), can physically and psychologically comfort the patients and the family members who provide the care.

Counseling may help family members who are dealing with anxieties about whether to use invasive nutritional support.

Chapter 4. Vitamin Deficiency, Dependency, and Toxicity

Introduction

Vitamins may be fat soluble (vitamins A, D, E, and K) or water soluble (B vitamins and vitamin C). The B vitamins include biotin, folate, niacin, pantothenic acid, riboflavin (B_2), thiamin (B_1), B_6 (eg, pyridoxine), and B_{12} (cobalamins). For dietary requirements, sources, functions, effects of deficiencies and toxicities, blood levels, and usual therapeutic dosages for vitamins, see Tables 4-1 and 4-2.

Dietary requirements for vitamins (and other nutrients) are expressed as daily recommended intake (DRI). There are 3 types of DRI:

- **Recommended daily allowance (RDA):** RDAs are set to meet the needs of 97 to 98% of healthy people.
- **Adequate intake (AI):** When data to calculate an RDA are insufficient, AIs are based on observed or experimentally determined estimates of nutrient intake by healthy people.
- **Tolerable upper intake level (UL):** ULs are the largest amount of a nutrient that most adults can ingest daily without risk of adverse health effects.

In developed countries, vitamin deficiencies result mainly from poverty, food faddism, drugs (see p. 7 and Table 4-3), alcoholism, or prolonged and inadequately supplemented parenteral feeding. Mild vitamin deficiency is common among frail and institutionalized elderly people who have protein-energy undernutrition. In developing countries, deficiencies can result from lack of access to nutrients. Deficiencies of water-soluble vitamins (except vitamin B_{12}) may develop after weeks to months of undernutrition. Deficiencies of fat-soluble vitamins and of vitamin B_{12} take > 1 yr to develop because the body stores them in relatively large amounts. Intake of vitamins sufficient to prevent classic vitamin deficiencies (like scurvy or beriberi) may not be adequate for optimum health. This area remains one of controversy and active research.

Vitamin dependency results from a genetic defect involving metabolism of a vitamin. In some cases, vitamin doses as high as 1000 times the DRI improve function of the altered metabolic pathway. Vitamin toxicity (hypervitaminosis) usually results from taking megadoses of vitamin A, D, C, B_6, or niacin.

Because many people eat irregularly, foods alone may provide suboptimal amounts of some vitamins. In these cases, the risk of certain cancers or other disorders may be increased. Because of this risk, routine daily multivitamin supplements are sometimes recommended.

Biotin and Pantothenic Acid

Biotin acts as a coenzyme for carboxylation reactions essential to fat and carbohydrate metabolism. Adequate intake for adults is 30 µg/day. Pantothenic acid is widely distributed in foods; it is an essential component of coenzyme A. Adults probably require about 5 mg/day. A beneficial role for pantothenic acid supplementation in lipid metabolism, RA, or athletic performance remains unproved. Isolated deficiency of biotin or pantothenic acid virtually never occurs.

Folate

Folate (folic acid) is now added to enriched grain foods in the US. Folate is also plentiful in various plant foods and meats, but its bioavailability is greater when it is in supplements

[**Table 4-1.** Recommended Daily Intakes for Vitamins]

or enriched foods than when it occurs naturally in food.

Folates are involved in RBC maturation and synthesis of purines and pyrimidines. They are required for development of the fetal nervous system. Absorption occurs in the duodenum and upper jejunum. Enterohepatic circulation of folate occurs. Folate supplements

[**Table 4-2.** Sources, Functions, and Effects of Vitamins]

do not protect against coronary artery disease or stroke (by lowering homocysteine levels); their role in reducing the risk of various cancers is unclear. The upper limit for folate intake is 1000 µg; higher doses (up to 5 mg) are recommended for women who have had a baby with a neural tube defect. Folate is essentially nontoxic.

Folate Deficiency

Folate deficiency is common. It may result from inadequate intake, malabsorption, or use of various drugs. Deficiency causes megaloblastic anemia (indistinguishable from that due to vitamin B_{12} deficiency). Maternal deficiency increases the risk of neural tube birth defects. Diagnosis requires laboratory testing to confirm. Measurement of neutrophil hypersegmentation is sensitive and readily available. Treatment with oral folate is usually successful.

Etiology and Pathophysiology

The most common causes are inadequate intake (usually in patients with undernutrition or alcoholism), increased demand (eg, due to pregnancy or breastfeeding), and impaired absorption (eg, in tropical sprue, due to certain drugs). Deficiency can also result from inadequate bioavailability and increased excretion (see
Table 4-4).

Prolonged cooking destroys folate, predisposing to inadequate intake. Intake is sometimes barely adequate (eg, in alcoholics). Liver stores provide only a several-month supply.

Alcohol interferes with folate absorption, metabolism, renal excretion, and enterohepatic reabsorption, as well as intake. 5-Fluorouracil, metformin, methotrexate, phenobarbital, phenytoin, sulfasalazine, triamterene, and trimethoprim impair folate metabolism.

In the US, many dietary staples (eg, cereals, grain products) are routinely enriched with folate, tending to reduce risk of deficiency.

[**Table 4-3.** Potential Vitamin-Drug Interactions]

Symptoms and Signs

Folate deficiency may cause glossitis, diarrhea, depression, and confusion. Anemia may develop insidiously and, because of compensatory mechanisms, be more severe than symptoms suggest.

Folate deficiency during pregnancy increases the risk of fetal neural tube defects and perhaps other brain defects (see p. 2992).

Diagnosis

• CBC and serum vitamin B_{12} and folate levels

CBC may indicate megaloblastic anemia indistinguishable from that of vitamin B_{12} deficiency. If serum folate is < 3 µg/L or ng/mL (< 7 nmol/L), deficiency is likely. Serum folate reflects folate status unless intake has recently increased or decreased. If intake has changed, erythrocyte (RBC) folate level better reflects tissue stores. A level of < 140 µg/L or ng/mL (< 305 nmol/L) indicates inadequate status. Also, an increase in the homocysteine level suggests tissue folate deficiency (but the level is also affected by

vitamin B_{12} and vitamin B_6 levels, renal insufficiency, and genetic factors). A normal methylmalonic acid (MMA) level may differentiate folate deficiency from vitamin B_{12} deficiency because MMA levels rise in vitamin B_{12} deficiency but not in folate deficiency.

Treatment

• Supplemental oral folate

Folate 400 to 1000 µg po once/day replenishes tissues and is usually successful even if deficiency has resulted from malabsorption. The normal requirement is 400 µg/day.

[Table 4-4. Causes of Folate Deficiency]

(CAUTION: *In patients with megaloblastic anemia, vitamin B_{12} deficiency must be ruled out before treating with folate. If vitamin B_{12} deficiency is present, folate supplementation can alleviate the anemia but does not reverse and may even worsen neurologic deficits.*) For pregnant women, the recommended daily allowance (RDA) is 600 µg/day. For women who have had a fetus or infant with a neural tube defect, the recommended dose is 1000 to 5000 µg/day.

Niacin

Niacin (nicotinic acid, nicotinamide) derivatives include nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which are coenzymes in oxidation-reduction reactions. They are vital in cell metabolism. Because dietary tryptophan can be metabolized to niacin, foods rich in tryptophan (eg, dairy products) can compensate for inadequate dietary niacin.

Niacin Deficiency

Dietary niacin deficiency (causing pellagra) is uncommon in developed countries. Clinical manifestations include the "three Ds": localized pigmented rash (dermatitis); gastroenteritis (diarrhea); and widespread neurologic deficits, including cognitive decline (dementia). Diagnosis is usually clinical, and dietary supplementation (oral or, if needed, IM) is usually successful.

Etiology

Primary deficiency results from extremely inadequate intake of both niacin and tryptophan, which usually occurs in areas where maize (Indian corn) constitutes a substantial part of the diet. Bound niacin, found in maize, is not assimilated in the GI tract unless it has been previously treated with alkali, as when tortillas are prepared. Corn protein is also deficient in tryptophan. The high incidence of pellagra in India among people who eat millet with a high leucine content has led to the hypothesis that amino acid imbalance may contribute to deficiency. Deficiencies of protein and many B vitamins commonly accompany primary niacin deficiency.

Secondary deficiency may be due to diarrhea, cirrhosis, or alcoholism. Pellagra also may occur in carcinoid syndrome (tryptophan is diverted to form 5-hydroxytryptophan and serotonin) and in Hartnup disease (absorption of tryptophan by the intestine and kidneys is defective).

Symptoms and Signs

Pellagra is characterized by skin, mucous membrane, CNS, and GI symptoms. Advanced pellagra can cause a symmetric photosensitive rash, stomatitis, glossitis, diarrhea, and mental aberrations. Symptoms may appear alone or in combination.

Skin symptoms include several types of lesions, which are usually bilaterally symmetric. The distribution of lesions—at pressure points or sun-exposed skin—is more pathognomonic than the form of the lesions. Lesions can develop in a glovelike distribution on the hands (pellagrous glove) or in a boot-shaped

distribution on the feet and legs (pellagrous boot). Sunlight causes Casal's necklace and butterfly-shaped lesions on the face.

Mucous membrane symptoms affect primarily the mouth but may also affect the vagina and urethra. Glossitis and stomatitis characterize acute deficiency. As the deficiency progresses, the tongue and oral mucous membranes become reddened, followed by pain in the mouth, increased salivation, and edema of the tongue. Ulcerations may appear, especially under the tongue, on the mucosa of the lower lip, and opposite the molar teeth.

GI symptoms early in the deficiency include burning in the pharynx and esophagus and abdominal discomfort and distention. Constipation is common. Later, nausea, vomiting, and diarrhea may occur. Diarrhea is often bloody because of bowel hyperemia and ulceration.

CNS symptoms include psychosis, encephalopathy (characterized by impaired consciousness), and cognitive decline (dementia). Psychosis is characterized by memory impairment, disorientation, confusion, and confabulation; the predominant symptom may be excitement, depression, mania, delirium, or paranoia.

Diagnosis

• Clinical evaluation

Diagnosis is clinical and may be straightforward when skin and mouth lesions, diarrhea, delirium, and dementia occur simultaneously. More often, the presentation is not so specific. Differentiating the CNS changes from those in thiamin deficiency is difficult. A history of a diet lacking niacin and tryptophan may help establish the diagnosis. A favorable response to treatment with niacin can usually confirm it. If available, laboratory testing can help confirm the diagnosis, particularly when the diagnosis is otherwise unclear. Urinary excretion of N^1-methylnicotinamide (NMN) is decreased; < 0.8 mg/day (< 5.8 µmol/day) suggests a niacin deficiency.

Treatment

• Nicotinamide and other nutrients

Because multiple deficiencies are common, a balanced diet, including other B vitamins (particularly riboflavin and pyridoxine), is needed. Nicotinamide is usually used to treat deficiency, because nicotinamide, unlike nicotinic acid (the most common form of niacin), does not cause flushing, itching, burning, or tingling sensations. Nicotinamide is given in doses ranging from 40 to 250 mg/day po in divided doses 3 to 4 times a day.

Niacin Toxicity

Niacin (nicotinic acid) in large amounts is sometimes used to lower low-density lipoprotein (LDL) cholesterol and triglyceride levels and to increase high-density lipoprotein (HDL) cholesterol levels. Symptoms may include flushing and, rarely, hepatotoxicity.

Immediate- and sustained-release preparations of niacin (but not nicotinamide) may improve lipid levels. Flushing, which is prostaglandin-mediated, is more common with immediate-release preparations. It may be more intense after alcohol ingestion, aerobic activity, sun exposure, and consumption of spicy foods. Flushing is minimized if niacin is taken after meals or if aspirin (325 mg) is taken 30 to 45 min before niacin. The chance of severe flushing can be reduced by starting immediate-release niacin at a low dose (eg, 50 mg tid) and increasing it very slowly. At intermediate doses (1000 mg/day), triglyceride levels decrease 15 to 20%, and HDL cholesterol levels increase 15 to 30%. Reductions in LDL cholesterol are modest (< 10%). Higher doses of niacin (3000 mg/day) reduce LDL cholesterol 15 to 20% but may cause jaundice, abdominal discomfort, blurred vision, worsening of hyperglycemia, and precipitation of preexisting gout. People with a liver disorder probably should not take high-dose niacin.

Hepatotoxicity may be more common with some sustained-release preparations. Some authorities

recommend checking levels of uric acid, serum glucose, and plasma transaminases every 6 to 8 wk until the dose of niacin has been stabilized.

Riboflavin

Riboflavin (vitamin B_2) is involved in carbohydrate metabolism as an essential coenzyme in many oxidation-reduction reactions. Riboflavin is essentially nontoxic.

Riboflavin Deficiency

Riboflavin deficiency usually occurs with other B-vitamin deficiencies. Symptoms and signs include sore throat, lesions of the lips and mucosa of the mouth, glossitis, conjunctivitis, seborrheic dermatitis, and normochromicnormocytic anemia. Diagnosis is usually clinical. Treatment consists of oral or, if needed, IM riboflavin.

Primary riboflavin deficiency results from inadequate intake of fortified cereals, milk, and other animal products. The most common causes of secondary deficiency are chronic diarrhea, malabsorption syndromes, liver disorders, hemodialysis, peritoneal dialysis, long-term use of barbiturates, and chronic alcoholism.

Symptoms and Signs

The most common signs are pallor and maceration of the mucosa at the angles of the mouth (angular stomatitis) and vermilion surfaces of the lips (cheilosis), eventually replaced by superficial linear fissures. The fissures can become infected with *Candida albicans*, causing grayish white lesions (perleche). The tongue may appear magenta. Seborrheic dermatitis develops, usually affecting the nasolabial folds, ears, eyelids, and scrotum or labia majora. These areas become red, scaly, and greasy.

Rarely, neovascularization and keratitis of the cornea occur, causing lacrimation and photophobia.

Diagnosis

The lesions characteristic of riboflavin deficiency are nonspecific. Riboflavin deficiency should be suspected if characteristic signs develop in a patient with other B vitamin deficiencies. Diagnosis can be confirmed by a therapeutic trial or laboratory testing, usually by measuring urinary excretion of riboflavin.

Treatment

Riboflavin 5 to 10 mg/day po is given until recovery. Other water-soluble vitamins should also be given.

Thiamin

Thiamin (vitamin B_1) is widely available in the diet. Thiamin is involved in carbohydrate, fat, amino acid, glucose, and alcohol metabolism. Thiamin is essentially nontoxic.

Thiamin Deficiency

Thiamin deficiency (causing beriberi) is most common among people subsisting on white rice or highly refined carbohydrates in developing countries and among alcoholics. Symptoms include diffuse polyneuropathy, high-output heart failure, and Wernicke-Korsakoff syndrome. Thiamin is given to help diagnose and treat the deficiency.

Etiology

Primary thiamin deficiency is caused by inadequate intake of thiamin. It is commonly due to a diet of highly refined carbohydrates (eg, polished rice, white flour, white sugar). It also develops when intake of other nutrients is inadequate; it often occurs with other B vitamin deficiencies.

Secondary thiamin deficiency is caused by increased demand (eg, due to hyperthyroidism, pregnancy, breastfeeding, strenuous exercise, or fever), impaired absorption (eg, due to prolonged diarrhea), or impaired metabolism (eg, due to hepatic insufficiency). In alcoholics, many mechanisms contribute to thiamin deficiency; they include decreased intake, impaired absorption and use, increased demand, and possibly an apoenzyme defect.

Pathophysiology

Deficiency causes degeneration of peripheral nerves, thalamus, mammillary bodies, and cerebellum. Cerebral blood flow is markedly reduced, and vascular resistance is increased.

The heart may become dilated; muscle fibers become swollen, fragmented, and vacuolized, with interstitial spaces dilated by fluid. Vasodilation occurs and can result in edema in the feet and legs. Arteriovenous shunting of blood increases. Eventually, high-output heart failure may occur.

Symptoms and Signs

Early symptoms are nonspecific: fatigue, irritability, poor memory, sleep disturbances, precordial pain, anorexia, and abdominal discomfort.

Dry beriberi refers to peripheral neurologic deficits due to thiamin deficiency. These deficits are bilateral and roughly symmetric, occurring in a stocking-glove distribution. They affect predominantly the lower extremities, beginning with paresthesias in the toes, burning in the feet (particularly severe at night), muscle cramps in the calves, pains in the legs, and plantar dysesthesias. Calf muscle tenderness, difficulty rising from a squatting position, and decreased vibratory sensation in the toes are early signs. Muscle wasting occurs. Continued deficiency worsens polyneuropathy, which can eventually affect the arms.

Wernicke-Korsakoff syndrome, which combines Wernicke's encephalopathy (see p. 1522) and Korsakoff's psychosis (see p. 1523), occurs in some alcoholics who do not consume foods fortified with thiamin. Wernicke's encephalopathy consists of psychomotor slowing or apathy, nystagmus, ataxia, ophthalmoplegia, impaired consciousness, and, if untreated, coma and death. It probably results from severe acute deficiency superimposed on chronic deficiency. Korsakoff's psychosis consists of mental confusion, dysphonia, and confabulation with impaired memory of recent events. It probably results from chronic deficiency and may develop after repeated episodes of Wernicke's encephalopathy.

Cardiovascular (wet) beriberi is myocardial disease due to thiamin deficiency. The first effects are vasodilation, tachycardia, a wide pulse pressure, sweating, warm skin, and lactic acidosis. Later, heart failure develops, causing orthopnea and pulmonary and peripheral edema. Vasodilation can continue, sometimes resulting in shock.

Infantile beriberi occurs in infants (usually by age 3 to 4 wk) who are breastfed by thiamin-deficient mothers. Heart failure (which may occur suddenly), aphonia, and absent deep tendon reflexes are characteristic.

Because thiamin is necessary for glucose metabolism, glucose infusions may precipitate or worsen symptoms of deficiency in thiamin-deficient people.

Diagnosis

• Favorable response to thiamin

Diagnosis is usually based on a favorable response to treatment with thiamin in a patient with symptoms or signs of deficiency. Similar bilateral lower-extremity polyneuropathies due to other disorders (eg, diabetes, alcoholism, vitamin B_{12} deficiency, heavy metal poisoning) do not respond to thiamin. Single-nerve neuritides (mononeuropathies—eg, sciatica) and multiple mononeuropathies (mononeuritis multiplex) are unlikely to result from thiamin deficiency.

Electrolytes, including Mg, should be measured to exclude other causes. For confirmation in equivocal cases, erythrocyte transketolase activity and 24-h urinary thiamin excretion may be measured.

Diagnosis of cardiovascular beriberi can be difficult if other disorders that cause heart failure are present. A therapeutic trial of thiamin can help.

Treatment

• Supplemental thiamin, with dose based on clinical manifestations

Ensuring that dietary supplies of thiamin are adequate is important regardless of symptoms. Because IV glucose can worsen thiamin deficiency, alcoholics and others at risk of thiamin deficiency should receive IV thiamin 100 mg before receiving IV glucose solutions.

For mild polyneuropathy, thiamin 10 to 20 mg po once/day is given for 2 wk. For moderate or advanced neuropathy, the dose is 20 to 30 mg/day; it should be continued for several weeks after symptoms disappear. For edema and congestion due to cardiovascular beriberi, thiamin 100 mg IV once/day is given for several days. Heart failure is also treated.

For Wernicke-Korsakoff syndrome, thiamin 50 to 100 mg IM or IV bid must usually be given for several days, followed by 10 to 20 mg once/day until a therapeutic response is obtained. Anaphylactic reactions to IV thiamin are rare. Symptoms of ophthalmoplegia may resolve in a day; improvement in patients with Korsakoff psychosis may take 1 to 3 mo. Recovery from neurologic deficits is often incomplete in Wernicke-Korsakoff syndrome and in other forms of thiamin deficiency.

Because thiamin deficiency often occurs with other B vitamin deficiencies, multiple water-soluble vitamins are usually given for several weeks. Patients should continue to consume a nutritious diet, supplying 1 to 2 times the daily recommended intake of vitamins; all alcohol intake should stop.

Vitamin A

Vitamin A (retinol) is required for the formation of rhodopsin, a photoreceptor pigment in the retina. Vitamin A helps maintain epithelial tissues. Normally, the liver stores 80 to 90% of the body's vitamin A. To use vitamin A, the body releases it into the circulation bound to prealbumin (transthyretin) and retinol-binding protein. β-Carotene and other provitamin carotenoids, contained in green leafy and yellow vegetables and deep- or bright-colored fruits, are converted to vitamin A. Carotenoids are absorbed better from vegetables when they are cooked or homogenized and served with some fats or oils.

Retinol activity equivalents (RAE) were developed because provitamin A carotenoids have less vitamin A activity than preformed vitamin A; 1 µg retinol = 3.33 IU.

Synthetic vitamin analogs (retinoids) are being used increasingly in dermatology. The possible protective role of β-carotene, retinol, and retinoids against some epithelial cancers is under study. However, risk of certain cancers may be increased after β-carotene supplementation.

Vitamin A Deficiency

Vitamin A deficiency can result from inadequate intake, fat malabsorption, or liver disorders. Deficiency impairs immunity and hematopoiesis and causes rashes and typical ocular effects (eg, xerophthalmia, night blindness). Diagnosis is based on typical ocular findings and low vitamin A levels. Treatment consists of vitamin A given orally or, if symptoms are severe or malabsorption is the cause, parenterally.

Etiology

Primary vitamin A deficiency is usually caused by prolonged dietary deprivation. It is endemic in areas such as southern and eastern Asia, where rice, devoid of β-carotene, is the staple food. Xerophthalmia due to primary deficiency is a common cause of blindness among young children in developing countries.

Secondary vitamin A deficiency may be due to decreased bioavailability of provitamin A carotenoids or to interference with absorption, storage, or transport of vitamin A. Interference with absorption or storage is likely in sprue, cystic fibrosis, pancreatic insufficiency, duodenal bypass, chronic diarrhea, bile duct obstruction, giardiasis, and cirrhosis. Vitamin A deficiency is common in prolonged protein-energy undernutrition not only because the diet is deficient but also because vitamin A storage and transport is defective. In children with complicated measles, vitamin A can shorten the duration of the disorder and reduce the severity of symptoms and risk of death.

Symptoms and Signs

Impaired dark adaptation of the eyes, which can lead to night blindness, is an early symptom. Xerophthalmia (which is nearly pathognomonic) results from keratinization of the eyes. It involves drying (xerosis) and thickening of the conjunctivae and corneas. Superficial foamy patches composed of epithelial debris and secretions on the exposed bulbar conjunctiva (Bitot's spots) develop. In advanced deficiency, the cornea becomes hazy and can develop erosions, which can lead to its destruction (keratomalacia).

Keratinization of the skin and of the mucous membranes in the respiratory, GI, and urinary tracts can occur. Drying, scaling, and follicular thickening of the skin and respiratory infections can result. Immunity is generally impaired.

The younger the patient, the more severe are the effects of vitamin A deficiency. Growth retardation and infections are common among children. Mortality rate can exceed 50% in children with severe vitamin A deficiency.

Diagnosis

• Serum retinol levels, clinical evaluation, and response to vitamin A

Ocular findings suggest the diagnosis. Dark adaptation can be impaired in other disorders (eg, zinc deficiency, retinitis pigmentosa, severe refractive errors, cataracts, diabetic retinopathy). If dark adaptation is impaired, rod scotometry and electroretinography are done to determine whether vitamin A deficiency is the cause.

Serum levels of retinol are measured. Normal range is 28 to 86 µg/dL (1 to 3 µmol/L). However, levels decrease only after the deficiency is advanced because the liver contains large stores of vitamin A. Also, decreased levels may result from acute infection, which causes retinol-binding protein and transthyretin (also called prealbumin) levels to decrease transiently. A therapeutic trial of vitamin A may help confirm the diagnosis.

Prevention

The diet should include dark green leafy vegetables, deep- or bright-colored fruits (eg, papayas, oranges), carrots, and yellow vegetables (eg, squash, pumpkin). Vitamin A-fortified milk and cereals, liver, egg yolks, and fish liver oils are helpful. Carotenoids are absorbed better when consumed with some dietary fat. If milk allergy is suspected in infants, they should be given adequate vitamin A in formula feedings. In developing countries, prophylactic supplements of vitamin A palmitate in oil 60,000 RAE (200,000 IU) po every 6 mo are advised for all children between 1 and 5 yr of age; infants < 6 mo can be given a one-time dose of 15,000 RAE (50,000 IU), and those aged 6 to 12 mo can be given a one-time dose of 30,000 RAE (100,000 IU).

Treatment

• Vitamin A palmitate

Dietary deficiency is traditionally treated with vitamin A palmitate in oil 60,000 IU po once/day for 2 days, followed by 4500 IU po once/day. If vomiting or malabsorption is present or xerophthalmia is probable, a

dose of 50,000 IU for infants < 6 mo, 100,000 IU for infants 6 to 12 mo, or 200,000 IU for children > 12 mo and adults should be given for 2 days, with a third dose at least 2 wk later. The same doses are recommended for infants and children with complicated measles. Infants born of HIV-positive mothers should receive 50,000 IU (15,000 RAE) within 48 h of birth. Prolonged daily administration of large doses, especially to infants, must be avoided because toxicity may result.

For pregnant or breastfeeding women, prophylactic or therapeutic doses should not exceed 10,000 IU (3000 RAE)/day to avoid possible damage to the fetus or infant.

Vitamin A Toxicity

Vitamin A toxicity can be acute (usually due to accidental ingestion by children) or chronic. Both types usually cause headache and increased intracranial pressure. Acute toxicity also causes nausea and vomiting. Chronic toxicity also causes changes in skin, hair, and nails; abnormal liver test results; and, in a fetus, birth defects. Diagnosis is usually clinical. Unless birth defects are present, adjusting the dose almost always leads to complete recovery.

Acute vitamin A toxicity in children may result from taking large doses (> 100,000 RAE [> 300,000 IU]), usually accidentally. In adults, acute toxicity has occurred when arctic explorers ingested polar bear or seal livers, which contain several million units of vitamin A.

Chronic toxicity in older children and adults usually develops after doses of > 30,000 RAE (> 100,000 IU)/day have been taken for months. Megavitamin therapy is a possible cause, as are massive daily doses (50,000 to 120,000 RAE [150,000 to 350,000 IU]) of vitamin A or its metabolites, which are sometimes given for nodular acne or other skin disorders. Adults who consume > 1500 RAE (> 4500 IU)/day of vitamin A may develop osteoporosis. Infants who are given excessive doses (6,000 to 20,000 RAE [18,000 to 60,000 IU]/day) of water-miscible vitamin A may develop toxicity within a few weeks. Birth defects occur in children of women receiving isotretinoin (which is related to vitamin A) for acne treatment during pregnancy.

Although carotene is converted to vitamin A in the body, excessive ingestion of carotene causes carotenemia, not vitamin A toxicity. Carotenemia is usually asymptomatic but may lead to carotenodermia, in which the skin becomes yellow. When taken as a supplement, β-carotene has been associated with increased cancer risk; risk does not seem to increase when carotenoids are consumed in fruits and vegetables.

Symptoms and Signs

Although symptoms may vary, headache and rash usually develop during acute or chronic toxicity. Acute toxicity causes increased intracranial pressure. Drowsiness, irritability, abdominal pain, nausea, and vomiting are common. Sometimes the skin subsequently peels.

Early symptoms of chronic toxicity are sparsely distributed, coarse hair; alopecia of the eyebrows; dry, rough skin; dry eyes; and cracked lips. Later, severe headache, pseudotumor cerebri, and generalized weakness develop. Cortical hyperostosis of bone and arthralgia may occur, especially in children. Fractures may occur easily, especially in the elderly. In children, toxicity can cause pruritus, anorexia, and failure to thrive. Hepatomegaly and splenomegaly may occur.

In carotenodermia, the skin (but not the sclera) becomes deep yellow, especially on the palms and soles.

Diagnosis

• Clinical evaluation

Diagnosis is clinical. Blood vitamin levels correlate poorly with toxicity. However, if clinical diagnosis is equivocal, laboratory testing may help. In vitamin A toxicity, fasting serum retinol levels may increase from normal (28 to 86 µg/dL [1 to 3 µmol/L]) to > 100 µg/dL (> 3.49 µmol/L), sometimes to > 2000 µg/dL (> 69.8 µmol/L). Hypercalcemia is common.

Differentiating vitamin A toxicity from other disorders may be difficult. Carotenodermia may also occur in severe hypothyroidism and anorexia nervosa, possibly because carotene is converted to vitamin A more slowly.

Prognosis

Complete recovery usually occurs if vitamin A ingestion stops. Symptoms and signs of chronic toxicity usually disappear within 1 to 4 wk. However, birth defects in the fetus of a mother who has taken megadoses of vitamin A are not reversible.

Treatment

Vitamin A is stopped.

Vitamin B_6

Vitamin B_6 includes a group of closely related compounds: pyridoxine, pyridoxal, and pyridoxamine. They are metabolized in the body to pyridoxal phosphate, which acts as a coenzyme in many important reactions in blood, CNS, and skin metabolism. Vitamin B_6 is important in heme and nucleic acid biosynthesis and in lipid, carbohydrate, and amino acid metabolism.

Vitamin B_6 Deficiency and Dependency

Because vitamin B_6 is present in most foods, dietary deficiency is rare. Secondary deficiency may result from various conditions. Symptoms can include peripheral neuropathy, a pellagra-like syndrome, anemia, and seizures, which, particularly in infants, may not resolve when treated with anticonvulsants. Impaired metabolism (dependency) is rare; it causes various symptoms, including seizures, intellectual disability, and anemia. Diagnosis is usually clinical; no laboratory test readily assesses vitamin B_6 status. Treatment consists of giving oral vitamin B_6 and, when possible, treating the cause.

Dietary deficiency, though rare, can develop because extensive processing can deplete foods of vitamin B_6. Secondary deficiency most often results from protein-energy undernutrition, malabsorption, alcoholism, use of pyridoxine-inactivating drugs (eg, anticonvulsants, isoniazid, cycloserine, hydralazine, corticosteroids, penicillamine), or excessive loss. Rarely, it results from increased metabolic demand (eg, in hyperthyroidism).

Rare inborn errors of metabolism can affect pyridoxine metabolism.

The role of vitamin B_6 deficiency in increasing plasma homocysteine levels and in contributing to vascular disorders is under study.

Symptoms and Signs

Deficiency causes a pellagra-like syndrome, with seborrheic dermatitis, glossitis, and cheilosis, and, in adults, can cause depression, confusion, EEG abnormalities, and seizures. Rarely, deficiency or dependency causes seizures in infants. Seizures, particularly in infants, may be refractory to treatment with anticonvulsants. Normocytic, microcytic, or sideroblastic anemia can also develop.

Diagnosis

• Clinical evaluation

Vitamin B_6 deficiency should be considered in any infant who has seizures, any patient who has seizures refractory to treatment with anticonvulsants, and any patient with deficiencies of other B vitamins,

particularly in patients with alcoholism or protein-energy undernutrition. Diagnosis is usually clinical. There is no single accepted laboratory test of vitamin B_6 status; measurement of serum pyridoxal phosphate is most common.

Treatment

• Pyridoxine

• Elimination of risk factors when possible

For secondary deficiency, causes (eg, use of pyridoxine-inactivating drugs, malabsorption) should be corrected if possible. Usually, pyridoxine 50 to 100 mg po once/day corrects the deficiency in adults. Most people taking isoniazid should also be given pyridoxine 30 to 50 mg/day. For deficiency due to increased metabolic demand, amounts larger than the daily recommended intake may be required. For most cases of inborn errors of metabolism, high doses of pyridoxine may be effective.

Vitamin B_6 Toxicity

The ingestion of megadoses (> 500 mg/day) of pyridoxine (eg, taken to treat carpal tunnel syndrome or premenstrual syndrome although efficacy is unproved) may cause peripheral neuropathy with deficits in a stocking-glove distribution, including progressive sensory ataxia and severe impairment of position and vibration senses. Senses of touch, temperature, and pain are less affected. Motor and central nervous systems are usually intact.

Diagnosis is clinical. Treatment is to stop taking vitamin B_6. Recovery is slow and, for some patients, incomplete.

Vitamin B_{12}

Cobalamin is a general term for compounds with biologic vitamin B_{12} activity. These compounds are involved in nucleic acid metabolism, methyl transfer, and myelin synthesis and repair. They are necessary for the formation of normal RBCs.

Food-bound vitamin B_{12} is released in the stomach's acid environment and is bound to R protein (haptocorrin). Pancreatic enzymes cleave this B_{12} complex (B_{12}-R protein) in the small intestine. After cleavage, intrinsic factor, secreted by parietal cells in the gastric mucosa, binds with vitamin B_{12}. Intrinsic factor is required for absorption of vitamin B_{12}, which takes place in the terminal ileum.

Vitamin B_{12} in plasma is bound to transcobalamins I and II. Transcobalamin II is responsible for delivering vitamin B_{12} to tissues. The liver stores large amounts of vitamin B_{12}. Enterohepatic reabsorption helps retain vitamin B_{12}. Liver vitamin B_{12} stores can normally sustain physiologic needs for 3 to 5 yr if B_{12} intake stops (eg, in people who become vegans) and for months to 1 yr if enterohepatic reabsorption capacity is absent.

Large amounts of vitamin B_{12} seem to be nontoxic but are not recommended for regular use (ie, as a general tonic).

Vitamin B_{12} Deficiency

Dietary vitamin B_{12} deficiency usually results from inadequate absorption, but deficiency can develop in vegans who do not take vitamin supplements. Deficiency causes megaloblastic anemia, damage to the white matter of the spinal cord and brain, and peripheral neuropathy. Diagnosis is usually made by measuring serum vitamin B_{12} levels. The Schilling test helps determine etiology. Treatment consists of oral or parenteral vitamin B_{12}. Folate (folic acid) should not be used instead of vitamin B_{12} because folate may alleviate the anemia but allow

neurologic deficits to progress.

Etiology

Inadequate vitamin B_{12} intake is possible in vegans but is otherwise unlikely. Breastfed babies of vegan mothers may develop vitamin B_{12} deficiency by age 4 to 6 mo because their

[
Table 4-5. Causes of Vitamin B_{12} Deficiency]

liver stores (which are normally extensive) are limited and their rapid growth rate results in high demand.

Vitamin B_{12} deficiency usually results from inadequate absorption (see Table 4-5 and p. 153), which, in the elderly, most commonly results from decreased acid secretion. In such cases, crystalline vitamin B_{12} (such as that available in vitamin supplements) can be absorbed, but food-bound vitamin B_{12} is not liberated and absorbed normally. Inadequate absorption may occur in blind loop syndrome (with overgrowth of bacteria) or fish tapeworm infestation; in these cases, bacteria or parasites use ingested vitamin B_{12} so that less is available for absorption. Vitamin B_{12} absorption may be inadequate if ileal absorptive sites are destroyed by inflammatory bowel disease or are surgically removed. Less common causes of inadequate vitamin B_{12} absorption include chronic pancreatitis, gastric surgery, malabsorption syndromes, AIDS, use of certain drugs (eg, antacids, metformin), repeated exposure to nitrous oxide, and a genetic disorder causing malabsorption in the ileum (Imerslund-Graesbeck syndrome).

Pernicious anemia is often used synonymously with vitamin B_{12} deficiency. However, pernicious anemia specifically refers to anemia resulting from vitamin B_{12} deficiency caused by an autoimmune metaplastic atrophic gastritis with loss of intrinsic factor (see p. 133). Patients with classic pernicious anemia, most commonly younger adults, are at increased risk of stomach and other GI cancers.

Subacute combined degeneration refers to degenerative changes in the nervous system due to vitamin B_{12} deficiency; they affect mostly brain and spinal cord white matter. Demyelinating or axonal peripheral neuropathies can occur.

Symptoms and Signs

Anemia usually develops insidiously. It is often more severe than its symptoms indicate because its slow evolution allows physiologic adaptation. Occasionally, splenomegaly and hepatomegaly occur. Various GI symptoms, including weight loss and poorly localized abdominal pain, may occur. Glossitis, usually described as burning of the tongue, is uncommon.

Neurologic symptoms develop independently from and often without hematologic abnormalities. In early stages, decreased position and vibratory sensation in the extremities is accompanied by mild to moderate weakness and hyporeflexia. In later stages, spasticity, extensor plantar responses, greater loss of position and vibratory sensation in the lower extremities, and ataxia emerge. These deficits may develop in a stocking-glove distribution. Tactile, pain, and temperature sensations are usually spared but may be difficult to assess in the elderly.

Some patients are also irritable and mildly depressed. Paranoia (megaloblastic madness), delirium, confusion, spastic ataxia, and, at times, postural hypotension may occur in advanced cases. The confusion may be difficult to differentiate from age-related dementias, such as Alzheimer's disease.

Diagnosis

• CBC and vitamin B_{12} and folate levels

• Sometimes methylmalonic acid levels or Schilling test

Diagnosis is based on CBC and vitamin B_{12} and folate levels. It is important to remember that severe neurologic disease may occur without anemia or macrocytosis.

CBC detects megaloblastic anemia. Tissue deficiency and macrocytic indexes may precede the development of anemia. A vitamin B_{12} level < 200 pg/mL (< 145 pmol/L) indicates vitamin B_{12} deficiency. The folate level is measured because vitamin B_{12} deficiency must be differentiated from folate deficiency as a cause of megaloblastic anemia; folate supplementation can mask vitamin B_{12} deficiency and may alleviate megaloblastic anemia but allow the neurologic deficits to progress or even accelerate.

When clinical judgment suggests vitamin B_{12} deficiency but the vitamin B_{12} level is low-normal (200 to 350 pg/mL [145 to 260 pmol/L]) or hematologic indexes are normal, other tests can be done. Measuring serum methylmalonic acid (MMA) levels may be useful. An elevated MMA level supports vitamin B_{12} deficiency but may be due to renal failure. MMA levels can also be used to monitor the response to treatment. MMA levels remain normal in folate deficiency; homocysteine levels may be elevated with either vitamin B_{12} or folate deficiency. Less commonly, holotranscobalamin II (transcobalamin II-B_{12} complex) content is measured; when holotranscobalamin II is < 40 pg/mL (< 30 pmol/L), vitamin B_{12} is deficient.

After deficiency is diagnosed, additional tests may be indicated for younger adults but usually not for the elderly. Unless dietary vitamin B_{12} is obviously inadequate, measurement of serum gastrin levels or autoantibodies to intrinsic factor may be done; sensitivity and specificity of these tests may be poor.

Schilling test: The Schilling test is useful only if diagnosing intrinsic factor deficiency is important, as in classic pernicious anemia. This test is not necessary for most elderly patients. The Schilling test measures absorption of free radiolabeled vitamin B_{12}. Radiolabeled vitamin B_{12} is given orally, followed in 1 to 6 h by 1000 µg (1 mg) of parenteral vitamin B_{12}, which reduces uptake of radiolabeled vitamin B_{12} by the liver. Absorbed radiolabeled vitamin B_{12} is excreted in urine, which is collected for 24 h. The amount excreted is measured, and the percentage of total radiolabeled vitamin B_{12} is determined. If absorption is normal, ≥ 9% of the dose given appears in the urine. Reduced urinary excretion (< 5% if kidney function is normal) indicates inadequate vitamin B_{12} absorption. Improved absorption with the subsequent addition of intrinsic factor to radiolabeled vitamin B_{12} confirms the diagnosis of pernicious anemia. The test is often difficult to do or interpret because of incomplete urine collection or renal insufficiency. In addition, because the Schilling test does not measure absorption of protein-bound vitamin B_{12}, the test does not detect defective liberation of vitamin B_{12} from foods, which is common among the elderly. The Schilling test repletes vitamin B_{12} and can mask deficiency, so it should be done only after all other diagnostic tests and therapeutic trials.

If malabsorption is identified, the Schilling test can be repeated after a 2-wk trial of an oral antibiotic. If antibiotic therapy corrects malabsorption, the likely cause is intestinal overgrowth of bacteria (eg, blind-loop syndrome).

Treatment

• Supplemental vitamin B_{12}

Vitamin B_{12} 1000 to 2000 µg po can be given once/day to patients who do not have severe deficiency or neurologic symptoms or signs. A nasal gel preparation of vitamin B_{12} is available at a higher price. Large oral doses can be absorbed by mass action, even when intrinsic factor is absent. If the MMA level (sometimes used to monitor treatment) does not decrease, patients may not be taking vitamin B_{12}. For more severe deficiency, vitamin B_{12} 1 mg IM is usually given 1 to 4 times/wk for several weeks until hematologic abnormalities are corrected; then it is given once/mo.

Although hematologic abnormalities are usually corrected within 6 wk (reticulocyte count should improve within 1 wk), resolution of neurologic symptoms may take much longer. Neurologic symptoms that persist

for months or years become irreversible. In most elderly people with vitamin B_{12} deficiency and dementia, cognition does not improve after treatment. Vitamin B_{12} treatment must be continued for life unless the pathophysiologic mechanism for the deficiency is corrected.

Infants of vegan mothers should receive supplemental vitamin B_{12} from birth.

Vitamin C

Vitamin C (ascorbic acid) plays a role in collagen, carnitine, hormone, and amino acid formation. It is essential for wound healing and facilitates recovery from burns. Vitamin C is also an antioxidant, supports immune function, and facilitates the absorption of iron.

Vitamin C Deficiency

In developed countries, vitamin C deficiency can occur as part of general undernutrition, but severe deficiency (causing scurvy) is uncommon. Symptoms include fatigue, depression, and connective tissue defects (eg, gingivitis, petechiae, rash, internal bleeding, impaired wound healing). In infants and children, bone growth may be impaired. Diagnosis is usually clinical. Treatment consists of oral vitamin C.

Severe deficiency results in scurvy, a disorder characterized by hemorrhagic manifestations and abnormal osteoid and dentin formation.

Etiology

In adults, primary deficiency is usually due to inadequate diet. The need for dietary vitamin C is increased by febrile illnesses, inflammatory disorders (particularly diarrheal disorders), achlorhydria, smoking, thyrotoxicosis, iron deficiency, cold or heat stress, surgery, burns, and protein deficiency. Heat (eg, sterilization of formulas, cooking) can destroy some of the vitamin C in food.

Pathophysiology

Formation of intercellular cement substances in connective tissues, bones, and dentin is defective, resulting in weakened capillaries with subsequent hemorrhage and defects in bone and related structures.

Bone tissue formation becomes impaired, which, in children, causes bone lesions and poor bone growth. Fibrous tissue forms between the diaphysis and the epiphysis, and costochondral junctions enlarge. Densely calcified fragments of cartilage are embedded in the fibrous tissue. Subperiosteal hemorrhages, sometimes due to small fractures, may occur in children or adults.

Symptoms and Signs

In adults, symptoms develop after weeks to months of vitamin C depletion. Lassitude, weakness, irritability, weight loss, and vague myalgias and arthralgias may develop early.

Later, symptoms related to defects in connective tissues develop. Follicular hyperkeratosis, coiled hair, and perifollicular hemorrhages may develop. Gums may become swollen, purple, spongy, and friable; they bleed easily in severe deficiency. Eventually, teeth become loose and avulsed. Secondary infections may develop. Wounds heal poorly and tear easily, and spontaneous hemorrhages may occur, especially as ecchymoses in the skin of the lower limbs or as bulbar conjunctival hemorrhage.

Other symptoms and signs include femoral neuropathy due to hemorrhage into femoral sheaths (which may mimic deep venous thrombosis), lower-extremity edema, and painful bleeding or effusions within joints.

Diagnosis

• Usually, skin or gingival findings and risk factors

Diagnosis is usually made clinically in a patient who has skin or gingival signs and is at risk of vitamin C deficiency. Laboratory confirmation may be available. Anemia is common. Bleeding, coagulation, and PT are normal.

Skeletal x-rays can help diagnose childhood (but not adult) scurvy. Changes are most evident at the ends of long bones, particularly at the knee. Early changes resemble atrophy. Loss of trabeculae results in a ground-glass appearance. The cortex thins. A line of calcified, irregular cartilage (white line of Fraenkel) may be visible at the metaphysis. A zone of rarefaction or a linear fracture proximal and parallel to the white line may be visible as only a triangular defect at the bone's lateral margin but is specific. The epiphysis may be compressed. Healing subperiosteal hemorrhages may elevate and calcify the periosteum.

Laboratory diagnosis, which requires measuring blood ascorbic acid, is sometimes done at academic centers. Levels of < 0.6 mg/dL (< 34 µmol/L) are considered marginal; levels of < 0.2 mg/dL (< 11 µmol/L) indicate vitamin C deficiency. Measurement of ascorbic acid levels in the WBC-platelet layer of centrifuged blood is not widely available or standardized.

In adults, scurvy must be differentiated from arthritis, hemorrhagic disorders, gingivitis, and protein-energy undernutrition. Hyperkeratotic hair follicles with surrounding hyperemia or hemorrhage are almost pathognomonic. Bleeding gums, conjunctival hemorrhages, most petechiae, and ecchymoses are nonspecific.

Treatment

• Nutritious diet with supplemental ascorbic acid

For scurvy in adults, ascorbic acid 100 to 500 mg po tid is given for 1 to 2 wk, until signs disappear, and followed by a nutritious diet supplying 1 to 2 times the daily recommended intake. In scurvy, therapeutic doses of ascorbic acid restore the functions of vitamin C in a few days. The symptoms and signs usually disappear over 1 to 2 wk. Chronic gingivitis with extensive subcutaneous hemorrhage persists longer.

Prevention

Vitamin C 75 mg po once/day for women and 90 mg po once/day for men prevents deficiency. Smokers should consume an additional 35 mg/day. Five servings of most fruits and vegetables (recommended daily) provide > 200 mg of vitamin C.

Vitamin C Toxicity

The upper limit for vitamin C intake is 2000 mg/day. Up to 10 g/day of vitamin C are sometimes taken for unproven health benefits, such as preventing or shortening the duration of viral infections or slowing or reversing the progression of cancer or atherosclerosis. Such doses may acidify the urine, cause nausea and diarrhea, interfere with the healthy antioxidant-prooxidant balance in the body, and, in patients with thalassemia or hemochromatosis, promote iron overload. Intake below the upper limit does not have toxic effects in healthy adults.

Vitamin D

Vitamin D has 2 main forms: D_2 (ergocalciferol) and D_3 (cholecalciferol); the latter is the naturally occurring form and the form used for low-dose supplementation. Vitamin D_3 is synthesized in skin by exposure to direct sunlight (ultraviolet B radiation) and obtained in the diet chiefly in fish liver oils and salt water fish. In some developed countries, milk and other foods are fortified with vitamin D. Human breast milk is low in vitamin D, containing an average of only 10% of the amount in fortified cow's milk. Requirements for vitamin D increase with age because skin synthesis declines. Sunscreen use and dark skin pigmentation also reduce skin synthesis of vitamin D.

Vitamin D is a prohormone with several active metabolites that act as hormones. Vitamin D is metabolized by the liver to 25(OH)D, which is then converted by the kidneys to $1,25(OH)_2D$ (1,25-dihydroxycholecalciferol, calcitriol, or active vitamin D hormone). 25(OH)D, the major circulating form, has some metabolic activity, but $1,25(OH)_2D$ is the most metabolically active. The conversion to $1,25(OH)_2D$ is regulated by its own concentration, parathyroid hormone (PTH), and serum concentrations of Ca and phosphate.

[
Table 4-6. Actions of Vitamin D and its Metabolites]

Vitamin D affects many organ systems (see Table 4-6), but mainly it increases Ca and phosphate absorption from the intestine and promotes normal bone formation and mineralization. Vitamin D and related analogs may be used to treat psoriasis, hypoparathyroidism, renal osteodystrophy, and possibly leukemia and breast, prostate, and colon cancers; they may also be used for immunosuppression.

Vitamin D Deficiency and Dependency

Inadequate exposure to sunlight predisposes to vitamin D deficiency. Deficiency impairs bone mineralization, causing rickets in children and osteomalacia in adults and possibly contributing to osteoporosis. Treatment usually consists of oral vitamin D; Ca and phosphate are supplemented as needed. Prevention is often possible. Rarely, hereditary disorders cause impaired metabolism of vitamin D (dependency).

Vitamin D deficiency is a common cause of rickets and osteomalacia, but these disorders may also result from other conditions, such as various renal tubular disorders, familial hypophosphatemic (vitamin D-resistant) rickets (see p. 2991), chronic metabolic acidosis, hypoparathyroidism (which reduces vitamin D absorption), inadequate dietary Ca, and disorders or drugs that impair the mineralization of bone matrix.

Vitamin D deficiency causes hypocalcemia, which stimulates production of PTH, causing hyperparathyroidism. Hyperparathyroidism increases absorption, bone mobilization, and renal conservation of Ca but increases excretion of phosphate. As a result, the serum level of Ca may be normal, but because of hypophosphatemia, bone mineralization is impaired.

Etiology

Vitamin D deficiency may result from the following.

Inadequate exposure or intake: Inadequate direct sunlight exposure (or sunscreen use) and inadequate intake usually occur simultaneously to result in clinical deficiency. Susceptible people include the elderly (who are often undernourished and are not exposed to enough sunlight), and certain communities (eg, women and children who are confined to the home or who wear clothing that covers the entire body and face). Inadequate vitamin D stores are common among the elderly, particularly those who are house-bound, institutionalized, or hospitalized or who have had a hip fracture. Recommended direct sunlight exposure is 5 to 15 min (suberythemal dose) to arms and legs, or face, arms and hands, at least 3 times a week.

Reduced absorption: Malabsorption can deprive the body of dietary vitamin D; only a small amount of 25(OH)D is recirculated enterohepatically.

Abnormal metabolism: Vitamin D deficiency may result from defects in the production of 25(OH)D or $1,25(OH)_2D$. People with a chronic renal disorder commonly develop rickets or osteomalacia because renal production of $1,25\ (OH)_2D$ is decreased and phosphate levels are elevated. Hepatic dysfunction can also interfere with production of active vitamin D metabolites.

Type I hereditary vitamin D-dependent rickets is an autosomal recessive disorder characterized by absent or defective conversion of 25(OH)D to $1,25(OH)_2D$ in the kidneys. X-linked familial hypophosphatemia

reduces vitamin D synthesis in the kidneys. Many anticonvulsants and glucocorticoid use increase the need for vitamin D supplementation.

Resistance to effects of vitamin D: Type II hereditary vitamin D-dependent rickets has several forms and is due to mutations in the $1,25(OH)_2D$ receptor. This receptor affects the metabolism of gut, kidney, bone, and other cells. In this disorder, $1,25(OH)_2D$ is abundant but ineffective because the receptor is not functional.

Symptoms and Signs

Vitamin D deficiency can cause muscle aches, muscle weakness, and bone pain at any age.

Vitamin D deficiency in a pregnant woman causes deficiency in the fetus. Occasionally, deficiency severe enough to cause maternal osteomalacia results in rickets with metaphyseal lesions in neonates. In young infants, rickets causes softening of the entire skull (craniotabes). When palpated, the occiput and posterior parietal bones feel like a ping pong ball. In older infants with rickets, sitting and crawling are delayed, as is fontanelle closure; there is bossing of the skull and costochondral thickening. Costochondral thickening can look like beadlike prominences along the lateral chest wall (rachitic rosary). In children 1 to 4 yr, epiphyseal cartilage at the lower ends of the radius, ulna, tibia, and fibula enlarges; kyphoscoliosis develops, and walking is delayed. In older children and adolescents, walking is painful; in extreme cases, deformities such as bowlegs and knock-knees develop.

Tetany is caused by hypocalcemia and may accompany infantile or adult vitamin D deficiency. Tetany may cause paresthesias of the lips, tongue, and fingers; carpopedal and facial spasm; and, if very severe, seizures. Maternal deficiency can cause tetany in neonates.

Osteomalacia predisposes to fractures. In the elderly, hip fractures may result from only minimal trauma.

Diagnosis

• Levels of 25(OH)D (D_2+D_3)

Diagnosis may be suspected based on any of the following:

• A history of inadequate sunlight exposure or dietary intake

• Symptoms and signs of rickets, osteomalacia, or neonatal tetany

• Characteristic bone changes seen on x-ray

X-rays of the radius and ulna plus serum levels of Ca, phosphate, alkaline phosphatase, PTH, and 25(OH)D are needed to differentiate vitamin D deficiency from other causes of bone demineralization.

Assessment of vitamin D status and serologic tests for syphilis can be considered for infants with craniotabes based on the history and physical, but most cases of craniotabes resolve spontaneously. Rickets can be distinguished from chondrodystrophy because the latter is characterized by a large head, short extremities, thick bones, and normal serum Ca, phosphate, and alkaline phosphatase levels.

Tetany due to infantile rickets may be clinically indistinguishable from seizures due to other causes. Blood tests and clinical history may help distinguish them.

Bone changes, seen on x-rays, precede clinical signs. In rickets, changes are most evident at the lower ends of the radius and ulna. The diaphyseal ends lose their sharp, clear outline; they are cup-shaped and show a spotty or fringy rarefaction. Later, because the ends of the radius and ulna have become noncalcified and radiolucent, the distance between them and the metacarpal bones appears increased. The bone matrix elsewhere also becomes more radiolucent. Characteristic deformities result from the bones bending at the cartilage-shaft junction because the shaft is weak. As healing begins, a thin white

line of calcification appears at the epiphysis, becoming denser and thicker as calcification proceeds. Later, the bone matrix becomes calcified and opacified at the subperiosteal level.

In adults, bone demineralization, particularly in the spine, pelvis, and lower extremities, can be seen on x-rays; the fibrous lamellae can also be seen, and incomplete ribbonlike areas of demineralization (pseudofractures, Looser's lines, Milkman's syndrome) appear in the cortex.

Because levels of serum 25(OH)D reflect body stores of vitamin D and correlate with symptoms and signs of vitamin D deficiency better than levels of other vitamin D metabolites, 25(OH)D (D_2+D_3) measurement is generally considered the best way to diagnose deficiency. Goal 25(OH)D levels are 30 to 40 ng/mL (about 75 to 100 nmol/L); whether higher levels may be beneficial remains uncertain.

If the diagnosis is unclear, serum levels of 1,25$(OH)_2$D and urinary Ca concentration can be measured. In severe deficiency, serum 1,25$(OH)_2$D is abnormally low, usually undetectable. Urinary Ca is low in all forms of the deficiency except those associated with acidosis.

In vitamin D deficiency, serum Ca may be low or, because of secondary hyperparathyroidism, may be normal. Serum phosphate usually decreases, and serum alkaline phosphatase usually increases. Serum PTH is elevated.

Type I hereditary vitamin D-dependent rickets results in normal serum 25(OH)D, low serum 1,25$(OH)_2$D and Ca, and normal or low serum phosphate.

Treatment

• Correction of Ca and phosphate deficiencies

• Supplemental vitamin D

Ca deficiency (which is common) and phosphate deficiency should be corrected. As long as Ca and phosphate intake is adequate, adults with osteomalacia and children with uncomplicated rickets can be cured by giving vitamin D 40 µg (1600 IU) po once/day. Serum 25(OH)D and 1,25$(OH)_2$D begin to increase within 1 or 2 days. Serum Ca and phosphate increase and serum alkaline phosphatase decreases within about 10 days. During the 3rd wk, enough Ca and phosphate are deposited in bones to be visible on x-rays. After about 1 mo, the dose can usually be reduced gradually to the usual maintenance level of 10 to 15 µg (400 to 600 IU) once/day. If tetany is present, vitamin D should be supplemented with IV Ca salts for up to 1 wk (see p. 841). Elderly patients may need 25 to ≥ 50 µg (1000 to ≥ 2000 IU) daily to maintain a 25(OH)D level > 30 ng/mL (> 75 nmol/L); this dose is higher than the recommended daily allowance (RDA) for people > 70 yr (600 IU) and may exceed the current upper limit of 2000 IU/day.

Because rickets and osteomalacia due to defective production of vitamin D metabolites are vitamin D-resistant, they do not respond to the doses usually effective for rickets due to inadequate intake. Endocrinologic evaluation is required because treatment depends on the specific defect. When 25(OH)D production is defective, vitamin D 50 µg (2000 IU) once/day increases serum levels and results in clinical improvement. Patients with kidney disorders often need 1,25$(OH)_2$D supplementation.

Type I hereditary vitamin D-dependent rickets responds to 1,25$(OH)_2$D 1 to 2 µg po once/day. Some patients with type II hereditary vitamin D-dependent rickets respond to very high doses (eg, 10 to 24 µg/day) of 1,25$(OH)_2$D; others require long-term infusions of Ca.

Prevention

Dietary counseling is particularly important in communities whose members are at risk of vitamin D deficiency. Fortifying unleavened chapati flour with vitamin D (125 µg/kg) has been effective among Indian immigrants in Britain. The benefits of sunlight exposure for vitamin D status must be weighed against the increased skin damage and skin cancer risks.

All breastfed infants should be given supplemental vitamin D 5 µg (200 IU) once/day from birth to 6 mo; at 6 mo, a more diversified diet is available. For adolescents at risk, a single IM dose of ergocalciferol 2.5 mg (100,000 IU) given in the fall can maintain adequate 25(OH)D levels throughout the winter. The recommended daily allowance (RDA) for vitamin D is 400 IU for people aged 51 to 70 and 600 IU for those >70; many consider this intake too low, and the 2005 Dietary Guidelines for Americans recommends that healthy older adults consume 1000 IU/day.

Vitamin D Toxicity

Usually, vitamin D toxicity results from taking excessive amounts. Marked hypercalcemia commonly causes symptoms. Diagnosis is typically based on elevated blood levels of 25(OH)D. Treatment consists of stopping vitamin D, restricting dietary Ca, restoring intravascular volume deficits, and, if toxicity is severe, giving corticosteroids or bisphosphonates.

Because synthesis of $1,25(OH)_2D$ (the most active metabolite of vitamin D) is tightly regulated, vitamin D toxicity usually occurs only if excessive doses (prescription or megavitamin) are taken. Vitamin D 1000 µg (40,000 IU)/day causes toxicity within 1 to 4 mo in infants. In adults, taking 1250 µg (50,000 IU)/day for several months can cause toxicity. Vitamin D toxicity can occur iatrogenically when hypoparathyroidism is treated too aggressively (see p. 844).

Symptoms and Signs

The main symptoms result from hypercalcemia. Anorexia, nausea, and vomiting can develop, often followed by polyuria, polydipsia, weakness, nervousness, pruritus, and eventually renal failure. Proteinuria, urinary casts, azotemia, and metastatic calcifications (particularly in the kidneys) can develop.

Diagnosis

• Hypercalcemia plus risk factors or elevated serum 25(OH)D levels

A history of excessive vitamin D intake may be the only clue differentiating vitamin D toxicity from other causes of hypercalcemia. Elevated serum Ca levels of 12 to 16 mg/dL (3 to 4 mmol/L) are a constant finding when toxic symptoms occur. Serum 25(OH)D levels are usually elevated > 150 ng/mL (> 375 nmol/L). Levels of $1,25(OH)_2D$, which need not be measured to confirm the diagnosis, may be normal.

Serum Ca should be measured often (weekly at first, then monthly) in all patients receiving large doses of vitamin D, particularly the potent $1,25(OH)_2D$.

Treatment

• IV hydration plus corticosteroids or bisphosphonates

After stopping vitamin D intake, hydration with IV normal saline and corticosteroids or bisphosphonates (which inhibit bone resorption) are used to reduce blood Ca levels.

Kidney damage or metastatic calcifications, if present, may be irreversible.

Vitamin E

Vitamin E is a group of compounds (including tocopherols and tocotrienols) that have similar biologic activities. The most biologically active is α-tocopherol, but β-, γ-, and δ-tocopherols, 4 tocotrienols, and several stereoisomers may also have important biologic activity. These compounds act as antioxidants, which prevent lipid peroxidation of polyunsaturated fatty acids in cellular membranes. Plasma tocopherol levels vary with total plasma lipid levels. Normally, the plasma α-tocopherol level is 5 to 20 µg/mL (11.6 to 46.4 µmol/L). High-dose vitamin E supplements do not protect against cardiovascular disorders;whether

supplements can protect against Alzheimer's disease, tardive dyskinesia, and prostate cancer among smokers is controversial.

Although the amount of vitamin E in many fortified foods and supplements is given in IU, current recommendations are to use mg.

Vitamin E Deficiency

Dietary vitamin E deficiency is common in developing countries; deficiency among adults in developed countries is uncommon and usually due to fat malabsorption. The main symptoms are hemolytic anemia and neurologic deficits. Diagnosis is based on measuring the ratio of plasma α-tocopherol to total plasma lipids; a low ratio suggests vitamin E deficiency. Treatment consists of oral vitamin E, given in high doses if there are neurologic deficits or if deficiency results from malabsorption.

Vitamin E deficiency causes fragility of RBCs and degeneration of neurons, particularly peripheral axons and posterior column neurons.

Etiology

In developing countries, the most common cause is inadequate intake of vitamin E. In developed countries, the most common causes are disorders that cause fat malabsorption, including abetalipoproteinemia (Bassen-Kornzweig syndrome, due to genetic absence of apolipoprotein B), chronic cholestatic hepatobiliary disease, pancreatitis, short bowel syndrome, and cystic fibrosis. A rare genetic form of vitamin E deficiency without fat malabsorption results from defective liver metabolism.

Symptoms and Signs

The main symptoms are mild hemolytic anemia and nonspecific neurologic deficits. Abetalipoproteinemia results in progressive neuropathy and retinopathy in the first 2 decades of life (see p. 904).

Vitamin E deficiency may contribute to retinopathy of prematurity (also called retrolental fibroplasia) in premature infants and to some cases of intraventricular and subependymal hemorrhage in neonates. Affected premature neonates have muscle weakness.

In children, chronic cholestatic hepatobiliary disease or cystic fibrosis causes neurologic deficits, including spinocerebellar ataxia with loss of deep tendon reflexes, truncal and limb ataxia, loss of vibration and position senses, ophthalmoplegia, muscle weakness, ptosis, and dysarthria.

In adults with malabsorption, vitamin E deficiency very rarely causes spinocerebellar ataxia because adults have large vitamin E stores in adipose tissue.

Diagnosis

• Low α-tocopherol level or low ratio of serum α-tocopherol to serum lipids

Without a history of inadequate intake or a predisposing condition, vitamin E deficiency is unlikely. Confirmation usually requires measuring the vitamin level. Measuring RBC hemolysis in response to peroxide can suggest the diagnosis but is nonspecific. Hemolysis increases as vitamin E deficiency impairs RBC stability.

Measuring the serum α-tocopherol level is the most direct method of diagnosis. In adults, vitamin E deficiency is suggested if the α-tocopherol level is < 5 μg/mL (< 11.6 μmol/L). Because abnormal lipid levels can affect vitamin E status, a low ratio of serum α-tocopherol to lipids (< 0.8 mg/g total lipid) is the most accurate indicator in adults with hyperlipidemia.

In children and adults with abetalipoproteinemia, serum α-tocopherol levels are usually undetectable.

Treatment

• Supplemental α-tocopherol

If malabsorption causes clinically evident deficiency, α-tocopherol 15 to 25 mg/kg po once/day should be given. However, larger doses given by injection are required to treat neuropathy during its early stages or to overcome the defect of absorption and transport in abetalipoproteinemia.

Prevention

Although premature neonates may require supplementation, human milk and commercial formulas have enough vitamin E for full-term neonates.

Vitamin E Toxicity

Many adults take relatively large amounts of vitamin E (α-tocopherol 400 to 800 mg/day) for months to years without any apparent harm. Occasionally, muscle weakness, fatigue, nausea, and diarrhea occur. The most significant risk is bleeding. However, bleeding is uncommon unless the dose is > 1000 mg/day or the patient takes oral coumarin or warfarin. Thus, the upper limit for adults aged ≥19 yr is 1000 mg for any form of α-tocopherol. Recent analyses of previous studies report that high vitamin E intakes may increase the risk of hemorrhagic stroke and premature death.

Vitamin K

Vitamin K_1 (phylloquinone) is dietary vitamin K. Dietary fat enhances its absorption. Infant formulas contain supplemental vitamin K. Vitamin K_2 refers to a group of compounds (menaquinones) synthesized by bacteria in the intestinal tract; the amount synthesized does not satisfy the vitamin K requirement.

Vitamin K controls the formation of coagulation factors II (prothrombin), VII, IX, and X in the liver. Other coagulation factors dependent on vitamin K are protein C, protein S, and protein Z; proteins C and S are anticoagulants. Metabolic pathways conserve vitamin K. Once vitamin K has participated in formation of coagulation factors, the reaction product, vitamin K epoxide, is enzymatically converted to the active form, vitamin K hydroquinone.

The actions of vitamin K-dependent proteins require Ca. The vitamin K-dependent proteins, osteocalcin and matrix γ-carboxy-glutamyl (Gla) protein, may have important roles in bone and other tissues. Forms of vitamin K are common therapy for osteoporosis in Japan and other countries.

Vitamin K Deficiency

Vitamin K deficiency results from extremely inadequate intake, fat malabsorption, or use of coumarin anticoagulants. Deficiency is particularly common among breastfed infants. It impairs clotting. Diagnosis is suspected based on routine coagulation study findings and confirmed by response to vitamin K. Treatment consists of vitamin K given orally or, when fat malabsorption is the cause or risk of bleeding is high, parenterally.

Vitamin K deficiency decreases levels of prothrombin and other vitamin K-dependent coagulation factors, causing defective coagulation and, potentially, bleeding.

Etiology

Worldwide, vitamin K deficiency causes infant morbidity and mortality. Vitamin K deficiency causes hemorrhagic disease of the newborn, which usually occurs 1 to 7 days postpartum. In affected neonates, birth trauma can cause intracranial hemorrhage. Neonates are prone to vitamin K deficiency because of the following:

• The placenta transmits lipids and vitamin K relatively poorly.

• The neonatal liver is immature with respect to prothrombin synthesis.

• Breast milk is low in vitamin K, containing about 2.5 µg/L (cow's milk contains 5000 µg/L).

• The neonatal gut is sterile during the first few days of life.

Late hemorrhagic disease (occurring 3 to 8 wk postpartum) is usually associated with breastfeeding, malabsorption, or a liver disorder. If the mother has taken phenytoin anticonvulsants, coumarin anticoagulants, or cephalosporin antibiotics, the risk of both types of hemorrhagic disease is increased.

In healthy adults, dietary vitamin K deficiency is uncommon because vitamin K is widely distributed in green vegetables and the bacteria of the normal gut synthesize menaquinones. However, biliary obstruction, malabsorption, cystic fibrosis, and resection of the small intestine can contribute to vitamin K deficiency.

Coumarin anticoagulants interfere with the synthesis of vitamin K-dependent coagulation proteins (factors II, VII, IX, and X) in the liver. Certain antibiotics (particularly some cephalosporins and other broad-spectrum antibiotics), salicylates, megadoses of vitamin E, and hepatic insufficiency increase risk of bleeding in patients with vitamin K deficiency.

Symptoms and Signs

Bleeding is the usual manifestation. Easy bruisability and mucosal bleeding (especially epistaxis, GI hemorrhage, menorrhagia, and hematuria) can occur. Blood may ooze from puncture sites or incisions.

Hemorrhagic disease of the newborn and late hemorrhagic disease in infants may cause cutaneous, GI, intrathoracic, or, in the worst cases, intracranial bleeding. If obstructive jaundice develops, bleeding—if it occurs—usually begins after the 4th or 5th day. It may begin as a slow ooze from a surgical incision, the gums, the nose, or GI mucosa, or it may begin as massive bleeding into the GI tract.

Diagnosis

• Usually, prolonged PT that decreases after phytonadione

Vitamin K deficiency or antagonism (due to coumarin anticoagulants) is suspected when abnormal bleeding occurs in a patient at risk. Blood coagulation studies can preliminarily confirm the diagnosis. PT, usually reported as the INR, is prolonged, but PTT, thrombin time, platelet count, bleeding time, and levels of fibrinogen, fibrin-split products, and D-dimer are normal. If phytonadione (USP generic name for vitamin K_1) 1 mg IV significantly decreases PT within 2 to 6 h, a liver disorder is not the likely cause, and the diagnosis of vitamin K deficiency is confirmed. Some centers can detect vitamin K deficiency more directly by measuring the serum vitamin level. The serum level of vitamin K_1 ranges from 0.2 to 1.0 ng/mL in healthy people consuming adequate quantities of vitamin K_1 (50 to 150 µg/day). Knowing vitamin K intake can help interpret serum levels; recent intake affects levels in serum but not in tissues.

More sensitive indicators of vitamin K status, such as PIVKA (*P*rotein *I*nduced in *V*itamin *K A*bsence or *A*ntagonism) and under-carboxylated osteocalcin, are under study.

Treatment

• Phytonadione

Whenever possible, phytonadione should be given po or sc. The usual adult dose is 5 to 20 mg. (Rarely, even when phytonadione is correctly diluted and given slowly, IV replacement can result in anaphylaxis or anaphylactoid reactions.) INR usually decreases within 6 to 12 h. The dose may be repeated in 6 to 8 h if INR has not decreased satisfactorily. Phytonadione 2.5 to 10 mg po is indicated for nonemergency correction of a prolonged INR in patients taking anticoagulants. Correction usually occurs within 6 to 8 h. When only partial correction of INR is desirable (eg, when INR should remain slightly elevated because of

a prosthetic heart valve), lower doses (eg, 1 to 2.5 mg) of phytonadione can be given.

In infants, bleeding due to deficiency can be corrected by giving phytonadione 1 mg sc or IM once. The dose is repeated if INR remains elevated. Higher doses may be necessary if the mother has been taking oral anticoagulants.

Prevention

Phytonadione 0.5 to 1 mg IM (or 0.3 mg/kg for preterm infants) is recommended for all neonates within 6 h of birth to reduce the incidence of intracranial hemorrhage due to birth trauma and of classic hemorrhagic disease of the newborn (increased bleeding risks 1 to 7 days after birth). It is also used prophylactically before surgery. Some clinicians recommend that pregnant women taking anticonvulsants receive phytonadione 10 mg po once/day for the 1 mo or 20 mg po once/day for the 2 wk before delivery. The low vitamin K_1 content in breast milk can be increased by increasing maternal dietary intake of phylloquinone to 5 mg/day.

Vitamin K Toxicity

Vitamin K_1 (phylloquinone) is not toxic when consumed orally, even in large amounts. However, menadione (a synthetic, water-soluble vitamin K precursor) can cause toxicity and should not be used to treat vitamin K deficiency.

Chapter 5. Mineral Deficiency and Toxicity

Introduction

Six macrominerals are required by people in gram amounts. Four (Na, K, Ca, and Mg) are cations; two (Cl and P) are accompanying anions (see p. 820). Daily requirements range from 0.3 to 2.0 g. Bone, muscle, heart, and brain function depend on these minerals.

Nine trace minerals (microminerals) are required by people in minute amounts: chromium, copper, iodine, iron, fluorine, manganese, molybdenum, selenium, and zinc. (For sources, functions, effects of deficiency and toxicity, and dietary requirements, see Tables 5-1 and 5-2.) All trace minerals are toxic at high levels; some minerals (arsenic, nickel, and chromium) may be carcinogens.

Mineral deficiencies (except of iodine, iron, and zinc) do not often develop spontaneously in adults on ordinary diets; infants are more vulnerable because their growth is rapid and intake varies. Trace mineral imbalances can result from hereditary disorders (eg, hemochromatosis, Wilson's disease), kidney dialysis, parenteral nutrition, or restrictive diets prescribed for people with inborn errors of metabolism.

Chromium

Only 1 to 3% of biologically active trivalent chromium (Cr) is absorbed. Normal plasma levels are 0.05 to 0.50 µg/L (1.0 to 9.6 nmol/L). Chromium potentiates insulin activity and increases the growth rate in undernourished children. Supplements do not enhance muscle size or strength in men.

Deficiency: Four patients receiving long-term TPN developed possible chromium deficiency, with glucose intolerance, weight loss, ataxia, and peripheral neuropathy. Symptoms resolved in 3 who were given trivalent chromium 150 to 250 mg.

Toxicity: High doses of trivalent chromium given parenterally cause skin irritation, but lower doses given orally are not toxic. Exposure to hexavalent chromium (CrO_3) in the workplace may irritate the skin, lungs, and GI tract and may cause perforation of the nasal septum and lung carcinoma.

Copper

Copper is a component of many body proteins; almost all of the body's copper is bound to copper proteins. Unbound (free) copper ions are toxic. Genetic mechanisms control the incorporation of copper into apoproteins and the processes that prevent toxic accumulation of copper in the body. Copper absorbed in excess of metabolic requirements is excreted through bile.

[**Table 5-1.** Trace Minerals]

Acquired Copper Deficiency

If the genetic mechanisms controlling copper metabolism are normal, dietary deficiency rarely causes clinically significant copper deficiency. The only reported causes are kwashiorkor, persistent infantile diarrhea (usually associated with a diet limited to milk), severe malabsorption (as in sprue), and excessive zinc intake.

Deficiency may cause neutropenia, impaired bone calcification, and hypochromic anemia not responsive to iron supplements.

Diagnosis is based on low serum levels of copper and ceruloplasmin, although these tests are not always reliable. Treatment is directed at the cause, and copper 1.5 to 3 mg/day po (usually as copper sulfate) is given.

Inherited Copper Deficiency

(Menkes Syndrome)

Inherited copper deficiency occurs in male infants who inherit a mutant X-linked gene. Incidence is about 1 in 50,000 live births. Copper is deficient in the liver, serum, and essential copper proteins, including cytochrome-c oxidase, ceruloplasmin, and lysyl oxidase.

Symptoms are severe intellectual disability, vomiting, diarrhea, protein-losing enteropathy, hypopigmentation, bone changes, and arterial rupture; the hair is sparse, steely, or kinky.

Diagnosis

• Serum copper and ceruloplasmin levels

• Serum levels of dopamine, norepinephrine, dihydroxyphenylacetic acid, and dihydroxyphenylglycol in infants at risk

Diagnosis is based on low copper and ceruloplasmin levels in serum, although these tests are not always reliable. Because early diagnosis and treatment seem to result in a better prognosis, the disorder is ideally detected before age 2 wk. However, diagnostic accuracy of these tests is limited. Thus, infants at risk (eg, those with a family history) can be screened by measuring dopamine, norepinephrine, dihydroxyphenylacetic acid, and dihydroxyphenylglycol in serum. A dihydroxyphenylacetic acid:dihydroxyphenylglycol ratio of > 4 seems to indicate deficiency, and a dopamine:norepinephrine ratio of > 0.2 seems to confirm it.

Treatment

• Copper histidine

Parenteral copper is usually given as copper histidine 250 µg sc bid to age 1 yr, then 250 µg sc once/day until age 3 yr; monitoring kidney function is essential during treatment. Despite early treatment, many children have abnormal neurodevelopment.

Acquired Copper Toxicity

Acquired copper toxicity can result from ingesting or absorbing excess copper (eg, from ingesting an acidic food or beverage that has had prolonged contact with a copper container). Self-limited gastroenteritis with nausea, vomiting, and diarrhea may occur.

[**Table 5-2.** Guidelines for Daily Intake of Minerals]

More severe toxicity results from ingestion (usually with suicidal intent) of gram quantities of a copper salt (eg, copper sulfate) or from absorption of large amounts through the skin (eg, if compresses saturated with a solution of a copper salt are applied to large areas of burned skin). Hemolytic anemia and anuria can result and may be fatal.

Indian childhood cirrhosis, non-Indian childhood cirrhosis, and idiopathic copper toxicity are probably identical disorders in which excess copper causes cirrhosis. All seem to be caused by ingesting milk that has been boiled or stored in corroded copper or brass vessels. Recent studies suggest that idiopathic copper toxicity may develop only in infants with an unknown genetic defect.

Diagnosis usually requires liver biopsy, which shows Mallory hyalin bodies.

Treatment

• Chelation

• Supportive measures

For copper toxicity due to ingesting grams of copper, prompt gastric lavage is done. Copper toxicity that causes complications such as hemolytic anemia, anuria, or hepatotoxicity is also treated with either oral penicillamine 250 mg q 6 h to 750 mg q 12 h (1000 to 1500 mg/day in 2 to 4 doses) or dimercaprol 3 to 5 mg/kg IM q 4 h for 2 days, then q 4 to 6 h (see also Table 340-4 and copper salts in Table 340-8). If used early, hemodialysis may be effective. Occasionally, copper toxicity is fatal despite treatment.

Inherited Copper Toxicity

(Wilson's Disease)

Inherited copper toxicity results in accumulation of copper in the liver and other organs. Hepatic or neurologic symptoms develop. Diagnosis is based on a low serum ceruloplasmin level, high urinary excretion of copper, and sometimes liver biopsy results. Treatment consists of a low-copper diet and chelation, usually with penicillamine or dimercaprol.

Wilson's disease is a progressive disorder of copper metabolism that affects 1 person in 30,000. Affected people are homozygous for the mutant recessive gene, located on chromosome 13. Heterozygous carriers, who constitute about 1.1% of the population, are asymptomatic.

Pathophysiology

The genetic defect impairs copper transport. The impaired transport decreases copper secretion into the bile, thus causing the copper overload and resultant accumulation in the liver, which begins at birth. The impaired transport also interferes with incorporation of copper into the copper protein ceruloplasmin, thus decreasing serum levels of ceruloplasmin.

Hepatic fibrosis develops, ultimately causing cirrhosis. Copper diffuses out of the liver into the blood, then into other tissues. It is most destructive to the brain but also damages the kidneys and reproductive organs and causes hemolytic anemia. Some copper is deposited in Descemet's membrane of the cornea, causing Kayser-Fleischer rings.

Symptoms and Signs

Symptoms usually develop between ages 5 and 40. In almost half of patients, particularly adolescents, the first symptom is hepatitis—acute, chronic active, or fulminant. But hepatitis may develop at any time. In about 40% of patients, particularly young adults, the first symptoms reflect CNS involvement. Motor deficits are common, including any combination of tremors, dystonia, dysarthria, dysphagia, chorea, drooling, and incoordination. Sometimes the first symptoms are cognitive or psychiatric abnormalities. In 5 to 10% of patients, the first symptom is incidentally noted gold or greenish gold Kayser-Fleischer rings or crescents (due to copper deposits in the cornea), amenorrhea or repeated miscarriages, or hematuria.

Diagnosis

• Slit-lamp examination for Kayser-Fleischer rings

• Serum ceruloplasmin and 24-h urinary copper excretion

• Sometimes confirmation by penicillamine provocation test or liver biopsy

Wilson's disease should be suspected in people < 40 with any of the following:

• An unexplained hepatic, neurologic, or psychiatric disorder

• An unexplained persistent elevation in hepatic transaminases

• A sibling, parent, or cousin with Wilson's disease

• Fulminant hepatitis

If Wilson's disease is suspected, slit-lamp examination for Kayser-Fleischer rings is required, and serum ceruloplasmin and copper levels and 24-h urinary copper excretion are measured. Transaminase levels are also often measured; high levels are consistent with the diagnosis.

Kayser-Fleischer rings: These rings plus typical motor neurologic abnormalities or a decrease in ceruloplasmin are nearly pathognomonic for Wilson's disease. Rarely, these rings occur in other liver disorders (eg, biliary atresia, primary biliary cirrhosis), but ceruloplasmin levels should be unaffected.

Ceruloplasmin: Serum ceruloplasmin (normally 20 to 35 mg/dL) is usually low in Wilson's disease but can be normal. It can also be low in heterozygous carriers and those with other liver disorders (eg, viral hepatitis, drug- or alcohol-induced liver disease). A low ceruloplasmin level in a patient with a Kayser-Fleischer ring is diagnostic. Also, a level of < 5 mg/dL is highly suggestive regardless of clinical findings.

Serum copper: Despite the copper accumulation in the body, serum copper levels are decreased because of the decreased ceruloplasmin levels.

Urinary copper excretion: In Wilson's disease, 24-h urinary copper excretion (normally, ≤ 30 µg/day) is usually > 100 µg/day. If serum ceruloplasmin is low and urinary copper excretion is high, diagnosis is clear. If levels are equivocal, measuring urinary copper excretion after penicillamine is given (penicillamine provocation test) may confirm the diagnosis; this test is not usually done in adults because cutoff values are not well-established.

Liver biopsy: In unclear cases (eg, elevated transaminases, no Kayser-Fleischer rings, indeterminate values for ceruloplasmin and urinary copper), the diagnosis is made by doing a liver biopsy to measure hepatic copper concentration. However, false-negative results may occur because of a sampling error (due to large variations in copper concentrations in the liver) or fulminant hepatitis (causing necrosis that releases large amounts of copper).

Screening: Because early treatment is most effective, screening is indicated for anyone who has a sibling, cousin, or parent with Wilson's disease. Screening consists of a slit-lamp examination and measurement of transaminase levels, serum copper and ceruloplasmin, and 24-h urine copper excretion. If any results are abnormal, liver biopsy is done to measure hepatic copper concentration. Infants should not be tested until after age 1 yr because ceruloplasmin levels are low during the first few months of life. Children < 6 yr with normal test results should be retested 5 to 10 yr later.

Genetic testing is under investigation.

Prognosis

Prognosis is usually good, unless disease is advanced before treatment begins. Untreated Wilson's disease is fatal, usually by age 30.

Treatment

• Penicillamine or another chelating drug if needed to remove accumulated copper

• Low-copper diet

• For maintenance, lifelong low-dose chelation therapy or oral zinc

Continual, lifelong treatment is mandatory regardless of whether symptoms are present. Accumulated copper should be removed with chelating drugs. A low-copper diet (eg, avoiding beef liver, cashews, black-eyed peas, vegetable juice, shellfish, mushrooms, and cocoa) and use of either low-dose chelation

therapy or oral zinc can prevent copper from accumulating.

Penicillamine is the most commonly used chelating drug but has considerable toxicity (eg, fever, rash, neutropenia, thrombocytopenia, proteinuria). Cross-reactivity may occur in people with penicillin allergy. Patients > 5 yr are given oral doses of 62.5 mg q 6 h to 250 mg q 12 h (250 to 500 mg/day in 2 to 4 doses) and slowly increased to a maximum of 250 mg q 6 h to 750 mg q 12 h (1000 to 1500 mg/day in 2 to 4 doses). Younger children are given 10 mg/kg bid or 6.7 mg/kg tid (20 mg/kg/d) po. Pyridoxine 25 mg po once/day is given with penicillamine. Occasionally, use of penicillamine is associated with worsening neurologic symptoms.

Trientine hydrochloride is an alternative treatment to penicillamine. Doses are 375 to 750 mg po bid or 250 to 500 mg po tid (750 to 1500 mg/day).

Zinc acetate 50 mg po tid can prevent reaccumulation of copper in patients who cannot tolerate penicillamine or trientine or who have neurologic symptoms that do not respond to the other drugs. (CAUTION: *Penicillamine or trientine must not be given with zinc because either drug can bind zinc, forming a compound with no therapeutic effect*.)

Poor long-term adherence to drug therapy is common. After 1 to 5 yr of therapy, lower dose maintenance drug therapy can be considered. Regular follow-up care with an expert in liver disease is recommended.

Liver transplantation may be lifesaving for patients who have Wilson's disease and fulminant hepatic failure or severe hepatic insufficiency refractory to drugs.

Fluorine

Most of the body's fluorine (F) is contained in bones and teeth. Fluoride (the ionic form of fluorine) is widely distributed in nature. The main source of fluoride is fluoridated drinking water.

Deficiency: Fluorine deficiency can lead to dental caries and possibly osteoporosis. Fluoridation of water that contains < 1 ppm (the ideal) reduces the incidence of dental caries. If a child's drinking water is not fluoridated, oral fluoride supplements can be prescribed.

Toxicity: Excess fluorine can accumulate in teeth and bones, causing fluorosis. Drinking water containing > 10 ppm is a common cause. Permanent teeth that develop during high fluoride intake are most likely to be affected. Exposure must be much greater to affect deciduous teeth.

The earliest signs are chalky white, irregularly distributed patches on the surface of the enamel; these patches become stained yellow or brown, producing a characteristic mottled appearance. Severe toxicity weakens the enamel, pitting its surface. Bony changes, including osteosclerosis, exostoses of the spine, and genu valgum, can develop but only in adults after prolonged high intake of fluoride.

No tests to diagnose toxicity are available.

Treatment involves reducing fluoride intake; eg, in areas with high fluoride water levels, patients should not drink fluoridated water or take fluoride supplements. Children should always be told not to swallow fluoridated toothpastes.

Iodine

In the body, iodine (I) is involved primarily in the synthesis of 2 thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3). Iodine occurs in the environment and in the diet primarily as iodide. In adults, about 80% of the iodide absorbed is trapped by the thyroid gland. Most environmental iodine occurs in seawater as iodide; a small amount enters the atmosphere and, through rain, enters ground water and soil near the sea. Thus, people living far from the sea and at higher altitudes are at particular risk of deficiency. Fortifying table salt with iodide (typically 70 µg/g) helps ensure adequate intake (150 µg/day). Requirements are higher for pregnant (220 µg/day) and breastfeeding (290 µg/day) women.

Iodine Deficiency

Deficiency is rare in areas where iodized salt is used but common worldwide. Iodine deficiency develops when iodide intake is < 20 µg/day. In mild or moderate deficiency, the thyroid gland, influenced by thyroid-stimulating hormone (TSH), hypertrophies to concentrate iodide in itself, resulting in colloid goiter. Usually, patients remain euthyroid; however, severe iodine deficiency in adults may cause hypothyroidism (endemic myxedema). It can decrease fertility and increase risk of stillbirth, spontaneous abortion, and prenatal and infant mortality. Severe maternal iodine deficiency retards fetal growth and brain development, sometimes resulting in birth defects, and, in infants, causes cretinism, which may include intellectual disability, deaf-mutism, difficulty walking, short stature, and sometimes hypothyroidism.

Diagnosis

• Assessment of thyroid structure and function

Diagnosis in adults and children is usually based on thyroid function, examination for goiter, and imaging tests identifying abnormalities in thyroid function and structure (see p. 776). All neonates should be screened by measuring the TSH level.

Treatment

• Iodide with or without levothyroxine

Infants with iodine deficiency are given L-thyroxine 3 µg/kg po once/day for a week plus iodide 50 to 90 µg po once/day for several weeks to quickly restore a euthyroid state. Children are treated with iodide 90 to 120 µg once/day. Adults are given iodide 150 µg once/day. Iodine deficiency can also be treated by giving levothyroxine. Serum TSH levels are monitored in all patients until the levels are normal (ie, < 5 µIU/mL).

Iodine Toxicity

Chronic toxicity may develop when intake is > 1.1 mg/day. Most people who ingest excess amounts of iodine remain euthyroid. Some people who ingest excess amounts of iodine, particularly those who were previously deficient, develop hyperthyroidism (Jod-Basedow phenomenon). Paradoxically, excess uptake of iodine by the thyroid may inhibit thyroid hormone synthesis (called Wolff-Chaikoff effect). Thus, iodine toxicity can eventually cause iodide goiter, hypothyroidism, or myxedema. Very large amounts of iodide may cause a brassy taste in the mouth, increased salivation, GI irritation, and acneiform skin lesions. Patients exposed to frequent large amounts of radiographic contrast dyes or the drug amiodarone also need to have their thyroid function monitored.

Diagnosis is usually based on thyroid function and imaging test findings (see p. 776), which are correlated with clinical data. Iodine excretion may be more specific but is not usually measured. Treatment consists of correcting thyroid abnormalities and, if intake is excessive, dietary modification.

Iron

Iron (Fe) is a component of hemoglobin, myoglobin, and many enzymes in the body. Heme iron, contained mainly in animal products, is absorbed much better than nonheme iron (eg, in plants and grains), which accounts for > 85% of iron in the average diet. However, absorption of nonheme iron is increased when it is consumed with animal protein and vitamin C.

Deficiency: Iron deficiency is one of the most common mineral deficiencies in the world. It may result from the following:

• Inadequate iron intake, common in infants, adolescent girls, and pregnant women

• Malabsorption (eg, celiac sprue)

• Chronic bleeding

Chronic bleeding due to colon cancer is a serious cause in middle-aged people and the elderly.

When deficiency is advanced, microcytic anemia develops (see p. 924).

In addition to anemia, iron deficiency may cause pica (a craving for nonfoods) and spoon nails and is associated with restless leg syndrome. Rarely, iron deficiency causes dysphagia due to postcricoid esophageal web.

Diagnosis involves CBC, serum ferritin, and possibly measurement of transferrin saturation (iron capacity).

All people with moderate or severe iron deficiency and some people with mild deficiency require iron supplementation.

Toxicity: Iron may accumulate in the body because of

• Iron therapy given in excessive amounts or for too long

• Repeated blood transfusions

• Chronic alcoholism

• Overdose of iron

Iron overload can also result from an inherited iron overload disease (hemochromatosis—see p. 1032), a potentially fatal but easily treatable genetic disorder in which too much iron is absorbed. Hemochromatosis affects > 1 million Americans.

An overdose of iron is toxic (see p. 3341), causing vomiting, diarrhea, and damage to the intestine and other organs.

Diagnosis is similar to that for iron deficiency.

Treatment often involves deferoxamine, which binds with iron and is excreted in urine.

Manganese

Manganese (Mn), necessary for healthy bone structure, is a component of several enzyme systems, including manganese-specific glycosyltransferases and phosphoenolpyruvate carboxykinase. Median intake is between 1.6 and 2.3 mg/day; absorption is 5 to 10%.

Deficiency has not been conclusively documented, although one experimental case in a volunteer resulted in transient dermatitis, hypocholesterolemia, and increased alkaline phosphatase levels.

Toxicity is usually limited to people who mine and refine ore; prolonged exposure causes neurologic symptoms resembling those of parkinsonism or Wilson's disease.

Molybdenum

Molybdenum (Mo) is a component of coenzymes necessary for the activity of xanthine oxidase, sulfite oxidase, and aldehyde oxidase.

Genetic and nutritional deficiencies of molybdenum have been reported but are rare. Genetic sulfite oxidase deficiency was described in 1967 in a child. It resulted from the inability to form the molybdenum coenzyme despite the presence of adequate molybdenum. The deficiency caused intellectual disability, seizures, opisthotonus, and lens dislocation.

Molybdenum deficiency resulting in sulfite toxicity occurred in a patient receiving long-term TPN. Symptoms were tachycardia, tachypnea, headache, nausea, vomiting, and coma. Laboratory tests showed high levels of sulfite and xanthine and low levels of sulfate and uric acid in the blood and urine. Ammonium molybdate 300 µg/day IV caused dramatic recovery.

A case of molybdenum toxicity may have occurred in 1961; it caused goutlike symptoms and abnormalities of the GI tract, liver, and kidneys.

Selenium

Selenium (Se) is a part of the enzyme glutathione peroxidase, which metabolizes hydro-peroxides formed from polyunsaturated fatty acids. Selenium is also a part of the enzymes that deiodinate thyroid hormones. Generally, selenium acts as an antioxidant that works with vitamin E. Some epidemiologic studies associate low selenium levels with cancer. In children with Down syndrome, selenium supplements may help prevent bacterial infections. Plasma levels vary from 8 to 25 µg/dL, depending on selenium intake. Diagnosis is usually clinical; sometimes blood glutathione peroxidase is measured.

Deficiency: Deficiency is rare, even in New Zealand and Finland, where selenium intake is 30 to 50 µg/day, compared with 100 to 250 µg/day in the US and Canada. In certain areas of China, where intake averages 10 to 15 µg/day, selenium deficiency predisposes patients to Keshan disease, an endemic viral cardiomyopathy affecting primarily children and young women. This cardiomyopathy can be prevented but not cured by sodium selenite supplements of 50 µg/day po. Patients receiving long-term TPN have developed selenium deficiency with muscle pain and tenderness that responded to a selenomethionine supplement. In Siberian Russia and China, growing children with selenium deficiency may develop chronic osteoarthropathy (Kashin-Beck disease). Selenium deficiency may contribute synergistically with iodine deficiency to the development of goiter and hypothyroidism.

Diagnosis is made clinically or sometimes by measuring glutathione peroxidase activity or plasma selenium, but neither of these tests is readily available. Treatment consists of sodium selenite 100 µg/day po.

Toxicity: At high doses (> 900 µg/day), selenium causes toxicity. Manifestations include hair loss, abnormal nails, dermatitis, peripheral neuropathy, nausea, diarrhea, fatigue, irritability, and a garlic odor of the breath. Toxic levels of plasma selenium are not well defined.

Zinc

Zinc (Zn) is contained mainly in bones, teeth, hair, skin, liver, muscle, leukocytes, and testes. Zinc is a component of several hundred enzymes, including many nicotinamide adenine dinucleotide (NADH) dehydrogenases, RNA and DNA polymerases, and DNA transcription factors as well as alkaline phosphatase, superoxide dismutase, and carbonic anhydrase. A diet high in fiber and phytate (eg, in whole-grain bread) reduces zinc absorption.

Deficiency: Dietary deficiency is unlikely in healthy people. Secondary zinc deficiency can develop in the following:

- Some patients with hepatic insufficiency (because the ability to retain zinc is lost)
- Patients taking diuretics
- Patients with diabetes mellitus, sickle cell disease, chronic renal failure, or malabsorption
- Patients with stressful conditions (eg, sepsis, burns, head injury)
- Elderly institutionalized and homebound patients (common)

Maternal zinc deficiency may cause fetal malformations and low birth weight.

Zinc deficiency in children causes impaired growth and impaired taste (hypogeusia). Other symptoms and signs in children include delayed sexual maturation and hypogonadism. In children or adults, symptoms include hypogonadism, alopecia, impaired immunity, anorexia, dermatitis, night blindness, anemia, lethargy, and impaired wound healing.

Zinc deficiency should be suspected in undernourished patients with typical symptoms or signs. However, because many of the symptoms and signs are nonspecific, clinical diagnosis of mild zinc deficiency is difficult. Laboratory diagnosis is also difficult. Low albumin levels, common in zinc deficiency, make serum zinc levels difficult to interpret; diagnosis usually requires the combination of low levels of zinc in serum and increased urinary zinc excretion. If available, isotope studies can measure zinc status more accurately.

Treatment consists of elemental zinc 15 to 120 mg/day po until symptoms and signs resolve.

Acrodermatitis enteropathica (a rare, once fatal autosomal recessive disorder) causes malabsorption of zinc. Psoriasiform dermatitis develops around the eyes, nose, and mouth; on the buttocks; and in an acral distribution. The disorder also causes hair loss, paronychia, impaired immunity, recurrent infection, impaired growth, and diarrhea. Symptoms and signs usually develop after infants are weaned from breast milk. In such cases, doctors suspect the diagnosis. If deficiency is diagnosed, zinc sulfate 30 to 150 mg/day po usually results in complete remission.

Toxicity: The recommended upper limit for zinc intake is 40 mg/day. Toxicity is rare. Ingesting doses of elemental zinc ranging from 100 to 150 mg/day for prolonged periods interferes with copper metabolism and causes low blood copper levels, RBC microcytosis, neutropenia, and impaired immunity; higher doses should be given only for short periods of time and the patient should be followed closely. Ingesting larger amounts (200 to 800 mg/day), usually by consuming acidic food or drink from a galvanized (zinc-coated) container, can cause anorexia, vomiting, and diarrhea. Metal fume fever, also called brass-founders' ague or zinc shakes, is caused by inhaling industrial zinc oxide fumes; it results in neurologic damage. Symptoms usually resolve after 12 to 24 h in a zinc-free environment.

Chapter 6. Obesity and the Metabolic Syndrome

Obesity

Obesity is excess body fat; consequences depend not only on the absolute amount but also on the distribution of the fat. Complications include cardiovascular disorders, diabetes mellitus, many cancers, cholelithiasis, fatty liver and cirrhosis, osteoarthritis, reproductive disorders in men and women, psychologic disorders, and premature death. Diagnosis is based on body mass index (BMI—calculated from height and weight) and waist circumference. BP, fasting plasma glucose, and lipid levels should be measured. Treatment includes physical activity, dietary and behavioral modification, and sometimes drugs or surgery.

Prevalence of obesity in the US is high and is increasing, particularly among children and adolescents (see Table 6-1).

Prevalence is more than twice as high at age 55 as at age 20. Obesity is twice as common among women in a lower socioeconomic group as among those in a higher group. Prevalence among black and white men does not differ significantly, but it is higher among black women than white women. More than 50% of black women ≥ 40 yr are obese; > 80% are overweight.

In the US, obesity and its complications cause as many as 300,000 premature deaths each year, making it second only to cigarette smoking as a preventable cause of death.

[**Table 6-1.** Changes in Prevalence of Obesity According to Nhanes]

Etiology

Almost all cases of obesity result from a combination of genetic predisposition and a chronic imbalance between energy intake, energy utilization for basic metabolic processes, and energy expenditure from physical activity.

Genetic factors: Heritability of BMI is about 66%. Genetic factors may affect the many signaling molecules and receptors used by parts of the hypothalamus and GI tract to regulate food intake (see Sidebar 6-1). Rarely, obesity results from abnormal levels of peptides that regulate food intake (eg, leptin) or abnormalities in their receptors (eg, melanocortin-4 receptor).

Genetic factors also regulate energy expenditure, including BMR, diet-induced thermogenesis, and nonvoluntary activity-associated thermogenesis. Genetic factors may have a greater effect on the distribution of body fat, particularly abdominal fat (see Metabolic Syndrome on p. 64), than on the amount of body fat.

Environmental factors: Weight is gained when caloric intake exceeds energy needs. Important determinants of energy intake include portion sizes and the energy density of the food. High-fat foods, processed foods, and diets high in refined carbohydrates, soft drinks, fruit juices, and alcohol promote weight gain. Diets high in fresh fruit and vegetables, fiber, and complex carbohydrates, with water as the main fluid consumed, minimize weight gain. A sedentary lifestyle promotes weight gain.

Regulatory factors: Prenatal maternal obesity, prenatal maternal smoking, intrauterine growth restriction, and insufficient sleep can disturb weight regulation. About 15% of women permanently gain ≥ 20 lb with each pregnancy. Obesity that persists beyond early childhood makes weight loss in later life more difficult.

Drugs, including corticosteroids, lithium, traditional antidepressants (tricyclics, tetracyclics, and monoamine oxidase inhibitors [MAOIs]), benzodiazepines, and antipsychotic drugs, often cause weight gain.

Uncommonly, weight gain is caused by one of the following disorders:

- Brain damage caused by a tumor (especially a craniopharyngioma) or an infection (particularly those affecting the hypothalamus), which can stimulate consumption of excess calories
- Hyperinsulinism due to pancreatic tumors
- Hypercortisolism due to Cushing's syndrome, which causes predominantly abdominal obesity
- Hypothyroidism (rarely a cause of substantial weight gain)

Sidebar 6-1 Pathways Regulating Food Intake

Preabsorptive and postabsorptive signals from the GI tract and changes in plasma nutrient levels provide short-term feedback to regulate food intake:

- GI hormones (eg, glucagon-like peptide 1 [GLP-1], cholecystokinin [CCK]) reduce food intake.
- Ghrelin, secreted primarily by the stomach, increases food intake.
- Leptin, secreted from adipose tissue, informs the brain as to how much fat is stored; high leptin levels correlate with increased body fat.

The hypothalamus integrates various signals involved in the regulation of energy balance and then activates pathways that increase or decrease food intake:

- Neuropeptide Y (NPY), agouti-related peptide (ARP), α-melanocyte-stimulating hormone (α-MSH), cocaine- and amphetamine-related transcript (CART), orexin, and melanin-concentrating hormone (MCH) increase food intake.
- Corticotropic hormone (CRH) and urocortin decrease it.

Eating disorders: At least 2 pathologic eating patterns may be associated with obesity:

- **Binge eating disorder** is consumption of large amounts of food quickly with a subjective sense of loss of control during the binge and distress after it (see p. 1537). This disorder does not include compensatory behaviors, such as vomiting. Prevalence is 1 to 3% among both sexes and 10 to 20% among people entering weight reduction programs. Obesity is usually severe, large amounts of weight are frequently gained or lost, and pronounced psychologic disturbances are present.
- **Night-eating syndrome** consists of morning anorexia, evening hyperphagia, and insomnia. At least 25 to 50% of daily intake occurs after the evening meal. About 10% of people seeking treatment for severe obesity may have this disorder. Rarely, a similar disorder is induced by use of a hypnotic such as zolpidem.

Similar but less extreme patterns, classified as eating disorders not otherwise specified (EDNOS), probably contribute to excess weight gain in more people. For example, nocturnal eating contributes to excess weight gain in many people who do not have night-eating syndrome.

Complications

Complications of obesity include the following:

- Metabolic syndrome
- Diabetes mellitus

- Cardiovascular disease
- Nonalcoholic steatohepatitis (fatty liver)
- Gallbladder disease
- Gastroesophageal reflux
- Obstructive sleep apnea
- Reproductive system disorders
- Many cancers
- Osteoarthritis
- Social and psychologic problems

Insulin resistance, dyslipidemias, and hypertension (the metabolic syndrome) develop, often leading to diabetes mellitus and coronary artery disease (see p. 64). These complications are more likely in patients with fat that is concentrated abdominally, a high serum triglyceride level, a family history of type 2 diabetes mellitus or premature cardiovascular disease, or a combination of these risk factors.

Obesity is also a risk factor for nonalcoholic steatohepatitis (which may lead to cirrhosis) and for reproductive system disorders, such as a low serum testosterone level in men and polycystic ovary syndrome in women.

Obstructive sleep apnea can result if excess fat in the neck compresses the airway during sleep. Breathing stops for moments, as often as hundreds of times a night (see p. 1903). This disorder, often undiagnosed, can cause loud snoring and excessive daytime sleepiness and increases the risk of hypertension, cardiac arrhythmias, and metabolic syndrome.

Obesity may cause the obesity-hypoventilation syndrome (Pickwickian syndrome). Impaired breathing leads to hypercapnia, reduced sensitivity to CO_2 in stimulating respiration, hypoxia, cor pulmonale, and risk of premature death. This syndrome may occur alone or secondary to obstructive sleep apnea.

Osteoarthritis and tendon and fascial disorders may result from obesity. Skin disorders are common; increased sweat and skin secretions, trapped in thick folds of skin, are conducive to fungal and bacterial growth, making intertriginous infections especially common. Being overweight probably predisposes to cholelithiasis, gout, deep venous thrombosis and pulmonary embolism, and many cancers (especially colon and breast cancers).

Obesity leads to social, economic, and psychologic problems as a result of prejudice, discrimination, poor body image, and low self-esteem. For example, people may be underemployed or unemployed.

Diagnosis

- BMI
- Waist circumference
- Sometimes body composition analysis

In adults, BMI, defined as weight (kg) divided by the square of the height (m^2), is used to screen for overweight or obesity. BMI of 25 to 29.9 kg/m^2 indicates overweight; BMI ≥ 30 kg/m^2 indicates obesity (see Table 6-2). However, BMI is a crude screening tool and has limitations in many subpopulations. BMI is

age- and race-specific; its use is limited in children and the elderly. In children and adolescents, overweight is BMI at the ≥ 95th percentile based on age- and sex-specific Centers for Disease Control and Prevention (CDC) growth charts at the CDC web site.

Asians, Japanese, and many aboriginal populations have a lower cut-off (23 kg/m^2) for overweight. In addition, BMI may be high in muscular athletes who lack excess body fat, and normal or low in formerly overweight people who have lost muscle mass.

The risk of metabolic and cardiovascular complications due to obesity is determined more accurately by the following:

• Other risk factors, particularly a family history of type 2 diabetes or premature cardiovascular disease

• Waist circumference

• Serum triglycerides

The waist circumference that increases risk of complications due to obesity varies by ethnic group and sex:

• White men: > 93 cm (> 36.6 in), particularly > 101 cm (> 39.8 in)

• White women: > 79 cm (> 31.1 in), particularly > 87 cm (> 34.2 in)

• Asian Indian men: > 78 cm (> 30.7 in), particularly > 90 cm (> 35.4 in)

• Asian Indian women: > 72 cm (> 28.3 in), particularly > 80 cm (> 31.5 in)

Body composition analysis: Body composition—the percentage of body fat and muscle—is also considered when obesity is diagnosed. Although probably unnecessary in routine clinical practice, body composition analysis can be helpful if clinicians question whether elevated BMI is due to muscle or excessive fat.

The percentage of body fat can be estimated by measuring skinfold thickness (usually over the triceps) or determining mid upper arm area (see p. 13).

Bioelectrical impedance analysis (BIA) can estimate percentage of body fat simply and noninvasively. BIA estimates percentage of total body water directly; percentage of body fat is derived indirectly. BIA is most reliable in healthy people and in people with only a few chronic disorders that do not change the percentage of total body water (eg, moderate obesity, diabetes mellitus). Whether measuring BIA poses risks in people with implanted defibrillators is unclear.

Underwater (hydrostatic) weighing is the most accurate method for measuring percentage of body fat. Costly and time-consuming, it is used more often in research than in clinical care. To be weighed accurately while submerged, people must fully exhale beforehand.

Imaging procedures, including CT, MRI, and dual-energy x-ray absorptiometry (DEXA), can also estimate the percentage and distribution of body fat but are usually used only for research.

Other testing: Obese patients should be screened for obstructive sleep apnea with an instrument such as the Epworth Sleepiness Scale and often the apnea-hypopnea index (total number of apnea or hypopnea episodes occurring per hour of sleep—see p. 1904). This disorder is often underdiagnosed, and obesity increases the risk.

Fasting glucose and lipid levels should be measured routinely in patients with a large waist circumference or a family history of type 2 diabetes mellitus or premature cardiovascular disease.

Prognosis

Untreated, obesity tends to progress. The probability and severity of complications are proportional to the absolute amount of fat, the distribution of the fat, and absolute muscle mass. After weight loss, most people return to their pretreatment weight within 5 yr, and

[**Table 6-2.** Body Mass Index (BMI)]

accordingly, obesity requires a lifelong management program similar to that for any other chronic disorder.

Treatment

• Nutrition management

• Physical activity

• Behavioral therapy

• Drugs (eg, sibutramine, orlistat)

• Bariatric surgery

Weight loss of even 5 to 10% improves overall health and well-being and in particular helps reduce risk of cardiovascular disorders and type 2 diabetes. Weight loss can lead to improvement in patients with obstructive sleep apnea, but sometimes a lot of weight must be lost for the disorder to resolve.

Support from health care practitioners, peers, and family members and various structured programs can help with weight loss and weight maintenance.

Nutrition: A normal eating pattern is important. People who miss breakfast tend to passively consume too many calories later in the day. Patients should eat small meals and avoid or carefully choose snacks. Low-fat (particularly very low saturated fat), high-fiber diets with modest calorie restriction (by 600 kcal/day) and substitution of some protein for carbohydrate seem to have the best long-term outcome. Fresh fruits and vegetables and salads should be substituted for refined carbohydrates and processed food, and water for soft drinks or juices. Alcohol consumption should be limited to moderate levels. Foods with a low glycemic index (see
Table 1-1 on p. 3) and marine fish oils or monounsaturated fats derived from plants (eg, olive oil) reduce the risk of cardiovascular disorders and diabetes. Low-fat dairy products are also part of a healthy diet. Patients need an adequate amount of vitamin D, preferably obtained by exercising outdoors in the sunshine.

Use of meal replacements has proven efficacy; use can be ongoing or intermittent. Diets that require unusual eating habits should be avoided. They are unlikely to be maintained, and weight increases when patients resume previous poor eating habits. Diets of < 1200 kcal/day cannot be sustained, but such diets are sometimes needed to achieve rapid short-term weight loss (eg, to prepare for surgery, to lessen obstructive sleep apnea). Diets of < 800 kcal/day do not produce greater weight loss and are less well tolerated.

Physical activity: Exercise increases energy expenditure, BMR, and diet-induced thermogenesis. Exercise also seems to regulate appetite to more closely match caloric needs. Other benefits include

• Increased insulin sensitivity

• Improved lipid profile

• Lower BP

• Better aerobic fitness

• Improved psychologic well-being

Strengthening (resistance) exercises increase muscle mass. Because muscle tissue burns more calories at rest than does fat tissue, increasing muscle mass produces lasting increases in BMR. Exercise that is interesting and enjoyable is more likely to be sustained. A combination of aerobic and resistance exercise is better than either alone.

Behavioral therapy: Behavioral therapy aims to improve eating habits and physical activity level. Rigid dieting is discouraged in favor of healthy eating. Common-sense measures include the following:

• Avoiding high-calorie snacks

• Choosing healthful foods when dining out

• Eating slowly

• Substituting a physically active hobby for a passive one

Social support, cognitive therapy, and stress management may help, particularly during the lapses usually experienced during any long-term weight loss program. Self-monitoring is useful, and maintenance of a diet diary is particularly effective.

Drugs: Drugs may be used if BMI is > 30 or if BMI is > 27 and patients have complications (eg, hypertension, insulin resistance). Most weight loss due to drug treatment is modest (5 to 10%) at best and occurs during the first 6 mo; not all patients benefit. Drugs are more useful for maintaining weight loss but must be continued indefinitely for weight loss to be maintained. Premenopausal women taking systemically acting drugs for weight control should use contraception.

Sibutramine is a centrally acting appetite suppressant that produces dose-related weight loss. The usual starting dose is 10 mg po once/day; the dose can be decreased to 5 mg or increased to 15 mg. Common adverse effects are headache, dry mouth, insomnia, and constipation; the most common serious one is hypertension. Cardiovascular disorders, particularly poorly controlled hypertension, are contraindications.

Orlistat inhibits intestinal lipase, decreasing fat absorption and improving serum glucose and lipids. Because orlistat is not absorbed, systemic effects are rare. Flatus, oily stools, and diarrhea are common but tend to resolve during the 2nd yr of treatment. A dose of 120 mg po tid should be taken with meals that include fat. A vitamin supplement should be taken at least 2 h before or after taking orlistat. Malabsorption and cholestasis are contraindications; irritable bowel syndrome and other GI disorders may make orlistat difficult to tolerate. Orlistat is available OTC.

Other OTC weight-loss drugs are not recommended. Some (eg, caffeine, ephedrine, guarana, phenylpropanolamine) may be marginally effective, but their adverse effects outweigh their advantages. Others (eg, brindleberry, L-carnitine, chitosan, pectin, grapeseed extract, horse chestnut, chromium picolinate, fucus vesiculosus, ginkgo biloba) have not been shown to be effective and may have adverse effects.

Surgery: Surgery is the most effective treatment for extremely obese patients (see p. 61).

Special Populations

Obesity is a particular concern in children and the elderly.

Children: Childhood obesity is even more worrisome than adult obesity. For obese children, complications are more likely because children are obese longer. About 20 to 25% of children and adolescents are overweight or obese. Risk factors for obesity in infants are low birth weight and maternal obesity, diabetes, and smoking. After puberty, food intake increases; in boys, the extra calories are used to increase protein deposition, but in girls, fat storage is increased.

For obese children, psychologic complications (eg, poor self-esteem, social difficulties, depression) and musculoskeletal complications can develop early. Some musculoskeletal complications, such as slipped capital femoral epiphyses, occur only in children. Other early complications may include obstructive sleep apnea, insulin resistance, hyperlipidemia, and nonalcoholic steatohepatitis. Risk of cardiovascular, respiratory, metabolic, hepatic, and other obesity-related complications increases when these children become adults.

Risk of obesity persisting into adulthood depends partly on when obesity first develops:

• During infancy: Low risk

• Between 6 mo and 5 yr: 25%

• After 6 yr: > 50%

• During adolescence if a parent is obese: > 80%

In children, preventing further weight gain, rather than losing weight, is a reasonable goal. Diet should be modified, and physical activity increased. Increasing general activities and play is more likely to be effective than a structured exercise program. Participating in physical activities during childhood may promote a lifelong physically active lifestyle. Drugs and surgery are avoided but, if complications of obesity are life threatening, may be warranted.

Measures that control weight and prevent obesity in children may benefit public health the most. Such measures should be implemented in the family, schools, and primary care programs.

The elderly: In the US, the percentage of obese elderly people has been increasing.

With aging, body fat increases and is redistributed to the abdomen, and muscle mass is lost, largely because of physical inactivity, but decreased androgens and growth hormone (which are anabolic) and inflammatory cytokines produced in obesity may also play a role.

Risk of complications depends on

• Body fat distribution (increasing with a predominantly abdominal distribution)

• Duration and severity of obesity

• Associated sarcopenia

Increased waist circumference, suggesting abdominal fat distribution, predicts morbidity (eg, hypertension, diabetes mellitus, coronary artery disease) and mortality risk better in the elderly than does BMI.

For the elderly, increased physical activity is usually preferable to dietary restriction unless restricted mobility prohibits activity; in such cases, caloric restriction may be needed to reduce weight enough to restore mobility. Physical activity also improves muscle strength, endurance, and overall well-being. Activity should include strengthening and endurance exercises.

Regardless of whether caloric restriction is considered necessary, nutrition should be optimized.

Weight-loss drugs such as sibutramine or fluoxetine are not recommended for the elderly because the possible benefits do not outweigh the adverse effects. However, orlistat may be useful for obese elderly patients, particularly those with diabetes mellitus or hypertension. Surgery is usually best avoided, although it has proven efficacy and benefits outweigh risks in carefully selected patients.

Prevention

Regular physical activity and healthy eating improve general fitness, can control weight, and help prevent obesity and diabetes mellitus. Even without weight loss, exercise decreases the risk of cardiovascular disorders. Dietary fiber decreases the risk of colon cancer and cardiovascular disorders. Sufficient and good-quality sleep, management of stress, and moderation of alcohol intake are also important.

Bariatric Surgery

Bariatric surgery is the surgical alteration of the stomach, intestine, or both to cause weight loss.

In the US, bariatric surgery is done over 200,000 times annually, accounting for almost two thirds of all bariatric operations done worldwide. Development of safer laparoscopic approaches has made this surgery more popular.

Indications

To qualify for bariatric surgery, patients should

- Have acceptable operative risk
- Be well-informed and motivated
- Have unsuccessfully tried all reasonable nonsurgical methods to lose weight and manage obesity-associated complications
- Have a BMI of > 40 kg/m^2 or a BMI > 35 kg/m^2 plus a serious complication (eg, diabetes, hypertension, obstructive sleep apnea, high-risk lipid profile) that could be expected to be meaningfully reduced with a weight loss of 5 to 10%

Contraindications include uncontrolled major depression or psychosis, binge eating disorders, current drug or alcohol abuse, severe coagulopathy, and inability to comply with nutritional requirements, including lifelong vitamin replacement (when indicated). Whether bariatric surgery is appropriate for patients < 18 or > 65 yr is controversial.

Procedures

- Restrictive procedures (adjustable gastric banding, vertical banded gastroplasty)
- Malabsorptive procedures (Roux-en-Y gastric bypass)

Most procedures can be done laparoscopically, but the approach depends on the type of procedure as well as patient weight. Morbidity and mortality tend to be lower with laparoscopic than with open surgery. However, if patients weigh ≥ 180 kg, open surgery is more likely to be successful. In about 8% of cases overall (fewer with experienced surgeons), surgery begun laparoscopically must be finished as open surgery.

Procedures can be restrictive, malabsorptive, or both.

Restrictive procedures: Restrictive procedures limit the volume of the stomach available for ingested food. This limited volume helps restrict food intake, probably because of earlier satiety. The effects can be partially defeated by patients who consume more high-calorie liquid foods (eg, milk shakes, alcohol), which pass through the restricted portion quicker.

Purely restrictive procedures include adjustable gastric banding and vertical banded gastroplasty.

[
Fig. 6-1. Adjustable gastric banding.]

Adjustable gastric banding accounts for about 15% of bariatric procedures done in the US; it is much more common in Europe and is growing in popularity in the US. It is the 2nd most common bariatric procedure. A band is placed around the upper part of the stomach to divide the stomach into a small upper pouch and a larger lower pouch. Saline can be injected into the band via a subcutaneous access port. When saline is injected, the band expands, decreasing the size of the passageway through the stomach. As a result, the upper pouch fills more quickly, sending a message to the brain that the stomach is full; patients eat smaller meals and lose substantial amounts of weight over time. This procedure is usually done laparoscopically. Saline can be removed to make the passageway larger. Even though weight loss from gastric banding is slightly less than that from Roux-en-Y, morbidity and mortality are much less and gastric banding can be reversed if necessary.

Vertical banded gastroplasty is no longer commonly done. A stapler is used to divide the stomach into a small upper pouch and a larger lower pouch. A nonexpandable plastic band is placed around the opening where the upper pouch empties into the lower pouch.

Malabsorptive procedures: Malabsorptive procedures, such as biliopancreatic diversion with a duodenal switch and Roux-en-Y gastric bypass, result in ingested food bypassing parts of the stomach and small intestine, creating malabsorption, which leads to weight loss. These procedures are also restrictive.

Roux-en-Y gastric bypass surgery accounts for about 80% of bariatric procedures in the US. It can often be done laparoscopically. A small part of the proximal stomach is detached from the rest, creating a stomach pouch of < 30 mL. Because stomach volume is smaller, satiety occurs earlier. Also, food bypasses part of the stomach and small intestine, where it is normally absorbed, reducing the amount of food and calories absorbed. The pouch is connected to the proximal jejunum with a narrow opening, producing even more restriction. The segment of bypassed proximal small intestine (and thus the bypassed stomach) is attached to the distal small intestine, enabling bile acids and pancreatic enzymes to mix with GI contents; this mixing limits malabsorption and nutritional deficiencies. Because a gastrojejunostomy is created, symptoms similar to the dumping-syndrome may occur after high glycemic loads; symptoms (light-headedness, diaphoresis, nausea, abdominal pain, diarrhea) may inhibit the consumption of such foods by adverse conditioning.

Biliopancreatic diversion with a duodenal switch accounts for < 5% of bariatric procedures done in the US. Part of the stomach is removed, causing restriction. The remaining part empties into the duodenum. The duodenum is cut

[
Fig. 6-2. Roux-en-Y gastric bypass surgery.]

and attached to the ileum, bypassing much of the small intestine, including the sphincter of Oddi (where bile acids and pancreatic enzymes enter); malabsorption results. This procedure is technically demanding but can sometimes be done laparoscopically. Malabsorption and nutritional deficiencies often develop.

Preoperative Evaluation

Evaluation should determine whether patients have a psychologic commitment to the lifestyle changes and whether operative risks are acceptable. Sleep apnea testing is done.

Extensive preoperative evaluation is probably unnecessary. However, for certain morbidly obese patients (BMI > 50 kg/m^2), examining the cardiac, pulmonary, GI, metabolic, and psychologic systems helps identify patients with acceptable operative risk and helps select the appropriate procedure. For these patients, routine preoperative tests may include

- **Liver function tests:** Increased liver enzymes, especially ALT, are common but do not contraindicate surgery.

- **Kidney function tests:** If renal blood flow and glomerular filtration rate are increased, proteinuria is

more likely and renal clearance of drugs may be increased. Thus, drug dosages may need to be adjusted.

- **ECG and echocardiography:** These tests are needed because identifying heart failure and pulmonary hypertension clinically in morbidly obese patients is difficult. Signs of heart failure (eg, increased jugular venous pressure, hepatomegaly, pulmonary crackles) are hard to identify when body fat is excessive. Pulmonary hypertension is also difficult to identify because many patients cannot exercise to the point where exertional dyspnea, fatigue, or syncope would result. Pulmonary hypertension is diagnosed if echocardiography shows tricuspid regurgitation and ECG shows tall R waves, right axis deviation, and right ventricular strain.

- **Sleep study:** Polysomnography (see p. 1706) can confirm obstructive sleep apnea, which is common, and determine its severity. An apnea-hypopnea index of > 30 signals high risk of morbidity and premature death. Obstructive sleep apnea does not contraindicate surgery but is done to help plan for use of continuous positive airway pressure (CPAP) postoperatively.

Risks

The most common perioperative complication is wound infection (in about 3%); the most common late complication is anastomotic stomach stenosis (in about 5%).

Other early complications include wound infection, incisional hernia, small-bowel obstruction, GI bleeding, ventral hernia, deep venous thrombosis, and pneumonia. These complications can cause significant morbidity, prolong hospitalization, and increase costs.

The most common cause of early (within about 6 wk) postoperative death (in up to 0.5%) is pulmonary embolism, followed by anastomotic leak. Tachycardia may be the only early sign of anastomotic leak. Less common causes of early postoperative death are MI, pneumonia, and bowel obstruction.

Later problems may include prolonged nausea and vomiting secondary to small-bowel obstruction, and anastomotic stenosis. Nutritional deficiencies (eg, protein-energy undernutrition, vitamin B_{12} deficiency) may result from inadequate intake, inadequate supplementation, or malabsorption. Malodorous flatulence, diarrhea, or both may develop, particularly after malabsorptive procedures. Ca and vitamin D absorption may be impaired, causing deficiencies and sometimes hypocalcemia and secondary hyperparathyroidism. With prolonged vomiting, thiamin deficiency may occur. After Roux-en-Y gastric bypass, iron deficiency may result. Patients may have symptoms of reflux, especially after biliopancreatic diversion with a duodenal switch. After rapid weight loss, cholelithiasis may develop.

Eating habits may be disordered. Adjusting to new eating habits can be difficult.

Prognosis

Overall, 30-day postoperative risk of death is 0.2 to 1%. Risk is higher in elderly patients and in patients who have had an open procedure, who are extremely morbidly obese (> 50 kg), or who have established organ failure. Risk of death may be lowest with laparoscopic adjustable gastric banding. Risk of death is almost 3 times higher in hospitals that do < 50 of these procedures/yr than in those that do >150 procedures/yr. The American Society of Bariatric Surgery may designate hospitals with better results as a Center of Excellence, based on resources and excellent short- and long-term outcomes.

In most patients, comorbidities (eg, insulin insensitivity, dyslipidemias, hypertension, obstructive sleep apnea, polycystic ovary syndrome, nonalcoholic steatohepatitis) tend to resolve.

Average loss of excess weight (real weight minus ideal weight) is about 60%, or about 40 to 60 kg in most patients. Depending on the procedure, excess weight loss can vary between 50% and 70%; loss tends to be lower with gastric banding and somewhat higher with Roux-en-Y gastric bypass. In many patients, weight loss, although initially rapid, plateaus after about 2 yr; then patients may slowly regain weight.

Mood and work and personal relationships usually improve.

Long-term follow-up data are not yet available because these procedures are relatively new.

Follow-up

Patients should be monitored every 4 to 6 wk while weight loss is rapid (usually about the first 6 mo after surgery), then every 6 to 12 mo. Weight and BP are checked, and eating habits are reviewed. Blood tests (usually CBC, electrolytes, glucose, BUN, creatinine, albumin, and protein) and liver function tests are done at each visit. If alkaline phosphatase is increased, parathyroid hormone level is measured; if parathyroid hormone level is abnormal, bone density is monitored. If weight loss exceeds about 9 kg (20 lb)/mo, visits should be scheduled at least monthly, and blood tests should include Mg, phosphorus, vitamin B_{12}, and iron levels. Nutritional supplementation is sometimes necessary.

Metabolic Syndrome

Metabolic syndrome (syndrome X, insulin resistance syndrome) is characterized by a clustering of risk factors for cardiovascular disease and type 2 diabetes mellitus. They commonly include excess intra-abdominal fat, insulin resistance, and ≥ 1 of the following: elevated serum triglyceride levels, decreased high-density lipoprotein (HDL) cholesterol level, and hypertension. Causes, complications, diagnosis, and treatment are similar to those of obesity.

In developed countries, metabolic syndrome is a serious problem. It is very common; in the US, > 40% of people > 50 yr may have it. Children and adolescents can develop

[
Table 6-3. Criteria Often Used for Diagnosis of Metabolic Syndrome*]

metabolic syndrome, but in these age groups, no definition is established.

Development of metabolic syndrome depends on distribution as well as amount of fat. Excess fat in the abdomen (called apple shape), particularly when it results in a high waist-to-hip ratio (reflecting a relatively low muscle-to-fat mass ratio), increases risk. The syndrome is less common among people who have excess subcutaneous fat around the hips (called pear shape) and a low waist-to-hip ratio (reflecting a higher muscle-to-fat mass ratio).

Excess abdominal fat leads to excess free fatty acids in the portal vein, increasing fat accumulation in the liver. Fat also accumulates in muscle cells. Insulin resistance develops, with hyperinsulinemia. Glucose metabolism is impaired, and dyslipidemias and hypertension develop. Serum uric acid levels are typically elevated, and a prothrombotic state (with increased levels of fibrinogen and plasminogen activator inhibitor I) and an inflammatory state develop. Patients have an increased risk of obstructive sleep apnea. Other risks include nonalcoholic steatohepatitis, chronic kidney disease, polycystic ovary syndrome (for women), and low serum testosterone, erectile dysfunction, or both (for men).

Diagnosis

• Waist circumference and BP

• Fasting plasma glucose and a lipid profile

Screening is important. A family history plus measurement of waist circumference and BP are part of routine care. If patients with a family history of type 2 diabetes mellitus, particularly those ≥ 40 yr, have a waist circumference greater than that recommended for race and sex, fasting plasma glucose and a lipid profile must be determined.

Metabolic syndrome has many different definitions, but it is most often diagnosed when ≥ 3 of the following are present: excess abdominal fat, a high fasting plasma glucose level, hypertension, a high triglyceride level, and a low HDL cholesterol level (see Table 6-3).

Treatment

• Healthy diet and exercise

• Sometimes metformin

• Management of cardiovascular risk factors

Optimally, the management approach results in weight loss based on a healthy diet and regular physical activity, which includes a combination of aerobic activity and resistance training, reinforced with behavioral therapy. Metformin, an insulin sensitizer, may be useful. Weight loss of ≈ 7% may be sufficient to reverse the syndrome, but if not, each feature of the syndrome should be managed to achieve recommended targets; available drug treatment is very effective.

Other cardiovascular risk factors (eg, smoking cessation) also need to be managed. Increased physical activity has cardiovascular benefits even if weight is not lost.

2 - Gastrointestinal Disorders

Chapter 7. Approach to the Patient With Upper GI Complaints

Introduction

Upper GI complaints include chest pain (see p. 2025), chronic and recurrent abdominal pain, dyspepsia, lump in the throat, halitosis (see p. 506), hiccups, nausea and vomiting, and rumination. Some upper GI complaints represent functional illness (ie, no physiologic cause found after extensive evaluation).

History: Using open-ended, interview-style questions, the physician identifies the location and quality of symptoms and any aggravating and alleviating factors. Psychologic stress factors must be specifically sought. Because a psychiatric disorder does not preclude physiologic disease, the significance of vague, dramatic, or bizarre complaints should not be minimized.

Patients report symptoms differently depending on their personality, the impact of the illness on their life, and sociocultural influences. For example, nausea and vomiting may be minimized or reported indirectly by a severely depressed patient but presented with dramatic urgency by a histrionic one.

Physical examination: Inspection of the abdomen with the patient supine may show a convex appearance when bowel obstruction, ascites, or, rarely, a large mass is present. Auscultation to assess bowel sounds and determine presence of bruits should follow. Percussion elicits hyperresonance (tympany) in the presence of bowel obstruction and dullness with ascites and can determine the span of the liver. Palpation proceeds systematically, beginning gently to identify areas of tenderness and, if tolerated, palpating deeper to locate masses or organomegaly. Digital rectal examination with testing for occult blood and (in women) pelvic examination complete the evaluation of the abdomen.

Testing: Patients with acute, nonspecific symptoms (eg, dyspepsia, nausea) and an unremarkable physical examination rarely require testing. Findings suggesting significant disease (alarm symptoms) should prompt further evaluation:

• Anorexia

• Anemia

• Blood in stool (gross or occult)

• Dysphagia

• Fever

• Hepatomegaly

• Pain that awakens patient

• Persistent nausea and vomiting

• Weight loss

Chronic or recurrent symptoms, even with an unremarkable examination, also warrant evaluation. Specific GI tests are discussed in Ch. 9.

Chronic and Recurrent Abdominal Pain

Chronic abdominal pain (CAP) persists for more than 3 mo either continuously or intermittently. Intermittent pain may be referred to as recurrent abdominal pain (RAP). Acute abdominal pain is discussed on p. 105. CAP occurs any time after 5 yr of age. Up to 10% of children require evaluation for RAP. About 2% of adults, predominantly women, have CAP (a much higher percentage of adults have

some type of chronic GI symptoms, including nonulcer dyspepsia and various bowel disturbances).

Nearly all patients with CAP have had prior medical evaluation that did not yield a diagnosis after history, physical, and basic testing.

Pathophysiology

Functional abdominal pain syndrome (FAPS) is pain that persists > 6 mo without evidence of physiologic disease, shows no relationship to physiologic events (eg, meals, defecation, menses), and interferes with daily functioning. FAPS is poorly understood but seems to involve altered nociception. Sensory neurons in the dorsal horn of the spinal cord may become abnormally excitable and hyperalgesic due to a combination of factors. Cognitive and psychologic factors (eg, depression, stress, culture, secondary gain, coping and support mechanisms) may cause efferent stimulation that amplifies pain signals, resulting in perception of pain with low level inputs and persistence of pain long after the stimulus has ceased. Additionally, the pain itself may function as a stressor, perpetuating a positive feedback loop.

In addition, menopause increases GI symptoms in several disorders including irritable bowel syndrome, inflammatory bowel disease, endometriosis, and nonulcer dyspepsia.

Etiology

Perhaps 10% of patients have an occult physiologic illness (see Table 7-1); the remainder have a functional process. However, determining whether a particular abnormality (eg, adhesions, ovarian cyst, endometriosis) is the cause of CAP symptoms or an incidental finding can be difficult.

Evaluation

History: History of present illness should elicit pain location, quality, duration, timing and frequency of recurrence, and factors that worsen or relieve pain (particularly eating or moving bowels). A specific inquiry as to whether milk and milk products cause abdominal cramps, bloating, or distention is needed, because lactose intolerance is common, especially among blacks.

Review of systems seeks concomitant GI symptoms such as gastroesophageal reflux, anorexia, bloating or "gas," nausea, vomiting, jaundice, melena, hematuria, hematemesis, weight loss, and mucus or blood in the stool. Bowel symptoms, such as diarrhea, constipation, and changes in stool consistency, color, or elimination pattern, are particularly important.

In adolescents, a diet history is important because ingestion of large amounts of cola beverages and fruit juices (which may contain significant quantities of fructose and sorbitol) can account for otherwise puzzling abdominal pain.

Past medical history should include nature and timing of any abdominal surgery and the results of previous tests that have been done and treatments that have been tried. A drug history should include details concerning prescription and illicit drug use as well as alcohol.

Family history of RAP, fevers, or both should be ascertained, as well as known diagnoses of sickle cell trait or disease, familial Mediterranean fever, and porphyria.

Physical examination: Review of vital signs should particularly note presence of fever or tachycardia.

General examination should seek presence of jaundice, skin rash, and peripheral edema. Abdominal examination should note areas of tenderness, presence of peritoneal findings (eg, guarding, rigidity, rebound), and any masses or organomegaly. Rectal examination and (in women) pelvic examination to locate tenderness, masses, and blood are essential.

Red flags: The following findings are of particular concern:

• Fever

• Anorexia, weight loss

• Pain that awakens patient

• Blood in stool or urine

• Jaundice

• Edema

• Abdominal mass or organomegaly

Interpretation of findings: Clinical examination alone infrequently provides a firm diagnosis.

Determining whether CAP is physiologic or functional can be difficult. Although the presence of red flag findings indicates a high likelihood of a physiologic cause, their absence does not rule it out. Other hints are that physiologic causes usually cause pain that is well localized, especially to areas other than the periumbilical region. Pain that wakes the patient is usually physiologic. Some findings suggestive of specific disorders are listed in Table 7-1.

Functional CAP may result in pain similar to that of physiologic origin. However, there are no associated red flag findings, and psychosocial features are often prominent. A history of physical or sexual abuse or an unresolved loss (eg, divorce, miscarriage, or death of a family member) may be a clue.

The Rome criteria for diagnosis of irritable bowel syndrome are the presence of abdominal pain or discomfort for at least 3 days/mo in the last 3 mo along with at least 2 of the following: (1) improvement with defecation; (2) onset (of each episode of discomfort) associated with a change in frequency of defecation; and (3) change in consistency of stool.

Testing: In general, simple tests (including urinalysis, CBC, liver tests, ESR, amylase, and lipase) should be done. Abnormalities in these tests, the presence of red flag findings, or specific clinical findings mandate further testing, even if previous assessments have been negative. Specific tests depend on the findings (see Table 7-1) but typically include CT of the abdomen and pelvis with contrast, upper GI endoscopy or colonoscopy, and perhaps small-bowel x-rays or stool testing.

The benefits of testing patients with no red flag findings are unclear. Those > 50 should probably have a colonoscopy; those ≤ 50 can be observed or have CT of the abdomen and pelvis with contrast if an imaging study is desired. Magnetic resonance cholangiopancreatography (MRCP), ERCP, and laparoscopy are rarely helpful in the absence of specific indications.

Between the initial evaluation and the follow-up visit, the patient (or family, if the patient is a child) should record any pain, including

[**Table 7-1.** Physiologic Causes of Chronic Abdominal Pain]

its nature, intensity, duration, and precipitating factors. Diet, defecation pattern, and any remedies tried (and the results obtained) should also be recorded. This record may reveal inappropriate behavior patterns and exaggerated responses to pain or otherwise suggest a diagnosis.

Treatment

Physiologic conditions are treated.

If the diagnosis of functional CAP is made, frequent examinations and tests should be avoided because they may focus on or magnify the physical complaints or imply that the physician lacks confidence in the diagnosis.

There are no modalities to cure functional CAP; however, many helpful measures are available. These measures rest on a foundation of a trusting, empathic relationship among the physician, patient, and family. Patients should be reassured that they are not in danger; specific concerns should be sought and addressed. The physician should explain the laboratory findings and the nature of the problem and describe how the pain is generated and how the patient perceives it (ie, that there is a constitutional tendency to feel pain at times of stress). It is important to avoid perpetuating the negative psychosocial consequences of chronic pain (eg, prolonged absences from school or work, withdrawal from social activities) and to promote independence, social participation, and self-reliance. These strategies help the patient control or tolerate the symptoms while participating fully in everyday activities.

Drugs such as aspirin, NSAIDs, H_2 receptor blockers, proton pump inhibitors, and tricyclic antidepressants can be effective. Opioids should be avoided because they invariably lead to dependency.

Cognitive methods (eg, relaxation training, biofeedback, hypnosis) may help by contributing to the patient's sense of well-being and control. Regular follow-up visits should be scheduled weekly, monthly, or bimonthly, depending on the patient's needs, and should continue until well after the problem has resolved. Psychiatric referral may be required if symptoms persist, especially if the patient is depressed or there are significant psychologic difficulties in the family.

School personnel should become involved for children who have CAP. Children can rest briefly in the nurse's office during the school day, with the expectation that they return to class after 15 to 30 min. The school nurse can be authorized to dispense a mild analgesic (eg, acetaminophen). The nurse can sometimes allow the child to call a parent, who should encourage the child to stay in school. However, once parents stop treating their child as special or ill, the symptoms may worsen before they abate.

Key Points

• Most cases represent a functional process.

• Red flag findings indicate a physiologic cause and need for further assessment.

• Testing is guided by clinical features.

• Repeated testing after physiologic causes are ruled out is usually counterproductive.

Dyspepsia

Dyspepsia is a sensation of pain or discomfort in the upper abdomen; it often is recurrent. It may be described as indigestion, gassiness, early satiety, postprandial fullness, gnawing, or burning.

Etiology

There are several common causes of dyspepsia (see Table 7-2).

Many patients have findings on testing (eg, duodenitis, pyloric dysfunction, motility disturbance, *Helicobacter pylori* gastritis, lactose deficiency, cholelithiasis) that correlate poorly with symptoms (ie, correction of the condition does not alleviate dyspepsia).

Nonulcer (functional) dyspepsia is defined as dyspeptic symptoms in a patient who has no abnormalities on physical examination and upper GI endoscopy.

Evaluation

History: History of present illness should elicit a clear description of the symptoms, including whether they are acute or chronic and recurrent. Other elements include timing and frequency of recurrence, any difficulty swallowing, and relationship of symptoms to eating or taking drugs. Factors that worsen

symptoms (particularly exertion, certain foods or alcohol) or relieve them (particularly eating or taking antacids) are noted.

Review of systems seeks concomitant GI symptoms such as anorexia, nausea, vomiting, hematemesis, weight loss, and bloody or black (melanotic) stools. Other symptoms include dyspnea and diaphoresis.

Past medical history should include known GI and cardiac diagnoses, cardiac risk factors (eg, hypertension, hypercholesterolemia), and the results of previous tests that have been done and treatments that have been tried. Drug history should include prescription and illicit drug use as well as alcohol.

Physical examination: Review of vital signs should note presence of tachycardia or irregular pulse.

General examination should note presence of pallor or diaphoresis, cachexia, or jaundice. Abdomen is palpated for tenderness, masses, and organomegaly. Rectal examination is done to detect gross or occult blood.

Red flags: The following findings are of particular concern:

[**Table 7-2.** Some Causes of Dyspepsia]

• Acute episode with dyspnea, diaphoresis, or tachycardia

• Anorexia

• Nausea or vomiting

• Weight loss

• Blood in the stool

• Dysphagia or odynophagia

• Failure to respond to therapy with H_2 blockers or proton pump inhibitors (PPIs)

Interpretation of findings: Some findings are helpful (see Table 7-2).

A patient presenting with a single, acute episode of dyspepsia is of concern, particularly if symptoms are accompanied by dyspnea, diaphoresis, or tachycardia; such patients may have acute coronary ischemia. Chronic symptoms that occur with exertion and are relieved by rest may represent angina.

GI causes are most likely to manifest as chronic complaints. Symptoms are sometimes classified as ulcer-like, dysmotility-like, or reflux-like; these classifications suggest but do not confirm an etiology. Ulcer-like symptoms consist of pain that is localized in the epigastrium, frequently occurs before meals, and is partially relieved by food, antacids, or H_2 blockers. Dysmotility-like symptoms consist of discomfort rather than pain, along with early satiety, postprandial fullness, nausea, vomiting, bloating, and symptoms that are worsened by food. Reflux-like symptoms consist of heartburn or acid regurgitation. However, symptoms often overlap.

Alternating constipation and diarrhea with dyspepsia suggests irritable bowel syndrome or excessive use of OTC laxatives or antidiarrheals.

[**Table 7-3.** Some Oral Drugs for Dyspepsia]

Testing: Patients in whom symptoms suggest acute coronary ischemia, particularly those with risk factors, should be sent to the emergency department for urgent evaluation, including ECG and serum cardiac markers.

For patients with chronic, nonspecific symptoms, routine tests include CBC (to exclude anemia caused by GI blood loss) and routine blood chemistries. If results are abnormal, additional tests (eg, imaging studies, endoscopy) should be considered. Because of the risk of cancer, patients > 45 and those with new-onset red flag findings should undergo upper GI endoscopy. For patients < 45 with no red flag findings, some authorities recommend empiric therapy for 2 to 4 wk with antisecretory agents followed by endoscopy in treatment failures. Others recommend screening for *H. pylori* infection with a C_{14}-urea breath test or stool assay (see p. 129). However, caution is required in using *H. pylori* or any other nonspecific findings to explain symptoms.

Esophageal manometry and pH studies are indicated if reflux symptoms persist after upper GI endoscopy and a 2- to 4-wk trial with a PPI.

Treatment

Specific conditions are treated. Patients without identifiable conditions are observed over time and reassured. Symptoms are treated with PPIs, H_2 blockers, or a cytoprotective agent (see Table 7-3). Prokinetic drugs (eg, metoclopramide, erythromycin) given as a liquid suspension also may be tried in patients with dysmotility-like dyspepsia. However, there is no clear evidence that matching the drug class to the specific symptoms (eg, reflux vs dysmotility) makes a difference. Misoprostol and anticholinergics are not effective in functional dyspepsia. Drugs that alter sensory perception (eg, tricyclic antidepressants) may be helpful.

Key Points

• Coronary ischemia is possible in a patient with acute "gas."

• Endoscopy is indicated for those > 45 or with red flag findings.

• Empiric treatment with an acid blocker is reasonable for those < 45 without red flag findings. Those who do not respond in 2 to 4 wk require further evaluation.

Hiccups

Hiccups (hiccough, singultus) are repeated involuntary spasms of the diaphragm followed by sudden closure of the glottis, which checks the inflow of air and causes the characteristic sound. Transient episodes are very common. Persistent (> 2 days) and intractable (> 1 mo) hiccups are uncommon but quite distressing.

Etiology

Hiccups follow irritation of afferent or efferent diaphragmatic nerves or of medullary centers that control the respiratory muscles, particularly the diaphragm. Hiccups are more common among men.

Cause is generally unknown, but transient hiccups are often caused by the following:

• Gastric distention

• Alcohol consumption

• Swallowing hot or irritating substances

Persistent and intractable hiccups have myriad causes (see Table 7-4).

Evaluation

History: History of present illness should note duration of hiccups, remedies tried, and relationship of

onset to recent illness or surgery.

Review of systems seeks concomitant GI symptoms such as gastroesophageal reflux and swallowing difficulties; thoracic symptoms such as cough, fever, or chest pain; and any neurologic symptoms.

Past medical history should query known GI and neurologic disorders. A drug history should include details concerning alcohol use.

Physical examination: Examination is usually unrewarding but should seek signs of chronic disease (eg, cachexia). A full neurologic examination is important.

Red flags: The following is of particular concern:

• Neurologic symptoms or signs

Interpretation of findings: Few findings are specific. Hiccups after alcohol consumption or surgery may well be related to those events. Other possible causes (see Table 7-4) are both numerous and rarely a cause of hiccups.

Testing: No specific evaluation is required for acute hiccups if routine history and physical examination are unremarkable; abnormalities are pursued with appropriate testing.

Patients with hiccups of longer duration and no obvious cause should have testing, probably including serum electrolytes, BUN and creatinine, chest x-ray, and ECG. Upper GI endoscopy and perhaps esophageal pH monitoring should be considered. If these are unremarkable, brain MRI and chest CT may be done.

[**Table 7-4.** Some Causes of Intractable Hiccups]

Treatment

Identified problems are treated (eg, proton pump inhibitors for gastroesophageal reflux disease, dilation for esophageal stricture).

For symptom relief, many simple measures can be tried, although none are more than slightly effective: $PaCO_2$ can be increased and diaphragmatic activity can be inhibited by a series of deep breath-holds or by breathing deeply in to and out of a paper bag. (CAUTION: *Plastic bags can cling to the nostrils and should not be used*.) Vagal stimulation by pharyngeal irritation (eg, swallowing dry bread, granulated sugar, or crushed ice; applying traction on the tongue; stimulating gagging) may work. Numerous other folk remedies exist.

Persistent hiccups are often recalcitrant to treatment. Many drugs have been used in anecdotal series. Baclofen, a γ-aminobutyric acid agonist (5 mg po q 6 h increasing to 20 mg/dose), may be effective. Other drugs include chlorpromazine 10 to 50 mg po tid as needed, metoclopramide 10 mg po bid to qid, and various anticonvulsants (eg, gabapentin). Additionally, an empiric trial of proton pump inhibitors may be given. For severe symptoms, chlorpromazine 25 to 50 mg IM or IV can be given. In intractable cases, the phrenic nerve may be blocked by small amounts of 0.5% procaine solution, with caution being taken to avoid respiratory depression and pneumothorax. Even bilateral phrenicotomy does not cure all cases.

Key Points

• The cause is usually unknown.

• Rarely, a serious disorder is present.

• Evaluation is typically unrewarding but should be pursued for hiccups of long duration.

• Numerous remedies exist, none with clear superiority (or perhaps even effectiveness).

Lump in Throat

Lump in the throat (globus sensation, globus hystericus) is the sensation of a lump or mass in the throat, unrelated to swallowing, when no mass is present. (If a mass is present, see p. 461.)

Etiology

No specific etiology or physiologic mechanism has been established. Some studies suggest that elevated cricopharyngeal (upper esophageal sphincter) pressure or abnormal hypopharyngeal motility occur during the time of symptoms. The sensation may also result from gastroesophageal reflux disease (GERD) or from frequent swallowing and drying of the throat associated with anxiety or another emotional state. Although not associated with stress factors or a specific psychiatric disorder, globus sensation may be a symptom of certain mood states (eg, grief, pride); some patients may have a predisposition to this response.

Disorders that can be confused with globus sensation include cricopharyngeal (upper esophageal) webs, symptomatic diffuse esophageal spasm, GERD, skeletal muscle disorders (eg, myasthenia gravis, myotonia dystrophica, polymyositis), and mass lesions in the neck or mediastinum that cause esophageal compression.

Evaluation

The main goal is to distinguish globus sensation from true dysphagia (see p. 120), which suggests a structural or motor disorder of the pharynx or esophagus.

History: History of present illness should elicit a clear description of the symptom, particularly as to whether there is any pain with swallowing, difficulty swallowing (including sensation of food sticking). Timing of symptoms is important, particularly whether it occurs with eating or drinking or is independent of those activities; association with emotional events should be queried specifically.

Review of systems seeks weight loss (as evidence of a swallowing disorder) and symptoms of muscle weakness.

Past medical history should include known neurologic diagnoses, particularly those causing weakness.

Physical examination: The neck and floor of the mouth are palpated for masses. The oropharynx is inspected (including by direct laryngoscopy). Swallowing (of water and a solid food such as crackers) should be observed. Neurologic examination with particular attention to motor function is important.

Red flags: The following findings are of particular concern:

- Neck or throat pain
- Weight loss
- Abrupt onset after age 50
- Pain, choking, or difficulty with swallowing
- Regurgitation of food
- Muscle weakness
- Palpable or visible mass
- Progressive worsening of symptoms

Interpretation of findings: Symptoms unrelated to swallowing, with no pain or difficulty with swallowing, or sensation of food sticking in the throat in a patient with a normal examination imply globus sensation. Any red flag findings or abnormal findings on examination suggest a mechanical or motor disorder of swallowing. Chronic symptoms that occur during unresolved or pathologic grief and that may be relieved by crying suggest globus sensation.

Testing: Those with findings typical of globus sensation need no testing. If the diagnosis is unclear or the clinician cannot adequately visualize the pharynx, testing as for dysphagia is done. Typical tests include plain or video esophagography, measurement of swallowing time, chest x-ray, and esophageal manometry.

Treatment

Treatment involves reassurance and sympathetic concern. No drug is of proven benefit. Underlying depression, anxiety, or other behavioral disturbances should be managed supportively, with psychiatric referral if necessary. At times, communicating to the patient the association between symptoms and mood state can be beneficial.

Key Points

- Globus symptoms are unrelated to swallowing.
- Tests are not needed unless symptoms are related to swallowing, examination is abnormal, or there are red flag findings.

Nausea and Vomiting

(For nausea and vomiting in infants and children, see p. 2746.)

Nausea, the unpleasant feeling of needing to vomit, represents awareness of afferent stimuli (including increased parasympathetic tone) to the medullary vomiting center. Vomiting is the forceful expulsion of gastric contents caused by involuntary contraction of the abdominal musculature when the gastric fundus and lower esophageal sphincter are relaxed.

Vomiting should be distinguished from regurgitation, the spitting up of gastric contents without associated nausea or forceful abdominal muscular contractions. Patients with achalasia or a Zenker's diverticulum may regurgitate undigested food without nausea.

Complications: Severe vomiting can lead to symptomatic dehydration and electrolyte abnormalities (typically a metabolic alkalosis with hypokalemia) or rarely to an esophageal tear, either partial (Mallory-Weiss) or complete (Boerhaave's syndrome). Chronic vomiting can result in undernutrition, weight loss, and metabolic abnormalities.

Etiology

Nausea and vomiting occur in response to conditions that affect the vomiting center. Causes may originate in the GI tract or CNS or may result from a number of systemic conditions (see Table 7-5).

The most common causes are the following:

- Gastroenteritis
- Drugs
- Toxins

Cyclic vomiting syndrome is an uncommon disorder characterized by severe, discrete attacks of vomiting or sometimes only nausea that occur at varying intervals, with normal health between episodes. It is most common in childhood (mean age of onset 5 yr) and tends to remit with adulthood. The condition may be associated with migraine headaches, possibly representing a migraine variant.

Evaluation

History: History of present illness should elicit frequency and duration of vomiting; its relation to possible precipitants such as drug or toxin ingestion, head injury, and motion (eg, car, plane, boat, amusement rides); and whether vomitus contained bile (bitter, yellow-green) or blood (red or "coffee ground" material). Important associated symptoms include presence of abdominal pain and diarrhea; the last passage of stool and flatus; and presence of headache, vertigo, or both.

Review of systems seeks symptoms of causative disorders such as amenorrhea, breast swelling (pregnancy); polyuria, polydipsia (diabetes); and hematuria, flank pain (kidney stones).

Past medical history should ascertain known causes such as pregnancy, diabetes, migraine, hepatic or renal disease, cancer (including timing of any chemotherapy or radiation therapy), and previous abdominal surgery (which may cause bowel obstruction due to adhesions). All drugs and substances ingested recently should be ascertained; certain substances may not manifest toxicity until several days after ingestion (eg, acetaminophen, some mushrooms).

Family history of recurrent vomiting should be noted.

Physical examination: Vital signs should particularly note presence of fever and signs of hypovolemia (eg, tachycardia, hypotension, or both).

General examination should seek presence of jaundice and skin rash.

On abdominal examination, the clinician should look for distention and surgical scars; listen for presence and quality of bowel sounds (eg, normal, high-pitched); percuss for tympany; and palpate for tenderness, peritoneal findings (eg, guarding, rigidity, rebound), and any masses, organomegaly, or hernias. Rectal examination and (in women) pelvic examination to locate tenderness, masses, and blood are essential.

Neurologic examination should particularly note mental status, nystagmus, meningismus (eg, stiff neck, Kernig's or Brudzinski's signs), and ocular signs of increased intracranial pressure (eg, papilledema, absence of venous pulsations, 3rd cranial nerve palsy) or subarachnoid hemorrhage (retinal hemorrhage).

Red flags: The following findings are of particular concern:

• Signs of hypovolemia

• Headache, stiff neck, or mental status change

• Peritoneal signs

• Distended, tympanitic abdomen

Interpretation of findings: Many findings are suggestive of a cause or group of causes (see Table 7-5). Vomiting occurring shortly after drug or toxin ingestion or exposure to motion in a patient with an unremarkable neurologic and abdominal examination can confidently be ascribed to those causes, as may vomiting in a woman with a known pregnancy and a benign examination. Acute vomiting accompanied by diarrhea in an otherwise

[**Table 7-5.** Some Causes of Nausea and Vomiting]

healthy patient with a benign examination is highly likely to be infectious gastroenteritis; further

assessment may be deferred.

Vomiting that occurs at the thought of food or that is not temporally related to eating suggests a psychogenic cause, as does personal or family history of functional nausea and vomiting. Patients should be questioned about the relationship between vomiting and stressful events because they may not recognize the association or even admit to feeling distress at those times.

Testing: All females of childbearing age should have a urine pregnancy test. Patients with severe vomiting, vomiting lasting over 1 day, or signs of dehydration on examination should have other laboratory tests (eg, electrolytes, BUN, creatinine, glucose, urinalysis, and sometimes liver tests). Patients with red flag findings should have testing appropriate to the symptoms (see Table 7-5).

The assessment of chronic vomiting usually includes the previously listed laboratory tests plus upper GI endoscopy, small-bowel x-rays, and tests to assess gastric emptying and antral-duodenal motility.

Treatment

Specific conditions, including dehydration, are treated. Even without significant dehydration, IV fluid therapy (0.9% saline 1 L, or 20 mL/kg in children) often leads to reduction of symptoms. In adults, various antiemetics are effective (see Table 7-6). Choice of agent varies somewhat with the cause and severity of symptoms. Typical use is the following:

• Motion sickness: Antihistamines, scopolamine patches, or both

• Mild to moderate symptoms: Prochlorperazine or metoclopramide

• Severe or refractory vomiting and vomiting caused by chemotherapy: 5-HT_3 antagonists

Obviously, only parenteral agents should be used in actively vomiting patients.

For psychogenic vomiting, reassurance indicates awareness of the patient's discomfort and a desire to work toward relief of symptoms, regardless of cause. Comments such as "nothing is wrong" or "the problem is emotional" should be avoided. Brief symptomatic treatment with antiemetics can be tried. If long-term management is necessary, supportive, regular office visits may help resolve the underlying problem.

Key Points

• Many episodes have an obvious cause and benign examination and require only symptomatic treatment.

• Physicians should be alert for signs of an acute abdomen or significant intracranial disorder.

• Pregnancy should always be considered in females of childbearing age.

Rumination

Rumination is the (usually involuntary) regurgitation of small amounts of food from the stomach (most often 15 to 30 min after eating) that are rechewed and, in most cases, again swallowed. Patients do not complain of nausea or abdominal pain.

[**Table 7-6.** Some Drugs for Vomiting]

Rumination is commonly observed in infants. The incidence in adults is unknown, because it is rarely reported by patients themselves.

Etiology

Patients with achalasia or a Zenker's diverticulum may regurgitate undigested food without nausea. In the majority of patients who do not have these obstructive esophageal conditions, the pathophysiology is poorly understood. The reverse peristalsis in ruminants has not been reported in humans. The disorder is probably a learned, maladaptive habit and may be part of an eating disorder. The person learns to open the lower esophageal sphincter and propel gastric contents into the esophagus and throat by increasing gastric pressure via rhythmic contraction and relaxation of the diaphragm.

Symptoms

Nausea, pain, and dysphagia do not occur. During periods of stress, the patient may be less careful about concealing rumination. Seeing the act for the first time, others may refer the patient to a physician. Rarely, patients regurgitate and expel enough food to lose weight.

Diagnosis

• Clinical evaluation

• Sometimes endoscopy, esophageal motility studies, or both

Rumination is usually diagnosed through observation. A psychosocial history may disclose underlying emotional stress. Endoscopy or an upper GI series is necessary to exclude disorders causing mechanical obstruction or Zenker's diverticulum. Esophageal manometry and tests to assess gastric emptying and antral-duodenal motility may be used to identify a motility disturbance.

Treatment

• Behavioral techniques

Treatment is supportive. Drug therapy generally does not help. Motivated patients may respond to behavioral techniques (eg, relaxation, biofeedback, training in diaphragmatic breathing [using the diaphragm instead of chest muscles to breathe]). Psychiatric consultation may be helpful.

Functional GI Illness

Often, no physiologic cause for GI complaints is found, even after extensive evaluation. Such patients are said to have functional illness, which accounts for 30 to 50% of referrals to gastroenterologists. Functional illness may manifest with upper and/or lower GI symptoms.

The reasons for functional symptoms are not clear. Some evidence suggests that such patients have visceral hypersensitivity, a disturbance of nociception in which they experience discomfort caused by sensations (eg, luminal distention, peristalsis) that other people do not find distressing. In some patients, psychologic conditions such as anxiety (with or without aerophagia), conversion disorder, somatization in depression, or hypochondriasis are associated with GI symptoms. Psychologic theories hold that functional symptoms may satisfy certain psychologic needs. For example, some patients with chronic illness derive secondary benefits from being sick. For such patients, successful treatment of symptoms may lead to development of other symptoms.

Many referring physicians and GI specialists find functional GI complaints difficult to understand and treat, and uncertainty may lead to frustration and judgmental attitudes. Physicians should avoid ordering repeated studies or multiple drug trials for the insistent patient with inexplicable complaints. When symptoms are not suggestive of serious illness, the physician should wait rather than embark on another diagnostic or therapeutic plan. In time, new information may direct evaluation and management. Functional complaints are sometimes present in patients with physiologic disease (eg, peptic ulcer, esophagitis); such symptoms may not remit even when a physiologic illness is addressed.

Chapter 8. Approach to the Patient With Lower GI Complaints

Introduction

Lower GI complaints include constipation, diarrhea, gas and bloating, abdominal pain (see also p. 105), and rectal pain or bleeding (see Ch. 21). As with upper GI complaints, lower GI complaints result from physiologic illness or represent a functional disorder (ie, no radiologic, biochemical, or pathologic abnormalities found even after extensive evaluation). The reasons for functional symptoms are not clear. Evidence suggests that patients with functional symptoms may have disturbances of motility, nociception, or both; ie, they perceive as uncomfortable certain sensations (eg, luminal distention, peristalsis) that other people do not find distressing.

No bodily function is more variable and subject to external influences than defecation. Bowel habits vary considerably from person to person and are affected by age, physiology, diet, and social and cultural influences. Some people have unwarranted preoccupation with bowel habits. In Western society, normal stool frequency ranges from 2 to 3/day to 2 to 3/wk. Changes in stool frequency, consistency, volume, or composition (ie, presence of blood, mucus, pus, or excess fatty material) may indicate disease.

Constipation

Constipation is difficult or infrequent passage of stool, hardness of stool, or a feeling of incomplete evacuation.

Many people incorrectly believe that daily defecation is necessary and complain of constipation if stools occur less frequently. Others are concerned with the appearance (size, shape, color) or consistency of stools. Sometimes the major complaint is dissatisfaction with the act of defecation or the sense of incomplete evacuation after defecation. Constipation is blamed for many complaints (abdominal pain, nausea, fatigue, anorexia) that are actually symptoms of an underlying problem (eg, irritable bowel syndrome [IBS], depression). Patients should not expect all symptoms to be relieved by a daily bowel movement, and measures to aid bowel habits should be used judiciously.

Obsessive-compulsive patients often feel the need to rid the body daily of "unclean" wastes. Such patients often spend excessive time on the toilet or become chronic users of cathartics.

Etiology

Acute constipation suggests an organic cause, whereas chronic constipation may be organic or functional (see
Table 8-1).

In many patients, constipation is associated with sluggish movement of stool through the colon. This delay may be due to drugs, organic conditions, or a disorder of defecatory function (ie, pelvic floor dysfunction). Patients with disordered defecation do not generate adequate rectal propulsive forces, do not relax the puborectalis and the external anal sphincter during defecation, or both. In IBS, patients have symptoms (eg, abdominal discomfort and altered bowel habits) but generally normal colonic transit and anorectal functions. However, IBS-disordered defecation may coexist.

Excessive straining, perhaps secondary to pelvic floor dysfunctions, may contribute to anorectal pathology (eg, hemorrhoids, anal fissures, and rectal prolapse) and possibly even to syncope. Fecal impaction, which may cause or develop from constipation, is also common among elderly patients, particularly with prolonged bed rest or decreased physical activity. It is also common after barium has been given by mouth or enema.

Changes with aging: Constipation is common among elderly people because of low-fiber diets, lack of exercise, coexisting medical conditions, and use of constipating drugs. Many elderly people have misconceptions about normal bowel habits and use laxatives regularly. Other changes that predispose the elderly to constipation include increased rectal compliance and impaired rectal sensation (such that larger rectal volumes are needed to elicit the desire to defecate).

Evaluation

History: A lifetime history of the patient's stool frequency, consistency, need to strain or use perineal maneuvers (eg, pushing on the perineum, gluteal region, or recto-vaginal wall) during defecation, and satisfaction after defecation should be obtained, including frequency and duration of laxative or enema use. Some patients deny previous constipation

[**Table 8-1.** Causes of Constipation]

but, when questioned specifically, admit to spending 15 to 20 min per bowel movement. The presence, amount, and duration of blood in the stool should also be elicited.

Symptoms of metabolic (eg, hypothyroidism, diabetes mellitus) and neurologic (eg, spinal cord injury) disorders and systemic symptoms (eg, weight loss) should also be sought. Prescription and nonprescription drug use should be assessed, with specific questioning about anticholinergic and opioid drugs.

Physical examination: A general examination is done to look for signs of systemic disease, including fever and cachexia. Abdominal masses should be sought by palpation. A rectal examination should be done not only for fissures, strictures, blood, or masses (including fecal impaction) but also to evaluate anal resting tone (the puborectalis "lift" when patients squeeze the anal sphincter), perineal descent during simulated evacuation, and rectal sensation. Patients with defecatory disorders may have increased anal resting tone (or anismus), reduced (ie, < 2 cm) or increased (ie, > 4 cm) perineal descent, and/or paradoxical contraction of the puborectalis during simulated evacuation.

Red flags: Certain findings raise suspicion of a more serious etiology of chronic constipation:

• Distended, tympanitic abdomen

• Vomiting

• Blood in stool

• Weight loss

• Severe constipation of recent onset/worsening in elderly patients

Interpretation of findings: Certain symptoms (eg, a sense of anorectal blockage, prolonged or difficult defecation), particularly when associated with abnormal (ie, increased or reduced) perineal motion during simulated evacuation, suggest a defecatory disorder. A tense, distended, tympanitic abdomen, particularly when there is nausea and vomiting, suggests mechanical obstruction.

Patients with IBS typically have abdominal pain with disordered bowel habits (see p. 162). Chronic constipation with modest abdominal discomfort in a patient who has used laxatives for a long time suggests slow-transit constipation. Acute constipation coincident with the start of a constipating drug in patients without red flag findings suggests the drug is the cause. New-onset constipation that persists for weeks or occurs intermittently with increasing frequency or severity, in the absence of a known cause, suggests colonic tumor or other causes of partial obstruction. Excessive straining or prolonged or unsatisfactory defecation, with or without anal digitation, suggests a defecatory disorder. Patients with fecal impaction may have cramps and may pass watery mucus or fecal material around the impacted mass, mimicking diarrhea (paradoxic diarrhea).

Testing: Testing is guided by clinical presentation.

Constipation with a clear etiology (drugs, trauma, bed rest) may be treated symptomatically without further study. Patients with symptoms of bowel obstruction require flat and upright abdominal x-rays, possibly a water-soluble contrast enema to evaluate for colonic obstruction, and possibly a CT scan or barium x-ray

of the small intestine (see also p. 116). Most patients without a clear etiology should have sigmoidoscopy or colonoscopy and a laboratory evaluation (CBC, thyroid-stimulating hormone, fasting glucose, electrolytes, and Ca).

Further tests are usually reserved for patients with abnormal findings on the previously mentioned tests or who do not respond to symptomatic treatment. If the primary complaint is infrequent defecation, colonic transit times should be measured with radiopaque markers or scintigraphy. If the primary complaint is difficulty with defecation, anorectal manometry and rectal balloon expulsion should be assessed.

Treatment

• Possibly discontinuation of causative drugs (some may be necessary)

• Increase in dietary fiber

• Possibly trial with a brief course of osmotic laxatives

Any identified conditions should be treated.

Agents used to treat constipation are summarized in Table 8-2. Laxatives should be used judiciously. Some (eg, phosphate, bran, cellulose) bind drugs and interfere with absorption. Rapid fecal transit may rush some drugs and nutrients beyond their optimal absorptive locus. Contraindications to laxative and cathartic use include acute abdominal pain of unknown origin, inflammatory bowel disorders, intestinal obstruction, GI bleeding, and fecal impaction.

Diet and behavior: The diet should contain enough fiber (typically 15 to 20 g/day) to ensure adequate stool bulk. Vegetable fiber, which is largely indigestible and unabsorbable, increases stool bulk. Certain components of fiber also absorb fluid, making stools softer and facilitating their passage. Fruits and vegetables are recommended sources, as are cereals containing bran. Fiber supplementation is particularly effective in treating normal-transit constipation but is not very effective for slow-transit constipation or defecatory disorders.

[**Table 8-2.** Agents Used to Treat Constipation]

Behavioral changes may help. Patients should try to move their bowels at the same time daily, preferably 15 to 45 min after breakfast, because food ingestion stimulates colonic motility. Initial efforts at regular, unhurried bowel movements may be aided by glycerin suppositories.

Explanation is important, but it is difficult to convince obsessive-compulsive patients that their attitude toward defecation is abnormal. Physicians must explain that daily bowel movements are not essential, that the bowel must be given a chance to function, and that frequent use of laxatives or enemas (> once/3 days) denies the bowel that chance.

Types of laxatives: Bulking agents (eg, psyllium, Ca polycarbophil, methylcellulose) act slowly and gently and are the safest agents for promoting elimination. Proper use involves gradually increasing the dose—ideally taken tid or qid with sufficient liquid (eg, 500 mL/day of extra fluid) to prevent impaction—until a softer, bulkier stool results. Bloating may be reduced by gradually titrating the dose of dietary fiber to the recommended dose, or by switching to a synthetic fiber preparation such as methylcellulose.

Osmotic agents contain poorly absorbed polyvalent ions (eg, Mg, phosphate, sulfate), polymers (eg, polyethylene glycol), or carbohydrates (eg, lactulose, sorbitol) that remain in the bowel, increasing intraluminal osmotic pressure and thereby drawing water into the intestine. The increased volume stimulates peristalsis. These agents usually work within 3 h.

In general, osmotic laxatives are reasonably safe even when used regularly. However, Na phosphate should not be used for bowel cleansing because it may rarely cause acute renal failure even after a single use for bowel preparation. These events occurred primarily in elderly patients, those with preexisting renal disease, and those who were taking drugs that affect renal perfusion or function (eg, diuretics, ACE

inhibitors, angiotensin II receptor blockers). Also, Mg and phosphate are partially absorbed and may be detrimental in some conditions (eg, renal insufficiency). Na (in some preparations) may exacerbate heart failure. In large or frequent doses, these drugs may upset fluid and electrolyte balance. Another approach to cleansing the bowel for diagnostic tests or surgery or sometimes for chronic constipation uses large volumes of a balanced osmotic agent (eg, polyethylene glycol-electrolyte solution) given orally or via NGT.

Secretory or stimulant cathartics (eg, phenolphthalein, bisacodyl, anthraquinones, castor oil, anthraquinones) act by irritating the intestinal mucosa or by directly stimulating the submucosal and myenteric plexus. Although phenolphthalein was withdrawn from the US market after animal studies suggested the compound was carcinogenic, there is no epidemiologic evidence of this in humans. Bisacodyl is an effective rescue drug for chronic constipation. The anthraquinones senna, cascara sagrada, aloe, and rhubarb are common constituents of herbal and OTC laxatives. They pass unchanged to the colon where bacterial metabolism converts them to active forms. Adverse effects include allergic reactions, electrolyte depletion, melanosis coli, and cathartic colon. Melanosis coli is a brownish black colorectal pigmentation of unknown composition. Cathartic colon refers to alterations in colonic anatomy observed on barium enema in patients with chronic stimulant laxative use. It is unclear whether cathartic colon, which has been attributed to destruction of myenteric plexus neurons by anthraquinones, is caused by currently available agents or other neurotoxic agents (eg, podophyllin), which are no longer available. There does not seem to be an increased risk of colon cancer with long-term anthraquinone use.

Enemas can be used, including tap water and commercially prepared hypertonic solutions.

Emollient agents (eg, docusate, mineral oil) act slowly to soften stools, making them easier to pass. However, they are not potent stimulators of defecation. Docusate is a surfactant, which allows water to enter the fecal mass to soften and increase its bulk.

Fecal impaction: Fecal impaction is treated initially with enemas of tap water followed by small enemas (100 mL) of commercially prepared hypertonic solutions (eg, Na phosphate). If these do not work, manual fragmentation and disimpaction of the mass is necessary. This procedure is painful, so perirectal and intrarectal application of local anesthetics (eg, lidocaine 5% ointment or dibucaine 1% ointment) is recommended. Some patients require sedation.

Key Points

- Drug causes are common (eg, chronic laxative abuse, use of anticholinergic or opioid drugs).
- Clinicians should be wary of bowel obstruction when constipation is acute and severe.
- Symptomatic treatment is reasonable in the absence of red flag findings and after excluding pelvic floor dysfunction.

Dyschezia

(Disordered Evacuation; Dysfunction of Pelvic Floor or Anal Sphincters; Functional Defecatory Disorders; Dyssynergia)

Dyschezia is difficulty defecating. Patients sense the presence of stool and the need to defecate but are unable. It results from a lack of coordination of pelvic floor muscles and anal sphincters. Diagnosis requires anorectal testing. Treatment is difficult, but biofeedback may be of benefit.

Etiology

Normally, when a person tries to defecate, rectal pressure rises in coordination with relaxation of the external anal sphincter. This process may be affected by one or more dysfunctions (eg, impaired rectal contraction, excessive contraction of the abdominal wall, paradoxic anal contraction, failure of anal relaxation) of unclear etiology. Functional defecatory disorders may manifest at any age. In contrast,

Hirschsprung's disease, which is due to an absent recto-anal inhibitory reflex, is almost always diagnosed in infancy or childhood.

Symptoms and Signs

The patient may or may not sense that stool is present in the rectum. Despite prolonged straining, evacuation is tedious or impossible, frequently even for soft stool or enemas. Patients may complain of anal blockage and may digitally remove stool from their rectum or manually support their perineum or splint the vagina to evacuate. Actual stool frequency may or may not be decreased.

Diagnosis

Rectal and pelvic examinations may reveal hypertonia of the pelvic floor muscles and anal sphincters. With bearing down, patients may not demonstrate the expected anal relaxation and perineal descent. With excessive straining, the anterior rectal wall prolapses into the vagina in patients with impaired anal relaxation; thus rectoceles are usually a secondary rather than a primary disturbance. Long-standing dyschezia with chronic straining may cause a solitary rectal ulcer or varying degrees of rectal prolapse or excessive perineal descent or an enterocoele. Anorectal manometry and rectal balloon expulsion, occasionally supplemented by defecatory or magnetic resonance proctography, are necessary to diagnose the condition.

Treatment

Because treatment with laxatives is unsatisfactory, it is important to assess anorectal functions in patients with refractory constipation. Biofeedback therapy can improve coordination between abdominal contraction and pelvic floor relaxation during defecation, thereby alleviating symptoms. However, pelvic floor retraining for defecatory disorders is highly specialized and available at select centers only. A collaborative approach (physiotherapists, dietitians, behavior therapists, gastroenterologists) is necessary.

Diarrhea

(See also Chs. 17 and 19. For diarrhea in children, see p. 2737.)

Stool is 60 to 90% water. In Western society, stool amount is 100 to 200 g/day in healthy adults and 10 g/kg/day in infants, depending on the amount of unabsorbable dietary material (mainly carbohydrates). Diarrhea is defined as stool weight > 200 g/day. However, many people consider any increased stool fluidity to be diarrhea. Alternatively, many people who ingest fiber have bulkier but formed stools but do not consider themselves to have diarrhea.

Complications: Complications may result from diarrhea of any etiology. Fluid loss with consequent dehydration, electrolyte loss (Na, K, Mg, Cl), and even vascular collapse sometimes occur. Collapse can develop rapidly in patients who have severe diarrhea (eg, patients with cholera) or are very young, very old, or debilitated. HCO_3 loss can cause metabolic acidosis. Hypokalemia can occur when patients have severe or chronic diarrhea or if the stool contains excess mucus. Hypomagnesemia after prolonged diarrhea can cause tetany.

Etiology

Normally, the small intestine and colon absorb 99% of fluid resulting from oral intake and GI tract secretions—a total fluid load of about 9 of 10 L daily. Thus, even small reductions (ie, 1%) in intestinal water absorption or increases in secretion can increase water content enough to cause diarrhea.

There are a number of causes of diarrhea (see Table 8-3). Several basic mechanisms are responsible for most clinically significant diarrheas: increased osmotic load, increased secretions, and decreased contact time/surface area. In many disorders, more than one mechanism is active. For example, diarrhea in inflammatory bowel disease results from mucosal destruction, exudation into the lumen, and from multiple secretagogues and bacterial toxins that affect

enterocyte function.

[Table 8-3. Some Causes of Diarrhea*]

Osmotic load: Diarrhea occurs when unabsorbable, water-soluble solutes remain in the bowel and retain water. Such solutes include polyethylene glycol, Mg salts (hydroxide and sulfate), and Na phosphate, which are used as laxatives. Osmotic diarrhea occurs with sugar intolerance (eg, lactose intolerance caused by lactase deficiency). Ingesting large amounts of hexitols (eg, sorbitol, mannitol, xylitol) or high fructose corn syrups, which are used as sugar substitutes in candy, gum, and fruit juices, causes osmotic diarrhea because hexitols are poorly absorbed. Lactulose, which is used as a laxative, causes diarrhea by a similar mechanism. Overingesting certain foodstuffs (see Table 8-4) can cause osmotic diarrhea.

Increased secretions: Diarrhea occurs when the bowels secrete more electrolytes and water than they absorb. Causes of increased secretions include infections, unabsorbed fats, certain drugs, and various intrinsic and extrinsic secretagogues.

Infections (eg, gastroenteritis; discussed in Ch. 16) are the most common causes of secretory diarrhea. Infections combined with food poisoning are the most common causes of acute diarrhea (< 4 days in duration). Most enterotoxins block Na^+-H^+ exchange, which is an important driving force for fluid absorption in the small bowel and colon.

Unabsorbed dietary fat and bile acids (as in malabsorption syndromes and after ileal resection) can stimulate colonic secretion and cause diarrhea.

Drugs may stimulate intestinal secretions directly (eg, quinidine, quinine, colchicine, anthraquinone cathartics, castor oil, prostaglandins) or indirectly by impairing fat absorption (eg, orlistat).

Various endocrine tumors produce secretagogues, including vipomas (vasoactive intestinal peptide), gastrinomas (gastrin), mastocytosis (histamine), medullary carcinoma of the thyroid (calcitonin and prostaglandins), and carcinoid tumors (histamine, serotonin, and polypeptides). Some of these mediators (eg, prostaglandins, serotonin, related compounds) also accelerate intestinal transit, colonic transit, or both.

Reduced contact time/surface area: Rapid intestinal transit and diminished surface area impair fluid absorption and cause diarrhea. Common causes include small-bowel or large-bowel resection or bypass, gastric resection,

[Table 8-4. Dietary Factors that May Worsen Diarrhea]

and inflammatory bowel disease. Other causes include microscopic colitis (collagenous or lymphocytic colitis) and celiac sprue.

Stimulation of intestinal smooth muscle by drugs (eg, Mg-containing antacids, laxatives, cholinesterase inhibitors, SSRIs) or humoral agents (eg, prostaglandins, serotonin) also can speed transit.

Evaluation

History: Duration and severity of diarrhea, circumstances of onset (including recent travel, food ingested, source of water), drug use (including any antibiotics within the previous 3 mo), abdominal pain or vomiting, frequency and timing of bowel movements, changes in stool characteristics (eg, presence of blood, pus, or mucus; changes in color or consistency; evidence of steatorrhea), associated changes in weight or appetite, and rectal urgency or tenesmus should be noted. Simultaneous occurrence of diarrhea in close contacts should be ascertained.

Physical examination: Fluid and hydration status should be evaluated. A full examination with attention to the abdomen and a digital rectal examination for sphincter competence and occult blood testing are important.

Red flags: Certain findings raise suspicion of an organic or more serious etiology of diarrhea:

• Blood or pus

• Fever

• Signs of dehydration

• Chronic diarrhea

• Weight loss

Interpretation of findings: Acute, watery diarrhea in an otherwise healthy person is likely to be of infectious etiology, particularly when travel, possibly tainted food, or an outbreak with a point-source is involved. Acute bloody diarrhea with or without hemodynamic instability in an otherwise healthy person suggests an enteroinvasive infection. Diverticular bleeding and ischemic colitis also manifest with acute bloody diarrhea. Recurrent bouts of bloody diarrhea in a younger person suggest inflammatory bowel disease. In the absence of laxative use, large-volume diarrhea (eg, daily stool volume > 1 L/day) strongly suggests an endocrine cause in patients with normal GI anatomy. A history of oil droplets in stool, particularly if associated with weight loss, suggests malabsorption.

Diarrhea that consistently follows ingestion of certain foods (eg, fats) suggests food intolerance. Recent antibiotic use should raise suspicion for antibiotic-associated diarrhea, including *Clostridium difficile* colitis.

The symptoms can help identify the affected part of the bowel. Generally, in small-bowel diseases, stools are voluminous and watery or fatty. In colonic diseases, stools are frequent, sometimes small in volume, and possibly accompanied by blood, mucus, pus, and abdominal discomfort. In irritable bowel syndrome (IBS), abdominal discomfort is relieved by defecation, associated with more loose or frequent stools, or both. However, these symptoms alone do not discriminate IBS from other diseases (eg, inflammatory bowel disease). Patients with IBS or rectal mucosal involvement often have marked urgency, tenesmus, and small, frequent stools (see p. 163).

Extra-abdominal findings that suggest an etiology include skin lesions or flushing (mastocytosis), thyroid nodules (medullary carcinoma of the thyroid), right-sided heart murmur (carcinoid), lymphadenopathy (lymphoma, AIDS), and arthritis (inflammatory bowel disease, celiac disease).

Testing: Acute diarrhea (< 4 days) typically does not require testing. Exceptions are patients with signs of dehydration, bloody stool, fever, severe pain, hypotension, or toxic features—particularly those who are very young or very old. These patients should have a CBC and measurement of electrolytes, BUN, and creatinine. Stool samples should be collected for microscopy, culture, fecal leukocyte testing, and, if antibiotics have been taken recently, *C. difficile* toxin assay.

Chronic diarrhea (> 4 wk) requires evaluation, as does a shorter (1 to 3 wk) bout of diarrhea in immunocompromised patients or those who appear significantly ill. Initial stool testing should include culture, fecal leukocytes (detected by smear or measurement of fecal lactoferrin), microscopic examination for ova and parasites, pH (bacterial fermentation of unabsorbed carbohydrate lowers stool pH < 6.0), fat (by Sudan stain), and electrolytes (Na and K). If no standard pathogens are found, specific tests for *Giardia* antigen and *Aeromonas*, *Plesiomonas*, coccidia, and microsporidia should be requested. Sigmoidoscopy or colonoscopy with biopsies should follow to look for inflammatory causes.

If no diagnosis is apparent and Sudan stain is positive for fat, fecal fat excretion should be measured, followed by small-bowel enteroclysis or CT enterography (structural disease) and endoscopic small-bowel biopsy (mucosal disease). If evaluation still yields negative findings, assessment of pancreatic structure and function (see p. 142) should be considered for patients who have unexplained steatorrhea. Infrequently, capsule endoscopy may uncover lesions, predominantly Crohn's disease or NSAID enteropathy, not identified by other modalities.

The stool osmotic gap, which is calculated 290 - 2 × (stool Na + stool K), indicates whether diarrhea is secretory or osmotic. An osmotic gap < 50 mEq/L indicates secretory diarrhea; a larger gap suggests osmotic diarrhea. Patients with osmotic diarrhea may have covert Mg laxative ingestion (detectable by stool Mg levels) or carbohydrate malabsorption (diagnosed by hydrogen breath test, lactase assay, and dietary review).

Undiagnosed secretory diarrhea requires testing (eg, plasma gastrin, calcitonin, vasoactive intestinal peptide levels, histamine, urinary 5-hydroxyindole acetic acid [5-HIAA]) for endocrine-related causes. A review for symptoms and signs of thyroid disease and adrenal insufficiency should be done. Surreptitious laxative abuse must be considered; it can be ruled out by a fecal laxative assay.

Treatment

• Fluid and electrolytes for dehydration

• Possibly antidiarrheals for nonbloody diarrhea in patients without systemic toxicity

Severe diarrhea requires fluid and electrolyte replacement to correct dehydration, electrolyte imbalance, and acidosis. Parenteral fluids containing NaCl, KCl, and glucose are generally required. Salts to counteract acidosis (Na lactate, acetate, HCO_3) may be indicated if serum HCO_3 is < 15 mEq/L. An oral glucose-electrolyte solution can be given if diarrhea is not severe and nausea and vomiting are minimal (see p. 2809). Oral and parenteral fluids are sometimes given simultaneously when water and electrolytes must be replaced in massive amounts (eg, in cholera).

Diarrhea is a symptom. When possible, the underlying disorder should be treated, but symptomatic treatment is often necessary. Diarrhea may be decreased by oral loperamide 2 to 4 mg tid or qid (preferably given 30 min before meals), diphenoxylate 2.5 to 5 mg (tablets or liquid) tid or qid, codeine phosphate 15 to 30 mg bid or tid, or paregoric (camphorated opium tincture) 5 to 10 mL once/day to qid.

Because antidiarrheals may exacerbate *C. difficile* colitis or increase the likelihood of hemolytic-uremic syndrome in *Shiga* toxin-producing *Escherichia coli* infection, they should not be used in bloody diarrhea of unknown cause. Their use should be restricted to patients with watery diarrhea and no signs of systemic toxicity. However, there is little evidence to justify previous concerns about prolonging excretion of possible bacterial pathogens with antidiarrheals.

Psyllium or methylcellulose compounds provide bulk. Although usually prescribed for constipation, bulking agents given in small doses decrease the fluidity of liquid stools. Kaolin, pectin, and activated attapulgite adsorb fluid. Osmotically active dietary substances (see Table 8-4) and stimulatory drugs should be avoided.

Key Points

• In patients with acute diarrhea, stool examination (cultures, ova and parasites, *C. difficile* cytotoxin) is only necessary for those who have prolonged symptoms (ie, > 1 wk) or red flag findings.

• Antidiarrheals should be used cautiously if there is a possibility of *C. difficile*, *Salmonella*, or shigellosis.

Gas-Related Complaints

The gut contains < 200 mL of gas, whereas daily gas expulsion averages 600 to 700 mL after consuming a standard diet plus 200 g of baked beans. About 75% of flatus is derived from colonic bacterial fermentation of ingested nutrients and endogenous glycoproteins. Gases include hydrogen (H_2), methane (CH_4), and carbon dioxide (CO_2). Flatus odor correlates with H_2 sulphide concentrations. Swallowed air (aerophagia) and diffusion from the blood into the lumen also contribute to intestinal gas. Gas diffuses between the lumen and the blood in a direction that depends on the difference in partial

pressures. Thus, most nitrogen (N_2) in the lumen originates from the bloodstream, and most H_2 in the bloodstream originates from the lumen.

Etiology

There are 3 main gas-related complaints: excessive belching, distention (bloating), and excessive flatus, each with a number of causes (see Table 8-5). Infants 2 to 4 mo of age with recurrent crying spells often appear to observers to be in pain, which in the past has been attributed to abdominal cramping or gas and termed colic. However, studies show no increase in H_2 production or in mouth-to-cecum transit times in colicky infants. Hence, the cause of infantile colic remains unclear (see p. 2725).

Excessive belching: Belching (eructation) results from swallowed air or from gas generated by carbonated beverages. Aerophagia occurs normally in small amounts during eating and drinking, but some people unconsciously swallow air repeatedly while eating or smoking and at other times, especially when anxious or in an attempt to induce belching. Excessive salivation increases aerophagia and may be associated with various GI disorders (eg, gastroesophageal reflux disease), ill-fitting dentures, certain drugs, gum chewing, or nausea of any cause.

Most swallowed air is eructated. Only a small amount of swallowed air passes into the small bowel; the amount is apparently influenced by position. In an upright person, air is readily belched; in a supine person, air trapped above the stomach fluid tends to be propelled into the duodenum. Excessive eructation may also be voluntary; patients who belch after taking antacids may attribute the relief of symptoms to belching rather than to antacids and may intentionally belch to relieve distress.

Distention (bloating): Abdominal bloating may occur in isolation or along with other GI symptoms in patients with functional disorders (eg, aerophagia, nonulcer dyspepsia, gastroparesis, irritable bowel syndrome) or organic disorders (eg, ovarian cancer, colon cancer). However, excessive intestinal gas is not clearly linked to these complaints. In most healthy people, 1 L/h of gas can be infused into the gut with minimal symptoms. It is likely that many symptoms are incorrectly attributed to "too much gas."

On the other hand, some patients with recurrent GI symptoms often cannot tolerate small quantities of gas: Retrograde colonic distention by balloon inflation or air instillation during colonoscopy often elicits severe discomfort in some patients (eg, those with irritable bowel syndrome) but minimal symptoms in others. Similarly, patients with eating disorders (eg, anorexia nervosa, bulimia) often misperceive and are particularly stressed by symptoms such as bloating. Thus, the basic abnormality in patients with gas-related symptoms may be a hypersensitive intestine. Altered motility may contribute further to symptoms.

Excessive flatus: There is great variability in the quantity and frequency of rectal gas passage. As with stool frequency, people who complain of flatulence often have a misconception of what is normal. The average number of gas passages is about 13 to 21/day. Objectively recording flatus frequency (using a diary kept by the patient) is a first step in evaluation.

Flatus is a metabolic byproduct of intestinal bacteria; almost none originates from swallowed air or back-diffusion of gases (primarily N_2) from the bloodstream. Bacterial metabolism yields significant volumes of H_2, CH_4, and CO_2.

H_2 is produced in large quantities in patients with malabsorption syndromes and after ingestion of certain fruits and vegetables containing indigestible carbohydrates (eg, baked beans), sugars (eg, fructose), or sugar alcohols (eg, sorbitol). In patients with disaccharidase deficiencies (most commonly lactase deficiency), large amounts of disaccharides pass into the colon and are fermented to H_2. Celiac disease, tropical sprue, pancreatic insufficiency, and other causes of carbohydrate malabsorption should also be considered in cases of excess colonic gas.

CH_4 is also produced by colonic bacterial metabolism of the same foods (eg, dietary fiber). However, about 10% of people have bacteria that produce CH_4 but not H_2.

CO_2 is also produced by bacterial metabolism and generated in the reaction of HCO_3^- and H^+. H^+ may come from gastric HCl or from fatty acids released during digestion of fats—the latter sometimes produces several hundred mEq of H^+. The acid products released by bacterial fermentation of unabsorbed carbohydrates in the colon may also react with HCO_3^- to produce CO_2. Although bloating may occasionally occur, the rapid diffusion of CO_2 into the blood generally prevents distention.

[Table 8-5. Some Causes of Gas-Related Complaints]

Diet accounts for much of the variation in flatus production among individuals, but poorly understood factors (eg, differences in colonic flora and motility) may also play a role.

Despite the flammable nature of the H_2 and CH_4 in flatulence, working near open flames is not hazardous. However, gas explosion, even with fatal outcome, has been reported during jejunal and colonic surgery and colonoscopy, when diathermy was used during procedures in patients with incomplete bowel cleaning.

Evaluation

History: Patients with belching should have the history directed at finding the cause of aerophagia, especially dietary causes.

In patients complaining of gas, bloating, or flatus, the relationship between symptoms and meals (both timing and type and amount of food), bowel movements, and exertion should be explored. Certain patients, particularly in the acute setting, may use the term "gas" to describe their symptoms of coronary ischemia. Changes in frequency and color and consistency of stool are sought. History of weight loss is noted.

Physical examination: The examination is generally normal, but in patients with bloating or flatus, signs of an underlying organic disorder should be sought on abdominal, rectal, and (for women) pelvic examination.

Red flags: The following findings are of concern:

• Weight loss

• Blood in stool (occult or gross)

Interpretation of findings: Chronic, recurrent bloating or distention relieved by defecation and associated with change in frequency or consistency of stool but without red flag findings suggests irritable bowel syndrome.

Long-standing symptoms in an otherwise well young person who has not lost weight are unlikely to be caused by serious physiologic disease, although an eating disorder should be considered, particularly in young women. Bloating accompanied by diarrhea, weight loss, or both (or only after ingestion of certain foods) suggests a malabsorption syndrome.

Testing: Testing is not indicated for belching unless other symptoms suggest a particular disorder. Testing for carbohydrate intolerance (eg, lactose, fructose) with breath tests should be considered particularly when the history suggests significant consumption of these sugars. Testing for small-bowel bacterial overgrowth should also be considered, particularly in patients who also have diarrhea, weight loss, or both, preferably by aerobic and anaerobic culture of small-bowel aspirates obtained during upper GI endoscopy. Testing for bacterial overgrowth with H_2 breath tests, generally glucose-H_2 breath tests, is prone to false-positive (ie, with rapid transit) and false-negative (ie, when there are no H_2-producing bacteria) results. New, persistent bloating in middle-aged or older women (or those with an abnormal pelvic examination) should prompt pelvic ultrasonography to rule out ovarian cancer.

Treatment

Belching and bloating are difficult to relieve because they are usually caused by unconscious aerophagia or increased sensitivity to normal amounts of gas. Aerophagia may be reduced by eliminating gum and carbonated beverages, cognitive behavioral techniques to prevent air swallowing, and management of associated upper GI diseases (eg, peptic ulcer). Foods containing unabsorbable carbohydrates should be avoided. Even lactose-intolerant patients generally tolerate up to 1 glass of milk drunk in small amounts throughout the day. The mechanism of repeated belching should be explained and demonstrated. When aerophagia is troublesome, behavioral therapy to encourage open-mouth, diaphragmatic breathing and minimize swallowing may be effective.

Sidebar 8-1 Essay on Flatulence

(First printed in the 14th Edition of *The Merck Manual*)

Flatulence, which can cause great psychosocial distress, is unofficially described according to its salient characteristics: (1) the "slider" (crowded elevator type), which is released slowly and noiselessly, sometimes with devastating effect; (2) the open sphincter, or "pooh" type, which is said to be of higher temperature and more aromatic; (3) the staccato or drumbeat type, pleasantly passed in privacy; and (4) the "bark" type (described in a personal communication) is characterized by a sharp exclamatory eruption that effectively interrupts (and often concludes) conversation. Aromaticity is not a prominent feature. Rarely, this usually distressing symptom has been turned to advantage, as with a Frenchman referred to as "Le Petomane," who became affluent as an effluent performer who played tunes with the gas from his rectum on the Moulin Rouge stage.

Drugs provide little benefit. Results with simethicone, an agent that breaks up small gas bubbles, and various anticholinergics are poor. Some patients with dyspepsia and postprandial upper abdominal fullness benefit from antacids, a low dose of tricyclic antidepressants (eg, nortriptyline 10 to 50 mg po once/day), or both to reduce visceral hypersensitivity.

Complaints of excess flatus are treated with avoidance of triggering substances (see Table 8-5). Roughage (eg, bran, psyllium seed) may be added to the diet to try to increase colonic transit; however, in some patients, worsening of symptoms may result. Activated charcoal can sometimes help reduce gas and unpleasant odor; however, it stains clothing and the oral mucosa. Charcoal-lined undergarments are available. Probiotics (eg, VSL#3) may also reduce bloating and flatulence by modulating intestinal bacterial flora. Antibiotics are useful in patients with documented bacterial overgrowth.

Functional bloating, distention, and flatus may run an intermittent, chronic course that is only partially relieved by therapy. When appropriate, reassurance that these problems are not detrimental to health is important.

Key Points

• Testing should be guided by the clinical features.

• Clinicians should be wary of new-onset, persistent symptoms in older patients.

Chapter 9. Diagnostic and Therapeutic GI Procedures

Introduction

Diagnostic tests and therapeutic procedures available for patients with GI disorders include acid-related tests, endoscopy, laparoscopy, manometry, nuclear scans, x-ray contrast studies, nasogastric or intestinal intubation, anoscopy and sigmoidoscopy, abdominal paracentesis, electrogastrography, and electrical impedance testing. CT, MRI, and ultrasonography are also commonly done for GI disorders, and sometimes angiography is used. The selection of procedures is discussed in subsequent chapters. ERCP, percutaneous transhepatic cholangiography, and liver biopsy are discussed in Ch. 24.

Acid-Related Tests

Acid-related tests are used to ascertain the effectiveness of acid-blocking drugs. All require nasogastric or nasoesophageal intubation. Complications are very rare. Patients must have nothing by mouth (npo) after midnight.

Ambulatory pH Monitoring

Ambulatory 24-h esophageal pH monitoring is currently the best available test for quantifying esophageal acid exposure. The principal indications are

• To document excessive acid exposure in patients without endoscopic evidence of esophagitis

• To evaluate the effectiveness of medical or surgical treatments

A thin tube containing a pH probe is positioned 5 cm above the lower esophageal sphincter. The patient records symptoms, meals, and sleep for 24 h. Esophageal acid exposure is defined by the percentage of the 24-h recording time that the pH is < 4.0. Values > 3.5% are considered abnormal. However, symptoms may not correlate with acid exposure or the presence of esophagitis. This may be because symptoms may result from nonacidic as well as acidic refluxate. Multichannel intraluminal impedance testing allows for recognition of major acid, minor acid, nonacid, and gas reflux, all of which can cause reflux symptoms.

Gastric Analysis

Samples of stomach contents obtained via NGT are used to measure gastric acid output in a basal and stimulated state. This information may be useful in a patient who develops a recurrent ulcer after surgical vagotomy for peptic ulcer disease. In this case, a positive acid response to stimulation (sham feeding) indicates an incomplete vagotomy. The test also is used to evaluate a patient with elevated serum gastrin levels. Hyperchlorhydria in the presence of elevated gastrin usually indicates Zollinger-Ellison syndrome. Hypochlorhydria in the presence of elevated gastrin indicates impairment of acid output, such as occurs in pernicious anemia, atrophic gastritis, and Menetrier's disease and after inhibition of gastric acid secretion by potent antisecretory drugs.

To do gastric analysis, an NGT is inserted and the gastric contents are aspirated and discarded. Gastric juice is then collected for 1 h, divided into four 15-min samples. These samples represent basal acid output.

Endoscopy

Flexible endoscopes equipped with video cameras can be used to view the upper GI tract from pharynx to upper duodenum and the lower GI tract from anus to cecum (and, sometimes, terminal ileum). Several other diagnostic and therapeutic interventions also can be done endoscopically. The potential to combine diagnosis and therapy in one procedure gives endoscopy a significant advantage over procedures that provide only imaging (eg, x-ray contrast studies, CT, MRI) and often outweighs endoscopy's higher cost and need for sedation.

Diagnostic procedures include the use of ultrasound-equipped endoscopes to evaluate blood flow or

provide imaging of lesions. Endoscopic ultrasound can provide information (eg, the depth and extent of lesions) that is not available via conventional endoscopy. Other diagnostic procedures include cell and tissue sample collection by brush or biopsy forceps.

Screening colonoscopy is recommended for patients at high risk of colon cancer and for everyone ≥ 50. Colonoscopy should be done every 10 yr for patients with no risk factors and with a normal initial colonoscopy. CT colonography (see p. 98) is an alternative to colonoscopy for screening for colonic tumors.

Therapeutic endoscopic procedures include removal of foreign bodies; hemostasis by thermal coagulation, laser photocoagulation, variceal banding, or sclerotherapy; debulking of tumors by laser or bipolar electrocoagulation; dilation of webs or strictures; stent placement; reduction of volvulus or intussusception; and decompression of acute or subacute colonic dilatation.

Absolute contraindications to endoscopy include

• Shock

• Acute MI

• Peritonitis

• Acute perforation

• Fulminant colitis

Relative contraindications include poor patient cooperation, coma (unless the patient is intubated), and cardiac arrhythmias or recent myocardial ischemia.

Patients taking anticoagulants or chronic NSAID therapy can safely undergo diagnostic endoscopy. However, if there is a possibility that biopsy or photocoagulation will be done, these drugs should be stopped for an appropriate interval before the procedure. Oral iron-containing drugs should be stopped 4 to 5 days before colonoscopy, because certain green vegetables interact with iron to form a sticky residue that is difficult to remove with a bowel preparation and interferes with visualization. The American Heart Association no longer recommends endocarditis prophylaxis for patients having GI endoscopy.

Routine preparations for endoscopy include no solids for 6 to 8 h and no liquids for 4 h before the procedure. Additionally, colonoscopy requires cleansing of the colon. A variety of regimens may be used, but all typically include a full or clear liquid diet for 24 to 48 h and some type of laxative, with or without an enema. A common laxative preparation involves having the patient drink a high-volume (4 L) balanced electrolyte solution over a period of 3 to 4 h before the procedure. Patients who cannot tolerate this solution may be given Mg citrate, Na phosphate, lactulose, or other laxatives. Enemas can be done with either Na phosphate or tap water. Phosphate preparations should not be used in patients with renal insufficiency.

Endoscopy generally requires IV sedation and, for upper endoscopy, topical anesthesia of the throat. Exceptions are anoscopy and sigmoidoscopy (see p. 98), which generally require nothing. The overall complication rate of endoscopy is 0.1 to 0.2%; mortality is about 0.03%. Complications are usually drug related (eg, respiratory depression); procedural complications (eg, aspiration, perforation, significant bleeding) are less common.

Video capsule endoscopy: In video capsule endoscopy (wireless video endoscopy), patients swallow a capsule containing a camera that transmits images to an external recorder. This noninvasive technology provides diagnostic imaging of the small bowel that is otherwise difficult to obtain. This procedure is particularly useful in patients with occult GI bleeding. Capsule endoscopy is more difficult in the colon; products and procedures are under development.

Laparoscopy

Diagnostic laparoscopy is a surgical procedure used to evaluate intra-abdominal or pelvic pathology (eg, tumor, endometriosis) in patients with acute or chronic abdominal pain and operability in patients with cancer. It also is used for lymphoma staging and liver biopsy.

Absolute contraindications include

- A coagulation or bleeding disorder
- Poor patient cooperation
- Peritonitis
- Intestinal obstruction
- Infection of the abdominal wall

Relative contraindications include severe cardiac or pulmonary disease, large abdominal hernias, multiple abdominal operations, and tense ascites.

CBC, coagulation studies, and type and Rh testing are done before laparoscopy. X-rays of the chest and abdomen (kidneys, ureters, and bladder) are also taken. Laparoscopy is done with sterile technique in an operating room or a well-equipped endoscopy suite. The patient is given local anesthesia plus IV sedation and analgesia with an opioid and short-acting sedative (eg, midazolam, propofol).

The procedure involves insertion of a pneumoperitoneum needle into the peritoneal cavity and infusion of nitrous oxide to distend the abdomen. After the opening is enlarged, a peritoneoscope is inserted into the abdomen and the abdominal contents are examined. Surgical instruments for biopsy and other procedures are inserted through separate openings. When the procedure is completed, the nitrous oxide is expelled by the patient with a Valsalva maneuver and the cannula is removed. Complications can include bleeding, bacterial peritonitis, and perforation of a viscus.

Manometry

Manometry is measurement of pressure within various parts of the GI tract. It is done by passing a catheter containing solid-state or liquid-filled pressure transducers through the mouth or anus into the lumen of the organ to be studied. Manometry typically is done to evaluate motility disorders in patients in whom structural lesions have been ruled out by other studies. Manometry is used in the esophagus, stomach and duodenum, sphincter of Oddi, and rectum. Aside from minor discomfort, complications are very rare. Patients must have nothing by mouth (npo) after midnight.

Esophageal manometry: This test is used to evaluate patients with dysphagia, heartburn, or chest pain. It measures the pressure in the upper and lower esophageal sphincters, determines the effectiveness and coordination of propulsive movements, and detects abnormal contractions. Manometry is used to diagnose achalasia, diffuse spasm, systemic sclerosis, and lower esophageal sphincter hypotension and hypertension. It also is used to evaluate esophageal function before certain therapeutic procedures (eg, antireflux surgery, pneumatic dilation for achalasia).

Gastroduodenal manometry: In this test, transducers are placed in the gastric antrum, duodenum, and proximal jejunum. Pressure is monitored for 5 to 24 h in both fasting and fed states. This test is used mainly in patients who have symptoms suggestive of dysmotility but normal gastric emptying studies.

Barostat: This is a pressure-sensing device that is placed in the stomach to measure gastric accommodation. The device consists of a plastic balloon and an electronic controller that varies the amount of air in the balloon to maintain constant pressure. This device is used mainly in research studies assessing sensory threshold and altered visceral perception, particularly in functional GI disorders.

Anorectal manometry: This test evaluates the anorectal sphincter mechanism and rectal sensation in

patients with incontinence (and sometimes constipation) by means of a pressure transducer in the anus. It can help diagnose Hirschsprung's disease and provide biofeedback training for fecal incontinence.

Nuclear Scans

Gastric emptying can be measured by having the patient ingest a radiolabeled meal (solid or liquid) and observing its passage out of the stomach with a gamma camera. Because this test cannot differentiate physical obstruction from gastroparesis, further diagnostic studies typically are done if emptying is delayed. The test also is useful in monitoring response to promotility drugs (eg, metoclopramide, erythromycin).

Bleeding scans use ^{99m}Tc-labeled RBCs, or occasionally ^{99m}Tc-labeled colloid, to determine the origin of lower GI hemorrhage before surgery or angiography. Active bleeding sites are identified by focal areas of tracer that conform to bowel anatomy, increase with time, and move with peristalsis. Bleeding scans are useful mainly for colonic bleeding in patients with significant hemorrhage and an unprepared bowel, in whom endoscopic visualization is difficult.

A **Meckel scan** identifies ectopic gastric mucosa (as in a Meckel's diverticulum) by using an injection of ^{99m}Tc pertechnetate, which is taken up by mucus-secreting cells of the gastric mucosa. Focal uptake outside of the stomach and in the small bowel indicates a Meckel's diverticulum.

X-Ray and Other Imaging Contrast Studies

X-ray and other imaging contrast studies visualize the entire GI tract from pharynx to rectum and are most useful for detecting mass lesions and structural abnormalities (eg, tumors, strictures). Single-contrast studies fill the lumen with radiopaque material, outlining the structure. Better, more detailed images are obtained from double-contrast studies, in which a small amount of high-density barium coats the mucosal surface and gas distends the organ and enhances contrast. The gas is injected by the operator in double-contrast barium enema, whereas in other studies, intrinsic GI tract gas is adequate. In all cases, patients turn themselves to properly distribute the gas and barium. Fluoroscopy can monitor the progress of the contrast material. Either video or plain films can be taken for documentation, but video is particularly useful when assessing motor disorders (eg, cricopharyngeal spasm, achalasia).

The main contraindication to x-ray contrast studies is suspected perforation, because free barium is highly irritating to the mediastinum and peritoneum; water-soluble contrast is less irritating and may be used if perforation is possible. Older patients may have difficulty turning themselves to properly distribute the barium and intraluminal gas.

Patients having upper GI x-ray contrast studies must have nothing by mouth (npo) after midnight. Patients having barium enema follow a clear liquid diet the day before, take an oral Na phosphate laxative in the afternoon, and take a bisacodyl suppository in the evening. Other laxative regimens are effective.

Complications are rare. Perforation can occur if barium enema is done in a patient with toxic megacolon. Barium impaction may be prevented by postprocedure oral fluids and sometimes laxatives.

An **upper GI examination** is best done as a biphasic study beginning with a double-contrast examination of the esophagus, stomach, and duodenum, followed by a single-contrast study using low-density barium. Glucagon 0.5 mg IV can facilitate the examination by causing gastric hypotonia.

A **small-bowel meal** is done by using fluoroscopy and provides a more detailed evaluation of the small bowel. Shortly before the examination, the patient is given metoclopramide 20 mg po to hasten transit of the contrast material.

Enteroclysis (small-bowel enema) provides still better visualization of the small bowel but requires intubation of the duodenum with a flexible, balloon-tipped catheter. A barium suspension is injected, followed by a solution of methylcellulose, which functions as a double-contrast agent that enhances visualization of the small-bowel mucosa.

A **barium enema** can be done as a single-or double-contrast study. Single-contrast barium enemas are used for potential obstruction, diverticulitis, fistulas, and megacolon. Double-contrast studies are preferred for detection of tumors.

CT scanning of the abdomen: CT scanning using oral and IV contrast allows excellent visualization of both the small bowel and colon as well as of other intra-abdominal structures.

CT enterography provides optimal visualization of the small-bowel mucosa; it is preferably done by using a multidetector CT (MDCT) scanner. Patients are given a large volume (1350 mL) of 0.1% barium sulfate before imaging. For certain indications (eg, obscure GI bleeding, small-bowel tumors, chronic ischemia), a biphasic contrast-enhanced MDCT study is done.

CT colonography (virtual colonoscopy) generates 3D and 2D images of the colon by using MDCT and a combination of oral contrast and gas distention of the colon. Viewing the high-resolution 3D images somewhat simulates the appearance of optical endoscopy, hence the name. Optimal CT colonography technique requires careful cleansing and distention of the colon. Residual stool causes problems similar to those encountered with barium enema because it simulates polyps or masses. Three-dimensional endoluminal images are useful to confirm the presence of a lesion and to improve diagnostic confidence.

CT enterography and CT colonoscopy have largely supplanted standard small-bowel series and barium enema examinations.

GI Procedures for the Generalist

Nasogastric or Intestinal Intubation

Nasogastric or intestinal intubation is used to decompress the stomach. It is used to treat gastric atony, ileus, or obstruction; remove ingested toxins, give antidotes (eg, activated charcoal), or both; obtain a sample of gastric contents for analysis (volume, acid content, blood); and supply nutrients.

Contraindications include

• Nasopharyngeal or esophageal obstruction

• Severe maxillofacial trauma

• Uncorrected coagulation abnormalities

Esophageal varices previously have been considered a contraindication, but evidence of adverse effects is lacking.

Several types of tubes are available. A Levin or Salem sump tube is used for gastric decompression or analysis and rarely for short-term feeding. A variety of long, thin, intestinal tubes are used for long-term enteral feeding (see p. 21).

For intubation, the patient sits upright or, if unable, lies in the left lateral decubitus position. A topical anesthetic sprayed in the nose and pharynx helps reduce discomfort. With the patient's head partially flexed, the lubricated tube is inserted through the nares and aimed back and then down to conform to the nasopharynx. As the tip reaches the posterior pharyngeal wall, the patient should sip water through a straw. Violent coughing with flow of air through the tube during respiration indicates that the tube is misplaced in the trachea. Aspiration of gastric juice verifies entry into the stomach. The position of larger tubes can be confirmed by instilling 20 to 30 mL of air and listening with the stethoscope under the left subcostal region for a rush of air.

Some smaller, more flexible intestinal feeding tubes require the use of stiffening wires or stylets. These tubes usually require fluoroscopic or endoscopic assistance for passage through the pylorus.

Complications are rare and include nasopharyngeal trauma with or without hemorrhage, pulmonary aspiration, traumatic esophageal or gastric hemorrhage or perforation, and (very rarely) intracranial or mediastinal penetration.

Anoscopy and Sigmoidoscopy

Anoscopy and sigmoidoscopy are used to evaluate symptoms referable to the rectum or anus (eg, bright rectal bleeding, discharge, protrusions, pain). There are no absolute contraindications. Patients with cardiac arrhythmias or recent myocardial ischemia should have the procedure postponed until the comorbid conditions improve; otherwise, patients will need cardiac monitoring. Per changes in American Heart Association guidelines, these procedures no longer require endocarditis prophylaxis.

The perianal area and distal rectum can be examined with a 7-cm anoscope, and the rectum and sigmoid with either a rigid 25-cm or a flexible 60-cm instrument. Flexible sigmoidoscopy is much more comfortable for the patient and readily permits photography and biopsy of tissue. Considerable skill is required to pass a rigid sigmoidoscope beyond the rectosigmoid junction (15 cm) without causing discomfort.

Sigmoidoscopy is done after giving an enema to empty the rectum. IV drugs are usually not needed. The patient is placed in the left lateral position. After external inspection and digital rectal examination, the lubricated instrument is gently inserted 3 to 4 cm past the anal sphincter. At this point, the obturator of the rigid sigmoidoscope is removed, and the instrument is inserted further under direct vision.

Anoscopy may be done without preparation. The anoscope is inserted its full length as described above for rigid sigmoidoscopy, usually with the patient in the left lateral position. Complications are exceedingly rare when the procedure is done properly.

Abdominal Paracentesis

Abdominal paracentesis is used to obtain ascitic fluid for testing. It also can be used to remove tense ascites causing respiratory difficulties or pain or as a treatment for chronic ascites.

Absolute contraindications include

- Severe, uncorrectable disorders of blood coagulation
- Intestinal obstruction
- An infected abdominal wall

Poor patient cooperation, surgical scarring over the puncture area, and severe portal hypertension with abdominal collateral circulation are relative contraindications.

CBC, platelet count, and coagulation studies are done before the procedure. After emptying the bladder, the patient sits in bed with the head elevated 45 to 90°. In patients with obvious and marked ascites, a point is located at the midline between the umbilicus and the pubic bone and is cleaned with an antiseptic solution and alcohol. In patients with moderate ascites, precise location of ascitic fluid by abdominal ultrasound is indicated. Under sterile technique, the area is anesthetized to the peritoneum with lidocaine 1%. For diagnostic paracentesis, an 18-gauge needle attached to a 50-mL syringe is inserted through the peritoneum (generally a popping sensation is noted). Fluid is gently aspirated and sent for cell count, protein or amylase content, cytology, or culture as needed. For therapeutic (large-volume) paracentesis, a 14-gauge cannula attached to a vacuum aspiration system is used to collect up to 8 L of ascitic fluid. Postprocedure hypotension caused by fluid redistribution is rare as long as interstitial (leg) edema is present.

Hemorrhage is the most common complication. Occasionally, with tense ascites, prolonged leakage of ascitic fluid occurs through the needle site.

Other Testing Procedures

Electrogastrography measures gastric electrical activity with adhesive cutaneous electrodes. This procedure is useful in patients with gastroparesis.

In **electrical impedance testing**, an electrical sensor is placed in the distal esophagus to assess nonacid reflux, which is common among patients receiving gastric antisecretory drugs and among infants with reflux disease.

Chapter 10. GI Bleeding

Introduction

GI bleeding can originate anywhere from the mouth to the anus and can be overt or occult. The manifestations depend on the location and rate of bleeding.

Hematemesis is vomiting of red blood and indicates upper GI bleeding, usually from an arterial source or varix. Coffee-ground emesis is vomiting of dark brown, granular material that resembles coffee grounds. It results from upper GI bleeding that has slowed or stopped, with conversion of red Hb to brown hematin by gastric acid.

Hematochezia is the passage of gross blood from the rectum and usually indicates lower GI bleeding but may result from vigorous upper GI bleeding with rapid transit of blood through the intestines.

Melena is black, tarry stool and typically indicates upper GI bleeding, but bleeding from a source in the small bowel or right colon may also be the cause. About 100 to 200 mL of blood in the upper GI tract is required to cause melena, which may persist for several days after bleeding has ceased. Black stool that does not contain occult blood may result from ingestion of iron, bismuth, or various foods and should not be mistaken for melena.

Chronic occult bleeding can occur from anywhere in the GI tract and is detectable by chemical testing of a stool specimen. Acute, severe bleeding also can occur from anywhere in the GI tract. Patients may present with signs of shock. Those with underlying ischemic heart disease may develop angina or MI because of hypoperfusion.

GI bleeding may precipitate portal-systemic encephalopathy (see p. 220) or hepatorenal syndrome (kidney failure secondary to liver failure—see p. 223).

Etiology

There are many possible causes (see Table 10-1), which are divided into upper GI (above the ligament of Treitz), lower GI, and small bowel.

Bleeding of any cause is more likely, and potentially more severe, in patients with chronic liver disease (eg, caused by alcohol abuse or chronic hepatitis), in those with hereditary coagulation disorders, or in those taking certain drugs. Drugs associated with GI bleeding include anticoagulants (eg, heparin, warfarin), those affecting platelet function (eg, aspirin and certain other NSAIDs, clopidogrel, SSRIs), and those affecting mucosal defenses (eg, NSAIDs).

Evaluation

Stabilization with airway management, IV fluids, or transfusions is essential before and during diagnostic evaluation.

History: History of present illness should attempt to ascertain quantity and frequency of blood passage. However, quantity can be difficult to assess because even small amounts (5 to 10 mL) of blood turn water in a toilet bowl an opaque red, and modest amounts of vomited blood appear huge to an anxious patient. However, most can distinguish among blood streaks, a few teaspoons, and clots.

Patients with hematemesis should be asked whether blood was passed with initial vomiting or only after an initial (or several) nonbloody emesis.

Patients with rectal bleeding should be asked whether pure blood was passed; whether it was mixed with stool, pus, or mucus; or whether blood simply coated the stool. Those with bloody diarrhea should be asked about travel or other possible exposure to GI pathogens.

[**Table 10-1.** Common Causes of GI Bleeding]

Review of symptoms should include presence of abdominal discomfort, weight loss, easy bleeding or bruising, previous colonoscopy results, and symptoms of anemia (eg, weakness, easy fatigability, dizziness).

Past medical history should inquire about previous GI bleeding (diagnosed or undiagnosed); known inflammatory bowel disease, bleeding diatheses, and liver disease; and use of any drugs that increase the likelihood of bleeding or chronic liver disease (eg, alcohol).

Physical examination: General examination focuses on vital signs and other indicators of shock or hypovolemia (eg, tachycardia, tachypnea, pallor, diaphoresis, oliguria, confusion) and anemia (eg, pallor, diaphoresis). Patients with lesser degrees of bleeding may simply have mild tachycardia (heart rate > 100). Orthostatic changes in pulse (a change of > 10 beats/min) or BP (a drop of ≥ 10 mm Hg) often develop after acute loss of ≥ 2 units of blood. However, orthostatic measurements are unwise in patients with severe bleeding (possibly causing syncope) and generally lack sensitivity and specificity as a measure of intravascular volume, especially in elderly patients.

External stigmata of bleeding disorders (eg, petechiae, ecchymoses) are sought, as are signs of chronic liver disease (eg, spider angiomas, ascites, palmar erythema) and portal hypertension (eg, splenomegaly, dilated abdominal wall veins).

A digital rectal examination is necessary to search for stool color, masses, and fissures. Anoscopy is done to diagnose hemorrhoids. Chemical testing of a stool specimen for occult blood completes the examination if gross blood is not present.

Red flags: Several findings suggest hypovolemia or hemorrhagic shock:

• Syncope

• Hypotension

• Pallor

• Diaphoresis

• Tachycardia

Interpretation of findings: The history and physical examination suggest a diagnosis in about 50% of patients, but findings are rarely diagnostic and confirmatory testing is required.

Epigastric abdominal discomfort relieved by food or antacids suggests peptic ulcer disease. However, many patients with bleeding ulcers have no history of pain. Weight loss and anorexia, with or without a change in stool, suggest a GI cancer. A history of cirrhosis or chronic hepatitis suggests esophageal varices. Dysphagia suggests esophageal cancer or stricture. Vomiting and retching before the onset of bleeding suggests a Mallory-Weiss tear of the esophagus, although about 50% of patients with Mallory-Weiss tears do not have this history.

A history of bleeding (eg, purpura, ecchymosis, hematuria) may indicate a bleeding diathesis (eg, hemophilia, hepatic failure). Bloody diarrhea, fever, and abdominal pain suggest ischemic colitis, inflammatory bowel disease (eg, ulcerative colitis, Crohn's disease), or an infectious colitis (eg, *Shigella*, *Salmonella*, *Campylobacter*, amebiasis). Hematochezia suggests diverticulosis or angiodysplasia. Fresh blood only on toilet paper or the surface of formed stools suggests internal hemorrhoids or fissures, whereas blood mixed with the stool indicates a more proximal source. Occult blood in the stool may be the first sign of colon cancer or a polyp, particularly in patients > 45 yr.

Blood in the nose or trickling down the pharynx suggests the nasopharynx as the source. Spider angiomas, hepatosplenomegaly, or ascites is consistent with chronic liver disease and hence possible esophageal varices. Arteriovenous malformations, especially of the mucous membranes, suggest

hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Cutaneous nail bed and GI telangiectasia may indicate systemic sclerosis or mixed connective tissue disease.

Testing: Several tests are done to help confirm the suspected diagnosis.

• CBC and often other laboratory studies

• NGT for all but those with minimal rectal bleeding

• Upper endoscopy for suspected upper GI bleeding

• Colonoscopy for lower GI bleeding (unless clearly caused by hemorrhoids)

CBC should be obtained in patients with occult blood loss. Those with more significant bleeding also require coagulation studies (eg, platelet count, PT, PTT) and liver function tests (eg, bilirubin, alkaline phosphatase, albumin, AST, ALT). Type and crossmatch are done if bleeding is ongoing. Hb and Hct may be repeated up to every 6 h in patients with severe bleeding. Additionally, one or more diagnostic procedures are typically required.

Nasogastric aspiration and lavage should be done in all patients with suspected upper GI bleeding (eg, hematemesis, coffee-ground emesis, melena, massive rectal bleeding). Bloody nasogastric aspirate indicates active upper GI bleeding, but about 10% of patients with upper GI bleeding have no blood in the nasogastric aspirate. Coffee-ground material indicates bleeding that is slow or stopped. If there is no sign of bleeding, and bile is returned, the NGT is removed; otherwise, it is left in place to monitor continuing or recurrent bleeding. Nonbloody, nonbilious return is considered a nondiagnostic aspirate.

Upper endoscopy (examination of the esophagus, stomach, and duodenum) should be done for upper GI bleeding. Because endoscopy may be therapeutic as well as diagnostic, it should be done rapidly for significant bleeding but may be deferred for 24 h if bleeding stops or is minimal. Upper GI barium x-rays have no role in acute bleeding, and the contrast used may obscure subsequent attempts at angiography. Angiography is useful in the diagnosis of upper GI bleeding and permits certain therapeutic maneuvers (eg, embolization, vasoconstrictor infusion).

Flexible sigmoidoscopy and anoscopy may be all that is required acutely for patients with symptoms typical of hemorrhoidal bleeding. All other patients with hematochezia should have colonoscopy, which can be done electively after routine preparation unless there is significant ongoing bleeding. In such patients, a rapid prep (5 to 10 L of polyethylene glycol solution delivered via NGT or by mouth over 3 to 4 h) often allows adequate visualization. If colonoscopy cannot visualize the source and ongoing bleeding is sufficiently rapid (> 0.5 to 1 mL/min), angiography may localize the source. Some angiographers first take a radionuclide scan to focus the examination, because angiography is less sensitive than the radionuclide scan.

Diagnosis of occult bleeding can be difficult, because heme-positive stools may result from bleeding anywhere in the GI tract. Endoscopy is the preferred method, with symptoms determining whether the upper or lower GI tract is examined first. Double-contrast barium enema and sigmoidoscopy can be used for the lower tract when colonoscopy is unavailable or the patient refuses it. If the results of upper endoscopy and colonoscopy are negative and occult blood persists in the stool, an upper GI series with small-bowel follow-through, small-bowel endoscopy (enteroscopy), capsule endoscopy, technetium-labeled colloid or RBC scan, and angiography should be considered.

Treatment

• Secure airway if needed

• IV fluid resuscitation

• Blood transfusion if needed

• In some, angiographic or endoscopic hemostasis

Hematemesis, hematochezia, or melena should be considered an emergency. Admission to an ICU, with consultation by both a gastroenterologist and a surgeon, is recommended for all patients with severe GI bleeding. General treatment is directed at maintenance of the airway and restoration of circulating volume. Hemostasis and other treatment depend on the cause of the bleeding.

Airway: A major cause of morbidity and mortality in patients with active upper GI bleeding is aspiration of blood with subsequent respiratory compromise. To prevent these problems, endotracheal intubation should be considered in patients who have inadequate gag reflexes or are obtunded or unconscious —particularly if they will be undergoing upper endoscopy.

Fluid resuscitation: IV fluids are initiated as for any patient with hypovolemia or hemorrhagic shock (see p. 2297): healthy adults are given normal saline IV in 500- to 1000-mL aliquots until signs of hypovolemia remit—up to a maximum of 2 L (for children, 20 mL/kg, that may be repeated once). Patients requiring further resuscitation should receive transfusion with packed RBCs. Transfusions continue until intravascular volume is restored and then are given as needed to replace ongoing blood loss. Transfusions in older patients or those with coronary artery disease may be stopped when Hct is stable at 30 unless the patient is symptomatic. Younger patients or those with chronic bleeding are usually not transfused unless Hct is < 23 or they have symptoms such as dyspnea or coronary ischemia.

Platelet count should be monitored closely; platelet transfusion may be required with severe bleeding. Patients who are taking antiplatelet drugs (eg, clopidogrel, aspirin) have platelet dysfunction, often resulting in increased bleeding. Platelet transfusion should be considered when patients taking these drugs have severe ongoing bleeding, although a residual circulating drug (particularly clopidogrel) may inactivate transfused platelets. Fresh frozen plasma should be transfused after every 4 units of packed RBCs.

Hemostasis: GI bleeding stops spontaneously in about 80% of patients. The remaining patients require some type of intervention. Specific therapy depends on the bleeding site. Early intervention to control bleeding is important to minimize mortality, particularly in elderly patients.

For peptic ulcer, ongoing bleeding or rebleeding is treated with endoscopic coagulation (with bipolar electrocoagulation, injection sclerotherapy, heater probes, or laser). Non-bleeding vessels that are visible within an ulcer crater are also treated. If endoscopy does not stop the bleeding, surgery is required to oversew the bleeding site. If medical management does not control gastric acid secretion, surgeons do acid-reduction surgery (see p. 136) at the same time.

Active variceal bleeding can be treated with endoscopic banding, injection sclerotherapy, or a transjugular intrahepatic portosystemic shunting (TIPS) procedure.

Severe, ongoing lower GI bleeding caused by diverticula or angiomas can sometimes be controlled colonoscopically by electrocautery, coagulation with a heater probe, or injection with dilute epinephrine. Polyps can be removed by snare or cautery. If these methods are ineffective or unfeasible, angiography with embolization or vasopressin infusion may be successful. However, because collateral blood flow to the bowel is limited, angiographic techniques have a significant risk of bowel ischemia or infarction unless super-selective catheterization techniques are used. In most series, the rate of ischemic complications is < 5%. Vasopressin infusion has about an 80% success rate for stopping bleeding, but bleeding recurs in about 50% of patients. Also, there is a risk of hypertension and coronary ischemia. Furthermore, angiography can be used to localize the source of bleeding more accurately. Surgery may be used in patients with continued bleeding (requiring > 4 units transfusion/24 h), but localization of the bleeding site is very important. Blind hemicolectomy (with no preoperative identification of the bleeding site) carries a much higher mortality risk than does directed segmental resection. However, assessment must be expeditious so that surgery is not unnecessarily delayed.

Acute or chronic bleeding of internal hemorrhoids stops spontaneously in most cases. Patients with refractory bleeding are treated via anoscopy with rubber band ligation, injection, coagulation, or surgery.

Geriatrics Essentials

In the elderly, hemorrhoids and colorectal cancer are the most common causes of minor bleeding. Peptic ulcer, diverticular disease, and angiodysplasia are the most common causes of major bleeding. Variceal bleeding is less common than in younger patients.

Massive GI bleeding is tolerated poorly by elderly patients. Diagnosis must be made quickly, and treatment must be started sooner than in younger patients, who can better tolerate repeated episodes of bleeding.

Key Points

• Rectal bleeding may result from upper or lower GI bleeding.

• Orthostatic changes in vital signs are unreliable markers for serious bleeding.

• About 80% of patients stop bleeding spontaneously; various endoscopic techniques are usually the first choice for the remainder.

Varices

Varices are dilated veins in the distal esophagus or proximal stomach caused by elevated pressure in the portal venous system, typically from cirrhosis. They may bleed massively but cause no other symptoms. Diagnosis is by upper endoscopy. Treatment is primarily with endoscopic banding and IV octreotide. Sometimes a transjugular intrahepatic portosystemic shunting procedure is needed.

Portal hypertension (see p. 218) results from a number of conditions, predominantly liver cirrhosis. If portal pressure remains higher than inferior vena caval pressure for a significant period, venous collaterals develop. The most dangerous collaterals occur in the distal esophagus and gastric fundus, causing engorged, serpentine submucosal vessels known as varices. These varices partially decompress portal hypertension but can rupture, causing massive GI bleeding. The trigger for variceal rupture is unknown, but bleeding almost never occurs unless the portal/systemic pressure gradient is > 12 mm Hg. Coagulopathies caused by liver disease may facilitate bleeding. NGT passage in a patient with varices has not been shown to trigger bleeding.

Symptoms and Signs

Patients typically present with sudden, painless, upper GI bleeding, often massive. Signs of shock may be present. Bleeding is usually from the distal esophagus, less often from the gastric fundus. Bleeding from gastric varices also may be acute but is more often subacute or chronic.

Bleeding into the GI tract may precipitate portal-systemic encephalopathy in patients with impaired hepatic function.

Diagnosis

• Endoscopy

• Evaluation for coagulopathy

Both esophageal and gastric varices are best diagnosed by endoscopy, which may also identify varices at high risk of bleeding (eg, those with red markings). Endoscopy is also critical to exclude other causes of acute bleeding (eg, peptic ulcer), even in patients known to have varices; perhaps as many as one third of patients with known varices who have upper GI bleeding have a nonvariceal source.

Because varices are typically associated with significant hepatic disease, evaluation for possible coagulopathy is important. Laboratory tests include CBC with platelets, PT, PTT, and liver function tests.

Bleeding patients should have type and crossmatch for 6 units of packed RBCs.

Prognosis

In about 80% of patients, variceal bleeding stops spontaneously. Nevertheless, mortality is high, often > 50%. Mortality depends primarily on severity of the associated liver disease rather than on the bleeding itself. Bleeding is often fatal in patients with severe hepatocellular impairment (eg, advanced cirrhosis), whereas patients with good hepatic reserve usually recover.

Surviving patients are at high risk of further variceal bleeding; typically, 50 to 75% have recurrence within 1 to 2 yr. Ongoing endoscopic or drug therapy significantly lowers this risk, but the overall effect on long-term mortality seems to be marginal, probably because of the underlying hepatic disease.

Treatment

• Fluid resuscitation

• Endoscopic banding (sclerotherapy second choice)

• IV octreotide

• Possibly a transjugular intrahepatic portosystemic shunting (TIPS) procedure

Management of hypovolemia and hemorrhagic shock is as described above and in Ch. 226. Patients with coagulation abnormalities (eg, elevated INR) should be given 1 to 2 units of fresh frozen plasma and 2.5 to 10 mg vitamin K IM (or IV if severe).

Because varices are invariably diagnosed during endoscopy, primary treatment is endoscopic. Endoscopic banding of varices is preferred over injection sclerotherapy. At the same time, IV octreotide (a synthetic analog of somatostatin, which may also be used) should be given. Octreotide increases splanchnic vascular resistance by inhibiting the release of splanchnic vasodilator hormones (eg, glucagon, vasoactive intestinal peptide). The usual dose is a 50 µg IV bolus, followed by infusion of 50 µg/h. Octreotide is preferred over previously used agents such as vasopressin and terlipressin, because it has fewer adverse effects.

If bleeding continues or recurs despite these measures, emergency techniques to shunt blood from the portal system to the vena cava can lower portal pressure and diminish bleeding. A TIPS procedure is the emergency intervention of choice. TIPS is an invasive radiologic procedure in which a guidewire is passed from the vena cava through the liver parenchyma into the portal circulation. The resultant passage is dilated by a balloon catheter, and a metallic stent is inserted, creating a bypass between the portal and hepatic venous circulations. Stent size is crucial. If the stent is too large, portal-systemic encephalopathy results because of diversion of too much portal blood flow from the liver. If the stent is too small, it is more likely to occlude. Surgical portacaval shunts, such as the distal spleno-renal shunt, work by a similar mechanism but are more invasive and have a higher immediate mortality.

Mechanical compression of bleeding varices with a Sengstaken-Blakemore tube or one of its variants causes considerable morbidity and should not be used as primary management. However, such a tube may provide life-saving tamponade pending decompression with a TIPS or surgical procedure. The tube is a flexible NGT with one gastric balloon and one esophageal balloon. After insertion, the gastric balloon is inflated with a fixed volume of air, and traction is applied to the tube to pull the balloon snugly against the gastroesophageal junction. This balloon is often sufficient to control bleeding, but if not, the esophageal balloon is inflated to a pressure of 25 mm Hg. The procedure is quite uncomfortable and may result in esophageal perforation and aspiration; thus, endotracheal intubation and IV sedation are often recommended.

Liver transplantation can also decompress the portal system but is a practical option only for patients already on a transplant list.

Long-term medical therapy of portal hypertension (with β-blockers and nitrates) is discussed elsewhere (see p. 219). Treatment of portal-systemic encephalopathy may be needed (see p. 220).

Vascular GI Lesions

Several distinct congenital or acquired syndromes involve abnormal mucosal or submucosal blood vessels in the GI tract. These vessels may cause recurrent bleeding, which is rarely massive. Diagnosis is by endoscopy and sometimes angiography. Treatment is endoscopic hemostasis; occasionally, angiographic embolization or surgical resection may be needed.

Vascular ectasias (angiodysplasias, arteriovenous malformations) are dilated, tortuous vessels that typically develop in the cecum and ascending colon. They occur mainly in people > 60 and are the most common cause of lower GI bleeding in that age group. They are thought to be degenerative and do not occur in association with other vascular abnormalities. Most patients have 2 or 3 lesions, which are typically 0.5 to 1.0 cm, bright red, flat or slightly raised, and covered by very thin epithelium. Vascular ectasias also occur in association with a number of systemic diseases (eg, renal failure, cirrhosis, CREST syndrome [calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias]—see p. 310) and after radiation to the bowel.

Gastric antral vascular ectasia (watermelon stomach) consists of large dilated veins running linearly along the stomach, creating a striped appearance suggestive of a watermelon. The condition occurs mainly in older women and is of unknown etiology.

Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome—see also p. 982) is an autosomal dominant disorder that causes multiple vascular lesions in various parts of the body, including the entire GI tract. GI bleeding rarely occurs before age 40.

Dieulafoy's lesion is an abnormally large artery that penetrates the gut wall, occasionally eroding through the mucosa and causing massive bleeding. It occurs mainly in the proximal stomach.

Arteriovenous malformations and **hemangiomas**, both congenital disorders of blood vessels, can occur in the GI tract but are rare.

Symptoms and Signs

Vascular lesions are painless. Patients often present with heme-positive stools or modest amounts of bright red blood from the rectum. Bleeding is often intermittent, sometimes with long periods between episodes. Patients with upper GI lesions may present with melena. Major bleeding is unusual.

Diagnosis

• Endoscopy

Vascular lesions are most commonly diagnosed endoscopically. If routine endoscopy is nondiagnostic, small-bowel endoscopy, capsule endoscopy, intraoperative endoscopy, or visceral angiography may be required. ^{99m}Tc-labeled RBC scans are less specific but may help localize the lesion enough to facilitate endoscopy or angiography.

Treatment

• Endoscopic coagulation

Endoscopic coagulation (with heater probe, laser, argon plasma, or bipolar electrocoagulation) is effective for many vascular lesions. Vascular ectasias often recur, although there is some evidence that oral estrogen-progesterone combinations may limit recurrence.

Mild recurrent bleeding can be treated simply with chronic iron therapy. More significant bleeding that is

unresponsive to endoscopic measures may require angiographic embolization or surgical resection. However, rebleeding occurs in about 15 to 25% of surgically treated patients.

Chapter 11. Acute Abdomen and Surgical Gastroenterology

Introduction

Acute abdomen refers to abdominal symptoms and signs of such severity or concern that disorders requiring surgery should be considered. The primary symptom is acute abdominal pain. Chronic abdominal pain is discussed in Ch. 7.

Acute Abdominal Pain

Abdominal pain is common and often inconsequential. Acute and severe abdominal pain, however, is almost always a symptom of intra-abdominal disease. It may be the sole indicator of the need for surgery and must be attended to swiftly: Gangrene and perforation of the gut can occur < 6 h from onset of symptoms in certain conditions (eg, interruption of the intestinal blood supply caused by a strangulating obstruction or an arterial embolus). Abdominal pain is of particular concern in patients who are very young or very old and those who have HIV infection or are taking immunosuppressants.

Textbook descriptions of abdominal pain have limitations because people react to pain differently. Some, particularly elderly people, are stoic, whereas others exaggerate their symptoms. Infants, young children, and some elderly people may have difficulty localizing the pain.

Pathophysiology

Visceral pain comes from the abdominal viscera, which are innervated by autonomic nerve fibers and respond mainly to the sensations of distention and muscular contraction—not to cutting, tearing, or local irritation. Visceral pain is typically vague, dull, and nauseating. It is poorly localized and tends to be referred to areas corresponding to the embryonic origin of the affected structure. Foregut structures (stomach, duodenum, liver, and pancreas) cause upper abdominal pain. Midgut structures (small bowel, proximal colon, and appendix) cause periumbilical pain. Hindgut structures (distal colon and GU tract) cause lower abdominal pain.

Somatic pain comes from the parietal peritoneum, which is innervated by somatic nerves, which respond to irritation from infectious, chemical, or other inflammatory processes. Somatic pain is sharp and well localized.

Referred pain is pain perceived distant from its source and results from convergence of nerve fibers at the spinal cord. Common examples of referred pain are scapular pain due to biliary colic, groin pain due to renal colic, and shoulder pain due to blood or infection irritating the diaphragm.

Peritonitis: Peritonitis is inflammation of the peritoneal cavity. The most serious cause is perforation of the GI tract (see p. 111), which causes immediate chemical inflammation followed shortly by infection from intestinal organisms. Peritonitis can also result from any abdominal condition that causes marked inflammation (eg, appendicitis, diverticulitis, strangulating intestinal obstruction, pancreatitis, pelvic inflammatory disease, mesenteric ischemia). Intraperitoneal blood from any source (eg, ruptured aneurysm, trauma, surgery, ectopic pregnancy) is irritating and results in peritonitis. Barium causes severe peritonitis and should never be given to a patient with suspected GI tract perforation. Peritoneo-systemic shunts, drains, and dialysis catheters in the peritoneal cavity predispose a patient to infectious peritonitis, as does ascitic fluid. Rarely, spontaneous bacterial peritonitis occurs, in which the peritoneal cavity is infected by blood-borne bacteria.

Peritonitis causes fluid shift into the peritoneal cavity and bowel, leading to severe dehydration and electrolyte disturbances. Adult respiratory distress syndrome can develop rapidly. Kidney failure, liver failure, and disseminated intravascular coagulation follow. The patient's face becomes drawn into the masklike appearance typical of hippocratic facies. Death occurs within days.

Etiology

Many intra-abdominal disorders cause abdominal pain (see

Fig. 11-1); some are trivial but some are immediately life threatening, requiring rapid diagnosis and surgery. These include ruptured abdominal aortic aneurysm (AAA), perforated viscus, mesenteric ischemia, and ruptured ectopic pregnancy. Others (eg, intestinal obstruction, appendicitis, severe acute pancreatitis) are also serious and nearly as urgent. Several extra-abdominal disorders also cause abdominal pain (see
Table 11-1).

Abdominal pain in neonates, infants, and young children has numerous causes not encountered in adults, including meconium peritonitis, pyloric stenosis, esophageal webs, volvulus of a gut with a common mesentery, imperforate anus, intussusception, and intestinal obstruction caused by atresia.

Evaluation

Evaluation of mild and severe pain follows the same process, although with severe abdominal pain, therapy sometimes proceeds simultaneously and involves early consultation with a surgeon. History and physical examination usually exclude all but a few possible causes, with final diagnosis confirmed by judicious use of laboratory and imaging tests. Life-threatening causes should always be ruled out before focusing on less serious diagnoses. In seriously ill patients with severe abdominal pain, the most important diagnostic measure may be expeditious surgical exploration. In mildly ill patients, watchful waiting may be best.

History: A thorough history usually suggests the diagnosis (see
Table 11-2). Of particular importance are pain location (see Fig. 11-1) and characteristics, history of similar symptoms, and associated symptoms. Concomitant symptoms such as gastroesophageal reflux, nausea, vomiting, diarrhea, constipation, jaundice, melena, hematuria, hematemesis, weight loss, and mucus or blood in the stool help direct subsequent evaluation. A drug history should include details concerning prescription and illicit drug use as well as alcohol. Many drugs cause GI upset. Prednisone or immunosuppressants may inhibit the inflammatory response to perforation or peritonitis and result in less pain and leukocytosis than might otherwise be expected. Anticoagulants can increase the chances of bleeding and hematoma formation. Alcohol predisposes to pancreatitis.

Known medical conditions and previous abdominal surgeries are important to ascertain. Women should be asked whether they are pregnant.

Physical examination: The general appearance is important. A happy, comfortable-appearing patient rarely has a serious problem, unlike one who is anxious, pale, diaphoretic, or in obvious pain. BP, pulse, state of consciousness, and other signs of peripheral perfusion must be evaluated. However, the focus

[**Fig. 11-1.** Location of abdominal pain and possible causes.]

[**Table 11-1.** Extra-Abdominal Causes of Abdominal Pain]

of the examination is the abdomen, beginning with inspection and auscultation, followed by palpation and percussion. Rectal examination and pelvic examination (for women) to locate tenderness, masses, and blood are essential.

Palpation begins gently, away from the area of greatest pain, detecting areas of particular tenderness, as well as the presence of guarding, rigidity, and rebound (all suggesting peritoneal irritation) and any masses. Guarding is an involuntary contraction of the abdominal muscles that is slightly slower and more sustained than the rapid, voluntary flinch exhibited by sensitive or anxious patients. Rebound is a distinct flinch upon brisk withdrawal of the examiner's hand. The inguinal area and all surgical scars should be palpated for hernias.

Red flags: Certain findings raise suspicion of a more serious etiology:

• Severe pain

• Signs of shock (eg, tachycardia, hypotension, diaphoresis, confusion)

• Signs of peritonitis

• Abdominal distention

Interpretation of findings: Distention, especially when surgical scars, tympany to percussion, and high-pitched peristalsis or borborygmi in rushes are present, strongly suggests bowel obstruction. Severe pain in a patient with a silent abdomen who is lying as still as possible suggests peritonitis; location of tenderness suggests etiology (eg, right upper quadrant suggests cholecystitis, right lower quadrant suggests appendicitis) but may not be diagnostic. Back pain with shock suggests ruptured AAA, particularly if there is a tender, pulsatile mass. Shock and vaginal bleeding in a pregnant woman suggest ruptured ectopic pregnancy. Ecchymoses of the costovertebral angles (Grey Turner's sign) or around the umbilicus (Cullen's sign) suggest hemorrhagic pancreatitis but are not very sensitive for this disorder.

History is often suggestive (see Table 11-2). Mild to moderate pain in the presence of active peristalsis of normal pitch suggests a nonsurgical disease (eg, gastroenteritis) but may also be the early manifestations of a more serious disorder. A patient who is writhing around trying to get comfortable is more likely to have an obstructive mechanism (eg, renal or biliary colic).

Previous abdominal surgery makes obstruction from adhesions more likely. Generalized atherosclerosis increases the possibility of MI, AAA, and mesenteric ischemia. HIV infection makes infectious causes and drug adverse effects likely.

Testing: Tests are selected based on clinical suspicion.

• Urine pregnancy test for all women of childbearing age

• Selected imaging tests based on suspected diagnosis

Standard tests (eg, CBC, chemistries, urinalysis) are often done but are of little value due to poor specificity; patients with significant disease may have normal results. Abnormal results do not provide a specific diagnosis (the urinalysis in particular may show pyuria or hematuria in a wide variety of conditions), and they can also occur in the absence of significant disease. An exception is serum lipase, which strongly suggests a diagnosis of acute pancreatitis. A bedside urine pregnancy test should be done for all women of childbearing age because a negative result effectively excludes ruptured ectopic pregnancy.

An abdominal series, consisting of flat and upright abdominal x-rays and upright chest x-rays (left lateral recumbent abdomen and anteroposterior chest x-ray for patients unable to stand), should be done when perforation or obstruction is suspected. However, these plain x-rays are seldom diagnostic for other conditions and need not be automatically done. Ultrasound should be done for suspected biliary tract disease or ectopic pregnancy (transvaginal

[**Table 11-2.** History in Patients with Acute Abdominal Pain]

probe). Ultrasound can also detect AAA but cannot reliably identify rupture. Noncontrast helical CT is the modality of choice for suspected renal stones. CT with oral contrast is diagnostic in about 95% of patients with significant abdominal pain and has markedly lowered the negative laparotomy rate. However, advanced imaging must not be allowed to delay surgery in patients with definitive symptoms and signs.

Treatment

Some clinicians feel that providing pain relief before a diagnosis is made interferes with their ability to evaluate. However, moderate doses of IV analgesics (eg, fentanyl 50 to 100 µg, morphine 4 to 6 mg) do not mask peritoneal signs and, by diminishing anxiety and discomfort, often make examination easier.

Key Points

• Life-threatening causes should be looked for first.

• Pregnancy should be ruled out in women of childbearing age.

• Signs of peritonitis, shock, and obstruction should be sought.

• Blood tests are of minimal value.

Acute Mesenteric Ischemia

Acute mesenteric ischemia is interruption of intestinal blood flow by embolism, thrombosis, or a low-flow state. It leads to mediator release, inflammation, and ultimately infarction. Abdominal pain is out of proportion to physical findings. Early diagnosis is difficult, but angiography and exploratory laparotomy have the most sensitivity; other imaging modalities often become positive only late in the disease. Treatment is by embolectomy, revascularization of viable segments, or resection; sometimes vasodilator therapy is successful. Mortality is high.

Pathophysiology

The intestinal mucosa has a high metabolic rate and, accordingly, a high blood flow requirement (normally receiving 20 to 25% of cardiac output), making it very sensitive to the effects of decreased perfusion. Ischemia disrupts the mucosal barrier, allowing release of bacteria, toxins, and vasoactive mediators, which in turn leads to myocardial depression, systemic inflammatory response syndrome (see p. 2299), multisystem organ failure, and death. Mediator release may occur even before complete infarction. Necrosis can occur as soon as 10 to 12 h after the onset of symptoms.

Three major vessels serve the abdominal contents: the celiac trunk, the superior mesenteric artery (SMA), and the inferior mesenteric artery (IMA). The celiac trunk supplies the esophagus, stomach, proximal duodenum, liver, gallbladder, pancreas, and spleen. The SMA supplies the distal duodenum, jejunum, ileum, and colon to the splenic flexure. The IMA supplies the descending colon and sigmoid colon and the rectum. Collateral vessels are abundant in the stomach, duodenum, and rectum; these areas rarely develop ischemia. The splenic flexure is a watershed between the SMA and IMA and is at particular risk of ischemia.

Etiology

Mesenteric blood flow may be disrupted on either the venous or arterial sides. In general, patients > 50 are at greatest risk and have the types of occlusions and risk factors shown in Table 11-3. However, many patients have no identifiable risk factors.

Symptoms and Signs

The early hallmark of mesenteric ischemia is severe pain but minimal physical findings. The abdomen remains soft, with little or no tenderness. Mild tachycardia may be present. Later, as necrosis develops, signs of peritonitis appear, with marked abdominal tenderness, guarding, rigidity, and no bowel sounds. The stool may be heme-positive (increasingly likely as ischemia progresses). The usual signs of shock develop and are frequently followed by death.

Sudden onset of pain suggests but is not diagnostic of an arterial embolism, whereas a more gradual onset is typical of venous thrombosis. Patients with a history of postprandial abdominal discomfort (which suggests intestinal angina) may have arterial thrombosis.

[**Table 11-3.** Causes of Acute Mesenteric Ischemia]

Diagnosis

• Clinical diagnosis more important than diagnostic tests

• Mesenteric angiography if diagnosis unclear

Early diagnosis is particularly important because mortality increases significantly once intestinal infarction has occurred. Mesenteric ischemia must be considered in any patient > 50 with known risk factors or predisposing conditions who develops sudden, severe abdominal pain.

Patients with clear peritoneal signs should proceed directly to the operating room for both diagnosis and treatment. For others, selective mesenteric angiography is the diagnostic procedure of choice. Other imaging studies and serum markers can show abnormalities but lack sensitivity and specificity early in the course of the disease when diagnosis is most critical. Plain abdominal x-rays are useful mainly in ruling out other causes of pain (eg, perforated viscus), although portal venous gas or pneumatosis intestinalis may be seen late in the disease. These findings also appear on CT, which may also directly visualize vascular occlusion—more accurately on the venous side. Doppler ultrasonography can sometimes identify arterial occlusion, but sensitivity is low. MRI is very accurate in proximal vascular occlusion, less so in distal vascular occlusion. Serum markers (eg, creatine kinase, lactate) rise with necrosis but are nonspecific findings that are seen later. Intestinal fatty acid binding protein in the urine may prove valuable in the future as an early marker.

Prognosis

If diagnosis and treatment take place before infarction occurs, mortality is low; after intestinal infarction, mortality approaches 70 to 90%. For this reason, clinical diagnosis of mesenteric ischemia should supersede diagnostic tests, which may delay treatment.

Treatment

• Surgical: Embolectomy, revascularization, or resection

• Angiographic: Vasodilators or thrombolysis

• Long-term anticoagulation or antiplatelet therapy

If diagnosis is made during exploratory laparotomy, options are surgical embolectomy, revascularization, and resection. A "second look" laparotomy may be needed to reassess the viability of questionable areas of bowel. If diagnosis is made by angiography, infusion of the vasodilator papaverine through the angiography catheter may improve survival in both occlusive and nonocclusive ischemia. A 60-mg bolus is given over 2 min, followed by an infusion of 30 to 60 mg/h. Papaverine is useful even when surgical intervention is planned and is sometimes given during and after surgical intervention as well. In addition, for arterial occlusion, thrombolysis or surgical embolectomy may be done. The development of peritoneal signs at any time during the evaluation suggests the need for immediate surgery. Mesenteric venous thrombosis without signs of peritonitis can be treated with papaverine followed by anticoagulation with heparin and then warfarin.

Patients with arterial embolism or venous thrombosis require long-term anticoagulation with warfarin. Patients with nonocclusive ischemia may be treated with antiplatelet therapy.

Acute Perforation

Any part of the GI tract may become perforated, releasing gastric or intestinal contents into the peritoneal space. Causes vary. Symptoms develop suddenly, with severe pain followed shortly by signs of shock. Diagnosis is usually made by the presence of free air in the abdomen on imaging studies. Treatment is with fluid resuscitation, antibiotics, and surgery. Mortality is high, varying with the underlying disorder and the patient's general health.

Etiology

Both blunt and penetrating trauma can result in perforation of any part of the GI tract (see Table 11-4). Swallowed foreign bodies, even sharp ones, rarely cause perforation unless they become

impacted, causing ischemia and necrosis from local pressure. Foreign bodies inserted via the anus may perforate the rectum.

Symptoms and Signs

Esophageal, gastric, and duodenal perforation tends to manifest suddenly and catastrophically, with abrupt onset of acute abdomen with severe generalized abdominal pain, tenderness, and peritoneal signs. Pain may radiate to the shoulder.

Perforation at other GI sites often occurs in the setting of other painful, inflammatory conditions. Because such perforations are often small initially and frequently walled off by the omentum, pain often develops gradually and may be localized. Tenderness also is more focal. Such findings can make it difficult to distinguish perforation from worsening of the underlying disorder or lack of response to treatment.

In all types of perforation, nausea, vomiting, and anorexia are common. Bowel sounds are quiet to absent.

Diagnosis

• Abdominal series

• If nondiagnostic, abdominal CT

An abdominal series (supine and upright abdominal x-rays and chest x-rays) may be diagnostic, showing free air under the diaphragm in 50 to 75% of cases. As time passes, this sign becomes more common. A lateral chest x-ray is more sensitive for free air than a posteroanterior x-ray. If the abdominal series is nondiagnostic, abdominal CT usually with oral and IV and/or rectal contrast may be helpful. Barium should not be used if perforation is suspected.

Treatment

• Surgery

• IV fluids and antibiotics

[Table 11-4. Some Causes of GI Tract Perforation]

If a perforation is noted, immediate surgery is necessary because mortality caused by peritonitis increases rapidly the longer treatment is delayed. If an abscess or an inflammatory mass has formed, the procedure may be limited to drainage of the abscess.

An NGT is inserted before operation. Patients with signs of volume depletion should have urine output monitored with a catheter. Fluid status is maintained by adequate IV fluid and electrolyte replacement. IV antibiotics effective against intestinal flora should be given (eg, cefotetan 1 to 2 g bid, or amikacin 5 mg/kg tid plus clindamycin 600 to 900 mg qid).

Appendicitis

Appendicitis is acute inflammation of the vermiform appendix, typically resulting in abdominal pain, anorexia, and abdominal tenderness. Diagnosis is clinical, often supplemented by CT or ultrasound. Treatment is surgical removal.

In the US, acute appendicitis is the most common cause of acute abdominal pain requiring surgery. Over 5% of the population develops appendicitis at some point. It most commonly occurs in the teens and 20s but may occur at any age.

Other conditions affecting the appendix include carcinoids, cancer, villous adenomas, and diverticula. The appendix may also be affected by Crohn's disease or ulcerative colitis with pancolitis.

Etiology

Appendicitis is thought to result from obstruction of the appendiceal lumen, typically by lymphoid hyperplasia, but occasionally by a fecalith, foreign body, or even worms. The obstruction leads to distention, bacterial overgrowth, ischemia, and inflammation. If untreated, necrosis, gangrene, and perforation occur. If the perforation is contained by the omentum, an appendiceal abscess results.

Symptoms and Signs

The classic symptoms of acute appendicitis are epigastric or periumbilical pain followed by brief nausea, vomiting, and anorexia; after a few hours, the pain shifts to the right lower quadrant. Pain increases with cough and motion. Classic signs are right lower quadrant direct and rebound tenderness located at McBurney's point (junction of the middle and outer thirds of the line joining the umbilicus to the anterior superior spine). Additional signs are pain felt in the right lower quadrant with palpation of the left lower quadrant (Rovsing sign), an increase in pain from passive extension of the right hip joint that stretches the iliopsoas muscle (psoas sign), or pain caused by passive internal rotation of the flexed thigh (obturator sign). Low-grade fever (rectal temperature 37.7 to 38.3° C [100 to 101° F]) is common.

Unfortunately, these classic findings appear in < 50% of patients. Many variations of symptoms and signs occur. Pain may not be localized, particularly in infants and children. Tenderness may be diffuse or, in rare instances, absent. Bowel movements are usually less frequent or absent; if diarrhea is a sign, a retrocecal appendix should be suspected. RBCs or WBCs may be present in the urine. Atypical symptoms are common among elderly patients and pregnant women; in particular, pain is less severe and local tenderness is less marked.

Diagnosis

• Clinical evaluation

• Abdominal CT if necessary

• Ultrasound an option to CT

When classic symptoms and signs are present, the diagnosis is clinical. In such patients, delaying laparotomy to do imaging tests only increases the likelihood of perforation and subsequent complications. In patients with atypical or equivocal findings, imaging studies should be done without delay. Contrast-enhanced CT has reasonable accuracy in diagnosing appendicitis and can also reveal other causes of an acute abdomen. Graded compression ultrasound can usually be done quickly and uses no radiation (of particular concern in children); however, it is occasionally limited by the presence of bowel gas and is less useful for recognizing nonappendiceal causes of pain. Appendicitis remains primarily a clinical diagnosis. Selective and judicious use of radiographic studies may reduce the rate of negative laparotomy.

Laparoscopy can be used for diagnosis as well as definitive treatment; it may be especially helpful in women with lower abdominal pain of unclear etiology. Laboratory studies typically show leukocytosis (12,000 to 15,000/µL), but this finding is highly variable; a normal WBC count should not be used to exclude appendicitis.

Prognosis

Without surgery or antibiotics, mortality is > 50%.

With early surgery, the mortality rate is < 1%, and convalescence is normally rapid and complete. With complications (rupture and development of an abscess or peritonitis), the prognosis is worse: Repeat operations and a long convalescence may follow.

Treatment

• Surgical removal

• IV fluids and antibiotics

Treatment of acute appendicitis is open or laparoscopic appendectomy; because treatment delay increases mortality, a negative appendectomy rate of 15% is considered acceptable. The surgeon can usually remove the appendix even if perforated. Occasionally, the appendix is difficult to locate: In these cases, it usually lies behind the cecum or the ileum and mesentery of the right colon. A contraindication to appendectomy is inflammatory bowel disease involving the cecum. However, in cases of terminal ileitis and a normal cecum, the appendix should be removed.

Appendectomy should be preceded by IV antibiotics. Third-generation cephalosporins are preferred. For nonperforated appendicitis, no further antibiotics are required. If the appendix is perforated, antibiotics should be continued until the patient's temperature and WBC count have normalized or continued for a fixed course, according to the surgeon's preference. If surgery is impossible, antibiotics—although not curative—markedly improve the survival rate. When a large inflammatory mass is found involving the appendix, terminal ileum, and cecum, resection of the entire mass and ileocolostomy are preferable. In late cases in which a pericolic abscess has already formed, the abscess is drained either by an ultrasound-guided percutaneous catheter or by open operation (with appendectomy to follow at a later date). A Meckel's diverticulum in a patient under the age of 40 should be removed concomitantly with the appendectomy unless extensive inflammation around the appendix prevents the procedure.

Hernias of the Abdominal Wall

A hernia of the abdominal wall is a protrusion of the abdominal contents through an acquired or congenital area of weakness or defect in the wall. Many hernias are asymptomatic, but some become incarcerated or strangulated, causing pain and requiring immediate surgery. Diagnosis is clinical. Treatment is elective surgical repair.

Abdominal hernias are extremely common, particularly among males, necessitating about 700,000 operations each year in the US.

Classification

Abdominal hernias are classified as either abdominal wall or groin hernias. Strangulated hernias are ischemic from physical constriction of their blood supply. Gangrene, perforation, and peritonitis may develop. Incarcerated and strangulated hernias cannot be reduced manually.

Abdominal wall hernias include umbilical hernias, epigastric hernias, Spigelian hernias, and incisional (ventral) hernias. Umbilical hernias (protrusions through the umbilical ring) are mostly congenital, but some are acquired in adulthood secondary to obesity, ascites, pregnancy, or chronic peritoneal dialysis. Epigastric hernias occur through the linea alba. Spigelian hernias occur through defects in the transversus abdominis muscle lateral to the rectus sheath, usually below the level of the umbilicus. Incisional hernias occur through an incision from previous abdominal surgery.

Groin hernias include inguinal hernias and femoral hernias. Inguinal hernias occur above the inguinal ligament. Indirect inguinal hernias traverse the internal inguinal ring into the inguinal canal, and direct inguinal hernias extend directly forward and do not pass through the inguinal canal. Femoral hernias occur below the inguinal ligament and go into the femoral canal.

About 75% of all abdominal hernias are inguinal. Incisional hernias comprise another 10 to 15%. Femoral and unusual hernias account for the remaining 10 to 15%.

Symptoms and Signs

Most patients complain only of a visible bulge, which may cause vague discomfort or be asymptomatic. Most hernias, even large ones, can be manually reduced with persistent gentle pressure; placing the patient in the Trendelenburg position may help. An incarcerated hernia cannot be reduced but has no

additional symptoms. A strangulated hernia causes steady, gradually increasing pain, typically with nausea and vomiting. The hernia itself is tender, and the overlying skin may be erythematous; peritonitis may develop depending on location, with diffuse tenderness, guarding, and rebound.

Diagnosis

• Clinical evaluation

The diagnosis is clinical. Because the hernia may be apparent only when abdominal pressure is increased, the patient should be examined in a standing position. If no hernia is palpable, the patient should cough or perform a Valsalva maneuver as the examiner palpates the abdominal wall. Examination focuses on the umbilicus, the inguinal area (with a finger in the inguinal canal in males), the femoral triangle, and any incisions that are present.

Inguinal masses that resemble hernias may be the result of adenopathy (infectious or malignant), an ectopic testis, or lipoma. These masses are solid and are not reducible. A scrotal mass may be a varicocele, hydrocele, or testicular tumor. Ultrasound may be done if physical examination is equivocal.

Prognosis

Congenital umbilical hernias rarely strangulate and are not treated; most resolve spontaneously within several years. Very large defects may be repaired electively after age 2 yr. Umbilical hernias in adults cause cosmetic concerns and can be electively repaired; strangulation and incarceration are unusual but, if happen, usually contain omentum rather than intestine.

Treatment

• Surgical repair

Groin hernias should be repaired electively because of the risk of strangulation, which results in higher morbidity (and possible mortality in elderly patients). Repair may be through a standard incision or laparoscopically.

An incarcerated or strangulated hernia of any kind requires urgent surgical repair.

Ileus

(Paralytic Ileus; Adynamic Ileus; Paresis)

Ileus is a temporary arrest of intestinal peristalsis. It occurs most commonly after abdominal surgery, particularly when the intestines have been manipulated. Symptoms are nausea, vomiting, and vague abdominal discomfort. Diagnosis is based on x-ray findings and clinical impression. Treatment is supportive, with nasogastric suction and IV fluids.

Etiology

In addition to postoperative causes, ileus also results from intraperitoneal or retroperitoneal inflammation (eg, appendicitis, diverticulitis, perforated duodenal ulcer), retroperitoneal or intra-abdominal hematomas (eg, ruptured abdominal aortic aneurysm, lumbar compression fracture), metabolic disturbances (eg, hypokalemia), or drugs (eg, opioids, anticholinergics, sometimes Ca channel blockers). Ileus sometimes occurs in association with renal or thoracic disease (eg, lower rib fractures, lower lobe pneumonias, MI).

Gastric and colonic motility disturbances after abdominal surgery are common. The small bowel is typically least affected, with motility and absorption returning to normal within hours after surgery. Stomach emptying is usually impaired for about 24 h or more. The colon is often most affected and may remain inactive for 48 to 72 h or more.

Symptoms and Signs

Symptoms and signs include abdominal distention, vomiting, and vague discomfort. Pain rarely has the classic colicky pattern present in mechanical obstruction. There may be obstipation or passage of slight amounts of watery stool. Auscultation reveals a silent abdomen or minimal peristalsis. The abdomen is not tender unless the underlying cause is inflammatory.

Diagnosis

• Clinical evaluation

• Sometimes x-rays

The most essential task is to distinguish ileus from intestinal obstruction. In both conditions, x-rays show gaseous distention of isolated segments of intestine. In postoperative ileus, however, gas may accumulate more in the colon than in the small bowel. Postoperative accumulation of gas in the small bowel often implies development of a complication (eg, obstruction, peritonitis). In other types of ileus, x-ray findings are similar to obstruction; differentiation can be difficult unless clinical features clearly favor one or the other. Water-soluble contrast studies may help differentiate.

Treatment

• NGT

• IV fluids

Treatment involves continuous nasogastric suction, npo status, IV fluids and electrolytes, a minimal amount of sedatives, and avoidance of opioids and anticholinergic drugs. Maintaining an adequate serum K level (> 4 mEq/L [> 4 mmol/L]) is especially important. Ileus persisting > 1 wk probably has a mechanical obstructive cause, and laparotomy should be considered. Sometimes colonic ileus can be relieved by colonoscopic decompression; rarely, cecostomy is required. Colonoscopic decompression is helpful in treating pseudo-obstruction (Ogilvie's syndrome), which consists of apparent obstruction at the splenic flexure, although no cause can be found by contrast enema or colonoscopy for the failure of gas and feces to pass this point. Some clinicians use IV neostigmine (requires cardiac monitoring) to treat Ogilvie's syndrome.

Intestinal Obstruction

Intestinal obstruction is significant mechanical impairment or complete arrest of the passage of contents through the intestine. Symptoms include cramping pain, vomiting, obstipation, and lack of flatus. Diagnosis is clinical, confirmed by abdominal x-rays. Treatment is fluid resuscitation, nasogastric suction, and, in most cases of complete obstruction, surgery.

Mechanical obstruction is divided into obstruction of the small bowel (including the duodenum) and obstruction of the large bowel. Obstruction may be partial or complete. About 85% of partial small-bowel obstructions resolve with nonoperative treatment, whereas about 85% of complete small-bowel obstructions require operation.

Etiology

Overall, the most common causes of mechanical obstruction are adhesions, hernias, and tumors. Other general causes are diverticulitis, foreign bodies (including gallstones), volvulus (twisting of bowel on its mesentery), intussusception (telescoping of one segment of bowel into another—see p. 2801), and fecal impaction. Specific segments of the intestine are affected differently (see Table 11-5).

Pathophysiology

In simple mechanical obstruction, blockage occurs without vascular compromise. Ingested fluid and food,

digestive secretions, and gas accumulate above the obstruction. The proximal bowel distends, and the distal segment collapses. The normal secretory and absorptive functions of the mucosa are depressed, and the bowel wall becomes edematous and congested. Severe intestinal distention is self-perpetuating and progressive, intensifying

[Table 11-5. Causes of Intestinal Obstruction]

the peristaltic and secretory derangements and increasing the risks of dehydration and progression to strangulating obstruction.

Strangulating obstruction is obstruction with compromised blood flow; it occurs in nearly 25% of patients with small-bowel obstruction. It is usually associated with hernia, volvulus, and intussusception. Strangulating obstruction can progress to infarction and gangrene in as little as 6 h. Venous obstruction occurs first, followed by arterial occlusion, resulting in rapid ischemia of the bowel wall. The ischemic bowel becomes edematous and infarcts, leading to gangrene and perforation. In large-bowel obstruction, strangulation is rare (except with volvulus).

Perforation may occur in an ischemic segment (typically small bowel) or when marked dilation occurs. The risk is high if the cecum is dilated to a diameter ≥ 13 cm. Perforation of a tumor or a diverticulum may also occur at the obstruction site.

Symptoms and Signs

Obstruction of the small bowel causes symptoms shortly after onset: abdominal cramps centered around the umbilicus or in the epigastrium, vomiting, and—in patients with complete obstruction—obstipation. Patients with partial obstruction may develop diarrhea. Severe, steady pain suggests that strangulation has occurred. In the absence of strangulation, the abdomen is not tender. Hyperactive, high-pitched peristalsis with rushes coinciding with cramps is typical. Sometimes, dilated loops of bowel are palpable. With infarction, the abdomen becomes tender and auscultation reveals a silent abdomen or minimal peristalsis. Shock and oliguria are serious signs that indicate either late simple obstruction or strangulation.

Obstruction of the large bowel usually causes milder symptoms that develop more gradually than those caused by small-bowel obstruction. Increasing constipation leads to obstipation and abdominal distention. Vomiting may occur (usually several hours after onset of other symptoms) but is not common. Lower abdominal cramps unproductive of feces occur. Physical examination typically shows a distended abdomen with loud borborygmi. There is no tenderness, and the rectum is usually empty. A mass corresponding to the site of an obstructing tumor may be palpable. Systemic symptoms are relatively mild, and fluid and electrolyte deficits are uncommon.

Volvulus often has an abrupt onset. Pain is continuous, sometimes with superimposed waves of colicky pain.

Diagnosis

• Abdominal series

Supine and upright abdominal x-rays should be taken and are usually adequate to diagnose obstruction. Although only laparotomy can definitively diagnose strangulation, careful serial clinical examination may provide early warning. Elevated WBCs and acidosis may indicate that strangulation has already occurred.

On plain x-rays, a ladderlike series of distended small-bowel loops is typical of small-bowel obstruction but may also occur with obstruction of the right colon. Fluid levels in the bowel can be seen in upright views. Similar, although perhaps less dramatic, x-ray findings and symptoms occur in ileus (paralysis of the intestine without obstruction—see p. 114); differentiation can be difficult. Distended loops and fluid levels may be absent with an obstruction of the upper jejunum or with closed-loop strangulating obstructions (as may occur with volvulus). Infarcted bowel may produce a mass effect on x-ray. Gas in the bowel wall (pneumatosis intestinalis) indicates gangrene.

In large-bowel obstruction, abdominal x-ray shows distention of the colon proximal to the obstruction. In cecal volvulus, there may be a large gas bubble in the mid-abdomen or left upper quadrant. With both cecal and sigmoidal volvulus, a contrast enema shows the site of obstruction by a typical "bird-beak" deformity at the site of the twist; the procedure may actually reduce a sigmoid volvulus. If contrast enema is not done, colonoscopy can be used to decompress a sigmoid volvulus but rarely works with a cecal volvulus.

Treatment

• Nasogastric suction

• IV fluids

• IV antibiotics if bowel ischemia suspected

Patients with possible intestinal obstruction should be hospitalized. Treatment of acute intestinal obstruction must proceed simultaneously with diagnosis. A surgeon should always be involved.

Supportive care is similar for small- and large-bowel obstruction: nasogastric suction, IV fluids (0.9% saline or lactated Ringer's solution for intravascular volume repletion), and a urinary catheter to monitor fluid output. Electrolyte replacement should be guided by test results, although in cases of repeated vomiting serum Na and K are likely to be depleted. If bowel ischemia or infarction is suspected, antibiotics should be given (eg, a 3rd-generation cephalosporin, such as cefotetan 2 g IV) before laparotomy.

Specific measures: Obstruction of the duodenum in adults is treated by resection or, if the lesion cannot be removed, palliative gastrojejunostomy (for treatment in children, see p. 2978).

Complete obstruction of the small bowel is preferentially treated with early laparotomy, although surgery can be delayed 2 or 3 h to improve fluid status and urine output in a very ill, dehydrated patient. The offending lesion is removed whenever possible. If a gallstone is the cause of obstruction, it is removed through an enterotomy, and cholecystectomy need not be done. Procedures to prevent recurrence should be done, including repair of hernias, removal of foreign bodies, and lysis of the offending adhesions. In some patients with early postoperative obstruction or repeated obstruction caused by adhesions, simple intubation with a long intestinal tube (many consider a standard NGT to be equally effective), rather than surgery, may be attempted in the absence of peritoneal signs.

Disseminated intraperitoneal cancer obstructing the small bowel is a major cause of death in adult patients with GI tract cancer. Bypassing the obstruction, either surgically or with endoscopically placed stents, may palliate symptoms briefly.

Obstructing colon cancers can often be treated by a single-stage resection and anastomosis. Other options include a diverting ileostomy and distal anastomosis. Occasionally, a diverting colostomy with delayed resection is required.

When diverticulitis causes obstruction, perforation is often present. Removal of the involved area may be very difficult but is indicated if perforation and general peritonitis are present. Resection and colostomy are done, and anastomosis is postponed.

Fecal impaction usually occurs in the rectum and can be removed digitally and with enemas. However, a fecal concretion alone or in a mixture (ie, with barium or antacids) that causes complete obstruction (usually in the sigmoid) requires laparotomy.

Treatment of cecal volvulus consists of resection and anastomosis of the involved segment or fixation of the cecum in its normal position by cecostomy in the frail patient. In sigmoidal volvulus, an endoscope or a long rectal tube can often decompress the loop, and resection and anastomosis may be deferred for a few days. Without a resection, recurrence is almost inevitable.

Intra-Abdominal Abscesses

Abscesses can occur anywhere in the abdomen and retroperitoneum. They mainly occur after surgery, trauma, or conditions involving abdominal infection and inflammation, particularly when peritonitis or perforation occurs. Symptoms are malaise, fever, and abdominal pain. Diagnosis is by CT. Treatment is with drainage, either surgical or percutaneous. Antibiotics are ancillary.

Etiology

Intra-abdominal abscesses are classified as intraperitoneal, retroperitoneal, or visceral (see Table 11-6). Many intra-abdominal abscesses develop after perforation of a hollow viscus or colonic cancer. Others develop by extension of infection or inflammation resulting from conditions such as appendicitis, diverticulitis, Crohn's disease, pancreatitis, pelvic inflammatory disease, or indeed any condition causing generalized peritonitis. Abdominal surgery, particularly that involving the digestive or biliary tract, is another significant risk factor: The peritoneum may be contaminated during or after surgery from such events as anastomotic leaks. Traumatic

[**Table 11-6.** Intra-Abdominal Abscesses]

abdominal injuries—particularly lacerations and hematomas of the liver, pancreas, spleen, and intestines—may develop abscesses, whether treated operatively or not.

The infecting organisms typically reflect normal bowel flora and are a complex mixture of anaerobic and aerobic bacteria. Most frequent isolates are aerobic gram-negative bacilli (eg, *Escherichia coli* and *Klebsiella*) and anaerobes (especially *Bacteroides fragilis*).

Undrained abscesses may extend to contiguous structures, erode into adjacent vessels (causing hemorrhage or thrombosis), rupture into the peritoneum or bowel, or form a cutaneous fistula. Subdiaphragmatic abscesses may extend into the thoracic cavity, causing an empyema, lung abscess, or pneumonia. An abscess in the lower abdomen may track down into the thigh or perirectal fossa. Splenic abscess is a rare cause of sustained bacteremia in endocarditis that persists despite appropriate antimicrobial therapy.

Symptoms and Signs

Abscesses may form within 1 wk of perforation or significant peritonitis, whereas postoperative abscesses may not occur until 2 to 3 wk after operation and, rarely, not for several months. Although manifestations vary, most abscesses cause fever and abdominal discomfort ranging from minimal to severe (usually near the abscess). Paralytic ileus, either generalized or localized, may develop. Nausea, anorexia, and weight loss are common.

Abscesses in Douglas' cul-de-sac, adjacent to the colon, may cause diarrhea. Contiguity to the bladder may result in urinary urgency and frequency and, if caused by diverticulitis, may create a colovesical fistula.

Subphrenic abscesses may cause chest symptoms such as nonproductive cough, chest pain, dyspnea, and shoulder pain. Rales, rhonchi, or a friction rub may be audible. Dullness to percussion and decreased breath sounds are typical when basilar atelectasis, pneumonia, or pleural effusion occurs.

Generally, there is tenderness over the location of the abscess. Large abscesses may be palpable as a mass.

Diagnosis

• Abdominal CT

• Rarely, radionuclide scanning

CT of the abdomen and pelvis with oral contrast is the preferred diagnostic modality for suspected abscess. Other imaging studies, if done, may show abnormalities; plain abdominal x-rays may reveal extraintestinal gas in the abscess, displacement of adjacent organs, a soft-tissue density representing the abscess, or loss of the psoas muscle shadow. Abscesses near the diaphragm may result in chest x-ray abnormalities such as ipsilateral pleural effusion, elevated or immobile hemidiaphragm, lower lobe infiltrates, and atelectasis.

CBC and blood cultures should be done. Leukocytosis occurs in most patients, and anemia is common.

Occasionally, radionuclide scanning with indium^{111}-labeled leukocytes may be helpful in identifying intra-abdominal abscesses.

Prognosis

Intra-abdominal abscesses have a mortality rate of 10 to 40%. Outcome depends mainly on the patient's primary illness or injury and general medical condition rather than on the specific nature and location of the abscess.

Treatment

• IV antibiotics

• Drainage: Percutaneous or surgical

All intra-abdominal abscesses require drainage, either by percutaneous catheters or surgery. Drainage through catheters (placed with CT or ultrasound guidance) may be appropriate given the following conditions: Few abscess cavities are present; the drainage route does not traverse bowel or uncontaminated organs, pleura, or peritoneum; the source of contamination is controlled; and the pus is thin enough to pass through the catheter.

Antibiotics are not curative but may limit hematogenous spread and should be given before and after intervention. Therapy requires drugs active against bowel flora, such as a combination of an aminoglycoside (eg, gentamicin 1.5 mg/kg q 8 h) and metronidazole 500 mg q 8 h. Single-agent therapy with cefotetan 2 g q 12 h is also reasonable. Patients previously given antibiotics or those who have hospital-acquired infections should receive drugs active against resistant aerobic gram-negative bacilli (eg, *Pseudomonas*) and anaerobes.

Nutritional support is important, with the enteral route preferred. Parenteral nutrition should begin early if the enteral route is not feasible.

Ischemic Colitis

Ischemic colitis is a transient reduction in blood flow to the colon.

Necrosis may occur but is usually limited to the mucosa and submucosa, only occasionally causing full-thickness necrosis necessitating surgery. It occurs mainly in older people (> 60) and is thought to be caused by small-vessel atherosclerosis.

Symptoms are milder and of slower onset than those of acute mesenteric ischemia and consist of left lower quadrant pain followed by rectal bleeding. Diagnosis is made by colonoscopy; angiography or magnetic resonance angiography is not indicated. Treatment is supportive with IV fluids, bowel rest, and antibiotics. Surgery is rarely required. About 5% of patients have a recurrence. Occasionally, strictures develop at the site of the ischemia several weeks later, necessitating surgical resection.

Chapter 12. Esophageal and Swallowing Disorders

Introduction

(See also Esophageal Cancer on p. 186 and Esophageal Atresia on p. 2975.)

The swallowing apparatus consists of the pharynx, upper esophageal (cricopharyngeal) sphincter, the body of the esophagus, and the lower esophageal sphincter (LES). The upper third of the esophagus and the structures proximal to it are composed of skeletal muscle; the distal esophagus and LES are composed of smooth muscle. These components work as an integrated system that transports material from the mouth to the stomach and prevents its reflux into the esophagus. Physical obstruction or disorders that interfere with motor function (motility disorders) can affect the system.

The patient's history suggests the diagnosis almost 80% of the time. The only physical findings in esophageal disorders are cervical and supraclavicular lymphadenopathy caused by metastasis, swellings in the neck caused by large pharyngeal diverticula or thyromegaly, and prolonged swallowing time (the time from the act of swallowing to the sound of the bolus of fluid and air entering the stomach—normally ≤ 12 sec—heard by auscultation with the stethoscope over the epigastrium). Watching the patient swallow may help diagnose aspiration or nasal regurgitation. Most esophageal disorders require specific tests for diagnosis.

Dysphagia

Dysphagia is difficulty swallowing. The condition results from impeded transport of liquids, solids, or both from the pharynx to the stomach. Dysphagia should not be confused with globus sensation (see p. 78), a feeling of having a lump in the throat, which is unrelated to swallowing and occurs without impaired transport.

Complications: Dysphagia can lead to tracheal aspiration of ingested material, oral secretions, or both. Aspiration can cause acute pneumonia; recurrent aspiration may eventually lead to chronic lung disease. Prolonged dysphagia often leads to inadequate nutrition and weight loss.

Etiology

Dysphagia is classified as oropharyngeal or esophageal, depending on where it occurs.

Oropharyngeal dysphagia: Oropharyngeal dysphagia is difficulty emptying material from the oropharynx into the esophagus; it results from abnormal function proximal to the esophagus. Patients complain of difficulty initiating swallowing, nasal regurgitation, and tracheal aspiration followed by coughing.

Most often, oropharyngeal dysphagia occurs in patients with neurologic conditions or muscular disorders that affect skeletal muscles (see Table 12-1).

Esophageal dysphagia: Esophageal dysphagia is difficulty passing food down the esophagus. It results from either a motility disorder or a mechanical obstruction (see Table 12-2).

Evaluation

History: History of present illness begins with duration of symptoms and acuity of onset. Patients should describe what substances cause difficulty and where they feel the disturbance is located. Specific concerns include whether patients have difficulty swallowing solids, liquids, or both; whether food comes out their nose; whether they drool or have food spill from their mouth; and whether they cough or choke while eating.

[**Table 12-1.** Some Causes of Oropharyngeal Dysphagia]

Review of symptoms should focus on symptoms suggestive of neuromuscular, GI, and connective tissue disorders and on the presence of complications. Important neuromuscular symptoms include weakness and easy fatigability, gait or balance disturbance, tremor, and difficulty speaking. Important GI symptoms include heartburn or other chest discomfort suggestive of reflux. Symptoms of connective tissue disorders include muscle and joint pain, Raynaud's phenomenon, and skin changes (eg, rash, swelling, thickening).

Past medical history should ascertain known diseases that may cause dysphagia (see Tables 12-1 and 12-2).

Physical examination: Examination focuses on findings suggestive of neuromuscular, GI, and connective tissue disorders and on the presence of complications.

General examination should evaluate nutritional status (including body weight). A complete neurologic examination is essential, with attention to any resting tremor, the cranial nerves (note the gag reflex may normally be absent; this absence is thus not a good marker of swallowing dysfunction), and muscle strength. Patients who describe easy fatigability should be observed performing a repetitive action (eg, blinking, counting aloud) for a rapid decrement in performance.

[**Table 12-2.** Some Causes of Esophageal Dysphagia]

The patient's gait should be observed, and balance should be tested. Skin is examined for rash and thickening or texture changes, particularly on the fingertips. Muscles are inspected for wasting and fasciculations and are palpated for tenderness. The neck is evaluated for thyromegaly or other mass.

Red flags: Any dysphagia is of concern, but certain findings are more urgent:

• Symptoms of complete obstruction (eg, drooling, inability to swallow anything)

• Dysphagia resulting in weight loss

• New focal neurologic deficit, particularly any objective weakness

Interpretation of findings: Dysphagia that occurs in conjunction with an acute neurologic event is likely the result of that event; new dysphagia in a patient with a stable, long-standing neurologic disorder may have another etiology. Dysphagia for solids alone suggests mechanical obstruction; however, a problem with both solids and liquids is nonspecific. Drooling and spilling food from the mouth while eating or nasal regurgitation suggests an oropharyngeal disorder. Regurgitation of a small amount of food on lateral compression of the neck is virtually diagnostic of pharyngeal diverticulum.

Patients who complain of difficulty getting food to leave the mouth or of food sticking in the lower esophagus are usually correct about the condition's location; the sensation of dysphagia in the upper esophagus is less specific.

Many findings suggest specific disorders (see Table 12-3) but are of varying sensitivity and specificity and thus do not rule in or out a given cause; however, they can guide testing.

Testing: A barium swallow (with a solid bolus, usually a marshmallow or tablet) should be done. If this test shows obstruction, endoscopy (and possibly biopsy) should be done to rule out malignancy. If the barium swallow is negative or suggestive of a motility disorder, esophageal motility studies should be done. Other tests for specific causes are done as suggested by findings.

Treatment

Treatment is directed at the specific cause. If complete obstruction occurs, emergent upper endoscopy is essential. If a stricture, ring, or web is found, careful endoscopic dilation is performed. Pending resolution,

patients with oropharyngeal dysphagia may benefit

[Table 12-3. Some Helpful Findings in Dysphagia]

from evaluation by a rehabilitation specialist. Sometimes patients benefit from changing head position while eating, retraining the swallowing muscles, doing exercises that improve the ability to accommodate a food bolus in the oral cavity, or doing strength and coordination exercises for the tongue. Patients with severe dysphagia and recurrent aspiration may require a gastrostomy tube.

Geriatrics Essentials

Chewing, swallowing, tasting, and communicating require intact, coordinated neuromuscular function in the mouth, face, and neck. Oral motor function in particular declines measurably with aging, even in healthy people. Decline in function may have many manifestations:

- Reduction in masticatory muscle strength and coordination is common, especially among patients with partial or complete dentures, and may lead to a tendency to swallow larger food particles, which can increase the risk of choking or aspiration.

- Drooping of the lower face and lips caused by decreased circumoral muscle tone and, in edentulous people, reduced bone support, is an aesthetic concern and can lead to drooling, spilling of food and liquids, and difficulty closing the lips while eating, sleeping, or resting. Sialorrhea (saliva leakage) is often the first symptom.

- Swallowing difficulties increase. It takes longer to move food from mouth to oropharynx, which increases the likelihood of aspiration.

After age-related changes, the most common causes of oral motor disorders are neuromuscular disorders (eg, cranial neuropathies caused by diabetes, stroke, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis). Iatrogenic causes also contribute. Drugs (eg, anticholinergics, diuretics), radiation therapy to the head and neck, and chemotherapy can greatly impair saliva production. Hyposalivation is a major cause of delayed and impaired swallowing.

Oral motor dysfunction is best managed with a multidisciplinary approach. Coordinated referrals to specialists in prosthetic dentistry, rehabilitative medicine, speech pathology, otolaryngology, and gastroenterology may be needed.

Key Points

- All patients complaining of esophageal dysphagia should undergo upper endoscopy to rule out cancer.

- If the upper endoscopy is normal, biopsies should be obtained to rule out eosinophilic esophagitis.

- Treatment is geared toward the cause.

Cricopharyngeal Incoordination

In cricopharyngeal incoordination, the cricopharyngeal muscle (the upper esophageal sphincter) is uncoordinated. It can cause a Zenker's diverticulum (see p. 125). Repeated aspiration of material from the diverticulum can lead to chronic lung disease. The condition can be treated by surgical section of the cricopharyngeal muscle.

Obstructive Disorders

(See also Benign Esophageal Tumors and Esophageal Cancer on p. 186.)

Lower Esophageal Ring

(Schatzki's Ring, B Ring)

A lower esophageal ring is a 2- to 4-mm mucosal stricture, probably congenital, causing a ringlike narrowing of the distal esophagus at the squamocolumnar junction.

These rings cause intermittent dysphagia for solids. This symptom can begin at any age but usually does not begin until after age 25. The swallowing difficulty comes and goes and is especially aggravated by meat and dry bread. Symptoms usually occur only when the esophageal lumen is < 12 mm in diameter and never when it is > 20 mm. If the distal esophagus is adequately distended, barium x-rays usually show the ring. Instructing the patient to chew food thoroughly is usually the only treatment required in wider rings, but narrow-lumen rings require dilation by endoscopy or bougienage. Surgical resection is rarely required.

Esophageal Web

(Plummer-Vinson Syndrome; Paterson-Kelly Syndrome; Sideropenic Dysphagia)

An esophageal web is a thin mucosal membrane that grows across the lumen.

Rarely, webs develop in patients with untreated severe iron-deficiency anemia; they develop even more rarely in patients without anemia. Webs usually occur in the upper esophagus, causing dysphagia for solids. They are best diagnosed by barium swallow. Webs resolve with treatment of the anemia but can be easily ruptured during esophagoscopy.

Dysphagia Lusoria

Dysphagia lusoria is caused by compression of the esophagus from any of several congenital vascular abnormalities.

The vascular abnormality is usually an aberrant right subclavian artery arising from the left side of the aortic arch, a double aortic arch, or a right aortic arch with left ligamentum arteriosum. The dysphagia may develop in childhood or later in life as a result of arteriosclerotic changes in the aberrant vessel. Barium swallow shows the extrinsic compression, but arteriography is necessary for absolute diagnosis. Most patients require no treatment, but surgical repair is sometimes done.

Motility Disorders

Achalasia

(Cardiospasm; Esophageal Aperistalsis; Megaesophagus)

Achalasia is a neurogenic esophageal motility disorder characterized by impaired esophageal peristalsis, a lack of lower esophageal sphincter relaxation during swallowing, and an elevation of lower esophageal sphincter resting pressure. Symptoms are slowly progressive dysphagia, usually to both liquids and solids, and regurgitation of undigested food. Evaluation typically includes barium swallow, endoscopy, and sometimes manometry. Treatments include dilation, chemical denervation, and surgical myotomy.

Achalasia is thought to be caused by a loss of ganglion cells in the myenteric plexus of the esophagus, resulting in denervation of esophageal muscle. Etiology of the denervation is unknown, although a viral cause is suspected, and certain tumors may cause achalasia either by direct obstruction or as a paraneoplastic process. Chagas disease, which causes destruction of autonomic ganglia, may result in achalasia.

Increased pressure at the lower esophageal sphincter (LES) causes obstruction with secondary dilation of the esophagus. Esophageal retention of undigested food is common.

Symptoms and Signs

Achalasia occurs at any age but usually begins between ages 20 and 60. Onset is insidious, and progression is gradual over months or years. Dysphagia for both solids and liquids is the major symptom. Nocturnal regurgitation of undigested food occurs in about 33% of patients and may cause cough and pulmonary aspiration. Chest pain is less common but may occur on swallowing or spontaneously. Mild to moderate weight loss occurs; when weight loss is pronounced, particularly in elderly patients whose symptoms of dysphagia developed rapidly, achalasia secondary to a tumor of the gastroesophageal junction should be considered.

Diagnosis

• Barium swallow

• Esophageal manometry

The preferred test is barium swallow, which shows absence of progressive peristaltic contractions during swallowing. The esophagus is dilated, often enormously, but is narrowed and beaklike at the LES. If esophagoscopy is done, there is dilation but no obstructing lesion. The esophagoscope usually passes readily into the stomach; resistance raises the possibility of an inapparent cancer or stricture. To exclude cancer, a retroflexed view of the gastric cardia, biopsies, and brushings for cytology should be obtained. Esophageal manometry is usually done and typically shows aperistalsis, increased LES pressure, and incomplete sphincteric relaxation during swallowing.

Achalasia must be differentiated from a distal stenosing carcinoma and a peptic stricture, particularly in patients with systemic sclerosis (see p. 309), in whom esophageal manometry may also show aperistalsis. Systemic sclerosis is usually accompanied by a history of Raynaud's phenomenon and symptoms of gastroesophageal reflux disease (GERD), due to low or absent LES pressure.

Achalasia due to cancer at the gastroesophageal junction can be diagnosed by CT of the chest and abdomen or by endoscopic ultrasound.

Prognosis

Pulmonary aspiration and the presence of cancer are the determining prognostic factors. Nocturnal regurgitation and coughing suggest aspiration. Pulmonary complications secondary to aspiration are difficult to manage. Incidence of esophageal cancer in patients with achalasia may be increased; this point is controversial.

Treatment

• Balloon dilation of the LES

• Alternatively, botulinum toxin injection or surgical myotomy

No therapy restores peristalsis; treatment aims at reducing the pressure (and thus the obstruction) at the LES. Pneumatic balloon dilation of the LES is indicated initially. Results are satisfactory in about 85% of patients, but repeated dilations may be needed. Esophageal rupture and secondary mediastinitis requiring surgical repair occur in < 2% of patients. Nitrates (eg, isosorbide dinitrate 5 to 10 mg sublingually before meals) or Ca channel blockers (eg, nifedipine 10 mg po tid) are of limited effectiveness but may reduce LES pressure enough to prolong the time between dilations.

Achalasia can also be treated by chemical denervation of cholinergic nerves in the distal esophagus by direct injection of botulinum toxin type A into the LES. Clinical improvement occurs in 70 to 80% of patients, but results may last only 6 mo to 1 yr.

A Heller myotomy, in which the muscular fibers in the LES are cut, is usually reserved for patients who do not respond to dilation; its success rate is about 85%. It can be done via laparoscopy or thoracoscopy and may be a viable alternative to dilation as primary therapy. Symptomatic GERD occurs after surgery in

about 15% of patients.

Symptomatic Diffuse Esophageal Spasm

(Spastic Pseudodiverticulosis; Rosary Bead or Corkscrew Esophagus)

Symptomatic diffuse esophageal spasm is part of a spectrum of motility disorders characterized variously by nonpropulsive contractions, hyperdynamic contractions, or elevated lower esophageal sphincter pressure. Symptoms are chest pain and sometimes dysphagia. Diagnosis is by barium swallow or manometry. Treatment is difficult but includes nitrates, Ca channel blockers, botulinum toxin injection, and antireflux therapy.

Abnormalities in esophageal motility correlate poorly with patient symptoms; similar abnormalities may cause different or no symptoms in different people. Furthermore, neither symptoms nor abnormal contractions are definitively associated with histopathologic abnormalities of the esophagus.

Symptoms and Signs

Diffuse esophageal spasm typically causes substernal chest pain with dysphagia for both liquids and solids. The pain may waken the patient from sleep. Very hot or cold liquids may aggravate the pain. Over many years, this disorder may evolve into achalasia.

Esophageal spasms can cause severe pain without dysphagia. This pain is often described as a substernal squeezing pain and may occur in association with exercise. Such pain may be indistinguishable from angina pectoris.

Some patients have symptoms that combine those of achalasia and diffuse spasm. One such combination has been called vigorous achalasia because it features both the food retention and aspiration of achalasia and the severe pain and spasm of diffuse spasm.

Diagnosis

• Barium swallow

• Esophageal manometry

• Possibly testing for coronary ischemia

Alternative diagnoses include coronary ischemia. Definitive confirmation of an esophageal origin for symptoms is difficult. Barium swallow may show poor progression of a bolus and disordered, simultaneous contractions or tertiary contractions. Severe spasms may mimic the radiographic appearance of diverticula but vary in size and position. Esophageal manometry (see p. 96) provides the most specific description of the spasms. Contractions are usually simultaneous, prolonged or multiphasic, and possibly of very high amplitude ("nutcracker esophagus"). However, spasms may not occur during testing. Lower esophageal sphincter (LES) pressure elevation or impaired relaxation is present in 30% of patients. Esophageal scintigraphy and provocative tests with drugs (eg, edrophonium chloride 10 mg IV) have not proved helpful.

Treatment

• Ca channel blockers

• Botulinum toxin injection

Esophageal spasms are often difficult to treat, and controlled studies of treatment methods are lacking. Anticholinergics, nitroglycerin, and long-acting nitrates have had limited success. Ca channel blockers given orally (eg, verapamil 80 mg tid, nifedipine 10 mg tid) may be useful, as may injection of botulinum toxin type A into the LES.

Medical management is usually sufficient, but pneumatic dilation and bougienage, or even surgical myotomy along the full length of the esophagus, may be tried in intractable cases.

Esophageal Diverticula

An esophageal diverticulum is an outpouching of mucosa through the muscular layer of the esophagus. It can be asymptomatic or cause dysphagia and regurgitation. Diagnosis is made by barium swallow; surgical repair is rarely required.

There are several types of esophageal diverticula, each of different origin.

- Zenker's (pharyngeal) diverticula are posterior outpouchings of mucosa and submucosa through the cricopharyngeal muscle, probably resulting from an incoordination between pharyngeal propulsion and cricopharyngeal relaxation.

- Midesophageal (traction) diverticula are caused by traction from mediastinal inflammatory lesions or, secondarily, by motility disorders.

- Epiphrenic diverticula occur just above the diaphragm and usually accompany a motility disorder (achalasia, diffuse esophageal spasm).

Symptoms and Signs

A Zenker's diverticulum fills with food that might be regurgitated when the patient bends or lies down. Aspiration pneumonitis may result if regurgitation is nocturnal. Rarely, the pouch becomes large, causing dysphagia and sometimes a palpable neck mass.

Traction and epiphrenic diverticula are rarely symptomatic, although their underlying cause may be.

Diagnosis

All diverticula are diagnosed by videotaped barium swallow.

Treatment

- Usually none

- Sometimes surgical resection

Specific treatment is usually not required, although resection is occasionally necessary for large or symptomatic diverticula. Diverticula associated with motility disorders require treatment of the primary disorder. For example, case reports suggest doing a cricopharyngeal myotomy when resecting a Zenker's diverticulum.

Gastroesophageal Reflux Disease

Incompetence of the lower esophageal sphincter allows reflux of gastric contents into the esophagus, causing burning pain. Prolonged reflux may lead to esophagitis, stricture, and rarely metaplasia or cancer. Diagnosis is clinical, sometimes with endoscopy, with or without acid testing. Treatment involves lifestyle modification, acid suppression using proton pump inhibitors, and sometimes surgical repair.

Gastroesophageal reflux disease (GERD) is common, occurring in 30 to 40% of adults. It also occurs frequently in infants, typically beginning at birth.

Etiology

The presence of reflux implies lower esophageal sphincter (LES) incompetence, which may result from a generalized loss of intrinsic sphincter tone or from recurrent inappropriate transient relaxations (ie, unrelated to swallowing). Transient LES relaxations are triggered by gastric distention or subthreshold pharyngeal stimulation.

Factors that contribute to the competence of the gastroesophageal junction include the angle of the cardioesophageal junction, the action of the diaphragm, and gravity (ie, an upright position). Factors contributing to reflux include weight gain, fatty foods, caffeinated or carbonated beverages, alcohol, tobacco smoking, and drugs. Drugs that lower LES pressure include anticholinergics, antihistamines, tricyclic antidepressants, Ca channel blockers, progesterone, and nitrates.

Complications: GERD may lead to esophagitis, peptic esophageal ulcer, esophageal stricture, Barrett's esophagus, and esophageal adenocarcinoma (see p. 186). Factors that contribute to the development of esophagitis include the caustic nature of the refluxate, the inability to clear the refluxate from the esophagus, the volume of gastric contents, and local mucosal protective functions. Some patients, particularly infants, aspirate the reflux material.

Symptoms and Signs

The most prominent symptom of GERD is heartburn, with or without regurgitation of gastric contents into the mouth. Infants present with vomiting, irritability, anorexia, and sometimes symptoms of chronic aspiration. Both adults and infants with chronic aspiration may have cough, hoarseness, or wheezing.

Esophagitis may cause odynophagia and even esophageal hemorrhage, which is usually occult but can be massive. Peptic stricture causes a gradually progressive dysphagia for solid foods. Peptic esophageal ulcers cause the same type of pain as gastric or duodenal ulcers, but the pain is usually localized to the xiphoid or high substernal region. Peptic esophageal ulcers heal slowly, tend to recur, and usually leave a stricture on healing.

Diagnosis

• Clinical diagnosis

• Endoscopy for those not responding to empiric treatment

• 24-h pH testing for those with typical symptoms but normal endoscopy

A detailed history points to the diagnosis. Patients with typical symptoms of GERD may be given a trial of therapy. Patients who do not improve, or have long-standing symptoms or symptoms of complications, should be studied. Endoscopy, with cytologic washings and biopsy of abnormal areas, is the test of choice. Endoscopic biopsy is the only test that consistently detects the columnar mucosal changes of Barrett's esophagus. Patients with unremarkable endoscopy findings who have typical symptoms despite treatment with proton pump inhibitors should undergo 24-h pH testing (see p. 95). Although barium swallow readily shows esophageal ulcers and peptic strictures, it is less useful for mild to moderate reflux; in addition, most patients with abnormalities require subsequent endoscopy. Esophageal manometry may be used to guide pH probe placement and to evaluate esophageal peristalsis before surgical treatment.

Treatment

• Head of bed elevated

• Coffee, alcohol, fats, and smoking avoided

• Proton pump inhibitors

Management of uncomplicated GERD consists of elevating the head of the bed about 15 cm (6 in) and avoiding the following: eating within 2 to 3 h of bedtime, strong stimulants of acid secretion (eg, coffee, alcohol), certain drugs (eg, anticholinergics), specific foods (eg, fats, chocolate), and smoking.

Drug therapy is with a proton pump inhibitor. For example, adults can be given omeprazole 20 mg, lansoprazole 30 mg, or esomeprazole 40 mg 30 min before breakfast. In some cases, proton pump inhibitors may be given bid. Infants and children may be given these drugs at an appropriate lower single daily dose (ie, omeprazole 20 mg in children > 3 yr, 10 mg in children < 3 yr; lansoprazole 15 mg in children ≤ 30 kg, 30 mg in children > 30 kg). These drugs may be continued long-term, but the dose should be adjusted to the minimum required to prevent symptoms. H_2 blockers (eg, ranitidine 150 mg at bedtime) or promotility agents (eg, metoclopramide 10 mg po 30 min before meals and at bedtime) are less effective.

Antireflux surgery (usually via laparoscopy) is done on patients with serious esophagitis, large hiatal hernias, hemorrhage, stricture, or ulcers. Esophageal strictures are managed by repeated balloon dilation.

Barrett's esophagus may or may not regress with medical or surgical therapy. Because Barrett's esophagus is a precursor to adenocarcinoma, endoscopic surveillance for malignant transformation is recommended every 1 to 2 yr. Surveillance has uncertain cost-effectiveness in patients with low-grade dysplasia but is important in high-grade dysplasia in patients who are unable to undergo surgical resection. Alternatively, Barrett's esophagus may be treated with endoscopic mucosal resection, photodynamic therapy, cryotherapy, or laser ablation.

Hiatus Hernia

Hiatus hernia is a protrusion of the stomach through the diaphragmatic hiatus. Most hernias are asymptomatic, but an increased incidence of acid reflux may lead to symptoms of gastroesophageal reflux disease (GERD). Diagnosis is by barium swallow. Treatment is directed at symptoms of GERD if present.

Etiology

Etiology is usually unknown, but a hiatus hernia is thought to be acquired through stretching of the fascial attachments between the esophagus and diaphragm at the hiatus (the opening through which the esophagus traverses the diaphragm).

Pathophysiology

In a sliding hiatus hernia (the most common type), the gastroesophageal junction and a portion of the stomach are above the diaphragm. In a paraesophageal hiatus hernia, the gastroesophageal junction is in the normal location, but a portion of the stomach is adjacent to the esophagus in the diaphragmatic hiatus. Hernias may also occur through other parts of the diaphragm (see p. 2977).

A sliding hiatus hernia is common and is an incidental finding on x-ray in > 40% of the population; therefore, the relationship of hernia to symptoms is unclear. Although most patients with GERD have some degree of hiatus hernia, < 50% of patients with hiatus hernia have GERD.

Symptoms and Signs

Most patients with a sliding hiatus hernia are asymptomatic, but chest pain and other reflux symptoms can occur. A paraesophageal hiatus hernia is generally asymptomatic but, unlike a sliding hiatus hernia, may incarcerate and strangulate. Occult or massive GI hemorrhage may occur with either type.

Diagnosis

• Barium swallow

A large hiatus hernia is often discovered incidentally on chest x-ray. Smaller hernias are diagnosed with a barium swallow.

Treatment

• Sometimes a proton pump inhibitor

An asymptomatic sliding hiatus hernia requires no specific therapy. Patients with accompanying GERD should be treated with a proton pump inhibitor. A paraesophageal hernia should be reduced surgically because of the risk of strangulation.

Infectious Esophageal Disorders

Esophageal infection occurs mainly in patients with impaired host defenses. Primary agents include *Candida albicans*, herpes simplex virus, and cytomegalovirus. Symptoms are odynophagia and chest pain. Diagnosis is by endoscopic visualization and culture. Treatment is with antifungal or antiviral drugs.

Esophageal infection is rare in patients with normal host defenses. Primary esophageal defenses include saliva, esophageal motility, and cellular immunity. Thus, at-risk patients include those with AIDS, organ transplants, alcoholism, diabetes, undernutrition, cancer, and motility disorders. *Candida* infection may occur in any of these patients. Herpes simplex virus (HSV) and cytomegalovirus (CMV) infections occur mainly in AIDS and transplant patients.

Candida: Patients with *Candida* esophagitis usually complain of odynophagia and, less commonly, dysphagia. About two thirds of patients have signs of oral thrush (thus its absence does not exclude esophageal involvement). Patients with odynophagia and typical thrush may be given empiric treatment, but if significant improvement does not occur in 5 to 7 days, endoscopic evaluation is required. Barium swallow is less accurate.

Treatment is with fluconazole 200 mg po or IV for one dose, then 100 mg po or IV q 24 h for 14 to 21 days. Alternatives include the azoles (eg, itraconazole, voriconazole, ketoconazole) or echinocandins (eg, caspofungin). Topical therapy has no role.

HSV and CMV: These infections are equally likely in transplant patients, but HSV occurs early after transplantation (reactivation) and CMV occurs 2 to 6 mo after. Among AIDS patients, CMV is much more common than HSV, and viral esophagitis occurs mainly when the CD4+ count is < 200/µL. Severe odynophagia results from either infection.

Endoscopy, with cytology or biopsy, is usually necessary for diagnosis. HSV is treated with IV acyclovir 5 mg/kg q 8 h for 7 days or valacyclovir 1 g po tid. CMV is treated with ganciclovir 5 mg/kg IV q 12 h for 14 to 21 days with maintenance at 5 mg/kg IV 5 days/wk in immunocompromised patients. Alternatives include foscarnet and cidofovir.

Mallory-Weiss Syndrome

Mallory-Weiss syndrome is a nonpenetrating mucosal laceration of the distal esophagus and proximal stomach caused by vomiting, retching, or hiccuping.

Initially described in alcoholics, Mallory-Weiss syndrome can occur in any patient who vomits forcefully. It is the cause of about 5% of episodes of upper GI hemorrhage. Most episodes of bleeding stop spontaneously; severe bleeding occurs in about 10% of patients who require significant intervention, such as transfusion or endoscopic hemostasis (by injection of ethanol, polidocanol, or epinephrine or by electrocautery). Intra-arterial infusion of pitressin or therapeutic embolization into the left gastric artery during angiography may also be used to control bleeding. Surgical repair is rarely required.

Esophageal Rupture

Esophageal rupture may be iatrogenic during endoscopic procedures or other instrumentation or may be spontaneous (Boerhaave's syndrome). Patients are seriously ill, with symptoms of mediastinitis. Diagnosis is by esophagography with a water-soluble contrast agent. Immediate

surgical repair and drainage are required.

Endoscopic procedures are the primary cause of esophageal rupture, but spontaneous rupture may occur, typically related to vomiting, retching, or swallowing a large food bolus. The most common site of rupture is the distal esophagus on the left side. Acid and other stomach contents cause a fulminant mediastinitis and shock. Pneumomediastinum is common.

Symptoms and Signs

Symptoms include chest and abdominal pain, vomiting, hematemesis, and shock. Subcutaneous emphysema is palpable in about 30% of patients. Mediastinal crunch (Hamman's sign), a crackling sound synchronous with the heartbeat, may be present.

Diagnosis

• Chest and abdominal x-rays

• Esophagography

Chest and abdominal x-rays showing mediastinal air, pleural effusion, or mediastinal widening suggest the diagnosis. Diagnosis is confirmed by esophagography with a water-soluble contrast agent, which avoids potential mediastinal irritation from barium. CT of the thorax detects mediastinal air and fluid but does not localize the perforation well. Endoscopy may miss a small perforation.

Treatment

• Surgical repair

Pending surgical repair, patients should receive broad-spectrum antibiotics (eg, gentamicin plus metronidazole or piperacillin/tazobactam) and fluid resuscitation as needed for shock. Even with treatment, mortality is high.

Chapter 13. Gastritis and Peptic Ulcer Disease

Introduction

Acid is secreted by parietal cells in the proximal two thirds (body) of the stomach. Gastric acid aids digestion by creating the optimal pH for pepsin and gastric lipase and by stimulating pancreatic bicarbonate secretion. Acid secretion is initiated by food: the thought, smell, or taste of food effects vagal stimulation of the gastrin-secreting G cells located in the distal one third (antrum) of the stomach. The arrival of protein to the stomach further stimulates gastrin output. Circulating gastrin triggers the release of histamine from enterochromaffin-like cells in the body of the stomach. Histamine stimulates the parietal cells via their H_2 receptors. The parietal cells secrete acid, and the resulting drop in pH causes the antral D cells to release somatostatin, which inhibits gastrin release (negative feedback control).

Acid secretion is present at birth and reaches adult levels (on a weight basis) by age 2. There is a decline in acid output in elderly patients who develop chronic gastritis, but acid output is otherwise maintained throughout life.

Normally, the GI mucosa is protected by several distinct mechanisms: (1) Mucosal production of mucus and HCO_3 creates a pH gradient from the gastric lumen (low pH) to the mucosa (neutral pH). The mucus serves as a barrier to the diffusion of acid and pepsin. (2) Epithelial cells remove excess hydrogen ions (H^+) via membrane transport systems and have tight junctions, which prevent back diffusion of H^+ ions. (3) Mucosal blood flow removes excess acid that has diffused across the epithelial layer. Several growth factors (eg, epidermal growth factor, insulin-like growth factor I) and prostaglandins have been linked to mucosal repair and maintenance of mucosal integrity.

Factors that interfere with these mucosal defenses (particularly NSAIDs and *Helicobacter pylori* infection) predispose to gastritis and peptic ulcer disease.

NSAIDs promote mucosal inflammation and ulcer formation (sometimes with GI bleeding) both topically and systemically. By inhibiting prostaglandin production via blockage of the enzyme cyclooxygenase (COX), NSAIDs reduce gastric blood flow, reduce mucus and HCO_3 secretion, and decrease cell repair and replication. Also, because NSAIDs are weak acids and are nonionized at gastric pH, they diffuse freely across the mucus barrier into gastric epithelial cells, where H^+ ions are liberated, leading to cellular damage. Because gastric prostaglandin production involves the COX-1 isoform, NSAIDs that are selective COX-2 inhibitors have fewer adverse gastric effects than other NSAIDs.

Helicobacter pylori Infection

***H. pylori* is a common gastric pathogen that causes gastritis, peptic ulcer disease, gastric adenocarcinoma, and low-grade gastric lymphoma. Infection may be asymptomatic or result in varying degrees of dyspepsia. Diagnosis is by urea breath test and testing of endoscopic biopsy samples. Treatment is with a proton pump inhibitor plus two antibiotics.**

H. pylori is a spiral-shaped, gram-negative organism that has adapted to thrive in acid. In developing countries, it commonly causes chronic infections and is usually acquired during childhood. In the US, infection is less common among children but increases with age: by age 60, about 50% of people are infected. Infection is most common among blacks, Hispanics, and Asians.

The organism has been cultured from stool, saliva, and dental plaque, which suggests oral-oral or fecal-oral transmission. Infections tend to cluster in families and in residents of custodial institutions. Nurses and gastroenterologists seem to be at high risk because bacteria can be transmitted by improperly disinfected endoscopes.

Pathophysiology

Effects of *H. pylori* infection vary depending on the location within the stomach. Antral-predominant

infection results in increased gastrin production, probably via local impairment of somatostatin release. Resultant hypersecretion of acid predisposes to prepyloric and duodenal ulcer. Body-predominant infection leads to gastric atrophy and decreased acid production, possibly via increased local production of IL-1β. Patients with body-predominant infection are predisposed to gastric ulcer and adenocarcinoma. Some patients have mixed infection of both antrum and body with varying clinical effects. Many patients with *H. pylori* infection have no noticeable clinical effects.

Ammonia produced by *H. pylori* enables the organism to survive in the acidic environment of the stomach and may erode the mucus barrier. Cytotoxins and mucolytic enzymes (eg, bacterial protease, lipase) produced by *H. pylori* may play a role in mucosal damage and subsequent ulcerogenesis.

Infected people are 3 to 6 times more likely to develop stomach cancer. *H. pylori* infection is associated with intestinal-type adenocarcinoma of the gastric body and antrum but not cancer of the gastric cardia. Other associated cancers include gastric lymphoma and mucosa-associated lymphoid tissue (MALT) lymphoma, a monoclonally restricted B-cell tumor.

Diagnosis

• For initial diagnosis: Serologic tests

• For confirmation of cure: Urea breath test or stool antigen assay

Screening of asymptomatic patients is not warranted. Tests are done during evaluation for peptic ulcer and gastritis. Posttreatment testing is typically done to confirm eradication of the organism. Different tests are preferred for initial diagnosis and posttreatment.

Noninvasive tests: Laboratory and office-based serologic assays for antibodies to *H. pylori* have sensitivity and specificity of > 85% and are considered the noninvasive tests of choice for initial documentation of *H. pylori* infection. However, because qualitative assays remain positive for up to 3 yr after successful treatment and because quantitative antibody levels do not decline significantly for 6 to 12 mo after treatment, serologic assays are not usually used to assess cure.

Urea breath tests use an oral dose of ^{13}C- or ^{14}C-labeled urea. In an infected patient, the organism metabolizes the urea and liberates labeled CO_2, which is exhaled and can be quantified in breath samples taken 20 to 30 min after ingestion of the urea. Sensitivity and specificity are > 90%. Urea breath tests are well suited for confirming eradication of the organism after therapy. False-negative results are possible with recent antibiotic use or concomitant proton pump inhibitor therapy; therefore, follow-up testing should be delayed ≥ 4 wk after antibiotic therapy and 1 wk after proton pump inhibitor therapy. H_2 blockers do not affect the test.

Stool antigen assays seem to have a sensitivity and specificity near that of urea breath tests, particularly for initial diagnosis; an office-based test is under development.

Invasive tests: Endoscopy is used to obtain mucosal biopsy samples for a rapid urease test (RUT) or histologic staining. Bacterial culture is of limited use because of the fastidious nature of the organism. Endoscopy is not recommended solely for diagnosis of *H. pylori;* noninvasive tests are preferred unless endoscopy is indicated for other reasons.

The RUT, in which presence of bacterial urease in the biopsy sample causes a color change on a special medium, is the diagnostic method of choice on tissue samples. Histologic staining of biopsy samples should be done for patients with negative RUT results but suspicious clinical findings, recent antibiotic use, or treatment with proton pump inhibitors. RUT and histologic staining each have a sensitivity and specificity of > 90%.

Treatment

• Antibiotics (various regimens) plus a proton pump inhibitor

Patients with complications (eg, gastritis, ulcer, cancer) should have the organism eradicated. Eradication of *H. pylori* can even cure some cases of MALT lymphoma (but not other infection-related cancers). Treatment of asymptomatic infection has been controversial, but the recognition of the role of *H. pylori* in cancer has led to a recommendation for treatment. Vaccines, both preventive and therapeutic (ie, as an adjunct to treatment of infected patients), are under development.

H. pylori eradication requires multidrug therapy, typically antibiotics plus acid suppressants. Proton pump inhibitors suppress *H. pylori*, and the increased gastric pH accompanying their use can enhance tissue concentration and efficacy of antimicrobials, creating a hostile environment for *H. pylori*.

Triple therapy is recommended. Oral omeprazole 20 mg bid or lansoprazole 30 mg bid, plus clarithromycin 500 mg bid, plus amoxicillin 1 g bid (or, for penicillin-allergic patients, metronidazole 500 mg bid) for 14 days, cures infection in > 95% of cases. This regimen has excellent tolerability. Ranitidine bismuth citrate 400 mg po bid may be substituted for the proton pump inhibitor.

Quadruple therapy with a proton pump inhibitor bid, tetracycline 500 mg and bismuth subsalicylate or subcitrate 525 mg qid, and metronidazole 500 mg tid is also effective but more cumbersome.

Infected patients with duodenal or gastric ulcer require continuation of the acid suppression for at least 4 wk.

Treatment is repeated if *H. pylori* is not eradicated. If two courses are unsuccessful, some authorities recommend endoscopy to obtain cultures for sensitivity testing.

Gastritis

Gastritis is inflammation of the gastric mucosa caused by any of several conditions, including infection (*Helicobacter pylori*), drugs (NSAIDs, alcohol), stress, and autoimmune phenomena (atrophic gastritis). Many cases are asymptomatic, but dyspepsia and GI bleeding sometimes occur. Diagnosis is by endoscopy. Treatment is directed at the cause but often includes acid suppression and, for *H. pylori* infection, antibiotics.

Gastritis is classified as erosive or nonerosive based on the severity of mucosal injury. It is also classified according to the site of involvement (ie, cardia, body, antrum). Gastritis can be further classified histologically as acute or chronic based on the inflammatory cell type. No classification scheme matches perfectly with the pathophysiology; a large degree of overlap exists. Some forms of gastritis involve acid-peptic and *H. pylori* disease. Additionally, the term is often loosely applied to nonspecific (and often undiagnosed) abdominal discomfort and gastroenteritis.

Acute gastritis is characterized by PMN infiltration of the mucosa of the antrum and body.

Chronic gastritis implies some degree of atrophy (with loss of function of the mucosa) or metaplasia. It predominantly involves the antrum (with subsequent loss of G cells and decreased gastrin secretion) or the corpus (with loss of oxyntic glands, leading to reduced acid, pepsin, and intrinsic factor).

Erosive Gastritis

Erosive gastritis is gastric mucosal erosion caused by damage to mucosal defenses. It is typically acute, manifesting with bleeding, but may be subacute or chronic with few or no symptoms. Diagnosis is by endoscopy. Treatment is supportive, with removal of the inciting cause. Certain ICU patients (eg, ventilator-bound, head trauma, burn, multisystem trauma) benefit from prophylaxis with acid suppressants.

Causes of erosive gastritis include NSAIDs, alcohol, stress, and less commonly radiation, viral infection (eg, cytomegalovirus), vascular injury, and direct trauma (eg, nasogastric tubes).

Superficial erosions and punctate mucosal lesions occur. These may develop as soon as 12 h after the

initial insult. Deep erosions, ulcers, and sometimes perforation may occur in severe or untreated cases. Lesions typically occur in the body, but the antrum may also be involved.

Acute stress gastritis, a form of erosive gastritis, occurs in about 5% of critically ill patients. The incidence increases with duration of ICU stay and length of time the patient is not receiving enteral feeding. Pathogenesis likely involves hypoperfusion of the GI mucosa, resulting in impaired mucosal defenses. Patients with head injury or burns may also have increased secretion of acid.

Symptoms and Signs

Patients with mild erosive gastritis are often asymptomatic, although some complain of dyspepsia, nausea, or vomiting. Often, the first sign is hematemesis, melena, or blood in the nasogastric aspirate, usually within 2 to 5 days of the inciting event. Bleeding is usually mild to moderate, although it can be massive if deep ulceration is present, particularly in acute stress gastritis. Acute and chronic erosive gastritis are diagnosed endoscopically.

Diagnosis

Acute and chronic erosive gastritis are diagnosed endoscopically.

Treatment

• For bleeding: Endoscopic hemostasis

• For acid suppression: A proton pump inhibitor or H_2 blocker

In severe gastritis, bleeding is managed with IV fluids and blood transfusion as needed. Endoscopic hemostasis should be attempted, with surgery (total gastrectomy) a fallback procedure. Angiography is unlikely to stop severe gastric bleeding because of the many collateral vessels supplying the stomach. Acid suppression should be started if the patient is not already receiving it.

For milder gastritis, removing the offending agent and using drugs to reduce gastric acidity (see p. 136) may be all that is required.

Prevention

Prophylaxis with acid-suppressive drugs can reduce the incidence of acute stress gastritis. However, it mainly benefits certain high-risk ICU patients, including those with severe burns, CNS trauma, coagulopathy, sepsis, shock, multiple trauma, mechanical ventilation for > 48 h, hepatic or renal failure, multiorgan dysfunction, and history of peptic ulcer or GI bleeding.

Prophylaxis consists of IV H_2 blockers, proton pump inhibitors, or oral antacids to raise intragastric pH > 4.0. Repeated pH measurement and titration of therapy are not required. Early enteral feeding also can decrease the incidence of bleeding.

Acid suppression is not recommended for patients simply taking NSAIDs unless they have previously had an ulcer.

Nonerosive Gastritis

Nonerosive gastritis refers to a variety of histologic abnormalities that are mainly the result of *H. pylori* infection. Most patients are asymptomatic. Diagnosis is by endoscopy. Treatment is eradication of *H. pylori* and sometimes acid suppression.

Pathology

Superficial gastritis: Lymphocytes and plasma cells mixed with neutrophils are the predominant infiltrating inflammatory cells. Inflammation is superficial and may involve the antrum, body, or both. It is

usually not accompanied by atrophy or metaplasia. Prevalence increases with age.

Deep gastritis: Deep gastritis is more likely to be symptomatic (eg, vague dyspepsia). Mononuclear cells and neutrophils infiltrate the entire mucosa to the level of the muscularis, but exudate or crypt abscesses seldom result, as might be expected by such infiltration. Distribution may be patchy. Superficial gastritis may be present, as may partial gland atrophy and metaplasia.

Gastric atrophy: Atrophy of gastric glands may follow in gastritis, most often longstanding antral (sometimes referred to as type B) gastritis. Some patients with gastric atrophy have autoantibodies to parietal cells, usually in association with corpus (type A) gastritis and pernicious anemia.

Atrophy may occur without specific symptoms. Endoscopically, the mucosa may appear normal until atrophy is advanced, when submucosal vascularity may be visible. As atrophy becomes complete, secretion of acid and pepsin diminishes and intrinsic factor may be lost, resulting in vitamin B_{12} malabsorption.

Metaplasia: Two types of metaplasia are common in chronic nonerosive gastritis: mucous gland and intestinal.

Mucous gland metaplasia (pseudopyloric metaplasia) occurs in the setting of severe atrophy of the gastric glands, which are progressively replaced by mucous glands (antral mucosa), especially along the lesser curve. Gastric ulcers may be present (typically at the junction of antral and corpus mucosa), but whether they are the cause or consequence of these metaplastic changes is not clear.

Intestinal metaplasia typically begins in the antrum in response to chronic mucosal injury and may extend to the body. Gastric mucosa cells change to resemble intestinal mucosa—with goblet cells, endocrine (enterochromaffin or enterochromaffin-like) cells, and rudimentary villi—and may even assume functional (absorptive) characteristics. Intestinal metaplasia is classified histologically as complete (most common) or incomplete. With complete metaplasia, gastric mucosa is completely transformed into small-bowel mucosa, both histologically and functionally, with the ability to absorb nutrients and secrete peptides. In incomplete metaplasia, the epithelium assumes a histologic appearance closer to that of the large intestine and frequently exhibits dysplasia. Intestinal metaplasia may lead to stomach cancer.

Symptoms and Signs

Most patients with *H. pylori*-associated gastritis are asymptomatic, although some have mild dyspepsia or other vague symptoms.

Diagnosis

• Endoscopy

Often, the condition is discovered during endoscopy done for other purposes. Testing of asymptomatic patients is not indicated. Once gastritis is identified, testing for *H. pylori* is appropriate.

Treatment

• Eradication of *H. pylori*

• Sometimes acid-suppressive drugs

Treatment of chronic nonerosive gastritis is *H. pylori* eradication (see p. 130). Treatment of asymptomatic patients is somewhat controversial given the high prevalence of *H. pylori*-associated superficial gastritis and the relatively low incidence of clinical sequelae (ie, peptic ulcer disease). However, *H. pylori* is a class J carcinogen; eradication removes the cancer risk. In *H. pylori*-negative patients, treatment is directed at symptoms using acid-suppressive drugs (eg, H_2 blockers, proton pump inhibitors) or antacids.

Postgastrectomy Gastritis

Postgastrectomy gastritis is gastric atrophy developing after partial or subtotal gastrectomy (except in cases of gastrinoma).

Metaplasia of the remaining corpus mucosa is common. The degree of gastritis is usually greatest at the lines of anastomosis.

Several mechanisms are responsible: bile reflux, which is common after such surgery, damages the gastric mucosa; loss of antral gastrin decreases stimulation of parietal and peptic cells, causing atrophy; and vagotomy may result in a loss of vagal trophic action.

There are no specific symptoms of gastritis. Postgastrectomy gastritis often progresses to severe atrophy and achlorhydria. Production of intrinsic factor may cease with resultant vitamin B_{12} deficiency (which may be worsened by bacterial overgrowth in the afferent loop). The relative risk of gastric adenocarcinoma seems to increase 15 to 20 yr after partial gastrectomy; however, given the low absolute incidence of postgastrectomy cancer, routine endoscopic surveillance is probably not cost effective, but upper GI symptoms or anemia in such patients should prompt endoscopy.

Uncommon Gastritis Syndromes

Menetrier's disease: This rare idiopathic disorder affects adults aged 30 to 60 and is more common among men. It manifests as a significant thickening of the gastric folds of the gastric body but not the antrum. Gland atrophy and marked foveolar pit hyperplasia occur, often accompanied by mucous gland metaplasia and increased mucosal thickness with little inflammation. Hypoalbuminemia (the most consistent laboratory abnormality) caused by GI protein loss may be present (protein-losing gastropathy). As the disease progresses, the secretion of acid and pepsin decreases, causing hypochlorhydria.

Symptoms are nonspecific and commonly include epigastric pain, nausea, weight loss, edema, and diarrhea. Differential diagnosis includes (1) lymphoma, in which multiple gastric ulcers may occur; (2) mucosa-associated lymphoid tissue (MALT) lymphoma, with extensive infiltration of monoclonal B lymphocytes; (3) Zollinger-Ellison syndrome with associated gastric fold hypertrophy; and (4) Cronkhite-Canada syndrome, a mucosal polypoid protein-losing syndrome associated with diarrhea. Diagnosis is made by endoscopy with deep mucosal biopsy or full-thickness laparoscopic gastric biopsy.

Various treatments have been used, including anticholinergics, antisecretory drugs, and corticosteroids, but none have proved fully effective. Partial or complete gastric resection may be necessary in cases of severe hypoalbuminemia.

Eosinophilic gastritis: Extensive infiltration of the mucosa, submucosa, and muscle layers with eosinophils often occurs in the antrum. It is usually idiopathic but may result from nematode infestation. Symptoms include nausea, vomiting, and early satiety. Diagnosis is by endoscopic biopsy of involved areas. Corticosteroids can be successful in idiopathic cases; however, if pyloric obstruction develops, surgery may be required.

Mucosa-associated lymphoid tissue (MALT) lymphoma: This rare condition is characterized by massive lymphoid infiltration of the gastric mucosa, which can resemble Menetrier's disease.

Gastritis caused by systemic disorders: Sarcoidosis, TB, amyloidosis, and other granulomatous diseases can cause gastritis, which is seldom of primary importance.

Gastritis caused by physical agents: Radiation and ingestion of corrosives (especially acidic compounds) can cause gastritis. Exposure to > 16 Gy of radiation causes marked deep gastritis, usually involving the antrum more than the corpus. Pyloric stenosis and perforation are possible complications of radiation-induced gastritis.

Infectious (septic) gastritis: Except for *H. pylori* infection, bacterial invasion of the stomach is rare and mainly occurs after ischemia, ingestion of corrosives, or exposure to radiation. On x-ray, gas outlines the

mucosa. The condition can manifest as an acute surgical abdomen and has a very high mortality rate. Surgery is often necessary.

Debilitated or immunocompromised patients may develop viral or fungal gastritis with cytomegalovirus, *Candida*, histoplasmosis, or mucormycosis; these diagnoses should be considered in patients with exudative gastritis, esophagitis, or duodenitis.

Autoimmune Metaplastic Atrophic Gastritis

Autoimmune metaplastic atrophic gastritis (AMAG) is an inherited autoimmune disease that attacks parietal cells, resulting in hypochlorhydria and decreased production of intrinsic factor. Consequences include atrophic gastritis, B_{12} malabsorption, and, frequently, pernicious anemia. Risk of gastric adenocarcinoma increases 3-fold. Diagnosis is by endoscopy. Treatment is with parenteral vitamin B_{12}.

Patients with AMAG have antibodies to parietal cells and their components (which include intrinsic factor and the proton pump H^+,K^+-ATPase). AMAG is inherited as an autosomal dominant trait. Some patients also develop Hashimoto's thyroiditis and 50% have thyroid antibodies; conversely, parietal cell antibodies are found in 30% of patients with thyroiditis.

The lack of intrinsic factor leads to vitamin B_{12} deficiency that can result in a megaloblastic anemia (pernicious anemia—see p. 932) or neurologic symptoms (subacute combined degeneration—see p. 38).

Hypochlorhydria leads to G-cell hyperplasia and elevated serum gastrin levels (often >1000 pg/mL). Elevated gastrin levels lead to enterochromaffin-like cell hyperplasia, which occasionally undergoes transformation to a carcinoid tumor.

In some patients, AMAG may be associated with chronic *Helicobacter pylori* infection, although the relationship is not clear. Gastrectomy and chronic acid suppression with proton pump inhibitors cause similar deficiencies of intrinsic factor secretion.

The areas of atrophic gastritis in the body and fundus may manifest metaplasia. Patients with AMAG have a 3-fold increased relative risk of developing gastric adenocarcinoma.

Diagnosis is made by endoscopic biopsy. Serum B_{12} levels should be obtained. Parietal cell antibodies can be detected but are not measured routinely. The issue of surveillance endoscopy for cancer screening is unsettled; follow-up examinations are unnecessary unless histologic abnormalities (eg, dysplasia) are present on initial biopsy or symptoms develop. No treatment is needed other than parenteral replacement of vitamin B_{12}.

Peptic Ulcer Disease

A peptic ulcer is an erosion in a segment of the GI mucosa, typically in the stomach (gastric ulcer) or the first few centimeters of the duodenum (duodenal ulcer), that penetrates through the muscularis mucosae. Nearly all ulcers are caused by *Helicobacter pylori* infection or NSAID use. Symptoms typically include burning epigastric pain that is often relieved by food. Diagnosis is by endoscopy and testing for *H. pylori*. Treatment involves acid suppression, eradication of *H. pylori* (if present), and avoidance of NSAIDs.

Ulcers may range in size from several millimeters to several centimeters. Ulcers are delineated from erosions by the depth of penetration; erosions are more superficial and do not involve the muscularis mucosae. Ulcers can occur at any age, including infancy and childhood, but are most common among middle-aged adults.

Etiology

H. pylori and NSAIDs disrupt normal mucosal defense and repair, making the mucosa more susceptible to acid. *H. pylori* infection is present in 50 to 70% of patients with duodenal ulcers and 30 to 50% of patients with gastric ulcers. If *H. pylori* is eradicated, only 10% of patients have recurrence of peptic ulcer disease, compared with 70% recurrence in patients treated with acid suppression alone. NSAIDs now account for > 50% of peptic ulcers.

Cigarette smoking is a risk factor for the development of ulcers and their complications. Also, smoking impairs ulcer healing and increases the incidence of recurrence. Risk correlates with the number of cigarettes smoked per day. Although alcohol is a strong promoter of acid secretion, no definitive data link moderate amounts of alcohol to the development or delayed healing of ulcers. Very few patients have hypersecretion of gastrin (Zollinger-Ellison syndrome—see p. 200).

A family history exists in 50 to 60% of children with duodenal ulcer.

Symptoms and Signs

Symptoms depend on ulcer location and patient age; many patients, particularly elderly patients, have few or no symptoms. Pain is most common, often localized to the epigastrium and relieved by food or antacids. The pain is described as burning or gnawing, or sometimes as a sensation of hunger. The course is usually chronic and recurrent. Only about half of patients present with the characteristic pattern of symptoms.

Gastric ulcer symptoms often do not follow a consistent pattern (eg, eating sometimes exacerbates rather than relieves pain). This is especially true for pyloric channel ulcers, which are often associated with symptoms of obstruction (eg, bloating, nausea, vomiting) caused by edema and scarring.

Duodenal ulcers tend to cause more consistent pain. Pain is absent when the patient awakens but appears in mid-morning, is relieved by food, but recurs 2 to 3 h after a meal. Pain that awakens a patient at night is common and is highly suggestive of duodenal ulcer. In neonates, perforation and hemorrhage may be the first manifestation of duodenal ulcer. Hemorrhage may also be the first recognized sign in later infancy and early childhood, although repeated vomiting or evidence of abdominal pain may be a clue.

Diagnosis

• Endoscopy

• Sometimes serum gastrin levels

Diagnosis of peptic ulcer is suggested by patient history and confirmed by endoscopy. Empiric therapy is often begun without definitive diagnosis. However, endoscopy allows for biopsy or cytologic brushing of gastric and esophageal lesions to distinguish between simple ulceration and ulcerating stomach cancer. Stomach cancer may manifest with similar manifestations and must be excluded, especially in patients who are > 45, have lost weight, or report severe or refractory symptoms. The incidence of malignant duodenal ulcer is extremely low, so biopsies of lesions in that area are generally not warranted. Endoscopy can also be used to definitively diagnose *H. pylori* infection, which should be sought when an ulcer is detected.

Gastrin-secreting cancer and Zollinger-Ellison syndrome should be considered when there are multiple ulcers, when ulcers develop in atypical locations (eg, postbulbar) or are refractory to treatment, or when the patient has prominent diarrhea or weight loss. Serum gastrin levels should be measured in these patients.

Complications

Hemorrhage: Mild to severe hemorrhage is the most common complication of peptic ulcer disease. Symptoms include hematemesis (vomiting of fresh blood or "coffee ground" material); passage of bloody stools (hematochezia) or black tarry stools (melena); and weakness, orthostasis, syncope, thirst, and sweating caused by blood loss.

Penetration (confined perforation): A peptic ulcer may penetrate the wall of the stomach. If adhesions prevent leakage into the peritoneal cavity, free penetration is avoided and confined perforation occurs. Still, the ulcer may penetrate into the duodenum and enter the adjacent confined space (lesser sac) or another organ (eg, pancreas, liver). Pain may be intense, persistent, referred to sites other than the abdomen (usually the back when caused by penetration of a posterior duodenal ulcer into the pancreas), and modified by body position. CT or MRI is usually needed to confirm the diagnosis. When therapy does not result in healing, surgery is required.

Free perforation: Ulcers that perforate into the peritoneal cavity unchecked by adhesions are usually located in the anterior wall of the duodenum or, less commonly, in the stomach. The patient presents with an acute abdomen. There is sudden, intense, continuous epigastric pain that spreads rapidly throughout the abdomen, often becoming prominent in the right lower quadrant and at times referred to one or both shoulders. The patient usually lies still because even deep breathing worsens the pain. Palpation of the abdomen is painful, rebound tenderness is prominent, abdominal muscles are rigid (boardlike), and bowel sounds are diminished or absent. Shock may ensue, heralded by increased pulse rate and decreased BP and urine output. Symptoms may be less striking in elderly or moribund patients and those receiving corticosteroids or immunosuppressants.

Diagnosis is confirmed if an x-ray or CT shows free air under the diaphragm or in the peritoneal cavity. Upright views of the chest and abdomen are preferred. The most sensitive view is the lateral x-ray of the chest. Severely ill patients may be unable to sit upright and should have a lateral decubitus x-ray of the abdomen. Failure to detect free air does not exclude the diagnosis.

Immediate surgery is required. The longer the delay, the poorer is the prognosis. When surgery is contraindicated, the alternatives are continuous nasogastric suction and broad-spectrum antibiotics.

Gastric outlet obstruction: Obstruction may be caused by scarring, spasm, or inflammation from an ulcer. Symptoms include recurrent, large-volume vomiting, occurring more frequently at the end of the day and often as late as 6 h after the last meal. Loss of appetite with persistent bloating or fullness after eating also suggests gastric outlet obstruction. Prolonged vomiting may cause weight loss, dehydration, and alkalosis.

If the patient's history suggests obstruction, physical examination, gastric aspiration, or x-rays may provide evidence of retained gastric contents. A succussion splash heard > 6 h after a meal or aspiration of fluid or food residue > 200 mL after an overnight fast suggests gastric retention. If gastric aspiration shows marked retention, the stomach should be emptied and endoscopy done or x-rays taken to determine site, cause, and degree of obstruction.

Edema or spasm caused by an active pyloric channel ulcer is treated with gastric decompression by nasogastric suction and acid suppression (eg, IV H_2 blockers). Dehydration and electrolyte imbalances resulting from protracted vomiting or continued nasogastric suctioning should be vigorously sought and corrected. Prokinetic agents are not indicated. Generally, obstruction resolves within 2 to 5 days of treatment. Prolonged obstruction may result from peptic scarring and may respond to endoscopic pyloric balloon dilation. Surgery is necessary to relieve obstruction in selected cases.

Recurrence: Factors that affect recurrence of ulcer include failure to eradicate *H. pylori*, continued NSAID use, and smoking. Less commonly, a gastrinoma (Zollinger-Ellison syndrome) may be the cause. The 3-yr recurrence rate for gastric and duodenal ulcers is < 10% when *H. pylori* is successfully eradicated but > 50% when it is not. Thus, a patient with recurrent disease should be tested for *H. pylori* and treated again if the tests are positive.

Although long-term treatment with H_2 blockers, proton pump inhibitors, or misoprostol reduces the risk of recurrence, their routine use for this purpose is not recommended. However, patients who require NSAIDs after having had a peptic ulcer are candidates for long-term therapy, as are those with a marginal ulcer or prior perforation or bleeding.

Stomach cancer: Patients with *H. pylori*-associated ulcers have a 3- to 6-fold increased risk of gastric cancer later in life. There is no increased risk of cancer with ulcers of other etiology.

Treatment

• Eradication of *H. pylori* (when present)

• Acid-suppressive drugs

Treatment of gastric and duodenal ulcers requires eradication of *H. pylori* when present (see p. 130) and a reduction of gastric acidity. For duodenal ulcers, it is particularly important to suppress nocturnal acid secretion.

Methods of decreasing acidity include a number of drugs, all of which are effective but which vary in cost, duration of therapy, and convenience of dosing. In addition, mucosal protective drugs (eg, sucralfate) and acid-reducing surgical procedures may be used. Drug therapy is discussed on p. 136.

Adjuncts: Smoking should be stopped, and alcohol consumption stopped or limited to small amounts of dilute alcohol. There is no evidence that changing the diet speeds ulcer healing or prevents recurrence. Thus, many physicians recommend eliminating only foods that cause distress.

Surgery: With current drug therapy, the number of patients requiring surgery has declined dramatically. Indications include perforation, obstruction, uncontrolled or recurrent bleeding, and, although rare, symptoms that do not respond to drug therapy.

Surgery consists of a procedure to reduce acid secretion, often combined with a procedure to ensure gastric drainage. The recommended operation for duodenal ulcer is highly selective, or parietal cell, vagotomy (which is limited to nerves at the gastric body and spares antral innervation, thereby obviating the need for a drainage procedure). This procedure has a very low mortality rate and avoids the morbidity associated with resection and traditional vagotomy. Other acid-reducing surgical procedures include antrectomy, hemigastrectomy, partial gastrectomy, and subtotal gastrectomy (ie, resection of 30 to 90% of the distal stomach). These are typically combined with truncal vagotomy. Patients who undergo a resective procedure or who have an obstruction require gastric drainage via a gastroduodenostomy (Billroth I) or gastrojejunostomy (Billroth II).

The incidence and type of postsurgical symptoms vary with the type of operation. After resective surgery, up to 30% of patients have significant symptoms, including weight loss, maldigestion, anemia, dumping syndrome, reactive hypoglycemia, bilious vomiting, mechanical problems, and ulcer recurrence.

Weight loss is common after subtotal gastrectomy; the patient may limit food intake because of early satiety (because the residual gastric pouch is small) or to prevent dumping syndrome and other postprandial syndromes. With a small gastric pouch, distention or discomfort may occur after a meal of even moderate size; patients should be encouraged to eat smaller and more frequent meals.

Maldigestion and steatorrhea caused by pancreaticobiliary bypass, especially with Billroth II anastomosis, may contribute to weight loss.

Anemia is common (usually from iron deficiency, but occasionally from vitamin B_{12} deficiency caused by loss of intrinsic factor or bacterial overgrowth) in the afferent limb, and osteomalacia may occur. IM vitamin B_{12} supplementation is recommended for all patients with total gastrectomy but may also be given to patients with subtotal gastrectomy if deficiency is suspected.

Dumping syndrome may follow gastric surgical procedures, particularly resections. Weakness, dizziness, sweating, nausea, vomiting, and palpitation occur soon after eating, especially hyperosmolar foods. This phenomenon is referred to as early dumping, the cause of which remains unclear but likely involves autonomic reflexes, intravascular volume contraction, and release of vasoactive peptides from the small intestine. Dietary modifications, with smaller, more frequent meals and decreased carbohydrate

intake, usually help.

Reactive hypoglycemia or **late dumping** (another form of the syndrome) results from rapid emptying of carbohydrates from the gastric pouch. Early high peaks in blood glucose stimulate excess release of insulin, which leads to symptomatic hypoglycemia several hours after the meal. A high-protein, low-carbohydrate diet and adequate caloric intake (in frequent small feedings) are recommended.

Mechanical problems (including gastroparesis and bezoar formation—see p. 138) may occur secondary to a decrease in phase III gastric motor contractions, which are altered after antrectomy and vagotomy. Diarrhea is especially common after vagotomy, even without a resection (pyloroplasty).

Ulcer recurrence, according to older studies, occurs in 5 to 12% after highly selective vagotomy and in 2 to 5% after resective surgery. Recurrent ulcers are diagnosed by endoscopy and generally respond to either proton pump inhibitors or H_2 blockers. For ulcers that continue to recur, the completeness of vagotomy should be tested by gastric analysis, *H. pylori* eliminated if present, and Zollinger-Ellison syndrome ruled out by serum gastrin studies.

Drug Treatment of Gastric Acidity

Drugs for decreasing acidity are used for peptic ulcer, gastroesophageal reflux disease (GERD—see p. 125), and many forms of gastritis. Some drugs are used in regimens for treating *H. pylori* infection. Drugs include proton pump inhibitors, H_2 blockers, antacids, and prostaglandins.

Proton pump inhibitors: These drugs are potent inhibitors of H^+,K^+-ATPase. This enzyme, located in the apical secretory membrane of the parietal cell, plays a key role in the secretion of H^+ (protons). These drugs can completely inhibit acid secretion and have a long duration of action. They promote ulcer healing and are also key components of *H. pylori* eradication regimens. Proton pump inhibitors have replaced H_2 blockers in most clinical situations because of greater rapidity of action and efficacy.

Proton pump inhibitors include esomeprazole, lansoprazole, and pantoprazole, all available orally and IV, and omeprazole and rabeprazole, available only orally in the US (see Table 13-1). Omeprazole is available without a prescription in the US. For uncomplicated duodenal ulcers, omeprazole 20 mg po once/day or lansoprazole 30 mg po once/day is given for 4 wk. Complicated duodenal ulcers (ie, multiple

[**Table 13-1.** Proton Pump Inhibitors]

ulcers, bleeding ulcers, those > 1.5 cm, or those occurring in patients with serious underlying illness) respond better to higher doses (omeprazole 40 mg once/day, lansoprazole 60 mg once/day or 30 mg bid). Gastric ulcers require treatment for 6 to 8 wk. Gastritis and GERD require 8 to 12 wk of therapy; GERD additionally requires long-term maintenance.

Long-term proton pump inhibitor therapy produces elevated gastrin levels, which lead to enterochromaffin-like cell hyperplasia. However, there is no evidence of dysplasia or malignant transformation in patients receiving this treatment. Some may develop vitamin B_{12} malabsorption.

H_2 blockers: These drugs (cimetidine, ranitidine, famotidine, available IV and orally; and nizatidine available orally) are competitive inhibitors of histamine at the H_2 receptor, thus suppressing gastrin-stimulated acid secretion and proportionately reducing gastric juice volume. Histamine-mediated pepsin secretion is also decreased.

H_2 blockers are well absorbed from the GI tract, with onset of action 30 to 60 min after ingestion and peak effects at 1 to 2 h. IV administration produces a more rapid onset of action. Duration of action is proportional to dose and ranges from 6 to 20 h. Doses should often be reduced in elderly patients.

For duodenal ulcers, once daily oral administration of cimetidine 800 mg, ranitidine 300 mg, famotidine 40

mg, or nizatidine 300 mg given at bedtime or after dinner for 6 to 8 wk is effective. Gastric ulcers may respond to the same regimen continued for 8 to 12 wk, but because nocturnal acid secretion is less important, morning administration may be equally or more effective. Children ≥ 40 kg may receive adult doses. Below that weight, the oral dosage is ranitidine 2 mg/kg q 12 h and cimetidine 10 mg/kg q 12 h. For GERD, H_2 blockers are now mostly used for pain management. Gastritis heals with famotidine or ranitidine given bid for 8 to 12 wk.

Cimetidine has minor antiandrogen effects expressed as reversible gynecomastia and, less commonly, erectile dysfunction with prolonged use. Mental status changes, diarrhea, rash, drug fever, myalgias, thrombocytopenia, and sinus bradycardia and hypotension after rapid IV administration have been reported with all H_2 blockers, generally in < 1% of treated patients but more commonly in elderly patients.

Cimetidine and, to a lesser extent, other H_2 blockers interact with the P-450 microsomal enzyme system and may delay metabolism of other drugs eliminated through this system (eg, phenytoin, warfarin, theophylline, diazepam, lidocaine).

Antacids: These agents neutralize gastric acid and reduce pepsin activity (which diminishes as gastric pH rises to > 4.0). In addition, some antacids adsorb pepsin. Antacids may interfere with the absorption of other drugs (eg, tetracycline, digoxin, iron).

Antacids relieve symptoms, promote ulcer healing, and reduce recurrence. They are relatively inexpensive but must be taken 5 to 7 times/day. The optimal antacid regimen for ulcer healing seems to be 15 to 30 mL of liquid or 2 to 4 tablets 1 h and 3 h after each meal and at bedtime. The total daily dosage of antacids should provide 200 to 400 mEq neutralizing capacity. However, antacids have been superseded by acid-suppressive therapy in the treatment of peptic ulcer and are used only for short-term symptom relief.

In general, there are 2 types of antacids: absorbable and nonabsorbable. Absorbable antacids (eg, Na bicarbonate, Ca carbonate) provide rapid, complete neutralization but may cause alkalosis and should be used only briefly (1 or 2 days). Nonabsorbable antacids (eg, aluminum or Mg hydroxide) have fewer systemic adverse effects and are preferred.

Aluminum hydroxide is a relatively safe, commonly used antacid. With chronic use, phosphate depletion occasionally develops as a result of binding of phosphate by aluminum in the GI tract. The risk of phosphate depletion increases in alcoholics, undernourished patients, and patients with renal disease (including those receiving hemodialysis). Aluminum hydroxide causes constipation.

Mg hydroxide is a more effective antacid than aluminum but may cause diarrhea. To limit diarrhea, many proprietary antacids combine Mg and aluminum antacids. Because small amounts of Mg are absorbed, Mg preparations should be used with caution in patients with renal disease.

Prostaglandins: Certain prostaglandins (especially misoprostol) inhibit acid secretion by decreasing the generation of cyclic AMP that is triggered by histamine stimulation of the parietal cell, and enhance mucosal defense. Synthetic prostaglandin derivatives are used predominantly to decrease the risk of NSAID-induced mucosal injury. Patients at high risk of NSAID-induced ulcers (ie, elderly patients, those with a history of ulcer or ulcer complication, those also taking corticosteroids) are candidates to take misoprostol 200 µg po qid with food along with their NSAID. Common adverse effects of misoprostol are abdominal cramping and diarrhea, which occur in 30% of patients. Misoprostol is a powerful abortifacient and is absolutely contraindicated in women of childbearing age who are not using contraception.

Sucralfate: This drug is a sucrose-aluminum complex that dissociates in stomach acid and forms a physical barrier over an inflamed area, protecting it from acid, pepsin, and bile salts. It also inhibits pepsin-substrate interaction, stimulates mucosal prostaglandin production, and binds bile salts. It has no effect on acid output or gastrin secretion. Sucralfate seems to have trophic effects on the ulcerated mucosa, possibly by binding growth factors and concentrating them at an ulcer site. Systemic absorption of sucralfate is negligible. Constipation occurs in 3 to 5% of patients. Sucralfate may bind to other drugs and interfere with their absorption.

Chapter 14. Bezoars and Foreign Bodies

Introduction

Food and other ingested materials may collect and form solid masses within the GI tract.

Bezoars

A bezoar is a tightly packed collection of partially digested or undigested material that is unable to exit the stomach. It often occurs in patients with abnormal gastric emptying, especially those that have diabetic gastroparesis, as well as after gastric surgery. Many bezoars are asymptomatic, but some cause symptoms of gastric outlet obstruction. Some can be dissolved enzymatically, others removed endoscopically, and some require surgery.

Partially digested agglomerations of vegetable matter are called phytobezoars; agglomerations of hair are called trichobezoars. Pharmacobezoars are concretions of medication (particularly common with sucralfate and aluminum hydroxide gel). Many other substances have been found in bezoars.

Etiology

Trichobezoars, which can weigh several kg, most commonly occur in patients with psychiatric disturbances who chew and swallow their own hair. Phytobezoars often occur in patients who have undergone a Billroth I or II partial gastrectomy, especially when accompanied by vagotomy. Hypochlorhydria, diminished antral motility, and incomplete mastication are the main predisposing factors; these factors are more common among the elderly, who are thus at higher risk of bezoar formation. Others include diabetic gastroparesis and gastroplasty for morbid obesity. Consumption of persimmons (a fruit containing the tannin shibuol, which polymerizes in the stomach) has been known to cause bezoars that require surgery in > 90% of cases. Persimmon bezoars often occur in epidemics in regions where the fruit is grown.

Symptoms and Signs

Most bezoars cause no symptoms, although postprandial fullness, nausea and vomiting, pain, and GI bleeding may occur.

Diagnosis

• Endoscopy

Bezoars are detectable as a mass lesion on most tests (eg, x-ray, ultrasound, CT) that may be done to evaluate upper GI symptoms. They may be mistaken for tumors; upper endoscopy is usually done. On endoscopy, bezoars have an unmistakable irregular surface and may range in color from yellow-green to gray-black. An endoscopic biopsy that yields hair or plant material is diagnostic.

Treatment

• Observation

• Sometimes manual removal via endoscopy

• Sometimes enzymatic therapy

If initial diagnosis is made by endoscopy, removal can be attempted at that time. Fragmentation with forceps, wire snare, jet spray, or even laser may break up bezoars, allowing them to pass or be extracted. Metoclopramide 40 mg IV over 24 h or 10 mg IM q 4 h for several days may increase peristalsis and aid gastric emptying of fragmented material.

If endoscopy was not initially done, treatment is based on symptoms. Asymptomatic patients that have a

bezoar discovered incidentally during testing for other reasons do not necessarily require intervention. In some cases, a trial of enzymatic therapy can be attempted. Enzymes include papain (10,000 U with each meal), meat tenderizer (5 mL [1 tsp] in 8 oz of clear liquid before each meal), or cellulase (10 g dissolved in 1 L water, consumed over 24 h for 2 to 3 days). If enzymatic therapy is unsuccessful, or if patients are symptomatic, endoscopic removal may be tried. Rocklike concretions and trichobezoars usually require laparotomy.

Foreign Bodies

A variety of foreign bodies may enter the GI tract. Many pass spontaneously, but some become impacted, causing symptoms of obstruction. Perforation may occur. The esophagus is the most common (75%) site of impaction. Nearly all impacted objects can be removed endoscopically, but surgery is occasionally necessary.

Undigestible objects may be intentionally swallowed by children and demented adults. Denture wearers, the elderly, and inebriated people are prone to accidentally swallowing inadequately masticated food (particularly meat), which may become impacted in the esophagus. Smugglers who swallow drug-filled balloons, vials, or packages to escape detection (body packers or body stuffers) may develop intestinal obstruction. The packaging may rupture, leading to drug overdose.

Esophageal foreign bodies: Foreign bodies usually lodge in an area of esophageal narrowing such as at the cricopharyngeus or aortic arch or just above the gastroesophageal junction. If obstruction is complete, patients retch or vomit. Some patients drool because they are unable to swallow secretions.

Immediate endoscopic removal is required for sharp objects, coins in the proximal esophagus, and any obstruction causing significant symptoms. Also, button batteries lodged in the esophagus may cause direct corrosive damage, low-voltage burns, and pressure necrosis and thus require prompt removal.

Other esophageal foreign bodies may be observed for a maximum of 12 to 24 h. Glucagon 1 mg IV sometimes relaxes the esophagus enough to allow spontaneous passage. Other methods, such as use of effervescent agents, meat tenderizer, and bougienage, are not recommended. Endoscopic removal is the treatment of choice. Removal is best achieved using a forceps, basket, or snare with an overtube placed in the esophagus to prevent aspiration.

Sometimes, foreign bodies scratch the esophagus but do not become lodged. In such cases, patients may report a foreign body sensation even though no foreign body is present.

Gastric and intestinal foreign bodies: Foreign bodies that pass through the esophagus are asymptomatic unless obstruction or perforation occurs. Of the foreign bodies that reach the stomach, 80 to 90% pass spontaneously, 10 to 20% require nonoperative intervention, and ≤ 1% require surgery. Thus, most intragastric foreign bodies can be ignored. However, objects larger than 5 × 2 cm rarely pass the stomach. Sharp objects should be retrieved from the stomach because 15 to 35% will cause intestinal perforation, but small round objects (eg, coins and button batteries) can simply be observed. The patient's stools should be searched, and if the object does not appear, x-rays are taken at 48-h intervals. A coin that remains in the stomach for > 4 wk or a battery showing signs of corrosion on x-ray that remains in the stomach for > 48 h should be removed. A hand-held metal detector can localize metallic foreign bodies and provide information comparable to that yielded by plain x-rays.

Patients with symptoms of obstruction or perforation require laparotomy. Ingested drug packages are of great concern because of the risk of leakage and consequent drug overdose. Patients with symptoms of drug toxicity should have immediate laparotomy with interim medical management of symptoms (eg, benzodiazepines for cocaine toxicity). Asymptomatic patients should be admitted to the hospital. Some clinicians advocate oral polyethylene glycol solution as a cathartic to enhance passage of the material; others suggest surgical removal. The best practice is unclear.

Most foreign objects that have passed into the small intestine usually traverse the GI tract without problem, even if they take weeks or months to do so. They tend to be held up just before the ileocecal valve or at any site of narrowing, as is present in Crohn's disease. Sometimes objects such as toothpicks

remain within the GI tract for many years, only to turn up in a granuloma or abscess.

Rectal foreign bodies: Gallstones, fecaliths, and swallowed foreign bodies (including toothpicks and chicken and fish bones) may lodge at the anorectal junction. Urinary calculi, vaginal pessaries, or surgical sponges or instruments may erode into the rectum. Foreign bodies, sometimes bizarre and/or related to sexual play, may be introduced intentionally but become lodged unintentionally. Some objects are caught in the rectal wall, and others are trapped just above the anal sphincter.

Sudden, excruciating pain during defecation should arouse suspicion of a penetrating foreign body, usually lodged at or just above the anorectal junction. Other manifestations depend on the size and shape of the foreign body, its duration in situ, and the presence of infection or perforation.

Foreign bodies usually become lodged in the mid rectum, where they cannot negotiate the anterior angulation of the rectum. They can be felt on digital examination. Abdominal examination and chest x-rays may be necessary to exclude possible intraperitoneal rectal perforation.

If the object can be palpated, a local anesthetic is given by sc and submucosal injections of 0.5% lidocaine or bupivacaine. The anus is dilated with a rectal retractor, and the foreign body is grasped and removed. If the object cannot be palpated, the patient should be hospitalized. Peristalsis usually moves the foreign body down to the mid rectum, and the above routine can be followed. Removal via a sigmoidoscope or proctoscope is rarely successful, and sigmoidoscopy usually forces the foreign body proximally, delaying its extraction. Regional or general anesthesia is infrequently necessary, and laparotomy with milking of the foreign body toward the anus or colotomy with extraction of the foreign body is rarely necessary. After extraction, sigmoidoscopy should be done to rule out significant rectal trauma or perforation. Removal of a rectal foreign body may be of high risk and should be done by a surgeon or gastroenterologist skilled in foreign body removal.

Chapter 15. Pancreatitis

Introduction

Pancreatitis is classified as either acute or chronic. Acute pancreatitis is inflammation that resolves both clinically and histologically. Chronic pancreatitis is characterized by histologic changes that are irreversible and progressive and that result in considerable loss of exocrine and endocrine pancreatic function. Patients with chronic pancreatitis may have a flare-up of acute disease.

Pancreatitis can affect both the exocrine and endocrine functions of the pancreas. Pancreatic acinar cells secrete bicarbonate and digestive enzymes into ducts that connect the pancreas to the duodenum at the ampulla of Vater (exocrine function). Pancreatic β-cells secrete insulin directly into the bloodstream (endocrine function).

Acute Pancreatitis

Acute pancreatitis is inflammation of the pancreas (and, sometimes, adjacent tissues) caused by the release of activated pancreatic enzymes. The most common triggers are biliary tract disease and chronic heavy alcohol intake. The condition ranges from mild (abdominal pain and vomiting) to severe (pancreatic necrosis and a systemic inflammatory process with shock and multiorgan failure). Diagnosis is based on clinical presentation and serum amylase and lipase levels. Treatment is supportive, with IV fluids, analgesics, and fasting.

Etiology

Biliary tract disease and alcoholism account for ≥ 80% of acute pancreatitis cases. The remaining 20% result from myriad causes (see
Table 15-1).

Pathophysiology

The precise mechanism by which obstruction of the sphincter of Oddi by a gallstone or microlithiasis (sludge) causes pancreatitis is unclear, although it probably involves increased ductal pressure. Prolonged alcohol intake (> 100 g/day for > 3 to 5 yr) may cause the protein of pancreatic enzymes to precipitate within small pancreatic ductules. Ductal obstruction by these protein plugs may cause premature activation of pancreatic enzymes. An alcohol binge in such patients can trigger pancreatitis, but the exact mechanism is not known.

A number of genetic mutations predisposing to pancreatitis have been identified. One, an autosomal dominant mutation of the cationic trypsinogen gene, causes pancreatitis in 80% of carriers; an obvious familial pattern is present. Other mutations have lesser penetrance and are not readily apparent clinically except through genetic testing. The genetic abnormality responsible for cystic fibrosis increases the risk of recurrent acute as well as chronic pancreatitis.

Regardless of the etiology, pancreatic enzymes (including trypsin, phospholipase A_2, and elastase) become activated within the gland itself. The enzymes can damage tissue and activate complement and the inflammatory cascade, producing cytokines. This process causes inflammation, edema, and sometimes necrosis. In mild pancreatitis, inflammation is confined to the pancreas; the mortality rate is < 5%. In severe pancreatitis, there is significant inflammation, with necrosis and hemorrhage of the gland and a systemic inflammatory response; the mortality rate is 10 to 50%. After 5 to 7 days, necrotic pancreatic tissue may become infected by enteric bacteria.

[**Table 15-1.** Some Causes of Acute Pancreatitis]

Activated enzymes and cytokines that enter the peritoneal cavity cause a chemical burn and third spacing of fluid; those that enter the systemic circulation cause a systemic inflammatory response that can result in acute respiratory distress syndrome and renal failure. The systemic effects are mainly the result of

increased capillary permeability and decreased vascular tone, which result from the released cytokines and chemokines. Phospholipase A_2 is thought to injure alveolar membranes of the lungs.

In about 40% of patients, collections of enzyme-rich pancreatic fluid and tissue debris form in and around the pancreas. In about half, the collections resolve spontaneously. In others, the collections become infected or form pseudocysts. Pseudocysts have a fibrous capsule without an epithelial lining. Pseudocysts may hemorrhage, rupture, or become infected.

Death during the first several days is usually caused by cardiovascular instability (with refractory shock and renal failure) or respiratory failure (with hypoxemia and at times adult respiratory distress syndrome). Occasionally, death results from heart failure secondary to an unidentified myocardial depressant factor. Death after the first week is usually caused by multiorgan system failure.

Symptoms and Signs

An acute attack causes steady, boring upper abdominal pain, typically severe enough to require large doses of parenteral opioids. The pain radiates through to the back in about 50% of patients; rarely, pain is first felt in the lower abdomen. Pain usually develops suddenly in gallstone pancreatitis; in alcoholic pancreatitis, pain develops over a few days. The pain usually persists for several days. Sitting up and leaning forward may reduce pain, but coughing, vigorous movement, and deep breathing may accentuate it. Nausea and vomiting are common.

The patient appears acutely ill and sweaty. Pulse rate is usually 100 to 140 beats/min. Respiration is shallow and rapid. BP may be transiently high or low, with significant postural hypotension. Temperature may be normal or even subnormal at first but may increase to 37.7 to 38.3° C (100 to 101° F) within a few hours. Sensorium may be blunted to the point of semicoma. Scleral icterus is occasionally present. The lungs may have limited diaphragmatic excursion and evidence of atelectasis.

About 20% of patients experience upper abdominal distention caused by gastric distention or displacement of the stomach by a pancreatic inflammatory mass. Pancreatic duct disruption may cause ascites (pancreatic ascites). Marked abdominal tenderness occurs, most often in the upper abdomen. There may be mild tenderness in the lower abdomen, but the rectum is not tender and the stool is usually negative for occult blood. Mild-to-moderate muscular rigidity may be present in the upper abdomen but is rare in the lower abdomen. Rarely, severe peritoneal irritation results in a rigid and boardlike abdomen. Bowel sounds may be hypoactive. Grey Turner's sign (ecchymoses of the flanks) and Cullen's sign (ecchymoses of the umbilical region) indicate extravasation of hemorrhagic exudate.

Infection in the pancreas or in an adjacent fluid collection should be suspected if the patient has a generally toxic appearance with elevated temperature and WBC count or if deterioration follows an initial period of stabilization.

Diagnosis

• Serum markers (amylase, lipase)

• Once pancreatitis is diagnosed, CT usually done

Pancreatitis is suspected whenever severe abdominal pain occurs, especially in a patient with significant alcohol use or known gallstones. Conditions causing similar symptoms include perforated gastric or duodenal ulcer, mesenteric infarction, strangulating intestinal obstruction, dissecting aneurysm, biliary colic, appendicitis, diverticulitis, inferior wall MI, and hematoma of the abdominal muscles or spleen.

Diagnosis is made by clinical suspicion, serum markers (amylase and lipase), and the absence of other causes for the patient's symptoms. Thus, a broad range of tests is done, typically including CBC, electrolytes, Ca, Mg, glucose, BUN, creatinine, amylase, and lipase. Other routine tests include ECG and an abdominal series (chest, flat, and upright abdomen). A urine dipstick for trypsinogen-2 has sensitivity and specificity of > 90% for acute pancreatitis. Ultrasound and CT are not generally done specifically to diagnose pancreatitis but are often used to evaluate acute abdominal pain (see p.

108).

Laboratory tests: Serum amylase and lipase concentrations increase on the first day of acute pancreatitis and return to normal in 3 to 7 days. Lipase is more specific for pancreatitis, but both enzymes may be increased in renal failure and various abdominal conditions (eg, perforated ulcer, mesenteric vascular occlusion, intestinal obstruction). Other causes of increased serum amylase include salivary gland dysfunction, macroamylasemia, and tumors that secrete amylase. Both amylase and lipase levels may remain normal if destruction of acinar tissue during previous episodes precludes release of sufficient amounts of enzymes. The serum of patients with hypertriglyceridemia may contain a circulating inhibitor that must be diluted before an elevation in serum amylase can be detected.

Amylase:creatinine clearance ratio does not have sufficient sensitivity or specificity to diagnose pancreatitis. It is generally used to diagnose macroamylasemia when no pancreatitis exists. In macroamylasemia, amylase bound to serum immunoglobulin falsely elevates the serum amylase level.

Fractionation of total serum amylase into pancreatic type (p-type) isoamylase and salivary-type (s-type) isoamylase increases the accuracy of serum amylase. However, the level of p-type also increases in renal failure and in other severe abdominal conditions in which amylase clearance is altered.

The WBC count usually increases to 12,000 to 20,000/µL. Third-space fluid losses may increase the Hct to as high as 50 to 55%, indicating severe inflammation. Hyperglycemia may occur. Serum Ca concentration falls as early as the first day because of the formation of Ca "soaps" secondary to excess generation of free fatty acids, especially by pancreatic lipase. Serum bilirubin increases in 15 to 25% of patients because pancreatic edema compresses the common bile duct.

Imaging: Plain x-rays of the abdomen may disclose calcifications within pancreatic ducts (evidence of prior inflammation and hence chronic pancreatitis), calcified gallstones, or localized ileus in the left upper quadrant or the center of the abdomen (a "sentinel loop" of small bowel, dilation of the transverse colon, or duodenal ileus). Chest x-ray may reveal atelectasis or a pleural effusion (usually left-sided or bilateral but rarely confined to the right pleural space).

Ultrasound should be done if gallstone pancreatitis is suspected (and another etiology is not obvious) to detect gallstones or dilation of the common bile duct (which indicates biliary tract obstruction). Edema of the pancreas may be visualized, but overlying gas frequently obscures the pancreas.

CT with IV contrast is generally done to identify necrosis, fluid collections, or pseudocysts once pancreatitis has been diagnosed. It is particularly recommended for severe pancreatitis or if a complication ensues (eg, hypotension or progressive leukocytosis and elevation of temperature). IV contrast facilitates the recognition of pancreatic necrosis; however, it may cause pancreatic necrosis in areas of low perfusion (ie, ischemia). Thus, contrast-enhanced CT should be done only after the patient has been adequately hydrated.

If pancreatic infection is suspected, fluid obtained by percutaneous CT-guided needle aspiration of cysts or areas of fluid collection or necrosis may reveal organisms on Gram stain or culture. The diagnosis is supported by positive blood cultures and, particularly, by the presence of air bubbles in the retroperitoneum on abdominal CT. The advent of magnetic resonance cholangiopancreatography (MRCP) may make the selection of pancreatic imaging simpler.

Prognosis

In edematous pancreatitis, mortality is < 5%. In pancreatitis with necrosis and hemorrhage, mortality is 10 to 50%. In pancreatic infection, mortality is usually 100% without extensive surgical debridement or drainage of the infected area.

CT findings correlate with prognosis. If CT is normal or shows only mild pancreatic edema (Balthazar class A or B), the prognosis is excellent. Patients with peripancreatic inflammation or one area of fluid collection (classes C and D) have a 10 to 15% incidence of abscess formation; the incidence is over 60% in patients with two or more areas of fluid collection (class E).

Ranson's prognostic signs help predict the prognosis of acute pancreatitis. Five of Ranson's signs can be documented at admission:

• Age > 55 yr

• Plasma glucose > 200 mg/dL (> 11.1 mmol/L)

• Serum LDH > 350 IU/L

• AST > 250 UL

• WBC count > 16,000/µL

The rest of Ranson's signs are determined within 48 h of admission:

• Hct decrease > 10%

• BUN increase > 5 mg/dL (> 1.78 mmol/L)

• Serum Ca < 8 mg/dL (< 2 mmol/L)

• Pao_2 < 60 mm Hg (< 7.98 kPa)

• Base deficit > 4 mEq/L (> 4 mmol/L)

• Estimated fluid sequestration > 6 L

Mortality increases with the number of positive signs: If < 3 signs are positive, the mortality rate is < 5%; if ≥ 3 are positive, mortality is 15 to 20%.

The APACHE II index (see
Table 222-4 on p. 2248), calculated on the second hospital day, also correlates with prognosis.

Treatment

• Fluid resuscitation

• Fasting

• Drugs, including adequate analgesia and acid blockers

• Antibiotics for pancreatic necrosis

• Drainage of infected pseudocysts or areas of necrosis

Adequate fluid resuscitation is essential; up to 6 to 8 L/day of fluid containing appropriate electrolytes may be required. Inadequate fluid therapy increases the risk of pancreatic necrosis.

Fasting is indicated until acute inflammation subsides (ie, cessation of abdominal tenderness and pain, normalization of serum amylase, return of appetite, feeling better). Fasting can last from a few days in mild pancreatitis to several weeks. TPN should be initiated in severe cases within the first few days to prevent undernutrition.

Pain relief requires parenteral opioids, which should be given in adequate doses. Although morphine may cause the sphincter of Oddi to contract, this is of doubtful clinical significance. Antiemetic agents (eg, prochlorperazine 5 to 10 mg IV q 6 h) should be given to alleviate vomiting. An NGT is required only if significant vomiting persists or ileus is present.

Parenteral H_2 blockers or proton pump inhibitors are given. Efforts to reduce pancreatic secretion with drugs (eg, anticholinergics, glucagon, somatostatin, octreotide) have no proven benefit.

Severe acute pancreatitis should be treated in an ICU, particularly in patients with hypotension, oliguria, Ranson's score ≥ 3, APACHE II ≥ 8, or pancreatic necrosis on CT > 30%. In the ICU, vital signs and urine output are monitored hourly; metabolic parameters (Hct, glucose, and electrolytes) are reassessed every 8 h; ABG is determined as needed; central venous pressure line or Swan-Ganz catheter measurements are determined every 6 h if the patient is hemodynamically unstable or if fluid requirements are unclear. CBC, platelet count, coagulation parameters, total protein with albumin, BUN, creatinine, Ca, and Mg are measured daily.

Hypoxemia is treated with humidified O_2 via mask or nasal prongs. If hypoxemia persists or adult respiratory distress syndrome develops, assisted ventilation may be required. Glucose > 170 to 200 mg/dL (9.4 to 11.1 mmol/L) should be treated cautiously with sc or IV insulin and carefully monitored. Hypocalcemia generally is not treated unless neuromuscular irritability occurs; 10 to 20 mL of 10% Ca gluconate in 1 L of IV fluid is given over 4 to 6 h. Chronic alcoholics and patients with documented hypomagnesemia should receive Mg sulfate 1 g/L of replacement fluid for a total of 2 to 4 g, or until levels normalize. If renal failure occurs, serum Mg levels are monitored and IV Mg is given cautiously. With restoration of normal Mg levels, serum Ca levels usually return to normal.

Heart failure should be treated (see p. 2126). Prerenal azotemia should be treated by increased fluid replacement. Renal failure may require dialysis (usually peritoneal).

Antibiotic prophylaxis with imipenem can prevent infection of sterile pancreatic necrosis, although the effect on reducing mortality is unclear. Infected areas of pancreatic necrosis require surgical debridement, but infected fluid collections outside the pancreas may be drained percutaneously. A pseudocyst that is expanding rapidly, infected, bleeding, or likely to rupture requires drainage. Whether drainage is percutaneous, surgical, or endoscopic depends on location of the pseudocyst and institutional expertise. Peritoneal lavage to wash out activated pancreatic enzymes and inflammatory mediators has no proven benefit.

Surgical intervention during the first several days is justified for severe blunt or penetrating trauma or uncontrolled biliary sepsis. Although > 80% of patients with gallstone pancreatitis pass the stone spontaneously, ERCP with sphincterotomy and stone removal is indicated for patients who do not improve after 24 h of treatment. Patients who spontaneously improve generally undergo elective laparoscopic cholecystectomy. Elective cholangiography remains controversial.

Chronic Pancreatitis

Chronic pancreatitis is persistent inflammation of the pancreas that results in permanent structural damage with fibrosis and ductal strictures, followed by a decline in exocrine and endocrine function. It can occur as the result of chronic alcohol abuse but may be idiopathic. Initial symptoms are recurrent attacks of pain. Later in the disease, some patients develop malabsorption and glucose intolerance. Diagnosis is usually made by imaging studies such as ERCP, endoscopic ultrasound, or secretin pancreatic function testing. Treatment is supportive, with dietary modification, analgesics, and enzyme supplements. In some cases, surgical treatment is helpful.

Etiology

In the US, 70 to 80% of cases result from alcoholism, and 15 to 25% are idiopathic. However, recent data suggest that alcohol is becoming less of a cause. Less common causes include hereditary pancreatitis, hyperparathyroidism, and obstruction of the main pancreatic duct caused by stenosis, stones, or cancer. In India, Indonesia, and Nigeria, idiopathic calcific pancreatitis occurs among children and young adults (tropical pancreatitis).

Pathophysiology

Similar to acute pancreatitis, the mechanism of disease may be ductal obstruction by protein plugs. The protein plugs may result from excess secretion of glycoprotein-2 or a deficiency of lithostatin, a protein in pancreatic fluid that inhibits Ca precipitation. If obstruction is chronic, persistent inflammation leads to fibrosis and alternating areas of ductal dilation and stricture, which may become calcified. Neuronal sheath hypertrophy and perineural inflammation occur and may contribute to chronic pain.

After several years, progressive fibrosis leads to loss of exocrine and endocrine function. Diabetes develops in 20 to 30% of patients within 10 to 15 yr of onset.

Symptoms and Signs

Most patients present with episodic abdominal pain. About 10 to 15% have no pain and present with malabsorption. Pain is epigastric, severe, and may last many hours or several days. Episodes typically subside spontaneously after 6 to 10 yr as the acinar cells that secrete pancreatic digestive enzymes are progressively destroyed. When lipase and protease secretions are reduced to < 10% of normal, the patient develops steatorrhea, passing greasy stools or even oil droplets, and creatorrhea (the presence of undigested muscle fibers in the feces). Symptoms of glucose intolerance may appear at this time.

Diagnosis

• Clinical suspicion

• Abdominal CT

• Sometimes magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasonography, or ERCP

Diagnosis can be difficult because amylase and lipase levels are frequently normal because of significant loss of pancreatic function. In a patient with a typical history of alcohol abuse and recurrent episodes of acute pancreatitis, detection of pancreatic calcification on plain x-ray of the abdomen may be sufficient. However, such calcifications typically occur late in the disease and then are visible in only about 30% of patients. In patients without a typical history, pancreatic cancer must be excluded as the cause of pain: abdominal CT is recommended. CT can show calcifications and other pancreatic abnormalities (eg, pseudocyst or dilated ducts) but still may be normal early in the disease.

The primary options for patients with normal CT findings include ERCP, endoscopic ultrasonography, and secretin pancreatic function testing. These tests are quite sensitive, but ERCP precipitates acute pancreatitis in about 5% of patients. MRCP may prove an acceptable alternative.

Late in the disease, tests of pancreatic exocrine function become abnormal. A 72-h test for stool fat is diagnostic for steatorrhea but cannot establish a cause. The secretin test collects pancreatic secretions via a duodenal tube for analysis but is done in only a few centers. Levels of serum trypsinogen and fecal chymotrypsin and elastase may be decreased. In the bentiromide test and the pancreolauryl test, substances are given orally, and urine is analyzed for cleavage products generated by pancreatic enzymes. All such exocrine tests are less sensitive than ERCP or endoscopic ultrasonography early in the disease.

Treatment

• IV fluids

• Fasting

• Drugs, including adequate analgesia and acid blockers

• Pancreatic enzyme supplements

• Sometimes drainage of pseudocysts (surgical or endoscopic)

A relapse requires treatment similar to acute pancreatitis with fasting, IV fluids, and analgesics. When feeding resumes, the patient must eschew alcohol and consume a low-fat (< 25 g/day) diet (to reduce secretion of pancreatic enzymes). An H_2 blocker or proton pump inhibitor may reduce acid-stimulated release of secretin, thereby decreasing the flow of pancreatic secretions. Too often, these measures do not relieve pain, requiring increased amounts of opioids, with the threat of addiction. Medical treatment of chronic pancreatic pain is often unsatisfactory.

Pancreatic enzyme supplementation may reduce chronic pain by inhibiting the release of cholecystokinin, thereby reducing the secretion of pancreatic enzymes. Supplementation is more likely to be successful in mild idiopathic pancreatitis than in alcoholic pancreatitis. Enzymes are also used to treat steatorrhea. Various preparations are available, and a dose providing at least 30,000 U of lipase should be used. Non-enteric coated tablets should be used, and they should be taken with meals. An H_2 blocker or proton pump inhibitor should be given to prevent acid breakdown of the enzymes.

Favorable clinical responses include weight gain, fewer bowel movements, elimination of oil droplet seepage, and improved well-being. Clinical response can be documented by showing a decrease in stool fat after enzyme therapy. If steatorrhea is particularly severe and refractory to these measures, medium-chain triglycerides can be provided as a source of fat (they are absorbed without pancreatic enzymes), reducing other dietary fats proportionally. Supplementation with fat-soluble vitamins (A, D, K) should be given, including vitamin E, which may minimize inflammation.

Surgical treatment may be effective for pain relief. A pancreatic pseudocyst, which may cause chronic pain, can be decompressed into a nearby structure to which it firmly adheres (eg, the stomach) or into a defunctionalized loop of jejunum (via a Roux-en-Y cystojejunostomy). If the main pancreatic duct is dilated > 5 to 8 mm, a lateral pancreaticojejunostomy (Puestow procedure) relieves pain in about 70 to 80% of patients. If the duct is not dilated, a partial resection is similarly effective; either distal pancreatectomy (for extensive disease at the tail of the pancreas) or Whipple procedure (for extensive disease at the head of the pancreas) is done. Operative approaches should be reserved for patients who have stopped using alcohol and who can manage diabetes that may be intensified by pancreatic resection.

Some pseudocysts can be drained endoscopically. Endoscopic ultrasound-guided denervation of the celiac plexus with alcohol and bupivacaine may provide pain relief. If there is significant stricture at the papilla or distal pancreatic duct, ERCP with sphincterotomy, stent placement, or dilatation may be effective.

Oral hypoglycemic drugs rarely help treat diabetes caused by chronic pancreatitis. Insulin should be given cautiously because the coexisting deficiency of glucagon secretion by α-cells means that the hypoglycemic effects of insulin are unopposed and prolonged hypoglycemia may occur.

Patients are at increased risk of pancreatic cancer. Worsening of symptoms, especially with development of a pancreatic duct stricture, should prompt an evaluation for cancer. Evaluation may include brushing strictures for cytologic analysis or measuring serum markers (eg, CA 19-9, carcinoembryonic antigen).

Chapter 16. Gastroenteritis

Introduction

(See also Food Allergy on p. 1118 and Mushroom Poisoning on p. 3336.)

Gastroenteritis is inflammation of the lining of the stomach and small and large intestines. Most cases are infectious, although gastroenteritis may occur after ingestion of drugs and chemical toxins (eg, metals, plant substances). Symptoms include anorexia, nausea, vomiting, diarrhea, and abdominal discomfort. Diagnosis is clinical or by stool culture, although immunoassays are increasingly used. Treatment is symptomatic, although parasitic and some bacterial infections require specific anti-infective therapy.

Gastroenteritis is usually uncomfortable but self-limited. Electrolyte and fluid loss is usually little more than an inconvenience to an otherwise healthy adult but can be grave for people who are very young (see p. 2806), elderly, or debilitated or who have serious concomitant illnesses. Worldwide, an estimated 3 to 6 million children die each year from infectious gastroenteritis.

Etiology

Infectious gastroenteritis may be caused by viruses, bacteria, or parasites. Many specific organisms are discussed further in the Infectious Diseases section.

Viruses: The viruses most commonly implicated are

• Rotavirus

• Norovirus

Viruses are the most common cause of gastroenteritis in the US. They infect enterocytes in the villous epithelium of the small bowel. The result is transudation of fluid and salts into the intestinal lumen; sometimes, malabsorption of carbohydrates worsens symptoms by causing osmotic diarrhea. Diarrhea is watery. Inflammatory diarrhea (dysentery), with fecal WBCs and RBCs or gross blood, is uncommon. Four categories of viruses cause most gastroenteritis: rotavirus and calicivirus (predominantly the norovirus [formerly Norwalk virus]) cause the majority of viral gastroenteritis, followed by astrovirus and enteric adenovirus.

Rotavirus is the most common cause of sporadic, severe, dehydrating diarrhea in young children (peak incidence, 3 to 15 mo). Rotavirus is highly contagious; most infections occur by the fecal-oral route. Adults may be infected after close contact with an infected infant. The illness in adults is generally mild. Incubation is 1 to 3 days. In temperate climates, most infections occur in the winter. Each year in the US, a wave of rotavirus illness begins in the Southwest in November and ends in the Northeast in March.

Norovirus most commonly infects older children and adults. Infections occur year-round. Norovirus is the principal cause of sporadic viral gastroenteritis in adults and of epidemic viral gastroenteritis in all age groups; large waterborne and food-borne outbreaks occur. Person-to-person transmission also occurs because the virus is highly contagious. Incubation is 24 to 48 h.

Astrovirus can infect people of all ages but usually infects infants and young children. Infection is most common in winter. Transmission is by the fecal-oral route. Incubation is 3 to 4 days.

Adenoviruses are the 4th most common cause of childhood viral gastroenteritis. Infections occur year-round, with a slight increase in summer. Children < 2 yr are primarily affected. Transmission is by the fecal-oral route. Incubation is 3 to 10 days.

In immunocompromised patients, additional viruses (eg, cytomegalovirus, enterovirus) can cause gastroenteritis.

Bacteria: The bacteria most commonly implicated are

• *Salmonella*

• *Campylobacter*

• *Shigella*

• *Escherichia coli* (especially serotype O157:H7)

Bacterial gastroenteritis is less common than viral. Bacteria cause gastroenteritis by several mechanisms. Certain species (eg, *Vibrio cholerae*, enterotoxigenic strains of *E. coli*) adhere to intestinal mucosa without invading and produce enterotoxins. These toxins impair intestinal absorption and cause secretion of electrolytes and water by stimulating adenylate cyclase, resulting in watery diarrhea. *Clostridium difficile* produces a similar toxin when overgrowth follows antibiotic use (see p. 1292).

Some bacteria (eg, *Staphylococcus aureus*, *Bacillus cereus*, *Clostridium perfringens*) produce an exotoxin that is ingested in contaminated food. The exotoxin can cause gastroenteritis without bacterial infection. These toxins generally cause acute nausea, vomiting, and diarrhea within 12 h of ingestion of contaminated food. Symptoms abate within 36 h.

Other bacteria (eg, *Shigella*, *Salmonella*, *Campylobacter*, some *E. coli* subtypes) invade the mucosa of the small bowel or colon and cause microscopic ulceration, bleeding, exudation of protein-rich fluid, and secretion of electrolytes and water. The invasive process and its results can occur whether or not the organism produces an enterotoxin. The resulting diarrhea contains WBCs and RBCs and sometimes gross blood.

Salmonella and *Campylobacter* are the most common bacterial causes of diarrheal illness in the US. Both infections are most frequently acquired through undercooked poultry; unpasteurized milk is also a possible source. *Campylobacter* is occasionally transmitted from dogs or cats with diarrhea. *Salmonella* can be transmitted by undercooked eggs and by contact with reptiles. Species of *Shigella* are the 3rd most common bacterial cause of diarrhea in the US and are usually transmitted person to person, although food-borne epidemics occur. *Shigella dysenteriae* type 1 (not present in the US) produces Shiga toxin, which can cause hemolytic-uremic syndrome (see p. 961).

Several different subtypes of *E. coli* cause diarrhea. The epidemiology and clinical manifestations vary greatly depending on the subtype: (1) Enterohemorrhagic *E. coli* is the most clinically significant subtype in the US. It produces Shiga toxin, which causes bloody diarrhea (hemorrhagic colitis). *E. coli* O157:H7 is the most common strain of this subtype in the US. Undercooked ground beef, unpasteurized milk and juice, and contaminated water are possible sources. Person-to-person transmission is common in the day care setting. Hemolytic-uremic syndrome is a serious complication that develops in 2 to 7% of cases, most commonly among the young and old. (2) Enterotoxigenic *E. coli* produces two toxins (one similar to cholera toxin) that cause watery diarrhea. This subtype is the most common cause of traveler's diarrhea. (3) Enteropathogenic *E. coli* causes watery diarrhea. Once a common cause of diarrhea outbreaks in nurseries, this subtype is now rare. (4) Enteroinvasive *E. coli* causes bloody or nonbloody diarrhea, primarily in the developing world. It is rare in the US.

Several other bacteria cause gastroenteritis, but most are uncommon in the US. *Yersinia enterocolitica* can cause gastroenteritis or a syndrome that mimics appendicitis. It is transmitted by undercooked pork, unpasteurized milk, or contaminated water. Several *Vibrio* species (eg, *V. parahaemolyticus*) cause diarrhea after ingestion of undercooked seafood. *V. cholerae* sometimes causes severe dehydrating diarrhea in the developing world. *Listeria* causes food-borne gastroenteritis. *Aeromonas* is acquired from swimming in or drinking contaminated fresh or brackish water. *Plesiomonas shigelloides* can cause diarrhea in patients who have eaten raw shellfish or traveled to tropical regions of the developing world.

Parasites: The parasites most commonly implicated are

• *Giardia*

• *Cryptosporidium*

Certain intestinal parasites, notably *Giardia intestinalis* (*lamblia*—see p. 1371), adhere to or invade the intestinal mucosa, causing nausea, vomiting, diarrhea, and general malaise. Giardiasis occurs in every region of the US and throughout the world. The infection can become chronic and cause a malabsorption syndrome. It is usually acquired via person-to-person transmission (often in day care centers) or from contaminated water.

Cryptosporidium parvum causes watery diarrhea sometimes accompanied by abdominal cramps, nausea, and vomiting. In healthy people, the illness is self-limited, lasting about 2 wk. In immunocompromised patients, illness may be severe, causing substantial electrolyte and fluid loss. *Cryptosporidium* is usually acquired through contaminated water.

Other parasites that can cause symptoms similar to those of cryptosporidiosis include *Cyclospora cayetanensis* and, in immunocompromised patients, *Cystoisospora* (*Isospora*) *belli*, and a collection of organisms referred to as microsporidia (eg, *Enterocytozoon bieneusi*, *Encephalitozoon intestinalis*). *Entamoeba histolytica* (amebiasis) is a common cause of subacute bloody diarrhea in the developing world and occasionally occurs in the US.

Symptoms and Signs

The character and severity of symptoms vary. Generally, onset is sudden, with anorexia, nausea, vomiting, borborygmi, abdominal cramps, and diarrhea (with or without blood and mucus). Malaise, myalgias, and prostration may occur. The abdomen may be distended and mildly tender; in severe cases, muscle guarding may be present. Gas-distended intestinal loops may be palpable. Borborygmi are present even without diarrhea (an important differential feature from paralytic ileus). Persistent vomiting and diarrhea can result in intravascular fluid depletion with hypotension and tachycardia. In severe cases, shock, with vascular collapse and oliguric renal failure, occurs.

If vomiting is the main cause of fluid loss, metabolic alkalosis with hypochloremia can occur. If diarrhea is more prominent, acidosis is more likely. Both vomiting and diarrhea can cause hypokalemia. Hyponatremia may develop, particularly if hypotonic fluids are used in replacement therapy.

In viral infections, watery diarrhea is the most common symptom; stools rarely contain mucus or blood. Rotavirus gastroenteritis in infants and young children may last 5 to 7 days. Vomiting occurs in 90% of patients, and fever > 39° C (> 102.2° F) occurs in about 30%. Norovirus typically causes acute onset of vomiting, abdominal cramps, and diarrhea, with symptoms lasting only 1 to 2 days. In children, vomiting is more prominent than diarrhea, whereas in adults, diarrhea usually predominates. Patients may also experience fever, headache, and myalgias. The hallmark of adenovirus gastroenteritis is diarrhea lasting 1 to 2 wk. Affected infants and children may have mild vomiting that typically starts 1 to 2 days after the onset of diarrhea. Low-grade fever occurs in about 50% of patients. Astrovirus causes a syndrome similar to mild rotavirus infection.

Bacteria that cause invasive disease (eg, *Shigella*, *Salmonella*) are more likely to result in fever, prostration, and bloody diarrhea. Bacteria that produce an enterotoxin (eg, *S. aureus*, *B. cereus*, *C. perfringens*) usually cause watery diarrhea.

Parasitic infections typically cause subacute or chronic diarrhea. Most cause nonbloody diarrhea; an exception is *E. histolytica*, which causes amebic dysentery. Fatigue and weight loss are common when diarrhea is persistent.

Diagnosis

• Clinical evaluation

• Stool testing in select cases

Other GI disorders that cause similar symptoms (eg, appendicitis, cholecystitis, ulcerative colitis) must be excluded. Findings suggestive of gastroenteritis include copious, watery diarrhea; ingestion of potentially contaminated food (particularly during a known outbreak), untreated surface water, or a known GI irritant; recent travel; or contact with similarly ill people. *E. coli* O157:H7-induced diarrhea is notorious for appearing to be a hemorrhagic rather than an infectious process, manifesting as GI bleeding with little or no stool. Hemolyticuremic syndrome may follow as evidenced by renal failure and hemolytic anemia (see p. 961). Recent oral antibiotic use (within 3 mo) must raise suspicion for *C. difficile* infection (see p. 1292).

Stool testing: If a rectal examination shows occult blood or if watery diarrhea persists > 48 h, stool examination (fecal WBCs, ova, parasites) and culture are indicated. However, for the diagnosis of giardiasis or cryptosporidiosis, stool antigen detection using an enzyme immunoassay has a higher sensitivity. Rotavirus and enteric adenovirus infections can be diagnosed using commercially available rapid assays that detect viral antigen in the stool, but these are usually done only to document an outbreak.

All patients with grossly bloody diarrhea should be tested for *E. coli* O157:H7, as should patients with nonbloody diarrhea during a known outbreak. Specific cultures must be requested because this organism is not detected on standard stool culture media. Alternatively, a rapid enzyme assay for the detection of Shiga toxin in stool can be done; a positive test indicates infection with *E. coli* O157:H7 or one of the other serotypes of enterohemorrhagic *E. coli*. (NOTE: *Shigella* species in the US do not produce Shiga toxin.)

Adults with grossly bloody diarrhea should usually have sigmoidoscopy with cultures and biopsy. Appearance of the colonic mucosa may help diagnose amebic dysentery, shigellosis, and *E. coli* O157:H7 infection, although ulcerative colitis may cause similar lesions. Patients with recent antibiotic use should have a stool assay for *C. difficile* toxin.

General tests: Serum electrolytes, BUN, and creatinine should be obtained to evaluate hydration and acid-base status in patients who appear seriously ill. CBC is nonspecific, although eosinophilia may indicate parasitic infection.

Treatment

• Oral or IV rehydration

• Consideration of antidiarrheal agents if there is no suspicion of *C. difficile* or *E. coli* O157:H7 infection

• Antibiotics only in select cases

Supportive treatment is all that is needed for most patients. Bed rest with convenient access to a toilet or bedpan is desirable. Oral glucose-electrolyte solutions, broth, or bouillon may prevent dehydration or treat mild dehydration. Even if vomiting, the patient should take frequent small sips of such fluids: vomiting may abate with volume replacement. For patients with *E. coli* O157:H7 infection, rehydration with isotonic IV fluids may attenuate the severity of any renal injury should hemolytic-uremic syndrome develop. Children may become dehydrated more quickly and should be given an appropriate rehydration solution (several are available commercially—see also p. 2809). Carbonated beverages and sports drinks lack the correct ratio of glucose to Na and thus are not appropriate for children < 5 yr. If the child is breastfed, breastfeeding should continue. If vomiting is protracted or if severe dehydration is prominent, IV replacement of volume and electrolytes is necessary (see p. 2297).

When the patient can tolerate fluids without vomiting and the appetite has begun to return, food may be gradually restarted. There is no demonstrated benefit from restriction to bland food (eg, cereal, gelatin, bananas, toast). Some patients have temporary lactose intolerance.

Antidiarrheal agents are safe for patients > 5 yr with watery diarrhea (as shown by heme-negative stool). However, antidiarrheals may cause deterioration of patients with *C. difficile* or *E. coli* O157:H7 infection and thus should not be given to any patient with recent antibiotic use or heme-positive stool, pending specific diagnosis. Effective antidiarrheals include loperamide 4 mg po initially, followed by 2 mg po for each subsequent episode of diarrhea (maximum of 6 doses/day or 16 mg/day), or diphenoxylate 2.5 to 5 mg tid or qid in tablet or liquid form.

If vomiting is severe and a surgical condition has been excluded, an antiemetic may be beneficial. Agents useful in adults include prochlorperazine 5 to 10 mg IV tid or qid, or 25 mg per rectum bid; and promethazine 12.5 to 25 mg IM tid or qid, or 25 to 50 mg per rectum qid. These drugs are usually avoided in children because of lack of demonstrated efficacy and the high incidence of dystonic reactions.

Antimicrobials: Empiric antibiotics are generally not recommended except for certain cases of traveler's diarrhea or when suspicion of *Shigella* or *Campylobacter* infection is high (eg, contact with a known case). Otherwise, antibiotics should not be given until stool culture results are known, particularly in children, who have a higher rate of infection with *E. coli* O157:H7 (antibiotics increase the risk of hemolytic-uremic syndrome in patients infected with *E. coli* O157:H7).

In proven bacterial gastroenteritis, antibiotics are not always required. They do not help with *Salmonella* and prolong the duration of shedding in the stool. Exceptions include immunocompromised patients, neonates, and patients with *Salmonella* bacteremia. Antibiotics are also ineffective against toxic gastroenteritis (eg, *S. aureus*, *B. cereus*, *C. perfringens*). Indiscriminate use of antibiotics fosters the emergence of drug-resistant organisms. However, certain infections do require antibiotics (see Table 16-1).

The use of probiotics, such as lactobacillus, is generally safe and may have some benefit in relieving symptoms. They can be given in the form of yogurt with active cultures.

[**Table 16-1.** Selected Oral Antibiotics for Infectious Gastroenteritis*]

For cryptosporidiosis, nitazoxanide may be helpful in immunocompetent patients. The dose is 100 mg po bid for children 1 to 3 yr, 200 mg po bid for children 4 to 11 yr, and 500 mg po bid for children ≥ 12 yr and adults.

Prevention

A new oral pentavalent rotavirus vaccine is available that is safe and effective against the majority of strains responsible for disease. This vaccine is now part of the recommended infant vaccination schedule and is given at 2, 4, and 6 mo of age (see p. 2718).

Prevention of infection is complicated by the frequency of asymptomatic infection and the ease with which many agents, particularly viruses, are transmitted from person to person. In general, proper procedures for handling and preparing food must be followed. Travelers must avoid potentially contaminated food and drink.

Breastfeeding affords some protection to neonates and infants. Caregivers should wash their hands thoroughly with soap and water after changing diapers, and diaper-changing areas should be disinfected with a freshly prepared solution of 1:64 household bleach (one fourth cup diluted in 1 gallon of water). Children with diarrhea should be excluded from child care facilities for the duration of symptoms. Children infected with enterohemorrhagic *E. coli* or *Shigella* should also have two negative stool cultures before readmission to the facility.

Traveler's Diarrhea

(Turista)

Traveler's diarrhea is gastroenteritis that is usually caused by bacteria endemic to local water.

Symptoms include vomiting and diarrhea. Diagnosis is mainly clinical. Treatment is with ciprofloxacin or azithromycin, loperamide, and replacement fluids.

Etiology

Traveler's diarrhea may be caused by any of several bacteria, viruses, or, less commonly, parasites. However, enterotoxigenic *Escherichia coli* is most common. *E. coli* is common in the water supplies of areas that lack adequate purification. Infection is common among people traveling to developing countries. Norovirus infection has been a particular problem on some cruise ships.

Both food and water can be the source of infection. Travelers who avoid drinking local water may still become infected by brushing their teeth with an improperly rinsed toothbrush, drinking bottled drinks with ice made from local water, or eating food that is improperly handled or washed with local water. People taking drugs that decrease stomach acid (antacids, H_2 blockers, and proton pump inhibitors) are at risk of more severe illness.

Symptoms and Signs

Nausea, vomiting, borborygmi, abdominal cramps, and diarrhea begin 12 to 72 h after ingesting contaminated food or water. Severity is variable. Some people develop fever and myalgias. Most cases are mild and self-limited, although dehydration can occur, especially in warm climates.

Diagnosis

• Clinical evaluation

Specific diagnostic measures are usually not necessary. However, fever, severe abdominal pain, and bloody diarrhea suggest more serious disease and should prompt immediate evaluation.

Treatment

• Fluid replacement

• Sometimes antimotility drugs

• Rarely antibiotics (eg, ciprofloxacin, azithromycin)

The mainstay of treatment is fluid replacement and an antimotility drug such as loperamide 4 mg po initially, followed by 2 mg po for each subsequent episode of diarrhea (maximum of 6 doses/day or 16 mg/day), or diphenoxylate 2.5 to 5 mg po tid or qid in tablet or liquid form. Antimotility drugs are contraindicated in patients with fever or bloody stools and in children < 2 yr. Iodochlorhydroxyquin, which may be available in some developing countries, should not be used because it may cause neurologic damage.

Generally, antibiotics are not necessary for mild diarrhea. In patients with moderate to severe diarrhea (≥ 3 loose stools over 8 h), antibiotics are given, especially if vomiting, abdominal cramps, fever, or bloody stools are present. For adults, ciprofloxacin 500 mg po bid for 3 days or levofloxacin 500 mg po once/day for 3 days is recommended. Azithromycin 250 mg po once/day for 3 days or rifaximin 200 mg po tid for 3 days may also be used. For children, azithromycin 5 to 10 mg/kg po once/day for 3 days is preferred.

Prevention

Travelers should dine at restaurants with a reputation for safety and avoid foods and beverages from street vendors. They should consume only cooked foods that are still steaming hot, fruit that can be peeled, and carbonated beverages without ice served in sealed bottles (bottles of noncarbonated beverages can contain tap water added by unscrupulous vendors); uncooked vegetables should be avoided. Buffets and fast food restaurants pose an increased risk.

Prophylactic antibiotics are effective in preventing diarrhea, but because of concerns about adverse effects and development of resistance, they should probably be reserved for immunocompromised patients.

Drug- and Chemical-Related Gastroenteritis

Many drugs cause nausea, vomiting, and diarrhea as adverse effects. A detailed drug history must be obtained. In mild cases, cessation followed by reuse of the drug may establish a causal relationship. Commonly responsible drugs include antacids containing Mg, antibiotics, antihelminthics, cytotoxics (used in cancer therapy), colchicine, digoxin, heavy metals, laxatives, and radiation therapy. Use of antibiotics may lead to *Clostridium difficile*-induced diarrhea (see p. 1292).

Iatrogenic, accidental, or intentional heavy-metal poisoning frequently causes nausea, vomiting, abdominal pain, and diarrhea.

Laxative abuse, sometimes denied by patients, may lead to weakness, vomiting, diarrhea, electrolyte depletion, and metabolic disturbances.

Various plants and mushrooms cause a syndrome of gastroenteritis (see p. 3336).

Chapter 17. Malabsorption Syndromes

Introduction

Malabsorption is inadequate assimilation of dietary substances due to defects in digestion, absorption, or transport. Malabsorption can affect macronutrients (eg, proteins, carbohydrates, fats), micronutrients (eg, vitamins, minerals), or both, causing excessive fecal excretion, nutritional deficiencies, and GI symptoms.

Pathophysiology

Digestion and absorption occur in three phases: (1) intraluminal hydrolysis of fats, proteins, and carbohydrates by enzymes—bile salts enhance the solubilization of fat in this phase; (2) digestion by brush border enzymes and uptake of end-products; and (3) lymphatic transport of nutrients. Malabsorption occurs when any of these phases is impaired.

Fats: Pancreatic enzymes split long-chain triglycerides into fatty acids and monoglycerides, which combine with bile acids and phospholipids to form micelles that pass through jejunal enterocytes. Absorbed fatty acids are resynthesized and combined with protein, cholesterol, and phospholipid to form chylomicrons, which are transported by the lymphatic system. Medium-chain triglycerides are absorbed directly.

Unabsorbed fats trap fat-soluble vitamins (A, D, E, K) and possibly some minerals, causing deficiency. Bacterial overgrowth results in deconjugation and dehydroxylation of bile salts, limiting the absorption of fats. Unabsorbed bile salts stimulate the colon, causing diarrhea.

Carbohydrates: Enzymes on microvilli lyse carbohydrates and disaccharides into constituent monosaccharides. Colonic bacteria ferment unabsorbed carbohydrates into CO_2, methane, H_2, and short-chain fatty acids (butyrate, propionate, acetate, and lactate). These fatty acids cause diarrhea. The gases cause abdominal distention and bloating.

Proteins: Enterokinase, a brush border enzyme, activates trypsinogen into trypsin, which converts many pancreatic proteases into their active forms. Active pancreatic enzymes hydrolyze proteins into oligopeptides, which are absorbed directly or hydrolyzed into amino acids.

Etiology

Malabsorption has many causes (see Table 17-1). Some malabsorptive disorders (eg, celiac sprue) impair the absorption of most nutrients, vitamins, and trace minerals (global malabsorption); others (eg, pernicious anemia) are more selective.

[**Table 17-1.** Causes of Malabsorption]

Pancreatic insufficiency causes malabsorption if > 90% of function is lost. Increased luminal acidity (eg, Zollinger-Ellison syndrome) inhibits lipase and fat digestion. Cirrhosis and cholestasis reduce hepatic bile synthesis or delivery of bile salts to the duodenum, causing malabsorption. Other causes are discussed elsewhere in this chapter.

Symptoms and Signs

The effects of unabsorbed substances include diarrhea, steatorrhea, abdominal bloating, and gas. Other symptoms result from nutritional deficiencies. Patients often lose weight despite adequate food intake.

Chronic diarrhea is the most common symptom and is what usually prompts evaluation of the patient. Steatorrhea—fatty stool, the hallmark of malabsorption—occurs when > 7 g/day of fat are excreted. Steatorrhea causes foul-smelling, pale, bulky, and greasy stools.

Severe vitamin and mineral deficiencies occur in advanced malabsorption; symptoms are related to the

specific nutrient deficiency (see Table 17-2). Vitamin B_{12} deficiency may occur in blind loop syndrome or after extensive resection of the distal ileum or stomach.

Amenorrhea may result from undernutrition and is an important manifestation of celiac sprue in young women.

Diagnosis

• Diagnosis typically clinically apparent

• Blood tests to screen for consequences of malabsorption

• Stool fat testing to confirm malabsorption (if unclear)

• Cause diagnosed with endoscopy, contrast x-rays, or other tests based on findings

Malabsorption is suspected in a patient with chronic diarrhea, weight loss, and anemia. The etiology is sometimes obvious. For example, those with malabsorption due to chronic pancreatitis usually have had prior bouts of acute pancreatitis. Patients with celiac sprue can present with classic lifelong diarrhea exacerbated by gluten products and may have dermatitis herpetiformis. Those with cirrhosis and pancreatic cancer can present with jaundice. Abdominal distention, excessive flatus, and watery diarrhea occurring 30 to 90 min after carbohydrate ingestion suggest deficiency of a disaccharidase enzyme, usually lactase. Previous extensive abdominal operations suggest short bowel syndrome.

If the history suggests a specific cause, testing should be directed to that condition (see Fig. 17-1). If no cause is readily apparent, blood tests can be used as screening tools (eg, CBC, RBC indices, ferritin, vitamin B_{12}, folate, Ca, albumin, cholesterol, PT). These results may suggest a diagnosis and direct further investigation.

[**Table 17-2.** Symptoms of Malabsorption]

Macrocytic anemia should prompt measurement of serum folate and B_{12} levels. Folate deficiency is common in mucosal disorders involving the proximal small bowel (eg, celiac sprue, tropical sprue, Whipple's disease). Low B_{12} levels can occur in pernicious anemia, chronic pancreatitis, bacterial overgrowth, and terminal ileal disease. A combination of low B_{12} and high folate levels is suggestive of bacterial overgrowth, because intestinal bacteria use vitamin B_{12} and synthesize folate.

Microcytic anemia suggests iron deficiency, which may occur with celiac sprue. Albumin is a general indicator of nutritional state. Low albumin can result from poor intake, decreased synthesis in cirrhosis, or protein wasting. Low serum carotene (a precursor of vitamin A) suggests malabsorption if intake is adequate.

Confirming malabsorption: Tests to confirm malabsorption are appropriate when symptoms are vague and the etiology is not apparent. Most tests for malabsorption assess fat malabsorption because it is relatively easy to measure. Confirmation of carbohydrate malabsorption is not helpful once steatorrhea is documented. Tests for protein malabsorption are rarely used because fecal nitrogen is difficult to measure.

[**Fig. 17-1.** Suggested evaluation for malabsorption.]

[**Table 17-3.** Small-Bowel Mucosal Histology in Certain Malabsorptive Disorders]

Direct measurement of fecal fat from a 72-h stool collection is the gold standard for establishing steatorrhea but unnecessary with gross steatorrhea of obvious cause. However, this test is available routinely in only a few centers. Stool is collected for a 3-day period during which the patient consumes ≥

100 g fat/day. Total fat in the stool is measured. Fecal fat > 7 g/day is abnormal. Although severe fat malabsorption (fecal fat ≥ 40 g/day) suggests pancreatic insufficiency or small-bowel mucosal disease, this test cannot determine the specific cause of malabsorption. Because the test is messy, unpleasant, and time consuming, it is unacceptable to most patients and difficult to do.

Sudan III staining of a stool smear is a simple and direct, but nonquantitative, screening test for fecal fat. Acid steatocrit is a gravimetric assay done on a single stool sample; it has a reported high sensitivity and specificity (using 72-h collection as the standard). Near-infrared reflectance analysis (NIRA) simultaneously tests stool for fat, nitrogen, and carbohydrates and may become the preferred test in the future.

Measurement of elastase and chymotrypsin in the stool can also help differentiate pancreatic and intestinal causes of malabsorption; both are decreased in pancreatic exocrine insufficiency.

The D-xylose absorption test, if available, can be done if the etiology is not obvious. It is the best noninvasive test to assess intestinal mucosal integrity and differentiate mucosal from pancreatic disease. This test has a reported specificity of 98% and sensitivity of 91% for small-bowel malabsorption.

D-Xylose is absorbed by passive diffusion and does not require pancreatic enzymes for digestion. A normal D-xylose test in the presence of moderate to severe steatorrhea indicates pancreatic exocrine insufficiency rather than small-bowel mucosal disease. Bacterial overgrowth syndrome can cause abnormal results because the enteric bacteria metabolize pentose, thus decreasing the D-xylose available for absorption.

After fasting, the patient is given 25 g of D-xylose in 200 to 300 mL of water po. Urine is collected over 5 h, and a venous sample is obtained after 1 h. Serum D-xylose < 20 mg/dL or < 4 g in the urine sample indicates abnormal absorption. Falsely low levels can also occur in renal diseases, portal hypertension, ascites, or delayed gastric emptying time. This test is rarely used today. In addition, an abnormal D-xylose test will require an endoscopic examination with biopsies of the small-bowel mucosa. As a result, small-bowel biopsy has replaced this test to establish intestinal mucosal disease.

Diagnosing the cause of malabsorption: More specific diagnostic tests (eg, upper endoscopy, colonoscopy, barium x-rays) are indicated to diagnose several causes of malabsorption.

Endoscopy with small-bowel biopsy is done when mucosal disease of the small bowel is suspected or if the D-xylose test is abnormal in a patient with massive steatorrhea. Aspirate from the small bowel can be sent for bacterial culture and colony count to document bacterial overgrowth. Histologic features on small-bowel biopsy (see Table 17-3) can establish the specific mucosal disease.

Small-bowel x-rays (eg, small-bowel follow-through, enteroclysis) can detect anatomic conditions that predispose to bacterial overgrowth. These include jejunal diverticula, fistulas, surgically created blind loops and anastomoses, ulcerations, and strictures. Abdominal flat plate x-ray may show pancreatic calcifications indicative of chronic pancreatitis. Barium contrast studies of the small bowel are neither sensitive nor specific but may have findings suggestive of mucosal disease (eg, dilated small-bowel loops, thinned or thickened mucosal folds, coarse fragmentation of the barium column).

Tests for pancreatic insufficiency (eg, secretin stimulation test, bentiromide test, pancreolauryl test, serum trypsinogen, fecal elastase, fecal chymotrypsin—see p. 145) are done if history is suggestive but are not sensitive for mild pancreatic disease.

The ^{14}C-xylose breath test helps diagnose bacterial overgrowth. ^{14}C-xylose is given orally, and the exhaled $^{14}CO_2$ concentration is measured. Catabolism of ingested xylose by the overgrowth flora causes $^{14}CO_2$ to appear in exhaled breath.

The H_2 breath test measures the exhaled H_2 produced by the bacterial degradation of carbohydrates. In patients with disaccharidase deficiencies, enteric bacteria degrade nonabsorbed carbohydrates in the

colon, increasing exhaled H_2. The lactose-H_2 breath test is useful only to confirm lactase deficiency (see p. 158) and is not used as an initial diagnostic test in the work-up of malabsorption.

The Schilling test assesses malabsorption of vitamin B_{12}. Its 4 stages determine whether the deficiency results from pernicious anemia, pancreatic exocrine insufficiency, bacterial overgrowth, or ileal disease.

- Stage 1: The patient is given 1 µg of radiolabeled cyanocobalamin po concurrent with 1000 µg of nonlabeled cobalamin IM to saturate hepatic binding sites. A 24-h urine collection is analyzed for radioactivity; urinary excretion of < 8% of the oral dose indicates malabsorption of cobalamin.

- Stage 2: If stage 1 is abnormal, the test is repeated with the addition of intrinsic factor. Pernicious anemia is present if this normalizes absorption.

- Stage 3: Stage 3 is done after adding pancreatic enzymes; normalization in this stage indicates cobalamin malabsorption secondary to pancreatic insufficiency.

- Stage 4: Stage 4 is done after antimicrobial therapy with anaerobic coverage; normalization after antibiotics suggests bacterial overgrowth.

Cobalamin deficiency secondary to ileal disease or ileal resection results in abnormalities in all stages.

Tests for less common causes of malabsorption include serum gastrin (Zollinger-Ellison syndrome), intrinsic factor and parietal cell antibodies (pernicious anemia), sweat chloride (cystic fibrosis), lipoprotein electrophoresis (abetalipoproteinemia), and serum cortisol (Addison's disease).

Bacterial Overgrowth Syndrome

Small-bowel bacterial overgrowth can occur from alterations in intestinal anatomy or GI motility, or lack of gastric acid secretion. This condition can lead to vitamin deficiencies, fat malabsorption, and undernutrition. Diagnosis is by breath test or quantitative culture of intestinal fluid aspirate. Treatment is with oral antibiotics.

Under normal conditions, the proximal small bowel contains < 10^5 bacteria/mL, mainly gram-positive aerobic bacteria. This low bacterial count is maintained by normal peristalsis, normal gastric acid secretion, mucus, secretory IgA, and an intact ileocecal valve.

Etiology

Usually, bacterial overgrowth occurs when anatomic alterations promote stasis of intestinal contents. These conditions include small-bowel diverticulosis, surgical blind loops, postgastrectomy states (especially in the afferent loop of a Billroth II), strictures, or partial obstruction. Intestinal motility disorders associated with diabetic neuropathy, systemic sclerosis, amyloidosis, and idiopathic intestinal pseudo-obstruction can also impair bacterial clearance. Achlorhydria and idiopathic changes in intestinal motility may cause bacterial overgrowth in elderly people.

Pathophysiology

The excess bacteria consume nutrients, including vitamin B_{12} and carbohydrates, leading to caloric deprivation and vitamin B_{12} deficiency. However, because the bacteria produce folate, this deficiency is rare. The bacteria deconjugate bile salts, causing failure of micelle formation and subsequent fat malabsorption. Severe bacterial overgrowth also damages the intestinal mucosa. Fat malabsorption and mucosal damage can cause diarrhea.

Symptoms and Signs

Many patients are asymptomatic and present with only weight loss or nutrient deficiencies. Some have significant diarrhea or steatorrhea.

Diagnosis

• ^{14}C-xylose breath test or quantitative culture of intestinal aspirate

• Upper GI series with small-bowel follow-through

Some clinicians advocate response to empiric antibiotic therapy as a diagnostic test. However, because bacterial overgrowth can mimic other malabsorptive disorders (eg, Crohn's disease) and adverse effects of the antibiotics can worsen symptoms, establishing a definitive etiology is preferred.

The standard for diagnosis is quantitative culture of intestinal fluid aspirate showing bacterial count > 10^5/mL. This method, however, requires endoscopy. Breath tests, using substrates like glucose, lactulose, and xylose, are noninvasive and easy to do. The ^{14}C-xylose breath test seems to perform better than the other breath tests. In addition, an upper GI series with small-bowel follow-through should be done to identify predisposing anatomic lesions.

Treatment

• Oral antibiotics (various)

Treatment is with 10 to 14 days of oral antibiotics. Empiric regimens include tetracycline 250 mg qid, amoxicillin/clavulanic acid 250 to 500 mg tid, cephalexin 250 mg qid, trimethoprim/sulfamethoxazole 160/800 mg bid, and metronidazole 250 to 500 mg tid or qid. Antibiotics should be changed based on culture and sensitivity results. Underlying conditions and nutritional deficiencies (eg, vitamin B_{12}) should be corrected.

Carbohydrate Intolerance

Carbohydrate intolerance is the inability to digest certain carbohydrates due to a lack of one or more intestinal enzymes. Symptoms include diarrhea, abdominal distention, and flatulence. Diagnosis is clinical and by an H_2 breath test. Treatment is removal of the causative disaccharide from the diet.

Pathophysiology

Disaccharides are normally split into monosaccharides by disaccharidases (eg, lactase, maltase, isomaltase, sucrase [invertase]) located in the brush border of small-bowel enterocytes. Undigested disaccharides cause an osmotic load that attracts water and electrolytes into the bowel, causing watery diarrhea. Bacterial fermentation of carbohydrates in the colon produces gases (H_2, CO_2, and methane), resulting in excessive flatus, bloating and distention, and abdominal pain.

Etiology

Enzyme deficiencies can be congenital, acquired (primary), or secondary. Congenital deficiencies are rare.

Acquired lactase deficiency (primary adult hypolactasia) is the most common form of carbohydrate intolerance. Lactase levels are high in neonates, permitting digestion of milk; in most ethnic groups (80% of blacks and Hispanics, almost 100% of Asians), the levels decrease in the post-weaning period rendering older children and adults unable to digest significant amounts of lactose. However, 80 to 85% of whites of Northwest European descent produce lactase throughout life and are thus able to digest milk and milk products. It is unclear why the normal state of > 75% of the world's population should be labeled a "deficiency."

Secondary lactase deficiency occurs in conditions that damage the small-bowel mucosa (eg, celiac sprue,

tropical sprue, acute intestinal infections). In infants, temporary secondary disaccharidase deficiency may complicate enteric infections or abdominal surgery. Recovery from the underlying disease is followed by an increase in activity of the enzyme.

Symptoms and Signs

Symptoms and signs are similar in all disaccharidase deficiencies. A child who cannot tolerate lactose develops diarrhea after ingesting significant amounts of milk and may not gain weight. An affected adult may have watery diarrhea, bloating, excessive flatus, nausea, borborygmi, and abdominal cramps after ingesting lactose. The patient often recognizes this early in life and avoids eating dairy products. Symptoms typically require ingestion of more than the equivalent of 8 to 12 oz of milk. Diarrhea may be severe enough to purge other nutrients before they can be absorbed. Symptoms may be similar to and can be confused with irritable bowel syndrome (see p. 162).

Diagnosis

• Clinical diagnosis

• H_2 breath test for confirmation

Lactose intolerance can usually be diagnosed with a careful history supported by dietary challenge. Patients usually have a history of intolerance to milk and dairy foods. The diagnosis is also suggested if the stool from chronic or intermittent diarrhea is acidic (pH < 6) and can be confirmed by an H_2 breath or a lactose tolerance test.

In the H_2 breath test, 50 g of lactose is given orally and the H_2 produced by bacterial metabolism of undigested lactose is measured with a breath meter at 2, 3, and 4 h postingestion. Most affected patients have an increase in expired H_2 of > 20 ppm over baseline. Sensitivity and specificity are > 95%.

The lactose tolerance test is less specific. Oral lactose (1.0 to 1.5 g/kg body weight) is given. Serum glucose is measured before ingestion and 60 and 120 min after. Lactose-intolerant patients develop diarrhea, abdominal bloating, and discomfort within 20 to 30 min, and their serum glucose levels do not rise > 20 mg/dL (< 1.1 mmol/L) above baseline. Low lactase activity in a jejunal biopsy specimen is diagnostic, but endoscopy is needed to obtain a specimen and is not routine.

Treatment

• Dietary restriction

Carbohydrate malabsorption is readily controlled by avoiding dietary sugars that cannot be absorbed (ie, following a lactose-free diet in cases of lactase deficiency). However, because the degree of lactose malabsorption varies greatly, many patients can ingest up to 12 oz (18 g of lactose) of milk daily without symptoms. Yogurt is usually tolerated because it contains an appreciable amount of lactase produced by intrinsic *Lactobacilli*.

For symptomatic patients wishing to drink milk, lactose in milk can be predigested by the addition of a commercially prepared lactase, and pretreated milk is now available. Enzyme supplements should be an adjunct to, not a substitute for, dietary restriction. Lactose-intolerant patients must take Ca supplements (1200 to 1500 mg/day).

Celiac Sprue

(Nontropical Sprue; Gluten Enteropathy; Celiac Disease)

Celiac sprue is an immunologically mediated disease in genetically susceptible people caused by intolerance to gluten, resulting in mucosal inflammation, which causes malabsorption. Symptoms usually include diarrhea and abdominal discomfort. Diagnosis is by small-bowel

biopsies showing characteristic though not specific pathologic changes of villous atrophy that resolve with a strict gluten-free diet.

Etiology

Celiac sprue is a hereditary disorder caused by sensitivity to the gliadin fraction of gluten, a protein found in wheat; similar proteins are present in rye and barley. In a genetically susceptible person, gluten-sensitive T cells are activated when gluten-derived peptide epitopes are presented. The inflammatory response causes characteristic mucosal villous atrophy in the small bowel.

Epidemiology: Celiac sprue mainly affects whites of northern European descent. Prevalence estimates based on serologic screens (sometimes confirmed by biopsy) indicate the disorder is present in about 1/300 in Europe and perhaps 1/250 in the US overall (but there may be significant variation among regions in the US).

The disease affects about 10 to 20% of 1st-degree relatives. Female:male ratio is 2:1. Onset is generally in childhood but may occur later.

Symptoms and Signs

The clinical presentation varies; no typical presentation exists. Some patients are asymptomatic or have only signs of nutritional deficiency. Others have significant GI symptoms.

Celiac sprue can manifest in infancy and childhood after introduction of cereals into the diet. The child has failure to thrive, apathy, anorexia, pallor, generalized hypotonia, abdominal distention, and muscle wasting. Stools are soft, bulky, clay-colored, and offensive. Older children may present with anemia or failure to grow normally.

In adults, lassitude, weakness, and anorexia are most common. Mild and intermittent diarrhea is sometimes the presenting symptom. Steatorrhea ranges from mild to severe (7 to 50 g fat/day). Some patients have weight loss, rarely enough to become underweight. Anemia, glossitis, angular stomatitis, and aphthous ulcers are usually seen in these patients. Manifestations of vitamin D and Ca deficiencies (eg, osteomalacia, osteopenia, osteoporosis) are common. Both men and women may have reduced fertility.

About 10% have dermatitis herpetiformis, an intensely pruritic papulovesicular rash that is symmetrically distributed over the extensor areas of the elbows, knees, buttocks, shoulders, and scalp. This rash can be induced by a high-gluten diet. Celiac sprue is also associated with diabetes mellitus, autoimmune thyroid disease, and Down syndrome.

Diagnosis

• Serologic markers

• Small-bowel biopsy

The diagnosis is suspected clinically and by laboratory abnormalities suggestive of malabsorption. Family incidence is a valuable clue. Celiac sprue should be strongly considered in a patient with iron deficiency without obvious GI bleeding.

Confirmation requires a small-bowel biopsy from the second portion of the duodenum. Findings include lack or shortening of villi (villous atrophy), increased intraepithelial cells, and crypt hyperplasia. However, such findings can also occur in tropical sprue, severe intestinal bacterial overgrowth, eosinophilic enteritis, lactose intolerance, and lymphoma.

Because biopsy lacks specificity, serologic markers can aid diagnosis. Anti-tissue transglutaminase antibody (AGA) and anti-endomysial antibody (EMA—an antibody against an intestinal connective tissue protein) each have sensitivity and specificity > 90%. These markers can also be used to screen

populations with high prevalence of celiac sprue, including 1st-degree relatives of affected patients and patients with diseases that occur at a greater frequency in association with celiac sprue. If either test is positive, the patient should have a diagnostic small-bowel biopsy. If both are negative, celiac sprue is extremely unlikely. These antibodies decrease in titer in patients on a gluten-free diet and thus are useful in monitoring dietary compliance.

Other laboratory abnormalities often occur and should be sought. They include anemia (iron-deficiency anemia in children and folate-deficiency anemia in adults); low albumin, Ca, K, and Na; and elevated alkaline phosphatase and PT.

Malabsorption tests are not specific for celiac sprue. If done, common findings include steatorrhea of 10 to 40 g/day and abnormal results with D-xylose and (in severe ileal disease) Schilling tests.

Prognosis

Mortality is 10 to 30% without a gluten-free diet. With proper diet, mortality is < 1%, mainly in adults who have severe disease at the outset. Complications include refractory sprue, collagenous sprue, and intestinal lymphomas. Intestinal lymphomas affect 6 to 8% of patients with celiac sprue, usually manifesting after 20 to 40 yr of disease. The incidence of other GI cancers (eg, carcinoma of the esophagus or oropharynx, small-bowel adenocarcinoma) also increases. Adherence to a gluten-free diet can significantly reduce the risk of cancer.

Treatment

• Gluten-free diet

• Supplements to replace any serious deficiencies

Treatment is a gluten-free diet (avoiding foods containing wheat, rye, or barley). Gluten is so widely used (eg, in commercial soups, sauces, ice creams, hot dogs) that a patient needs a detailed list of foods to avoid. Patients are encouraged to consult a dietitian and join a celiac support group. The response to a gluten-free diet is usually rapid, and symptoms resolve in 1 to 2 wk. Ingesting even small amounts of food containing gluten may prevent remission or induce relapse.

Small-bowel biopsy should be repeated after 3 to 4 mo of a gluten-free diet. If abnormalities persist, other causes of villous atrophy (eg, lymphoma) should be considered. Lessening of symptoms and improvement in small-bowel morphology are accompanied by a decrease in AGA and EMA titers.

Supplementary vitamins, minerals, and hematinics may be given, depending on the deficiencies. Mild cases may not require supplementation, whereas severe cases may require comprehensive replacement. For adults, replacement includes ferrous sulfate 300 mg po once/day to tid, folate 5 to 10 mg po once/day, Ca supplements, and any standard multivitamin. Sometimes children (but rarely adults) who are seriously ill on initial diagnosis require bowel rest and TPN.

If a patient responds poorly to gluten withdrawal, either the diagnosis is incorrect or the disease has become refractory. Corticosteroids can control symptoms in the latter case.

Infection and Infestation

Acute bacterial, viral, and parasitic infections may cause transient malabsorption, probably as a result of temporary, superficial damage to the villi and microvilli. Chronic bacterial infections of the small bowel are uncommon, apart from blind loops, systemic sclerosis, and diverticula. Intestinal bacteria may use up dietary vitamin B_{12} and other nutrients, perhaps interfere with enzyme systems, and cause mucosal injury.

Intestinal Lymphangiectasia

(Idiopathic Hypoproteinemia)

Intestinal lymphangiectasia is obstruction or malformation of the intramucosal lymphatics of the small bowel. It primarily affects children and young adults. Symptoms include those of malabsorption, with edema and growth retardation. Diagnosis is by small-bowel biopsy. Treatment is usually supportive.

Malformation of the lymphatic system is congenital or acquired. Congenital cases usually manifest in children and young adults (mean age of onset: 11 yr). Males and females are equally affected. In acquired cases, the defect may be secondary to retroperitoneal fibrosis, constrictive pericarditis, pancreatitis, neoplastic tumors, and infiltrative disorders that block the lymphatics.

Impaired lymphatic drainage leads to increased pressure and leakage of lymph into the intestinal lumen. Impairment of chylomicron and lipoprotein absorption results in malabsorption of fats and protein. Because carbohydrates are not absorbed through the lymphatic system, their uptake is not impaired.

Symptoms and Signs

Early manifestations include massive and often asymmetric peripheral edema, intermittent diarrhea, nausea, vomiting, and abdominal pain. Some patients have mild to moderate steatorrhea. Chylous pleural effusions (chylothorax) and chylous ascites may be present. Growth is retarded if onset is in the first decade of life.

Diagnosis

• Endoscopic small-bowel biopsy

• Sometimes contrast lymphangiography

Diagnosis usually requires endoscopic small-bowel biopsy, which shows marked dilation and ectasia of the mucosal and submucosal lymphatic vessels. Alternatively, contrast lymphangiography (injection of contrast material via the pedal vein) can show abnormal intestinal lymphatics.

Laboratory abnormalities include lymphocytopenia and low levels of serum albumin, cholesterol, IgA, IgM, IgG, transferrin, and ceruloplasmin. Barium studies may show thickened, nodular mucosal folds that resemble stacked coins. D-Xylose absorption is normal. Intestinal protein loss can be shown by using chromium-51-labeled albumin.

Treatment

• Supportive care

• Sometimes surgical resection or repair

Abnormal lymphatics cannot be corrected. Supportive treatment includes a low-fat (< 30 g/day), high-protein diet containing medium-chain triglyceride supplements. Supplemental Ca and fat-soluble vitamins are given. Intestinal resection or anastomosis of the abnormal lymphatics to the venous channels may be beneficial. Pleural effusions should be drained by thoracentesis.

Short Bowel Syndrome

Short bowel syndrome is malabsorption resulting from extensive resection of the small bowel. Symptoms depend on the length and function of the remaining small bowel, but diarrhea can be severe, and nutritional deficiencies are common. Treatment is with small feedings, antidiarrheals, and sometimes TPN or intestinal transplantation.

Common reasons for extensive resection are Crohn's disease, mesenteric infarction, radiation enteritis, cancer, volvulus, and congenital anomalies.

Because the jejunum is the primary digestive and absorptive site for most nutrients, jejunal resection significantly reduces nutrient absorption. In response, the ileum adapts by increasing the length and absorptive function of its villi, resulting in gradual improvement of nutrient absorption.

The ileum is the site of vitamin B_{12} and bile acid absorption. Severe diarrhea and bile acid malabsorption result when > 100 cm of the ileum is resected. Notably, there is no compensatory adaptation of the remaining jejunum. Consequently, malabsorption of fat, fat-soluble vitamins, and vitamin B_{12} occurs. In addition, unabsorbed bile acids in the colon result in secretory diarrhea. Preservation of the colon can significantly reduce water and electrolyte losses. Resection of the terminal ileum and ileocecal valve can predispose to bacterial overgrowth.

Treatment

• TPN

• Eventual oral feeding if > 100 cm of jejunum remain

• Antidiarrheals, cholestyramine, proton pump inhibitors, vitamin supplements

In the immediate postoperative period, diarrhea is typically severe, with significant electrolyte losses. Patients typically require TPN and intensive monitoring of fluid and electrolytes (including Ca and Mg). An oral iso-osmotic solution of Na and glucose (similar to WHO oral rehydration formula—see p. 2809) is slowly introduced in the postoperative phase once the patient stabilizes and stool output is < 2 L/day.

Patients with extensive resection (< 100 cm of remaining jejunum) and those with excessive fluid and electrolyte losses require TPN for life.

Patients with > 100 cm of jejunum left can achieve adequate nutrition through oral feeding. Fat and protein in the diet are usually well tolerated, unlike carbohydrates, which contribute a significant osmotic load. Small feedings reduce the osmotic load. Ideally, 40% of calories should consist of fat.

Patients who have diarrhea after meals should take antidiarrheals (eg, loperamide) 1 h before eating. Cholestyramine 2 to 4 g taken with meals reduces diarrhea associated with bile acid malabsorption. Monthly IM injections of vitamin B_{12} should be given to patients with a documented deficiency. Most patients should take supplemental vitamins, Ca, and Mg.

Gastric acid hypersecretion can develop, which can deactivate pancreatic enzymes; thus, most patients are given H_2 blockers or proton pump inhibitors.

Small-bowel transplantation is advocated for patients who are not candidates for long-term TPN and in whom adaptation does not occur.

Tropical Sprue

Tropical sprue is an acquired disease, probably of infectious etiology, characterized by malabsorption and megaloblastic anemia. Diagnosis is clinical and by small-bowel biopsy. Treatment is with tetracycline and folate for 6 mo.

Etiology

Tropical sprue occurs chiefly in the Caribbean, southern India, and Southeast Asia, affecting both natives and visitors. The illness is rare in visitors spending < 1 mo in areas where the disease is endemic. Although etiology is unclear, it is thought to result from chronic infection of the small bowel by toxigenic strains of coliform bacteria. Malabsorption of folate and vitamin B_{12} deficiency result in megaloblastic anemia. The incidence of tropical sprue is decreasing, perhaps because of increasing use of antibiotics for acute traveler's diarrhea.

Symptoms and Signs

Patients commonly have acute diarrhea with fever and malaise. A chronic phase of milder diarrhea, nausea, anorexia, abdominal cramps, and fatigue follows. Steatorrhea is common. Nutritional deficiencies, especially of folate and vitamin B_{12}, eventually develop after several months to years. The patient may also have weight loss, glossitis, stomatitis, and peripheral edema.

Diagnosis

• Endoscopy with small-bowel biopsy

• Blood tests to screen for consequences of malabsorption

Tropical sprue is suspected in people who live in or have visited areas where the disease is endemic and who have megaloblastic anemia and symptoms of malabsorption. The definitive test is upper GI endoscopy with small-bowel biopsy. Characteristic histologic changes (see Table 17-3) usually involve the entire small bowel and include blunting of the villi with infiltration of chronic inflammatory cells in the epithelium and lamina propria. Celiac disease and parasitic infection must be ruled out.

Additional laboratory studies (eg, CBC; albumin; Ca; PT; iron, folate, and B_{12} levels) help evaluate nutritional status. Barium small-bowel follow-through may show segmentation of the barium, dilation of the lumen, and thickening of the mucosal folds. D-Xylose absorption is abnormal in > 90% of cases. However, these tests are not specific or essential for diagnosis.

Treatment

• Long-term tetracycline

Treatment is tetracycline 250 mg po qid for 1 or 2 mo, then bid for up to 6 mo, depending on disease severity and response to treatment. Folate 5 to 10 mg po once/day should be given for the first month along with vitamin B_{12} 1 mg IM weekly for several weeks. Megaloblastic anemia promptly abates, and the clinical response is dramatic. Other nutritional replacements are given as needed. Relapse may occur in 20%. Failure to respond after 4 wk of therapy suggests another condition.

Whipple's Disease

(Intestinal Lipodystrophy)

Whipple's disease is a rare systemic illness caused by the bacterium *Tropheryma whippelii*. Main symptoms are arthritis, weight loss, and diarrhea. Diagnosis is by small-bowel biopsy. Treatment is with a minimum 1 yr of trimethoprim/sulfamethoxazole.

Whipple's disease predominately affects white men aged 30 to 60. Although it affects many parts of the body (eg, heart, lung, brain, serous cavities, joints, eye, GI tract), the mucosa of the small bowel is almost always involved. Affected patients may have subtle defects of cell-mediated immunity that predispose to infection with *T. whippelii*. About 30% of patients have HLA-B27.

Symptoms and Signs

Clinical presentation varies depending on the organ systems affected. Usually, the first symptoms are arthritis and fever. Intestinal symptoms (eg, watery diarrhea, steatorrhea, abdominal pain, anorexia, weight loss) usually manifest later, sometimes years after the initial complaint. Gross or occult intestinal bleeding may occur. Severe malabsorption may be present in patients diagnosed late in the clinical course. Other findings include increased skin pigmentation, anemia, lymphadenopathy, chronic cough, serositis, peripheral edema, and CNS symptoms.

Diagnosis

• Endoscopy with small-bowel biopsy

The diagnosis may be missed in patients without prominent GI symptoms. Whipple's disease should be suspected in middle-aged white men who have arthritis and abdominal pain, diarrhea, weight loss, or other symptoms of malabsorption. Such patients should have upper endoscopy with small-bowel biopsy; the intestinal lesions are specific and diagnostic. The most severe and consistent changes are in the proximal small bowel. Light microscopy shows periodic acid-Schiff-positive macrophages that distort the villus architecture. Gram-positive, acid fast-negative bacilli (*T. whippelii*) are seen in the lamina propria and in the macrophages. Confirmation by electron microscopy is recommended.

Whipple's disease should be differentiated from intestinal infection with *Mycobacterium avium-intracellulare* (MAI), which has similar histologic findings. However, MAI stains positive with acid fast. PCR testing may be useful for confirmation.

Treatment

• Antibiotics

• Late relapse a possibility

Untreated disease is progressive and fatal. Many antibiotics are curative (eg, tetracycline, trimethoprim/sulfamethoxazole, chloramphenicol, ampicillin, penicillin, cephalosporins). Treatment is initiated with ceftriaxone (2 g IV daily) or with procaine (1.2 million units IM once/day) or penicillin G (1.5 to 6 million units IV q 6 h) plus streptomycin (1.0 g IM once/day for 10 to 14 days). This regimen is followed by a long-term course of trimethoprim/sulfamethoxazole (160/800 mg po bid for 1 yr). Sulfa-allergic patients may substitute oral penicillin VK or ampicillin. Prompt clinical improvement occurs, with fever and joint pains resolving in a few days. Intestinal symptoms usually abate within 1 to 4 wk.

Some authorities do not recommend repeat small-bowel biopsies because macrophages may persist for years after treatment. However, others recommend repeat biopsy after 1 yr. In the latter approach, electron microscopy is needed to document bacilli (not just macrophages). Relapses are common and may occur years later. If relapse is suspected, small-bowel biopsies should be done (regardless of affected organ systems) to determine presence of free bacilli.

Chapter 18. Irritable Bowel Syndrome

(Spastic Colon)

Irritable bowel syndrome (IBS) is characterized by abdominal discomfort or pain that is accompanied by at least two of the following: relief by defecation, change in frequency of stool, or change in consistency of stool. The cause is unknown, and the pathophysiology is incompletely understood. Diagnosis is clinical. Treatment is symptomatic, consisting of dietary management and drugs, including anticholinergics and agents active at serotonin receptors.

Etiology

The cause of IBS is unknown. No anatomic cause can be found on laboratory tests, x-rays, and biopsies. Emotional factors, diet, drugs, or hormones may precipitate or aggravate GI symptoms. Historically, the disorder was often considered as purely psychosomatic. Although psychosocial factors are involved, IBS is better understood as a combination of psychosocial and physiologic factors.

Psychosocial factors: Psychologic distress is common among patients with IBS, especially among those who seek medical care. Some patients have anxiety disorders, depression, or a somatization disorder. Sleep disturbances also coexist. However, stress and emotional conflict do not always coincide with symptom onset and recurrence. Some patients with IBS seem to have a learned aberrant illness behavior (ie, they express emotional conflict as a GI complaint, usually abdominal pain). The physician evaluating patients with IBS, particularly those with refractory symptoms, should investigate for unresolved psychologic issues, including the possibility of sexual or physical abuse. Psychosocial factors also affect the outcome in IBS.

Physiologic factors: A variety of physiologic factors seem to be involved in IBS symptoms. Factors include altered motility, visceral hyperalgesia, and various genetic and environmental factors.

Visceral hyperalgesia refers to hypersensitivity to normal amounts of intraluminal distention and heightened perception of pain in the presence of normal quantities of intestinal gas; it may result from remodeling of neural pathways in the brain-gut axis. Some patients (perhaps 1 in 7) have reported their IBS symptoms began after an episode of acute gastroenteritis (termed postinfectious IBS). A subset of patients with IBS has autonomic dysfunctions. However, many patients have no demonstrable physiologic abnormalities, and even in those that do, the abnormalities may not correlate with symptoms.

Constipation may be explained by slower colonic transit, and diarrhea may be explained by faster colonic transit. Some patients with constipation have fewer colonic high amplitude-propagated contractions, which propel colonic contents over several segments. Conversely, excess sigmoid motor activity may retard transit in functional constipation.

Postprandial abdominal discomfort may be attributed to an exaggerated gastro-colonic reflex (the colonic contractile response to a meal), the presence of colonic high amplitude-propagated contractions, increased intestinal sensitivity (visceral hyperalgesia), or a combination of these. Fat ingestion may exaggerate hypersensitivity.

Hormonal fluctuations affect bowel functions in women. Rectal sensitivity is increased during menses but not during other phases of the menstrual cycle. The effects of sex steroids on GI transit are subtle. The role of small-bowel bacterial overgrowth in IBS is controversial.

Symptoms and Signs

IBS tends to begin in the teens and 20s, causing bouts of symptoms that recur at irregular periods. Onset in late adult life is less common but not rare. Symptoms rarely rouse the sleeping patient. Symptoms are often triggered by food, particularly fats, or by stress.

Patients have abdominal discomfort, which varies considerably but is often located in the lower quadrant, steady or cramping in nature, and relieved by defecation. In addition, abdominal discomfort is temporally

associated with alterations in stool frequency (increased in diarrhea-predominant IBS and decreased in constipation-predominant IBS) and consistency (ie, loose or lumpy and hard). Pain or discomfort related to defecation is likely to be of bowel origin; that associated with exercise, movement, urination, or menstruation usually has a different cause. Although bowel patterns are relatively consistent in most patients, it is not unusual for patients to alternate between constipation and diarrhea. Patients may also have symptoms of abnormal stool passage (straining, urgency, or feeling of incomplete evacuation), pass mucus, or complain of bloating or abdominal distention. Many patients also have symptoms of dyspepsia. Extraintestinal symptoms (eg, fatigue, fibromyalgia, sleep disturbances, chronic headaches) are common.

Diagnosis

• Clinical evaluation, based on Rome criteria

• Screening for organic causes with basic laboratory tests and sigmoidoscopy or colonoscopy

• Other tests for patients with red flag findings (rectal blood, weight loss, fever)

Diagnosis is based on characteristic bowel patterns, time and character of pain, and exclusion of other disease processes through physical examination and routine diagnostic tests. Diagnostic testing should be more intensive when the following red flag findings are present either at initial presentation or at any time after diagnosis: older age, fever, weight loss, rectal bleeding, vomiting. Because patients with IBS can develop organic conditions, testing for other conditions should also be considered in patients who develop alarm symptoms or markedly different symptoms during the course of IBS. Common illnesses that may be confused with IBS include lactose intolerance, drug-induced diarrhea, post-cholecystectomy diarrhea, laxative abuse, parasitic diseases (eg, giardiasis), eosinophilic gastritis or enteritis, microscopic colitis, and early inflammatory bowel disease. However, uninflamed colonic diverticula do not cause symptoms, and their presence should not be considered explanatory.

The bimodal age distribution of patients with inflammatory bowel disease makes it imperative to evaluate both younger and older patients. In patients > 60 with acute symptoms, ischemic colitis should be considered. Patients with constipation and no anatomic lesion should be evaluated for hypothyroidism and hyperparathyroidism. If the patient's symptoms suggest malabsorption, tropical sprue, celiac disease, and Whipple's disease must be considered. Defecatory disorders should be considered as a cause of constipation in patients who report symptoms of difficult defecation. Rare causes of diarrhea include hyperthyroidism, medullary cancer of the thyroid, or carcinoid syndrome, gastrinoma, vipoma, and Zollinger-Ellison syndrome. However, secretory diarrhea caused by vasoactive intestinal peptide (VIP), calcitonin, or gastrin is typically accompanied by stool volumes > 1000 mL daily.

History: Particular attention should be given to the character of the pain, bowel habits, familial interrelationships, and drug and dietary histories. Equally important are the patient's overall emotional state, interpretation of personal problems and quality of life. The quality of the patient-physician interaction is key to diagnostic and therapeutic efficacy.

The **Rome criteria** are standardized symptom-based criteria for diagnosing IBS. The Rome criteria require the presence of abdominal pain or discomfort for at least 3 days/mo in the last 3 mo along with ≥ 2 of the following: (1) improvement with defecation, (2) onset (of each episode of discomfort) associated with a change in frequency of defecation, or (3) change in consistency of stool.

Physical examination: Patients generally appear to be healthy. Palpation of the abdomen may reveal tenderness, particularly in the left lower quadrant, at times associated with a palpable, tender sigmoid. A digital rectal examination, including a test for occult blood, should be done on all patients. In women, a pelvic examination helps rule out ovarian tumors and cysts or endometriosis, which may mimic IBS.

Testing: The diagnosis of IBS can reasonably be made using the Rome criteria as long as patients have no red flag findings, such as rectal bleeding, weight loss, and fever, or other findings that might suggest another etiology. Many patients with IBS are overtested; however, CBC, biochemical profile (including liver tests), ESR, stool examination for ova and parasites (in those with diarrhea predominance), thyroid-stimulating hormone and Ca for those with constipation, and flexible sigmoidoscopy or colonoscopy

should be done. During flexible fiber-optic proctosigmoidoscopy, introduction of the instrument and air insufflation frequently trigger bowel spasm and pain. The mucosal and vascular patterns in IBS usually appear normal. Colonoscopy is preferred for patients > 50 with a change in bowel habits, particularly those with no previous IBS symptoms, to exclude colonic polyps and tumors. In patients with chronic diarrhea, particularly older women, mucosal biopsy can rule out possible microscopic colitis.

Additional studies (such as ultrasound, CT, barium enema x-ray, upper GI esophagogastroduodenoscopy, and small-bowel x-rays) should be undertaken only when there are other objective abnormalities. Fecal fat excretion should be measured when there is a concern about steatorrhea. Testing for celiac sprue and small-bowel x-rays are recommended when malabsorption is suspected. Testing for carbohydrate intolerance should be considered in appropriate circumstances.

Intercurrent disease: Patients with IBS may subsequently develop additional GI disorders, and the clinician must not summarily dismiss their complaints. Changes in symptoms (eg, in the location, type, or intensity of pain; in bowel habits; in constipation and diarrhea) and new symptoms or complaints (eg, nocturnal diarrhea) may signal another disease process. Other symptoms that require investigation include fresh blood in the stool, weight loss, very severe abdominal pain or unusual abdominal distention, steatorrhea or noticeably foul-smelling stools, fever or chills, persistent vomiting, hematemesis, symptoms that wake the patient from sleep (eg, pain, the urge to defecate), and a steady progressive worsening of symptoms. Patients > 40 are more likely than younger patients to develop an intercurrent physiologic illness.

Treatment

• Support and understanding

• Normal diet, avoiding gas-producing and diarrhea-producing foods

• Increased fiber intake constipation

• Loperamide for diarrhea

• Possibly tricyclic antidepressants

Therapy is directed at specific symptoms. An effective therapeutic relationship is essential for effectively managing IBS. Patients should be invited to express not only their symptoms but also their understanding of their symptoms and the reasons prompting a visit to the health care practitioner (eg, fear of serious disease). Patients should be educated about the disorder (eg, normal bowel physiology and the bowel's hypersensitivity to stress and food) and reassured, after appropriate tests, about the absence of a serious or life-threatening disease. Appropriate therapeutic goals (eg, expectations regarding the normal course or variability in symptoms, adverse effects of drugs, the appropriate and available working relationship between the physician and the patient) should be established. Finally, patients can benefit by being actively involved in the management of their condition. When successful, this can enhance the patient's motivation to adhere to treatment, foster a more positive physician-patient relationship, and mobilize the coping resources of even the most chronically passive patients. Psychologic stress, anxiety, or mood disorders should be identified, evaluated, and treated. Regular physical activity helps relieve stress and assists in bowel function, particularly in patients with constipation.

Diet: In general, a normal diet should be followed. Meals should not be overly large, and eating should be slow and paced. Patients with abdominal distention and increased flatulence may benefit from reducing or eliminating beans, cabbage, and other foods containing fermentable carbohydrates. Reduced intake of sweeteners (eg, sorbitol, mannitol, fructose), which are constituents of natural and processed foods (eg, apple and grape juice, bananas, nuts, and raisins), may alleviate flatulence, bloating, and diarrhea. Patients with evidence of lactose intolerance should reduce their intake of milk and dairy products. A low-fat diet may reduce postprandial abdominal symptoms.

Dietary fiber supplements may soften stool and improve the ease of evacuation. A bland bulk-producing agent may be used (eg, raw bran, starting with 15 mL [1 tbsp] with each meal, supplemented with

increased fluid intake). Alternatively, psyllium hydrophilic mucilloid with two glasses of water may be used. However, excessive use of fiber can lead to bloating and diarrhea, so fiber doses must be individualized. Occasionally, flatulence may be reduced by switching to a synthetic fiber preparation (eg, methylcellulose).

Drug therapy: Drug therapy is directed toward the dominant symptoms. Anticholinergic drugs (eg, hyoscyamine 0.125 mg po 30 to 60 min before meals) may be used for their antispasmodic effects.

Serotonin receptor modulation may be of benefit. Tegaserod, a 5HT4 agonist, stimulates motility and alleviates constipation. In 2007, tegaserod was withdrawn from the market because, in clinical trials, it slightly increased the incidence of cardiovascular ischemic events (ie, MI, unstable angina pectoris, stroke) compared with placebo. Tegaserod has since been reintroduced under a restricted program. The chloride channel activator lubiprostone may help patients with constipation.

In patients with diarrhea, oral diphenoxylate 2.5 to 5 mg or loperamide 2 to 4 mg may be given before meals. The dose of loperamide should be titrated upward to reduce diarrhea while avoiding constipation. For many patients, tricyclic antidepressants (TCAs) help relieve symptoms of diarrhea, abdominal pain, and bloating. These drugs are thought to reduce pain by down-regulating the activity of spinal cord and cortical afferent pathways arriving from the intestine. Secondary amine TCAs (eg, nortriptyline, desipramine) are often better tolerated than parent tertiary amines (eg, amitriptyline, imipramine, doxepin) because of fewer anticholinergic, sedating antihistaminic, and α-adrenergic adverse effects. Treatment should begin with a very low dose of a TCA (eg, desipramine 10 to 25 mg once/day at bedtime), increasing as necessary and tolerated up to about 100 to 150 mg once/day. SSRIs are also useful, particularly for patients with anxiety or an affective disorder, but may exacerbate diarrhea. 5HT3 antagonists (eg, alosetron) may benefit female patients with severe diarrhea refractory to other drugs. Because alosetron is associated with ischemic colitis, its use is restricted.

Preliminary data suggest that certain probiotics (eg, *Bifidobacterium infantis*) alleviate IBS symptoms, particularly bloating. The beneficial effects of probiotics are not generic to the entire species but specific to certain strains. Certain aromatic oils (carminatives) can relax smooth muscle and relieve pain caused by cramps in some patients. Peppermint oil is the most commonly used agent in this class.

Psychologic therapies: Cognitive-behavioral therapy, standard psychotherapy, and hypnotherapy may help some IBS patients.

Chapter 19. Inflammatory Bowel Disease

Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis (UC), is a relapsing and remitting condition characterized by chronic inflammation at various sites in the GI tract, which results in diarrhea and abdominal pain.

Inflammation results from a cell-mediated immune response in the GI mucosa. The precise etiology is unknown, but evidence suggests that the normal intestinal flora trigger an immune reaction in patients with a multifactorial genetic predisposition (perhaps involving abnormal epithelial barriers and mucosal immune defenses). No specific environmental, dietary, or infectious causes have been identified. The immune reaction involves the release of inflammatory mediators, including cytokines, interleukins, and tumor necrosis factor (TNF).

Although Crohn's disease and UC are similar, they can be distinguished in most cases (see Table 19-1). About 10% of colitis cases are considered indeterminate. The term colitis applies only to inflammatory disease of the colon (eg, ulcerative, granulomatous, ischemic, radiation-induced, infectious). Spastic (mucous) colitis is a misnomer sometimes applied to a functional disorder, irritable bowel syndrome (see p. 162).

Epidemiology: IBD affects people of all ages but usually begins before age 30, with peak incidence from 14 to 24. IBD may have a second smaller peak between ages 50 and 70; however, this later peak may include some cases of ischemic colitis.

IBD is most common among people of Northern European and Anglo-Saxon origin and is 2 to 4 times more common among Ashkenazi Jews than in non-Jewish whites. The incidence is lower in central and southern Europe and lower still in South America, Asia, and Africa. However, the incidence is increasing among blacks and Latin Americans living in North America. Both sexes are equally affected. First-degree relatives of patients with IBD have a 4- to 20-fold increased risk; their absolute risk may be as high as 7%. Familial tendency is much higher in Crohn's disease than in UC.

[**Table 19-1.** Differentiating Crohn's Disease and Ulcerative Colitis]

Several gene mutations conferring a higher risk of Crohn's disease (and some possibly related to UC) have been identified.

Cigarette smoking seems to contribute to development or exacerbation of Crohn's disease but decreases risk of UC. NSAIDs may exacerbate IBD.

Extraintestinal Manifestations

Crohn's disease and UC both affect organs other than the intestines. Most extraintestinal manifestations are more common in UC and Crohn's colitis than in Crohn's disease limited to the small bowel. Extraintestinal manifestations are categorized in 3 ways:

1. Disorders that usually parallel (ie, wax and wane with) IBD flare-ups. These disorders include peripheral arthritis, episcleritis, aphthous stomatitis, erythema nodosum, and pyoderma gangrenosum. Arthritis tends to involve large joints and be migratory and transient. One or more of these parallel disorders develops in more than one third of patients hospitalized with IBD.

2. Disorders that are clearly associated with IBD but appear independently of IBD activity. These disorders include ankylosing spondylitis, sacroiliitis, uveitis, and primary sclerosing cholangitis. Ankylosing spondylitis occurs more commonly in IBD patients with the HLA-B27 antigen. Most patients with spinal or sacroiliac involvement have evidence of uveitis and vice versa. Primary sclerosing cholangitis, which is a risk factor for cancer of the biliary tract, is strongly associated with UC or Crohn's colitis. Cholangitis may appear before or concurrently with the bowel disease or even 20 yr after colectomy. Liver disease (eg, fatty liver, autoimmune hepatitis, pericholangitis, cirrhosis) occurs in 3 to

5% of patients, although minor abnormalities in liver function tests are more common. Some of these conditions (eg, primary sclerosing cholangitis) may precede IBD by many years and, when diagnosed, should prompt an evaluation for IBD.

3. Disorders that are consequences of disrupted bowel physiology. These disorders occur mainly in severe Crohn's disease of the small bowel. Malabsorption may result from extensive ileal resection and cause deficiencies of fat-soluble vitamins, vitamin B_{12}, or minerals, resulting in anemia, hypocalcemia, hypomagnesemia, clotting disorders, and bone demineralization. In children, malabsorption retards growth and development. Other disorders include kidney stones from excessive dietary oxalate absorption, hydroureter and hydronephrosis from ureteral compression by the intestinal inflammatory process, gallstones from impaired ileal reabsorption of bile salts, and amyloidosis secondary to long-standing inflammatory and suppurative disease.

Thromboembolic disease may occur as a result of multiple factors in all 3 categories.

Treatment

• Supportive care

• 5-Aminosalicylic acid

• Corticosteroids

• Immunomodulating drugs

• Anticytokine drugs

• Sometimes antibiotics (eg, metronidazole, ciprofloxacin) and probiotics

Several classes of drugs are helpful for IBD. Details of their selection and use are discussed under each disorder.

5-Aminosalicylic acid (5-ASA, mesalamine): 5-ASA blocks production of prostaglandins and leukotrienes and has other beneficial effects on the inflammatory cascade. Because 5-ASA is active only intraluminally and is rapidly absorbed by the proximal small bowel, it must be formulated for delayed absorption when given orally. Sulfasalazine, the original agent in this class, delays absorption by complexing 5-ASA with a sulfa moiety, sulfapyridine. The complex is cleaved by bacterial flora in the lower ileum and colon, releasing the 5-ASA. The sulfa moiety, however, causes numerous adverse effects (eg, nausea, dyspepsia, headache), interferes with folate (folic acid) absorption, and occasionally causes serious adverse reactions (eg, hemolytic anemia or agranulocytosis and, rarely, hepatitis or pneumonitis). Reversible decreases in sperm count and motility occur in up to 80% of men. If used, sulfasalazine should be given with food, initially in a low dosage (eg, 0.5 g po bid) and gradually increased over several days to 1 to 2 g bid to tid. Patients should take daily folate supplements 1 mg po and have CBC and liver tests every 6 to 12 mo. Acute interstitial nephritis secondary to mesalamine occurs rarely; periodic monitoring of renal function is advisable because most cases are reversible if recognized early.

Newer drugs that complex 5-ASA with other vehicles seem almost equally effective but have fewer adverse effects. Olsalazine (a 5-ASA dimer) and balsalazide (5-ASA conjugated to an inactive compound) are cleaved by bacterial azoreductases (as is sulfasalazine). These drugs are activated mainly in the colon and are less effective for proximal small-bowel disease. Olsalazine dosage is 500 to 1500 mg po bid, and balsalazide is 2.25 g po tid. Olsalazine sometimes causes diarrhea, especially in patients with pancolitis. This problem is minimized by gradual escalation of dose and administration with meals.

Other forms of 5-ASA use delayed-release coatings. Asacol (typical dose 800 to 1200 mg po tid) is 5-ASA coated with an acrylic polymer whose pH solubility delays release of the drug until entry into the distal ileum and colon. Pentasa (1 g po qid) is 5-ASA encapsulated in ethylcellulose microgranules that release 35% of the drug in the small bowel. Two once/day formulations of mesalamine (Lialda, Apriso) are available; this less frequent dosing may improve adherence.

5-ASA is also available as a suppository (500 or 1000 mg at bedtime or bid) or enema (4 g at bedtime or bid) for proctitis and left-sided colon disease. These rectal preparations are effective for both acute treatment and long-term maintenance in proctitis and left-sided colon disease, and they have incremental benefit in combination with oral 5-ASA.

Corticosteroids: Corticosteroids are useful for acute flare-ups of most forms of IBD when 5-ASA compounds are inadequate. However, corticosteroids are not appropriate for maintenance. IV hydrocortisone 300 mg/day or methylprednisolone 60 to 80 mg/day by continuous drip or in divided doses is used for severe disease; oral prednisone or prednisolone 40 to 60 mg once/day may be used for moderate disease. Treatment is continued until symptoms remit (usually 7 to 28 days) and then tapered by 5 to 10 mg weekly to 20 mg once/day. Treatment is then further tapered by 2.5 to 5 mg weekly while instituting maintenance therapy with 5-ASA or immunomodulators. Adverse effects of short-term corticosteroids in high doses include hyperglycemia, hypertension, insomnia, hyperactivity, and acute psychotic episodes.

Hydrocortisone enemas or foam may be used for proctitis and left-sided colon disease; as an enema, 100 mg in 60 mL of isotonic solution is given once/day or bid. The enema should be retained in the bowel as long as possible; instillation at night, with the patient lying on the left side with hips elevated, may prolong retention and extend distribution. Treatment, if effective, should be continued daily for about 2 to 4 wk, then every other day for 1 to 2 wk, and then gradually discontinued over 1 to 2 wk.

Budesonide is a corticosteroid with a high (> 90%) first-pass liver metabolism; thus, oral administration may have a significant effect on GI tract disease but minimal adrenal suppression. Oral budesonide has fewer adverse effects than prednisolone but is not as rapidly effective and is typically used for less severe disease. Budesonide may be effective in maintaining remission for 3 to 6 mo but has not yet proved effective for long-term maintenance. Dosage is 9 mg once/day. It is also available outside the US as an enema.

Immunomodulating drugs: Azathioprine and its metabolite 6-mercaptopurine inhibit T-cell function. They are effective long-term and may diminish corticosteroid requirements and maintain remission for years. These drugs often require 1 to 3 mo to produce clinical benefits, so corticosteroids cannot be withdrawn until at least the 2nd month. Dosage of azathioprine is usually 2.5 to 3.0 mg/kg po once/day and 6-mercaptopurine 1.5 to 2.5 mg/kg po once/day but varies depending on individual metabolism. Signs of bone marrow suppression must be monitored with regular WBC count (biweekly for 1 mo, then every 1 to 2 mo). Pancreatitis or high fever occurs in about 3 to 5% of patients; either is an absolute contraindication to rechallenge. Hepatotoxicity is rarer and can be screened by blood tests every 6 to 12 mo. Newly available blood tests that measure the activity of one of the enzymes that metabolize azathioprine and 6-mercaptopurine and that directly measure metabolite levels may sometimes be helpful in ensuring safe and effective drug dosages.

Methotrexate 15 to 25 mg po or sc weekly is of benefit to many patients with corticosteroid-refractory or corticosteroid-dependent Crohn's disease, even those who have not responded to azathioprine or 6-mercaptopurine. Adverse effects include nausea, vomiting, and asymptomatic liver function test abnormalities. Folate 1 mg po once/day may diminish some of the adverse effects. Alcohol use, obesity, diabetes, and possibly psoriasis are risk factors for hepatotoxicity. Patients with these conditions should have a liver biopsy after a total dose of 1.5 g, but otherwise, concerns over hepatotoxicity are too often exaggerated. Pulmonary toxicity can also occur with methotrexate therapy.

Cyclosporine, which blocks lymphocyte activation, may benefit patients with severe UC unresponsive to corticosteroids and who may otherwise require colectomy. Its only well-documented use in Crohn's disease is for patients with refractory fistulas or pyoderma. Initial dose is 4 mg/kg IV in continuous infusion over 24 h; responders are converted to an oral dose of 6 to 8 mg/kg once/day with early introduction of azathioprine or 6-mercaptopurine. Long-term use (> 6 mo) is contraindicated by multiple adverse effects (eg, renal toxicity, seizures, opportunistic infections, hypertension, neuropathy). Generally, patients are not offered cyclosporine unless there is a reason to avoid the safer curative option of colectomy. If the drug is used, trough blood levels should be kept between 200 to 400 ng/mL and *Pneumocystis jirovecii* prophylaxis should be considered during the period of concomitant corticosteroid, cyclosporine, and

antimetabolite treatment. Tacrolimus, an immunosuppressant also used in transplant patients, seems as effective as cyclosporine.

Anticytokine drugs: Infliximab, certolizumab, and adalimumab are antibodies to TNF. These agents may be useful in Crohn's disease; additionally infliximab may be beneficial in UC for refractory or corticosteroid-dependent disease. Several anti-interleukin antibodies and interleukins may decrease the inflammatory response and are being studied for Crohn's disease. An antibody to leukocyte adhesion molecules (natalizumab) is approved as monotherapy for the most refractory cases of Crohn's disease; other analogs (eg, vedolizumab) are also being studied.

Infliximab is given as a single IV infusion of 5 mg/kg over 2 h. Monotherapy with infliximab is clearly effective for both induction and maintenance of remission, but some studies suggest better short-term results when infliximab is initiated in combination with a thiopurine (eg, azathioprine). Ideally, infliximab would eventually be stopped and patients would be maintained on the antimetabolite, but this strategy has not been validated in controlled studies. Corticosteroid tapering may begin after 2 wk. The initial infliximab infusion is usually followed by repeat infusions at weeks 2 and 6. Subsequently, it is given every 8 wk or at intervals determined by the patient's clinical course. Adverse effects during infusion (infusion reaction) include immediate hypersensitivity reactions (eg, rash, itching, sometimes anaphylactoid reactions), fever, chills, headache, and nausea. Delayed hypersensitivity reactions have also occurred. Anti-TNF drugs given subcutaneously (eg, adalimumab) do not cause infusion reactions, although they may cause local erythema, pain, and itching (injection site reaction). Patients who are intolerant or who have lost their initial response to infliximab may respond to adalimumab therapy.

Several patients have died of sepsis after infliximab use, so it is contraindicated when uncontrolled bacterial infection is present. Furthermore, TB reactivation has been attributed to this drug; therefore, screening by PPD and chest x-ray is required before its use. Lymphoma, demyelinating disease, and liver and hematologic toxicity are other potential concerns with anti-TNF antibody treatment. Other anticytokine, anti-integrin, and growth factors are under investigation, as is leukopheresis therapy to deplete activated immunocytes.

Antibiotics and probiotics: Antibiotics may be helpful in Crohn's disease but are of limited use in UC. Metronidazole 500 to 750 mg po tid for 4 to 8 wk may control mild Crohn's disease and help heal fistulas. However, adverse effects (particularly neurotoxicity) often preclude completion of treatment. Ciprofloxacin 500 to 750 mg po bid may prove less toxic. Many experts recommend metronidazole and ciprofloxacin in combination. Rifaximin, a nonabsorbable antibiotic, at a dose of 200 mg po tid is also being studied as treatment for active Crohn's disease.

Various nonpathogenic microorganisms (eg, commensal *Escherichia coli*, *Lactobacillus* species, *Saccharomyces*) given daily serve as probiotics and may be effective in preventing pouchitis (see p. 176), but other therapeutic roles have yet to be clearly defined. Therapeutic infestation with the parasite *Trichuris suis* has been tried in an effort to stimulate T2-helper cell immunity and may decrease disease activity in UC.

Supportive care: Most patients and their families are interested in diet and stress management. Although there are anecdotal reports of clinical improvement on certain diets, including one with rigid carbohydrate restrictions, controlled trials have shown no benefit. Stress management may be helpful.

Crohn's Disease

(Regional Enteritis; Granulomatous Ileitis or Ileocolitis)

Crohn's disease is a chronic transmural inflammatory disease that usually affects the distal ileum and colon but may occur in any part of the GI tract. Symptoms include diarrhea and abdominal pain. Abscesses, internal and external fistulas, and bowel obstruction may arise. Extraintestinal symptoms, particularly arthritis, may occur. Diagnosis is by colonoscopy and barium contrast studies. Treatment is with 5-aminosalicylic acid, corticosteroids, immunomodulators, anticytokines, antibiotics, and often surgery.

Pathophysiology

Crohn's disease begins with crypt inflammation and abscesses, which progress to tiny focal aphthoid ulcers. These mucosal lesions may develop into deep longitudinal and transverse ulcers with intervening mucosal edema, creating a characteristic cobblestoned appearance to the bowel.

Transmural spread of inflammation leads to lymphedema and thickening of the bowel wall and mesentery. Mesenteric fat typically extends onto the serosal surface of the bowel. Mesenteric lymph nodes often enlarge. Extensive inflammation may result in hypertrophy of the muscularis mucosae, fibrosis, and stricture formation, which can lead to bowel obstruction. Abscesses are common, and fistulas often penetrate into adjoining structures, including other loops of bowel, the bladder, or psoas muscle. Fistulas may even extend to the skin of the anterior abdomen or flanks. Independently of intra-abdominal disease activity, perianal fistulas and abscesses occur in 25 to 33% of cases; these complications are frequently the most troublesome aspects of Crohn's disease.

Noncaseating granulomas can occur in lymph nodes, peritoneum, the liver, and all layers of the bowel wall. Although pathognomonic when present, granulomas are not detected in about half of patients with Crohn's disease. The presence of granulomas does not seem to be related to the clinical course.

Segments of diseased bowel are sharply demarcated from adjacent normal bowel ("skip areas"); hence, the name regional enteritis. About 35% of Crohn's disease cases involve the ileum alone (ileitis); about 45% involve the ileum and colon (ileocolitis), with a predilection for the right side of the colon; and about 20% involve the colon alone (granulomatous colitis), most of which, unlike ulcerative colitis (UC), spare the rectum. Occasionally, the entire small bowel is involved (jejunoileitis). The stomach, duodenum, or esophagus is clinically involved only rarely, although microscopic evidence of disease is often detectable in the gastric antrum, especially in younger patients. In the absence of surgical intervention, the disease almost never extends into areas of small bowel that are not involved at first diagnosis.

There is an increased risk of cancer in affected small-bowel segments. Patients with colonic involvement have a long-term risk of colorectal cancer equal to that of UC, given the same extent and duration of disease.

Symptoms and Signs

The most common initial manifestation is chronic diarrhea with abdominal pain, fever, anorexia, and weight loss. The abdomen is tender, and a mass or fullness may be palpable. Gross rectal bleeding is unusual except in isolated colonic disease, which may manifest similarly to UC. Some patients present with an acute abdomen that simulates acute appendicitis or intestinal obstruction. About 33% of patients have perianal disease (especially fissures and fistulas), which is sometimes the most prominent or even initial complaint. In children, extraintestinal manifestations frequently predominate over GI symptoms; arthritis, FUO, anemia, or growth retardation may be a presenting symptom, whereas abdominal pain or diarrhea may be absent.

With recurrent disease, symptoms vary. Pain is most common and occurs with both simple recurrence and abscess formation. Patients with severe flare-up or abscess are likely to have marked tenderness, guarding, rebound, and a general toxic appearance. Stenotic segments may cause bowel obstruction, with colicky pain, distention, obstipation, and vomiting. Adhesions from previous surgery may also cause bowel obstruction, which begins rapidly, without the prodrome of fever, pain, and malaise typical of obstruction due to a Crohn's disease flare-up. An enterovesical fistula may produce air bubbles in the urine (pneumaturia). Draining cutaneous fistulas may occur. Free perforation into the peritoneal cavity is unusual.

Chronic disease causes a variety of systemic symptoms, including fever, weight loss, undernutrition, and extraintestinal manifestations (see p. 166).

The Vienna Classification and its recent Montreal modification categorize Crohn's disease into 3 principal patterns: (1) primarily inflammatory, which after several years commonly evolves into either (2) primarily stenotic or obstructing or (3) primarily penetrating or fistulizing. These different clinical patterns dictate

different therapeutic approaches. Some genetic studies suggest a molecular basis for this classification.

Diagnosis

• Barium x-rays of the stomach, small bowel, and colon

• Abdominal CT (conventional or CT enterography)

• Sometimes magnetic resonance (MR) enterography, upper endoscopy, and/or colonoscopy

Crohn's disease should be suspected in a patient with inflammatory or obstructive symptoms or in a patient without prominent GI symptoms but with perianal fistulas or abscesses or with otherwise unexplained arthritis, erythema nodosum, fever, anemia, or (in a child) stunted growth. A family history of Crohn's disease also increases the index of suspicion. Similar symptoms and signs (eg, abdominal pain, diarrhea) may be caused by other GI disorders. Differentiation from UC (see Table 19-1) may be an issue in the 20% of cases in which Crohn's disease is confined to the colon. However, because treatment is similar, this distinction is critical only when surgery or experimental therapy is contemplated.

Patients presenting with an acute abdomen (either initially or on relapse) should have flat and upright abdominal x-rays and an abdominal CT scan. These studies may show obstruction, abscesses or fistulas, and other possible causes of an acute abdomen (eg, appendicitis). Ultrasound may better delineate gynecologic pathology in women with lower abdominal and pelvic pain.

If initial presentation is less acute, an upper GI series with small-bowel follow-through and spot films of the terminal ileum is preferred over conventional CT. However, newer techniques of CT or MR enterography, which combine high-resolution CT or MR imaging with large volumes of ingested contrast, are becoming the procedures of choice in some centers. These imaging studies are virtually diagnostic if they show characteristic strictures or fistulas with accompanying separation of bowel loops. If findings are questionable, CT enteroclysis or video capsule enteroscopy may show superficial aphthous and linear ulcers. Barium enema x-ray may be used if symptoms seem predominantly colonic (eg, diarrhea) and may show reflux of barium into the terminal ileum with irregularity, nodularity, stiffness, wall thickening, and a narrowed lumen. Differential diagnoses in patients with similar x-ray findings include cancer of the cecum, ileal carcinoid, lymphoma, systemic vasculitis, radiation enteritis, ileocecal TB, and ameboma.

In atypical cases (eg, predominantly diarrhea, with minimal pain), evaluation is similar to suspected UC, with colonoscopy (including biopsy, sampling for enteric pathogens, and, when possible, visualization of the terminal ileum). Upper GI endoscopy may identify subtle gastroduodenal involvement even in the absence of upper GI symptoms.

Laboratory tests should be done to screen for anemia, hypoalbuminemia, and electrolyte abnormalities. Liver function tests should be done; elevated alkaline phosphatase and γ-glutamyl transpeptidase levels in patients with major colonic involvement suggest possible primary sclerosing cholangitis. Leukocytosis or increased levels of acute-phase reactants (eg, ESR, C-reactive protein) are nonspecific but may be used serially to monitor disease activity.

Perinuclear antineutrophil cytoplasmic antibodies are present in 60 to 70% of patients with UC and in only 5 to 20% of patients with Crohn's disease. Anti-*Saccharomyces cerevisiae* antibodies are relatively specific for Crohn's disease. However, these tests do not reliably separate the 2 diseases. They have uncertain value in cases of indeterminate colitis and are not recommended for routine diagnosis.

Prognosis

Established Crohn's disease is rarely cured but is characterized by intermittent exacerbations and remissions. Some patients have severe disease with frequent, debilitating periods of pain. However, with judicious medical therapy and, where appropriate, surgical therapy, most patients function well and adapt successfully. Disease-related mortality is very low. GI cancer, including cancer of the colon and small bowel, is the leading cause of excess Crohn's disease-related mortality.

Treatment

• Loperamide or antispasmodics for symptom relief

• 5-Aminosalicylic acid (5-ASA) or antibiotics

• Other drugs depending on symptoms and severity

• Sometimes surgery

Details of specific drugs and dosages are discussed on p. 167.

General management: Cramps and diarrhea may be relieved by oral administration of loperamide 2 to 4 mg or antispasmodic drugs up to 4 times/day (ideally before meals). Such symptomatic treatment is safe, except in cases of severe, acute Crohn's colitis, which may progress to toxic megacolon as in UC. Hydrophilic mucilloids (eg, methylcellulose or psyllium preparations) sometimes help prevent anal irritation by increasing stool firmness. Dietary roughage is to be avoided in stricturing disease or active colonic inflammation.

Mild to moderate disease: This category includes ambulatory patients who tolerate oral intake and have no signs of toxicity, tenderness, mass, or obstruction. 5-ASA (mesalamine) is commonly used as first-line treatment, although its benefits for small-bowel disease are modest at best. Pentasa is the most effective formulation for disease proximal to the terminal ileum; Asacol is effective in distal ileal disease. All formulations are roughly equivalent for Crohn's colitis, although none of the newer preparations rival sulfasalazine for efficacy on a dose-for-dose basis.

Antibiotics are considered a first-line agent by some clinicians, or they may be reserved for patients not responding to 4 wk of 5-ASA; their use is strictly empiric. With any of these drugs, 8 to 16 wk of treatment may be required.

Responders should receive maintenance therapy.

Moderate to severe disease: Patients without fistulas or abscesses but with significant pain, tenderness, fever, or vomiting, or those who have not responded to treatment for mild disease, require corticosteroids, either oral or parenteral, depending on severity of symptoms and frequency of vomiting. Oral prednisone or prednisolone may act more rapidly and reliably than oral budesonide, but budesonide has somewhat fewer adverse effects and is considered the corticosteroid of choice in many centers, especially in Europe. Patients not responding to corticosteroids, or those whose doses cannot be tapered, should receive azathioprine, 6-mercaptopurine, or possibly methotrexate. Infliximab is preferred by some as a second-line agent after corticosteroids, and even as a first-line agent in preference to corticosteroids, but it is contraindicated in active uncontrolled infection.

Obstruction is managed initially with nasogastric suction and IV fluids. Obstruction due to uncomplicated Crohn's disease should resolve within a few days and therefore does not require parenteral nutrition; absence of prompt response indicates a complication or another etiology and demands immediate surgery.

Fulminant disease or abscess: Patients with toxic appearance, high fever, persistent vomiting, rebound, or a tender or palpable mass must be hospitalized for administration of IV fluids and antibiotics. Abscesses must be drained, either percutaneously or surgically. IV corticosteroids should be given only when infection has been ruled out or controlled. If there is no response to corticosteroids and antibiotics within 5 to 7 days, surgery is usually indicated.

Fistulas: Fistulas are treated initially with metronidazole and ciprofloxacin. Patients who do not respond in 3 to 4 wk may receive an immunomodulator (eg, azathioprine, 6-mercaptopurine), with or without an induction regimen of infliximab for more rapid response. Cyclosporine is an alternative, but fistulas often relapse after treatment. Severe refractory perianal fistulas may require temporary diverting colostomy but almost invariably recur after reconnection; hence, diversion is more appropriately considered a

preparation for definitive surgery or at best an adjunct to infliximab rather than a primary treatment.

Maintenance therapy: Patients who require only 5-ASA or an antibiotic to achieve remission can be maintained on this drug. Patients requiring acute treatment with corticosteroids or infliximab generally require azathioprine, 6-mercaptopurine, methotrexate, or infliximab for maintenance. Systemically active corticosteroids are neither safe nor effective for long-term maintenance, although budesonide has been shown to delay relapse with fewer adverse effects. Patients who respond to infliximab for acute disease but who are not well maintained on antimetabolites may stay in remission with repeat doses of infliximab 5 to 10 mg/kg at 8-wk intervals. Monitoring during remission can be done by following symptoms and blood tests and does not require routine x-rays or colonoscopy (other than regular surveillance for dysplasia after 7 to 8 yr of disease).

Surgery: Even though about 70% of patients ultimately require an operation, surgery is always done reluctantly. It is best reserved for recurrent intestinal obstruction or intractable fistulas or abscesses. Resection of the involved bowel may ameliorate symptoms but does not cure the disease, which is likely to recur even after resection of all clinically apparent lesions. The recurrence rate, defined by endoscopic lesions at the anastomotic site, is > 70% at 1 yr and > 85% at 3 yr; defined by clinical symptoms, it is about 25 to 30% at 3 yr and 40 to 50% at 5 yr. Ultimately, further surgery is required in nearly 50% of cases. However, recurrence rates seem to be reduced by early postoperative prophylaxis with 6-mercaptopurine, metronidazole, or possibly infliximab or 5-ASA. Moreover, when surgery is done for appropriate indications, almost all patients have improved quality of life.

Ulcerative Colitis

Ulcerative colitis (UC) is a chronic inflammatory and ulcerative disease arising in the colonic mucosa, characterized most often by bloody diarrhea. Extraintestinal symptoms, particularly arthritis, may occur. Long-term risk of colon cancer is high. Diagnosis is by colonoscopy. Treatment is with 5-aminosalicylic acid, corticosteroids, immunomodulators, anticytokines, antibiotics, and occasionally surgery.

Pathophysiology

UC usually begins in the rectum. It may remain localized to the rectum (ulcerative proctitis) or extend proximally, sometimes involving the entire colon. Rarely, it involves most of the large bowel at once.

The inflammation caused by UC affects the mucosa and submucosa, and there is a sharp border between normal and affected tissue. Only in severe disease is the muscularis involved. In early cases, the mucous membrane is erythematous, finely granular, and friable, with loss of the normal vascular pattern and often with scattered hemorrhagic areas. Large mucosal ulcers with copious purulent exudate characterize severe disease. Islands of relatively normal or hyperplastic inflammatory mucosa (pseudopolyps) project above areas of ulcerated mucosa. Fistulas and abscesses do not occur.

Toxic or fulminant colitis occurs when transmural extension of ulceration results in localized ileus and peritonitis. Within hours to days, the colon loses muscular tone and begins to dilate. The terms toxic megacolon or toxic dilation are discouraged because the toxic inflammatory state and its complications can occur without frank megacolon (defined as transverse colon > 6 cm diameter during an exacerbation). Toxic colitis is a medical emergency that usually occurs spontaneously in the course of very severe colitis but is sometimes precipitated by opioid or anticholinergic antidiarrheal drugs. Colonic perforation may occur, which increases mortality significantly.

Symptoms and Signs

Bloody diarrhea of varied intensity and duration is interspersed with asymptomatic intervals. Usually an attack begins insidiously, with increased urgency to defecate, mild lower abdominal cramps, and blood and mucus in the stools. Some cases develop after an infection (eg, amebiasis, bacillary dysentery).

When ulceration is confined to the rectosigmoid, the stool may be normal or hard and dry, but rectal discharges of mucus loaded with RBCs and WBCs accompany or occur between bowel movements.

Systemic symptoms are absent or mild. If ulceration extends proximally, stools become looser and the patient may have > 10 bowel movements per day, often with severe cramps and distressing rectal tenesmus, without respite at night. The stools may be watery or contain mucus and frequently consist almost entirely of blood and pus.

Toxic or fulminant colitis manifests initially with sudden violent diarrhea, fever to 40° C (104° F), abdominal pain, signs of peritonitis (eg, rebound tenderness), and profound toxemia.

Systemic symptoms and signs, more common with extensive UC, include malaise, fever, anemia, anorexia, and weight loss. Extraintestinal manifestations (particularly joint and skin complications—see p. 167) are most common when systemic symptoms are present.

Diagnosis

• Stool cultures and microscopy (to exclude infectious causes)

• Sigmoidoscopy with biopsy

Initial presentation: Diagnosis is suggested by typical symptoms and signs, particularly when accompanied by extraintestinal manifestations or a history of previous similar attacks. UC should be distinguished from Crohn's disease (see Table 19-1) but more importantly from other causes of acute colitis (eg, infection; in elderly patients, ischemia).

In all patients, stool cultures for enteric pathogens should be done, and *Entamoeba histolytica* should be excluded by examination of fresh stool specimens. When amebiasis is suspected because of epidemiologic or travel history, serologic titers and biopsies should be done. History of prior antibiotic use or recent hospitalization should prompt stool assay for *Clostridium difficile* toxin. Patients at risk should be tested for HIV, gonorrhea, herpesvirus, chlamydia, and amebiasis. Opportunistic infections (eg, cytomegalovirus, *Mycobacterium avium-intracellulare*) or Kaposi's sarcoma must also be considered in immunosuppressed patients. In women using oral contraceptives, contraceptive-induced colitis is possible; it usually resolves spontaneously after hormone therapy is stopped.

Sigmoidoscopy should be done; it allows visual confirmation of colitis and permits direct sampling of stool or mucus for culture and microscopic evaluation, as well as biopsy of affected areas. Although visual inspection and biopsies may be nondiagnostic, because there is much overlap in appearance among different types of colitis, acute, self-limited, infectious colitis can usually be distinguished histologically from chronic idiopathic UC or Crohn's colitis. Severe perianal disease, rectal sparing, absence of bleeding, and asymmetric or segmental involvement of the colon indicate Crohn's disease rather than UC (see Table 19-1). Colonoscopy is usually unnecessary initially but should be done electively if inflammation has extended proximal to the reach of the sigmoidoscope.

Laboratory tests should be done to screen for anemia, hypoalbuminemia, and electrolyte abnormalities. Liver function tests should be done; elevated alkaline phosphatase and γ-glutamyl transpeptidase levels suggest possible primary sclerosing cholangitis. Perinuclear antineutrophil cytoplasmic antibodies are relatively specific (60 to 70%) for UC. Anti-*Saccharomyces cerevisiae* antibodies are relatively specific for Crohn's disease. However, these tests do not reliably separate the 2 diseases and are not recommended for routine diagnosis. Other possible laboratory abnormalities include leukocytosis, thrombocytosis, and elevated acute-phase reactants (eg, ESR, C-reactive protein).

X-rays are not diagnostic but occasionally show abnormalities. Plain x-rays of the abdomen may show mucosal edema, loss of haustration, and absence of formed stool in the diseased bowel. Barium enema shows similar changes, albeit more clearly, and may also show ulcerations, but the enema should not be done during an acute presentation. A shortened, rigid colon with an atrophic or pseudopolypoid mucosa is often seen after several years' illness. X-ray findings of thumbprinting and segmental distribution are more suggestive of intestinal ischemia or possibly Crohn's colitis rather than of UC.

Recurrent symptoms: Patients with known disease and a recurrence of typical symptoms should be examined, but extensive testing is not always required. Depending on duration and severity of symptoms,

sigmoidoscopy or colonoscopy may be done and a CBC obtained. Cultures, ova and parasite examination, and *C. difficile* toxin assay should be done when there are atypical features to the relapse or when there is an exacerbation after prolonged remission, during a contagious outbreak, after antibiotic exposure, or whenever the clinician is suspicious.

Fulminant symptoms: Patients require further evaluation during severe flare-ups. Flat and upright abdominal x-rays should be taken; they may show megacolon or intraluminal gas accumulated over a long, continuous, paralyzed segment of colon—a result of lost muscle tone. Colonoscopy and barium enema should be avoided because of the risk of perforation. CBC, ESR, electrolytes, PT, PTT, and type and crossmatch should be obtained.

The patient must be watched closely for progressive peritonitis or perforation. Percussion over the liver is important because loss of hepatic dullness may be the first clinical sign of free perforation, especially in a patient whose peritoneal signs are suppressed by high-dose corticosteroids. Abdominal x-rays are taken every 1 or 2 days to follow the course of colonic distention and to detect free or intramural air.

Prognosis

Usually, UC is chronic with repeated exacerbations and remissions. In about 10% of patients, an initial attack becomes fulminant with massive hemorrhage, perforation, or sepsis and toxemia. Complete recovery after a single attack occurs in another 10%.

Patients with localized ulcerative proctitis have the best prognosis. Severe systemic manifestations, toxic complications, and malignant degeneration are unlikely, and late extension of the disease occurs in only about 20 to 30%. Surgery is rarely required, and life expectancy is normal. The symptoms, however, may prove stubborn and refractory. Moreover, because extensive UC may begin in the rectum and spread proximally, proctitis should not be considered localized until it has been observed for ≥ 6 mo. Localized disease that later extends is often more severe and more refractory to therapy.

Colon cancer: The risk of colon cancer is proportional to the duration of disease and amount of colon affected, but not necessarily to the clinical severity of the attacks. Some recent studies suggest that sustained microscopic inflammation is a risk factor, and that use of aminosalicylate to control inflammation is protective. Cancer begins to appear by 7 yr from onset of illness in patients with extensive colitis. The cumulative likelihood of cancer is about 3% at 15 yr, 5% at 20 yr, and 9% at 25 yr, representing an annual risk of about 0.5 to 1% after the 10th yr. There is probably no higher absolute cancer risk among patients with childhood-onset colitis independent of the longer duration of disease. However, patients who have inflammatory bowel disease and primary sclerosing cholangitis are at a higher risk of cancer from the time of colitis diagnosis.

Regular colonoscopic surveillance, preferably during remission, is advised for patients with disease duration > 8 to 10 yr (except for those with isolated proctitis). Endoscopic biopsies should be taken every 10 cm throughout the colon. Newer techniques, especially chromoendoscopy, may better identify areas of suspicion in preference to totally random biopsies. Any grade of definite dysplasia within an area affected by colitis is liable to progress to more advanced neoplasia and even cancer and is a strong indication for total colectomy unless the dysplasia is strictly confined to a discrete, completely excisable polyp. It is important to distinguish definite neoplastic dysplasia from reactive or regenerative atypia secondary to inflammation. However, if the dysplasia is unequivocal, delaying colectomy in favor of repeated follow-up surveillance is a risky strategy. Pseudopolyps have no prognostic significance but may be difficult to distinguish from neoplastic polyps; thus, any suspect polyp should undergo excision biopsy.

The optimal frequency of colonoscopic surveillance has not been established, but some authorities recommend every 2 yr during the 2nd decade of disease and annually thereafter.

Long-term survival after diagnosis of colitis-related cancer is about 50%, a figure comparable to that for colorectal cancer in the general population.

Treatment

• Loperamide and dietary management for symptom relief

• 5-Aminosalicylic acid (5-ASA)

• Corticosteroids and other drugs depending on symptoms and severity

• Anticytokine drugs

• Sometimes surgery

Details of specific drugs and regimens are discussed on p. 167.

General management: Avoiding raw fruits and vegetables limits trauma to the inflamed colonic mucosa and may lessen symptoms. A milk-free diet may help but need not be continued if no benefit is noted. Loperamide 2 mg po bid to qid is indicated for relatively mild diarrhea; higher oral doses (4 mg in the morning and 2 mg after each bowel movement) may be required for more intense diarrhea. Antidiarrheal drugs must be used with extreme caution in severe cases because they may precipitate toxic dilation.

Mild left-sided disease: Patients with proctitis, or colitis that does not extend proximally beyond the splenic flexure, are treated with 5-ASA (mesalamine) enemas once/day or bid depending on severity. Suppositories are effective for more distal disease and are usually preferred by patients. Corticosteroid and budesonide enemas are slightly less effective but should be used if 5-ASA is unsuccessful or not tolerated. Once remission is achieved, dosage is slowly tapered to maintenance levels. Oral 5-ASA drugs theoretically have some incremental benefit in lessening the probability of proximal spread of disease.

Moderate or extensive disease: Patients with inflammation proximal to the splenic flexure or left-sided disease unresponsive to topical agents should receive an oral 5-ASA formulation in addition to 5-ASA enemas. High-dose corticosteroids are added for more severe symptoms; after 1 to 2 wk, the daily dose is reduced by about 5 to 10 mg each wk. Immunomodulater therapy with azathioprine or 6-mercaptopurine can be used in patients who are refractory to maximal doses of 5-ASA and would otherwise need long-term corticosteroid therapy. Additionally, infliximab is beneficial in some patients and may be considered for those refractory to immunomodulator or corticosteroid therapy as well as those who are corticosteroid dependent.

Severe disease: Patients with > 10 bloody bowel movements per day, tachycardia, high fever, or severe abdominal pain require hospitalization to receive high-dose IV corticosteroids. 5-ASA may be continued. IV fluids and blood transfusion are given as needed for dehydration and anemia. The patient must be observed closely for the development of toxic megacolon. Parenteral hyperalimentation is sometimes used for nutritional support but is of no value as primary therapy; patients who can tolerate food should eat.

Patients who do not respond within 3 to 7 days should be considered for IV cyclosporine or infliximab or else for surgery. Patients who do respond to a corticosteroid regimen are switched within a week or so to prednisone 60 mg po once/day, which may be gradually reduced at home based on clinical response. Patients who are started on IV cyclosporine and respond to therapy are switched to oral cyclosporine and concomitant azathioprine or 6-mercaptopurine. Oral cyclosporine is continued for about 3 to 4 mo, during which time corticosteroids are tapered and cyclosporine levels are closely monitored. Some clinicians recommend prophylaxis against *Pneumocystis jirovecii* pneumonia during the interval of overlapping treatment with corticosteroids, cyclosporine, and an antimetabolite.

Fulminant colitis: If fulminant colitis or toxic megacolon is suspected, the patient should (1) stop all antidiarrheal drugs; (2) take nothing by mouth and have inserted a long intestinal tube attached to intermittent suction; (3) receive aggressive IV fluid and electrolyte therapy with 0.9% NaCl, and potassium chloride and blood as needed; (4) be treated with high-dose IV corticosteroid or cyclosporine; and (5) receive antibiotics (eg, metronidazole 500 mg IV q 8 h and ciprofloxacin 500 mg IV q 12 h).

Having the patient roll over in bed from the supine to prone position every 2 to 3 h may help redistribute colonic gas and prevent progressive distention. Passage of a soft rectal tube may also be helpful but

must be done with extreme caution to avoid bowel perforation.

If intensive medical measures do not produce definite improvement within 24 to 48 h, immediate surgery is required or the patient may die of sepsis caused by bacterial translocation or even perforation.

Maintenance therapy: After effective treatment of a flare-up, corticosteroids are tapered based on clinical response and then stopped because they are ineffective as maintenance. Patients should remain on 5-ASA drugs indefinitely—oral or rectal, depending on location of disease—because stopping maintenance therapy often allows disease relapse. Dosage intervals for rectal preparations may be gradually lengthened to every 2nd or 3rd day.

Patients who cannot be withdrawn from corticosteroids should be given azathioprine or 6-mercaptopurine. Also, infliximab is becoming more widely accepted as maintenance therapy for UC as well as for Crohn's disease.

Surgery: Nearly one third of patients with extensive UC ultimately require surgery. Total proctocolectomy is curative: Life expectancy and quality of life are restored to normal, the disease does not recur (unlike Crohn's disease), and the risk of colon cancer is eliminated.

Emergency colectomy is indicated for massive hemorrhage, fulminating toxic colitis, or perforation. Subtotal colectomy with ileostomy and rectosigmoid closure or mucous fistula is usually the procedure of choice because most critically ill patients cannot tolerate more extensive surgery. The rectosigmoid stump may be electively removed later or may be used for ileoanal anastomosis with a pouch. The intact rectal stump should not be allowed to remain indefinitely because of the risk of disease activation and malignant transformation.

Elective surgery is indicated for cancer, symptomatic strictures, growth retardation in children, or, most commonly, intractable chronic disease resulting in invalidism or corticosteroid dependence. Colectomy is also done for high-grade and perhaps even low-grade mucosal dysplasia confirmed on pathologic consultation, unless the dysplasia is limited exclusively to a completely excisable polyp. Severe colitis-related extraintestinal manifestations (eg, pyoderma gangrenosum), now better controlled by intensive medical therapies, are only rarely indications for surgery.

The elective procedure of choice in patients with normal sphincter function is restorative proctocolectomy with ileoanal anastomosis. This procedure creates a pelvic reservoir or pouch from distal ileum, which is connected to the anus. The intact sphincter allows continence, typically with 8 to 10 bowel movements/day. Pouchitis is an inflammatory reaction occurring after this procedure in about 50% of patients. It is thought to be related to bacterial overgrowth and is treated with antibiotics (eg, quinolones). Probiotics may be protective. Most cases of pouchitis are readily controlled, but 5 to 10% prove refractory to all medical therapy and require conversion to a conventional (Brooke) ileostomy. For a minority of patients who are older, who have well-established families and lifestyles, who have poor sphincter tone or cannot tolerate frequent bowel movements, or who are simply unable or unwilling to face the consequences of frequent or chronic pouchitis, the Brooke ileostomy remains the procedure of choice.

In any event, the physical and emotional burdens imposed by any form of colon resection must be recognized, and care should be taken to see that the patient receives all the instructions and all the medical and psychologic support that is necessary before and after surgery.

Chapter 20. Diverticular Disease

Introduction

Diverticula are saclike mucosal outpouchings that protrude from a tubular structure. True diverticula contain all layers of the parent structure. False or pseudodiverticula are mucosal projections through the muscular layer. Esophageal (see p. 125) and Meckel's diverticula are true diverticula. Colonic diverticula are pseudodiverticula; they cause symptoms by trapping feces and becoming inflamed or infected, bleeding, or rupturing.

Diverticulosis

Diverticulosis is the presence of multiple diverticula in the colon, probably resulting from a lifelong low-fiber diet. Most diverticula are asymptomatic, but some become inflamed or bleed. Diagnosis is by colonoscopy or barium enema. Treatment varies depending on manifestation.

Diverticula occur anywhere in the large bowel—usually in the sigmoid but rarely below the peritoneal reflection of the rectum. They vary in diameter from 3 mm to > 3 cm. Patients with diverticula usually have several of them. Diverticulosis is uncommon in people < 40 but becomes common rapidly thereafter; essentially every 90-yr-old person has many diverticula. Giant diverticula, which are rare, range in diameter from 3 to 15 cm and may be single.

Pathophysiology

Diverticula are probably caused by increased intraluminal pressure leading to mucosal extrusion through the weakest points of the muscular layer of the bowel—areas adjacent to intramural blood vessels. Diverticula are more common among people who eat a low-fiber diet; however, the mechanism is not clear. One theory is that increased intraluminal pressure is required to move low-bulk stool through the colon. Another theory is that low-stool bulk causes a smaller diameter colon, which by Laplace's law would have increased pressure.

The etiology of giant diverticula is unclear. One theory is that a valvelike abnormality exists at the base of the diverticulum, so bowel gas can enter but escapes less freely.

Symptoms and Signs

Most (70%) diverticula are asymptomatic, 15 to 25% become painfully inflamed (diverticulitis), and 10 to 15% bleed painlessly. The bleeding is probably caused by erosion of the adjacent vessel by local trauma from impacted feces in the diverticulum. Although most diverticula are distal, 75% of bleeding occurs from diverticula proximal to the splenic flexure. In 33% of patients (5% overall), bleeding is serious enough to require transfusion.

Diagnosis

• Usually colonoscopy

Asymptomatic diverticula are usually found incidentally during barium enema or colonoscopy. Diverticulosis is suspected when painless rectal bleeding develops, particularly in an elderly patient. Evaluation of rectal bleeding typically includes colonoscopy, which can be done electively after routine preparation unless there is significant ongoing bleeding. In such patients, a rapid preparation (5 to 10 L of polyethylene glycol solution delivered via NGT over 3 to 4 h) often allows adequate visualization. If colonoscopy cannot visualize the source and ongoing bleeding is sufficiently rapid (> 0.5 to 1 mL/min), angiography may localize the source. Some angiographers first do a radionuclide scan to focus the examination.

Treatment

• High-fiber diet

• Sometimes angiographic or endoscopic treatment of bleeding

Treatment of diverticulosis aims at reducing segmental spasm. A high-fiber diet helps and may be supplemented by psyllium seed preparations or bran. Low-fiber diets are contraindicated. The intuitive injunction to avoid seeds or other dietary material that might become impacted in a diverticulum has no established medical basis. Antispasmodics (eg, belladonna) are not of benefit and may cause adverse effects. Surgery is unwarranted for uncomplicated disease. Giant diverticula, however, require surgery.

Diverticular bleeding stops spontaneously in 75% of patients. Treatment is often given during diagnostic procedures. If angiography was done for diagnosis, ongoing bleeding can be controlled in 70 to 90% of patients by intraarterial injection of vasopressin. In some cases, bleeding recurs within a few days and requires surgery. Angiographic embolization effectively stops bleeding but leads to bowel infarction in up to 20% of patients and is not recommended. Colonoscopy allows heat or laser coagulation of vessels or injection of epinephrine. If these measures fail to stop bleeding, segmental resection or subtotal colectomy is indicated.

Diverticulitis

Diverticulitis is inflammation of a diverticulum, which can result in phlegmon of the bowel wall, peritonitis, perforation, fistula, or abscess. The primary symptom is abdominal pain. Diagnosis is by CT. Treatment is with antibiotics (ciprofloxacin, or a 3rd-generation cephalosporin plus metronidazole) and occasionally surgery.

Diverticulitis occurs when a micro or macro perforation develops in a diverticulum, releasing intestinal bacteria. The resultant inflammation remains localized in about 75% of patients. The remaining 25% may develop abscess, free intraperitoneal perforation, bowel obstruction, or fistulas. The most common fistulas involve the bladder but may also involve the small bowel, uterus, vagina, abdominal wall, or even the thigh.

Diverticulitis is most serious in elderly patients, especially those taking prednisone or other drugs that increase the risk of infection. Nearly all serious diverticulitis occurs in the sigmoid.

Symptoms and Signs

Diverticulitis usually manifests with pain or tenderness in the left lower quadrant of the abdomen and fever. Peritoneal signs (eg, rebound or guarding) may be present, particularly with abscess or free perforation. Fistulas may manifest as pneumaturia, feculent vaginal discharge, or a cutaneous or myofascial infection of the abdominal wall, perineum, or upper leg. Patients with bowel obstruction have nausea, vomiting, and abdominal distention. Bleeding is uncommon.

Diagnosis

• Abdominal CT

• Colonoscopy after resolution

Clinical suspicion is high in patients with known diverticulosis. However, because other disorders (eg, appendicitis, colon or ovarian cancer) may cause similar symptoms, testing is required. Abdominal CT with oral and IV contrast is preferred, although findings in about 10% of patients cannot be distinguished from colon cancer. Colonoscopy, after resolution of the acute infection, is necessary for definitive diagnosis.

Treatment

• Varies with severity

• Liquid diet, oral antibiotics for mild disease

• IV antibiotics, npo for more severe disease

• CT-guided percutaneous drainage of abscess

• Sometimes surgery

A patient who is not very ill is treated at home with rest, a liquid diet, and oral antibiotics (eg, ciprofloxacin 500 mg bid amoxicillin/clavulanate 500 mg tid plus metronidazole 500 mg qid). Symptoms usually subside rapidly. The patient gradually advances to a soft low-fiber diet and a daily psyllium seed preparation. The colon should be evaluated after 2 to 4 wk with a colonoscopy or barium enema. After 1 mo, a high-fiber diet is resumed.

Patients with more severe symptoms (eg, pain, fever, marked leukocytosis) should be hospitalized, as should patients taking prednisone (who are at higher risk of perforation and general peritonitis). Treatment is bed rest, npo, IV fluids, and IV antibiotics (eg, ceftazidime 1 g IV q 8 h plus metronidazole 500 mg IV q 6 to 8 h).

About 80% of patients can be treated successfully without surgery. An abscess may respond to percutaneous drainage (CT guided). If response is satisfactory, the patient remains hospitalized until symptoms are relieved and a soft diet is resumed. A colonoscopy or barium enema is done ≥ 2 wk after symptoms have resolved.

Surgery: Surgery is required immediately for patients with free perforation or general peritonitis and for patients with severe symptoms that do not respond to nonsurgical treatment within 48 h. Increasing pain, tenderness, and fever are other signs that surgery is needed. Surgery should also be considered in patients with any of the following: ≥ 2 previous attacks of mild diverticulitis (or one attack in a patient < 50); a persistent tender mass; clinical, endoscopic, or x-ray signs suggestive of cancer; and dysuria associated with diverticulitis in men (or in women who have had a hysterectomy), because this symptom may presage perforation into the bladder.

The involved section of the colon is resected. The ends can be reanastomosed immediately in healthy patients without perforation, abscess, or significant inflammation. Other patients have a temporary colostomy with anastomosis carried out in a subsequent operation after inflammation resolves and the patient's general condition improves.

Meckel's Diverticulum

Meckel's diverticulum is a congenital sacculation of the distal ileum occurring in 2 to 3% of people. It is usually located within 100 cm of the ileocecal valve and often contains heterotopic gastric tissue, pancreatic tissue, or both. Symptoms are uncommon but include bleeding, bowel obstruction, and inflammation (diverticulitis). Diagnosis is difficult and often involves radionuclide scanning and barium studies. Treatment is surgical resection.

Pathophysiology

In early fetal life, the vitelline duct running from the terminal ileum to the umbilicus and yolk sac is normally obliterated by the 7th wk. If the portion connecting to the ileum fails to atrophy, a Meckel's diverticulum results. This congenital diverticulum arises from the antimesenteric margin of the intestine and contains all layers of the normal bowel. About 50% of diverticula also contain heterotopic tissue of the stomach (and thus contain parietal cells that secrete HCl), pancreas, or both.

Only about 2% of people with Meckel's diverticulum develop complications. Although diverticula are equally common among males and females, males are 2 to 3 times more likely to have complications. Complications include the following:

• Bleeding

• Obstruction

• Diverticulitis

• Tumors

Bleeding is more common among young children (< 5 yr) and occurs when acid secreted from ectopic gastric mucosa in the diverticulum ulcerates the adjacent ileum. Obstruction can occur at any age but is more common among older children and adults. In children, obstruction is most likely caused by intussusception of the diverticulum. Obstruction may also result from adhesions, volvulus, retained foreign bodies, tumors, or incarceration in a hernia (Littre's hernia). Acute Meckel's diverticulitis can occur at any age, but its incidence peaks in older children. Tumors, including carcinoids, are rare and occur mainly in adults.

Symptoms and Signs

In all ages, intestinal obstruction is manifested by cramping abdominal pain, nausea, and vomiting. Acute Meckel's diverticulitis is characterized by abdominal pain and tenderness typically localized below or to the left of the umbilicus; it is often accompanied by vomiting and is similar to appendicitis except for location of pain.

Children may present with repeated episodes of painless, bright red rectal bleeding, which is usually not severe enough to cause shock. Adults may also bleed, typically resulting in melena rather than frank blood.

Diagnosis

• Based on symptoms

• Radionuclide scan for bleeding

• CT for pain

Diagnosis is difficult, and tests are chosen based on presenting symptoms. If rectal bleeding is suspected to originate from a Meckel's diverticulum, a ^{99m}Tc pertechnetate scan may identify ectopic gastric mucosa and hence the diverticulum. Patients presenting with abdominal pain and focal tenderness should have a CT scan with oral contrast. If vomiting and signs of obstruction are predominant, flat and upright x-rays of the abdomen are done. Sometimes diagnosis is made only during surgical exploration for presumed appendicitis; whenever a normal appendix is found, Meckel's diverticulum should be suspected.

Treatment

• Surgery

Patients with intestinal obstruction caused by Meckel's diverticulum require early surgery. For detailed treatment of intestinal obstruction, see p. 117.

A bleeding diverticulum with an indurated area in the adjacent ileum requires resection of this section of the bowel and the diverticulum. A bleeding diverticulum without ileal induration requires only resection of the diverticulum.

Meckel's diverticulitis also requires resection. Small, asymptomatic diverticula encountered incidentally at laparotomy need not be removed.

Diverticular Disease of the Stomach and Small Bowel

Diverticula rarely involve the stomach but occur in the duodenum in up to 25% of people. Most duodenal

diverticula are solitary and occur in the second portion of the duodenum near the ampulla of Vater (periampullary). Jejunal diverticula occur in about 0.26% of patients and are more common among patients with disorders of intestinal motility. Meckel's diverticulum occurs in the distal ileum.

Duodenal and jejunal diverticula are asymptomatic in > 90% of cases and are usually detected incidentally during radiologic or endoscopic investigation of the upper GI tract for an unrelated disease. Rarely, small-bowel diverticula bleed or become inflamed, causing pain and nausea. Some even perforate. For poorly understood reasons, patients with periampullary diverticula are at increased risk of gallstones and pancreatitis. Treatment is surgical resection; however, the clinician should be cautious of recommending surgery for patients with a diverticulum and vague GI symptoms (eg, dyspepsia).

Chapter 21. Anorectal Disorders

Introduction

(See also Foreign Bodies on p. 139 and Anorectal Cancer on p. 195.)

The anal canal begins at the anal sphincter and ends at the anorectal junction (pectinate line, mucocutaneous junction, dentate line), where there are 8 to 12 anal crypts and 5 to 8 papillae. The canal is lined with anoderm, a continuation of the external skin. The anal canal and adjacent skin are innervated by somatic sensory nerves and are highly susceptible to painful stimuli. Venous drainage from the anal canal occurs through the caval system, but the anorectal junction can drain into both the portal and caval systems. Lymphatics from the anal canal pass to the internal iliac nodes, the posterior vaginal wall, and the inguinal nodes. The venous and lymphatic distributions determine how malignant disease and infection spread.

The rectum is a continuation of the sigmoid colon beginning at the level of the 3rd sacral vertebra and continuing to the anorectal junction. The rectal lining consists of red, glistening glandular mucosa, which has an autonomic nerve supply and is relatively insensitive to pain. Venous drainage occurs through the portal system. Lymphatic return from the rectum occurs along the superior hemorrhoidal vascular pedicle to the inferior mesenteric and aortic nodes.

The sphincteric ring encircling the anal canal is composed of the internal sphincter, the central portion of the levators, and components of the external sphincter. Anteriorly, it is more vulnerable to trauma, which can result in incontinence. The puborectalis forms a muscular sling around the rectum for support and assistance in defecation.

History: History should include the details of bleeding, pain, protrusion, discharge, swelling, abnormal sensations, bowel movements, incontinence, stool characteristics, use of cathartics and enemas, and abdominal and urinary symptoms. All patients should be asked about anal intercourse and other possible causes of trauma and infection.

Physical examination: Examination should be done gently and with good lighting. It consists of external inspection, perianal and intrarectal digital palpation, abdominal examination, and rectovaginal bidigital palpation. Anoscopy and rigid or flexible sigmoidoscopy to 15 to 60 cm above the anal verge are often included (see p. 98). Inspection, palpation, and anoscopy and sigmoidoscopy are best done with the patient in the left lateral (Sims') position or inverted on a tilt table. In cases of painful anal lesions, topical (lidocaine 5% ointment), regional, or even general anesthesia may be required. If it can be tolerated, a cleansing phosphate enema may facilitate sigmoidoscopy. Biopsies, smears, and cultures may be taken, and x-ray examination done if indicated.

Anal Fissure

(Fissure in Ano; Anal Ulcer)

An anal fissure is an acute longitudinal tear or a chronic ovoid ulcer in the squamous epithelium of the anal canal. It causes severe pain, sometimes with bleeding, particularly with defecation. Diagnosis is by inspection. Treatment is local hygiene, stool softeners, and sometimes botulinum toxin injection.

Anal fissures are believed to result from laceration by a hard or large stool, with secondary infection. Trauma (eg, anal intercourse) is a rare cause. The fissure may cause internal sphincter spasm, decreasing blood supply and perpetuating the fissure.

Symptoms and Signs

Anal fissures usually lie in the posterior midline but may occur in the anterior midline. Those off the midline may have specific etiologies, particularly Crohn's disease. An external skin tag (the sentinel pile) may be present at the lower end of the fissure, and an enlarged (hypertrophic) papilla may be present at

the upper end.

Infants may develop acute fissures, but chronic fissures are rare. Chronic fissures must be differentiated from cancer, primary lesions of syphilis, TB, and ulceration caused by Crohn's disease.

Fissures cause pain and bleeding. The pain typically occurs with or shortly after defecation, lasts for several hours, and subsides until the next bowel movement. Examination must be gentle but with adequate spreading of the buttocks to allow visualization.

Diagnosis

Diagnosis is made by inspection. Unless findings suggest a specific cause, further studies are not required.

Treatment

• Stool softeners

• Protective ointments, sitz baths

• Nitroglycerin ointment or botulinum toxin type A injection

Fissures often respond to conservative measures that minimize trauma during defecation (eg, stool softeners, psyllium, fiber). Healing is aided by use of protective zinc oxide ointments or bland suppositories (eg, glycerin) that lubricate the lower rectum and soften stool. Topical anesthetics (eg, benzocaine, lidocaine) and warm (not hot) sitz baths for 10 or 15 min after each bowel movement and prn give temporary relief.

Topical nitroglycerin 0.2% ointment, nifedipine cream 0.2% or 0.3%, arginine gel, and injections of botulinum toxin type A into the internal sphincter relax the anal sphincter and decrease maximum anal resting pressure, allowing healing. When conservative measures fail, surgery (internal anal sphincterotomy or controlled anal dilation) is needed to interfere with the cycle of internal anal sphincter spasm.

Anorectal Abscess

An anorectal abscess is a localized collection of pus in the perirectal spaces. Abscesses usually originate in an anal crypt. Symptoms are pain and swelling. Diagnosis is primarily by examination and CT or pelvic MRI for deeper abscesses. Treatment is surgical drainage.

An abscess may be located in various spaces surrounding the rectum and may be superficial or deep. A perianal abscess is superficial and points to the skin. An ischiorectal abscess is deeper, extending across the sphincter into the ischiorectal space below the levator ani; it may penetrate to the contralateral side, forming a "horseshoe" abscess. An abscess above the levator ani (ie, supralevator abscess) is quite deep and may extend to the peritoneum or abdominal organs; this abscess often results from diverticulitis or pelvic inflammatory disease. Crohn's disease (especially of the colon) sometimes causes anorectal abscess. A mixed infection usually occurs, with *Escherichia coli*, *Proteus vulgaris*, *Bacteroides*, streptococci, and staphylococci predominating.

Symptoms and Signs

Superficial abscesses can be very painful; perianal swelling, redness, and tenderness are characteristic. Deeper abscesses may be less painful but cause toxic symptoms (eg, fever, chills, malaise). There may be no perianal findings, but digital rectal examination may reveal a tender, fluctuant swelling of the rectal wall. High pelvirectal abscesses may cause lower abdominal pain and fever without rectal symptoms. Sometimes fever is the only symptom.

Diagnosis

• Clinical evaluation

• Rarely examination under anesthesia or CT

Patients who have a pointing cutaneous abscess, a normal digital rectal examination, and no signs of systemic illness do not require imaging. Those with any findings suggestive of a deeper abscess or Crohn's disease should have an examination under anesthesia at the time of drainage. Higher (supralevator) abscesses require CT to determine the intra-abdominal source of sepsis.

Treatment

• Incision and drainage

• Antibiotics for high-risk patients

Prompt incision and adequate drainage are required and should not wait until the abscess points. Many abscesses can be drained as an in-office procedure; deeper abscesses may require drainage in the operating room. Febrile, neutropenic, or diabetic patients or those with marked cellulitis should also receive antibiotics (eg, ciprofloxacin 500 mg IV q 12 h and metronidazole 500 mg IV q 8 h, ampicillin/sulbactam 1.5 g IV q 8 h). Antibiotics are not indicated for healthy patients with superficial abscesses. Anorectal fistulas may develop after drainage.

Anorectal Fistula

(Fistula in Ano)

An anorectal fistula is a tubelike tract with one opening in the anal canal and the other usually in the perianal skin. Symptoms are discharge and sometimes pain. Diagnosis is by examination and sigmoidoscopy. Treatment often requires surgery.

Fistulas arise spontaneously or occur secondary to drainage of a perirectal abscess. Predisposing causes include Crohn's disease and TB. Most fistulas originate in the anorectal crypts; others may result from diverticulitis, tumors, or trauma. Fistulas in infants are congenital and are more common among boys. Rectovaginal fistulas may be secondary to Crohn's disease, obstetric injuries, radiation therapy, or cancer.

Symptoms and Signs

A history of recurrent abscess followed by intermittent or constant discharge is usual. Discharge material is purulent, serosanguineous, or both. Pain may be present if there is infection. On inspection, one or more secondary openings can be seen. A cordlike tract can often be palpated. A probe inserted into the tract can determine the depth and direction and often the primary opening.

Diagnosis

• Clinical evaluation

• Sigmoidoscopy

Diagnosis is by examination. Sigmoidoscopy should follow to rule out Crohn's disease. Hidradenitis suppurativa, pilonidal sinus, dermal suppurative sinuses, and urethro-perineal fistulas must be differentiated from cryptogenic fistulas.

Treatment

• Various surgical procedures

• Medical treatment if caused by Crohn's disease

In the past, the only effective treatment was surgery, in which the primary opening and the entire tract are unroofed and converted into a "ditch." Partial division of the sphincters may be necessary. Some degree of incontinence may occur if a considerable portion of the sphincteric ring is divided. Alternatives to conventional surgery include advancement flaps, biologic plugs, and fibrin glue instillations into the fistulous tract.

If diarrhea or Crohn's disease is present, fistulotomy is inadvisable because of delayed wound healing. For patients with Crohn's disease, metronidazole, other appropriate antibiotics, and suppressive therapies can be given (see p. 171). Infliximab is very effective in closing fistulas caused by Crohn's disease.

Fecal Incontinence

Fecal incontinence is involuntary defecation.

Fecal incontinence can result from injuries or diseases of the spinal cord, congenital abnormalities, accidental injuries to the rectum and anus, procidentia, diabetes, severe dementia, fecal impaction, extensive inflammatory processes, tumors, obstetric injuries, and operations involving division or dilation of the anal sphincters.

Physical examination should evaluate gross sphincter function and perianal sensation and rule out fecal impaction. Anal sphincter ultrasonography, pelvic and perineal MRIs, pelvic floor electromyography, and anorectal manometry are also useful.

Treatment

• Program of stool regulation

• Perineal exercises, sometimes with biofeedback

• Sometimes a surgical procedure

Treatment includes a bowel management program to develop a predictable pattern of defecation. The program includes intake of adequate fluid and sufficient dietary bulk. Sitting on a toilet or using another customary defecatory stimulant (eg, coffee) encourages defecation. A suppository (eg, glycerin, bisacodyl) or a phosphate enema may also be used. If a regular defecatory pattern does not develop, a low-residue diet and oral loperamide may reduce the frequency of defecation.

Simple perineal exercises, in which the patient repeatedly contracts the sphincters, perineal muscles, and buttocks, may strengthen these structures and contribute to continence, particularly in mild cases. Biofeedback (to train the patient to use the sphincters maximally and to better appreciate physiologic stimuli) should be considered before recommending surgery in well-motivated patients who can understand and follow instructions and who have an anal sphincter capable of recognizing the cue of rectal distention. About 70% of such patients respond to biofeedback.

A defect in the sphincter can be sutured directly. When there is insufficient residual sphincter for repair, particularly in patients < 50 yr of age, a gracilis muscle can be transposed. Some centers attach a pacemaker to the gracilis muscle, as well as an artificial sphincter; these or other experimental procedures are available in only a few centers in the US, as research protocols. Alternatively, a Thiersch wire or other material can be used to encircle the anus. When all else fails, a colostomy can be considered.

Hemorrhoids

(Piles)

Hemorrhoids are dilated veins of the hemorrhoidal plexus in the lower rectum. Symptoms

include irritation and bleeding. Thrombosed hemorrhoids are painful. Diagnosis is by inspection or anoscopy. Treatment is symptomatic or with endoscopic banding, injection sclerotherapy, or sometimes surgery.

External hemorrhoids are located below the dentate line and are covered by squamous epithelium. Internal hemorrhoids are located above the dentate line and are lined by rectal mucosa. Hemorrhoids typically occur in the right anterior, right posterior, and left lateral zones. They occur in adults and children.

Symptoms and Signs

Hemorrhoids are often asymptomatic, or they may simply protrude. Pruritus ani is not commonly caused by hemorrhoids.

External hemorrhoids may become thrombosed, resulting in a painful, purplish swelling. Rarely, they ulcerate and cause minor bleeding. Cleansing the anal region may be difficult.

Internal hemorrhoids typically manifest with bleeding after defecation; blood is noted on toilet tissue and sometimes in the toilet bowl. Internal hemorrhoids may be uncomfortable but are not as painful as thrombosed external hemorrhoids. Internal hemorrhoids sometimes cause mucus discharge and a sensation of incomplete evacuation.

Strangulated hemorrhoids occur when protrusion and constriction occlude the blood supply. They cause pain that is occasionally followed by necrosis and ulceration.

Diagnosis

• Anoscopy

• Sometimes sigmoidoscopy or colonoscopy

Most painful hemorrhoids, thrombosed, ulcerated or not, are seen on inspection of the anus and rectum. Anoscopy is essential in evaluating painless or bleeding hemorrhoids. Rectal bleeding should be attributed to hemorrhoids only after more serious conditions are excluded (eg, by sigmoidoscopy or colonoscopy).

Treatment

• Stool softeners, sitz baths

• Rarely excision for thrombosed external hemorrhoids

• Injection sclerotherapy or rubber band ligation for internal hemorrhoids

Symptomatic treatment is usually all that is needed. It is accomplished with stool softeners (eg, docusate, psyllium), warm sitz baths (ie, sitting in a tub of tolerably hot water for 10 min) after each bowel movement and prn, anesthetic ointments containing lidocaine, or witch hazel (hamamelis) compresses (which soothe by an unknown mechanism). Pain caused by a thrombosed hemorrhoid can be treated with NSAIDs. Infrequently, simple excision of the hemorrhoid may relieve pain rapidly; after infiltration with 1% lidocaine, the thrombosed portion of the hemorrhoid is excised, and the defect is closed with an absorbable suture. Bleeding hemorrhoids can be treated by injection sclerotherapy with 5% phenol in vegetable oil. Bleeding should cease at least temporarily.

Rubber band ligation is used for larger, prolapsing internal hemorrhoids or those that do not respond to conservative management. With mixed internal and external hemorrhoids, only the internal component should be rubber band ligated. The internal hemorrhoid is grasped and withdrawn through a stretched 1/2-cm diameter band, which is released to ligate the hemorrhoid, resulting in its necrosis and sloughing. One hemorrhoid is ligated every 2 wk; 3 to 6 treatments may be required. Sometimes, multiple

hemorrhoids can be ligated at a single visit.

Infrared photocoagulation is useful for ablating small internal hemorrhoids, hemorrhoids that cannot be rubber band ligated because of pain sensitivity, or hemorrhoids that are not cured with rubber band ligation. Laser destruction, cryotherapy, and various types of electrodestruction are of unproven efficacy.

Surgical hemorrhoidectomy is required for patients who do not respond to other forms of therapy. Significant postoperative pain is common, as is urinary retention and constipation. Stapled hemorrhoidopexy is an alternative procedure for circumferential hemorrhoids, although its advantages and the indications have yet to be defined.

Levator Syndrome

Episodic rectal pain caused by spasm of the levator ani muscle.

Proctalgia fugax (fleeting pain in the rectum) and **coccydynia** (pain in the coccygeal region) are variants of levator syndrome. Rectal spasm causes pain, typically unrelated to defecation, usually lasting < 20 min. The pain may be brief and intense or a vague ache high in the rectum. It may occur spontaneously or with sitting and can waken the patient from sleep. The pain may feel as if it would be relieved by the passage of gas or a bowel movement. In severe cases, the pain can persist for many hours and recur frequently. The patient may have undergone various rectal operations for these symptoms, with no benefit.

Diagnosis

• Clinical evaluation

Physical examination can exclude other painful rectal conditions (eg, thrombosed hemorrhoids, fissures, abscesses). Physical examination is often normal, although tenderness or tightness of the levator muscle, usually on the left, may be present. Occasional cases are caused by low back or prostate disorders.

Treatment

• Analgesics, sitz baths

• Sometimes electrogalvanic stimulation

Treatment consists of explanations to the patient of the benign nature of the condition. An acute episode may be relieved by the passage of gas or a bowel movement, by a sitz bath, or by a mild analgesic. When the symptoms are more intense, physical therapy with electrogalvanic stimulation applied to the lower rectum is usually effective. Skeletal muscle relaxants or anal sphincter massage under local or regional anesthesia can be tried, but the benefit is unclear.

Pilonidal Disease

Pilonidal disease refers to an acute abscess or chronic draining sinus in the sacrococcygeal area.

Pilonidal disease usually occurs in young, hirsute, white males but can also occur in women. One or several midline or adjacent-to-the-midline pits or sinuses occur in the skin of the sacral region and may form a cavity, often containing hair. The lesion is usually asymptomatic; infected lesions are painful.

Treatment of an acute abscess is by incision and drainage. Usually, one or more chronic draining sinuses persist and must be extirpated by excision and primary closure or, preferably, by an open technique (eg, cystotomy, marsupialization). Antibiotics are generally not needed.

Proctitis

Proctitis is inflammation of the rectal mucosa, which may result from infection, inflammatory bowel disease, or radiation. Symptoms are rectal discomfort and bleeding. Diagnosis is by sigmoidoscopy, usually with cultures and biopsy. Treatment depends on etiology.

Proctitis may be a manifestation of sexually transmitted disease, certain enteric infections (eg, *Campylobacter*, *Shigella*, *Salmonella*), inflammatory bowel disease, or radiation treatments; it may be associated with prior antibiotic use. Sexually transmitted pathogens cause proctitis more commonly among homosexual men. Immunocompromised patients are at particular risk of infections with herpes simplex and cytomegalovirus.

Symptoms and Signs

Typically, patients report rectal bleeding or passage of mucus. Proctitis resulting from gonorrhea, herpes simplex, or cytomegalovirus may cause intense anorectal pain.

Diagnosis

• Proctoscopy or sigmoidoscopy

• Tests for syphilis and *Clostridium difficile*

Diagnosis requires proctoscopy or sigmoidoscopy, which may reveal an inflamed rectal mucosa. Small discrete ulcers and vesicles suggest herpes infection. Smears should be sent for culture of *Neisseria gonorrhoeae, Chlamydia* sp, enteric pathogens, and viral pathogens. Serologic tests for syphilis and stool tests for *C. difficile* toxin are done. Sometimes mucosal biopsy is needed. Colonoscopy may be valuable in some patients.

Treatment

• Various treatments depending on cause

Infective proctitis can be treated with antibiotics. Homosexual men with nonspecific proctitis may be treated empirically with ceftriaxone 125 mg IM once (or ciprofloxacin 500 mg po bid for 7 days), plus doxycycline 100 mg po bid for 7 days. Antibiotic-associated proctitis is treated with metronidazole (250 mg po qid) or vancomycin (125 mg po qid) for 7 to 10 days.

Radiation proctitis is usually effectively treated with topical formalin carefully applied to the affected mucosa. Alternative treatments include topical corticosteroids as foam (hydrocortisone 90 mg) or enemas (hydrocortisone 100 mg or methylprednisolone 40 mg) bid for 3 wk, or mesalamine (4 g) enema at bedtime for 3 to 6 wk. Mesalamine suppositories 500 mg once/day or bid, mesalamine 800 mg po tid, or sulfasalazine 500 to 1000 mg po qid for ≥ 3 wk alone or in combination with topical therapy may also be effective. Patients unresponsive to these forms of therapy may benefit from a course of systemic corticosteroids.

Pruritus Ani

Pruritus ani is anal and perianal itching.

The perianal skin tends to itch, which can result from numerous causes (see Table 21-1).

[**Table 21-1.** Causes of Pruritus Ani]

Occasionally, the irritation is misinterpreted by the patient as pain, so other causes of perianal pain (eg, abscess) should be ruled out.

Diagnosis is based on the appearance of the anal skin and relevant information from the history. The skin typically shows dullness and thickening, although the underlying pathology is often obscured by

excoriation caused by scratching and secondary infection. A scraping of local skin is taken to rule out a fungal infection, and a stool sample should be examined for ova and parasites. Visible lesions should be biopsied.

Foods suspected of causing pruritus ani should be eliminated from the diet. Clothing should be loose, and bed clothing light. After bowel movements, the patient should cleanse the anal area with absorbent cotton or plain soft tissue moistened with water. Liberal, frequent dusting with nonmedicated talcum powder or cornstarch helps combat moisture. Hydrocortisone acetate 1% ointment, applied sparingly qid, may relieve symptoms. Systemic causes and parasitic or fungal infections must be treated specifically.

Rectal Prolapse and Procidentia

Rectal prolapse is painless protrusion of the rectum through the anus. Procidentia is complete prolapse of the entire thickness of the rectum. Diagnosis is by inspection. Surgery is usually required in adults.

Transient, minor prolapse of just the rectal mucosa often occurs in otherwise normal infants. Mucosal prolapse in adults persists and may progressively worsen.

Procidentia is complete prolapse of the entire thickness of the rectum. The primary cause is unclear. Most patients are women > 60.

Symptoms and Signs

The most prominent symptom is protrusion. It may only occur while straining or while walking or standing. Rectal bleeding can occur, and incontinence is frequent. Pain is uncommon unless incarceration occurs.

Diagnosis

• Clinical evaluation

• Sigmoidoscopy, colonoscopy, or barium enema

To determine the full extent of the prolapse, the clinician should examine the patient while the patient is standing or squatting and straining. Rectal procidentia can be distinguished from hemorrhoids by the presence of circumferential mucosal folds. Anal sphincter tone is usually diminished. Sigmoidoscopy, colonoscopy, or barium enema x-rays of the colon must be done to search for other disease. Primary neurologic disorders (eg, spinal cord tumors) must be ruled out.

Treatment

• Elimination of causes of straining

• For infants and children: Sometimes strapping buttocks together

• For adults: Sometimes surgery

In infants and children, conservative treatment is most satisfactory. Causes of straining should be eliminated. Firmly strapping the buttocks together with tape between bowel movements usually facilitates spontaneous resolution of the prolapse. For simple mucosal prolapse in adults, the excess mucosa can be excised. For procidentia, an abdominal operation may be required. In patients who are very old or in poor health, a wire or synthetic plastic loop can encircle the sphincteric ring (Thiersch's procedure). Other perineal operations (eg, Delorme or Altemeier procedure) can be considered.

Chapter 22. Tumors of the GI Tract

Introduction

Various benign and malignant tumors can develop anywhere in the GI tract. Tumors of the mouth are discussed in Ch. 55.

Benign Esophageal Tumors

Although there are many types of benign esophageal tumors, most are of little consequence except for causing annoying swallowing symptoms (see p. 120) and rarely ulceration or bleeding. Leiomyoma, the most common, may be multiple but usually has an excellent prognosis.

Esophageal Cancer

The most common malignant tumor in the proximal two thirds of the esophagus is squamous cell carcinoma; adenocarcinoma is the most common in the distal one third. Symptoms are progressive dysphagia and weight loss. Diagnosis is by endoscopy, followed by CT and endoscopic ultrasound for staging. Treatment varies with stage and generally includes surgery with or without chemotherapy and radiation. Long-term survival is poor except for those with local disease.

Esophageal cancer accounts for an estimated 15,500 cases and 13,900 deaths in the US annually.

Squamous cell carcinoma: About 8000 cases occur annually in the US. It is more common in parts of Asia and in South Africa. In the US, it is 4 to 5 times more common among blacks than whites, and 2 to 3 times more common among men than women.

The primary risk factors are alcohol ingestion and tobacco use (in any form). Other factors include achalasia, human papillomavirus, lye ingestion (resulting in stricture), sclerotherapy, Plummer-Vinson syndrome, irradiation of the esophagus, and esophageal webs. Genetic causes are unclear, but 50% of patients with tylosis (hyperkeratosis palmaris et plantaris), an autosomal dominant disorder, have esophageal cancer by age 45, and 95% have it by age 55.

Adenocarcinoma: Adenocarcinoma occurs in the distal esophagus. Its incidence is increasing; it accounts for 50% of esophageal carcinoma in whites. It is 4 times more common among whites than blacks. Alcohol is not an important risk factor, but smoking is contributory. Adenocarcinoma of the distal esophagus is difficult to distinguish from adenocarcinoma of the gastric cardia invading the distal esophagus.

Most adenocarcinomas arise in Barrett's esophagus, which results from chronic gastroesophageal reflux disease and reflux esophagitis. In Barrett's esophagus, a metaplastic, columnar, glandular, intestine-like mucosa with brush border and goblet cells replaces the normal stratified squamous epithelium of the distal esophagus during the healing phase of acute esophagitis when healing takes place in the continued presence of stomach acid.

Other malignant tumors: Less common malignant tumors include spindle cell carcinoma (a poorly differentiated variant of squamous cell carcinoma), verrucous carcinoma (a well-differentiated variant of squamous cell carcinoma), pseudosarcoma, mucoepidermoid carcinoma, adenosquamous carcinoma, cylindroma (adenoid cystic carcinoma), primary oat cell carcinoma, choriocarcinoma, carcinoid tumor, sarcoma, and primary malignant melanoma.

Metastatic cancer constitutes 3% of esophageal cancer. Melanoma and breast cancer are most likely to metastasize to the esophagus; others include cancers of the head and neck, lung, stomach, liver, kidney, prostate, testis, and bone. These tumors usually seed the loose connective tissue stroma around the esophagus, whereas primary esophageal cancers begin in the mucosa or submucosa.

Symptoms and Signs

Early-stage esophageal cancer tends to be asymptomatic. When the lumen of the esophagus becomes constricted to < 14 mm, dysphagia commonly occurs. The patient first has difficulty swallowing solid food, then semisolid food, and finally liquid food and saliva; this steady progression suggests a growing malignant process rather than a spasm, benign ring, or peptic stricture. Chest pain may be present, usually radiating to the back.

Weight loss, even when the patient maintains a good appetite, is almost universal. Compression of the recurrent laryngeal nerve may lead to vocal cord paralysis and hoarseness. Compression of sympathetic nerves may lead to Horner's syndrome, and nerve compression elsewhere may cause spinal pain, hiccups, or paralysis of the diaphragm. Malignant pleural effusions or pulmonary metastasis may cause dyspnea. Intraluminal tumor involvement may cause odynophagia, vomiting, hematemesis, melena, iron deficiency anemia, aspiration, and cough. Fistulas between the esophagus and tracheobronchial tree may cause lung abscess and pneumonia. Other findings may include superior vena cava syndrome, malignant ascites, and bone pain.

Lymphatic spread to internal jugular, cervical, supraclavicular, mediastinal, and celiac nodes is common. The tumor usually metastasizes to lung and liver and occasionally to distant sites (eg, bone, heart, brain, adrenal glands, kidneys, peritoneum).

Diagnosis

• Endoscopy with biopsy

• Then CT and endoscopic ultrasound

There are no screening tests. Patients suspected of having esophageal cancer should have endoscopy with cytology and biopsy. Although barium x-ray may show an obstructive lesion, endoscopy is required for biopsy and tissue diagnosis.

Patients in whom esophageal cancer is identified require CT of the chest and abdomen to determine extent of tumor spread. If CT results are negative for metastasis, endoscopic ultrasound should be done to determine the depth of the tumor in the esophageal wall and regional lymph node involvement. Findings guide therapy and help determine prognosis.

Basic blood tests, including CBC, electrolytes, and liver function, should be done.

Prognosis

Prognosis depends greatly on stage, but overall is poor (5-yr survival: < 5%) because many patients present with advanced disease. Patients with cancer restricted to the mucosa have about an 80% survival rate, which drops to < 50% with submucosal involvement, 20% with extension to the muscularis propria, 7% with extension to adjacent structures, and < 3% with distant metastases.

Treatment

• Surgical resection, often combined with chemotherapy and radiation

Treatment decisions depend on tumor staging, size, location, and the patient's wishes (many choose to forgo aggressive treatment).

General principles: Patients with stage 0, I, or IIa disease (see Table 22-1) respond well to surgical resection; preoperative chemotherapy and radiation provide additional benefit. Those with stage IIb and III have poor survival with surgery alone; response and survival are enhanced by preoperative (neoadjuvant) use of radiation and chemotherapy to reduce tumor volume before surgery. Patients unable or unwilling to undergo surgery may receive some benefit from combined radiation and chemotherapy. Radiation or chemotherapy alone is of little benefit. Patients with stage IV disease require palliation and should not undergo surgery.

After treatment, patients are screened for recurrence by endoscopy and CT of the neck, chest, and abdomen at 6-mo intervals for 3 yr and annually thereafter.

Patients with Barrett's esophagus require intense long-term treatment for gastroesophageal reflux disease (see p. 125) and endoscopic surveillance for malignant transformation at 3- to 12-mo intervals depending on the degree of metaplasia.

Surgery: En bloc resection for cure requires removal of the entire tumor, proximal and distal margins of normal tissue, all potentially malignant lymph nodes, and a portion of the proximal stomach sufficient to contain the distal draining lymphatics. The procedure requires gastric pull-up with esophagogastric anastomosis, small-bowel interposition, or colonic interposition. Pyloroplasty is required to ensure proper gastric drainage because esophagectomy necessarily results in bilateral vagotomy. This extensive surgery may be poorly tolerated by patients > 75 yr, particularly those

[**Table 22-1.** Staging Esophageal Cancer*]

with underlying cardiac or pulmonary disease (ejection fraction < 40%, or forced expiratory volume in 1 sec [FEV_1] < 1.5 L/min). Overall, operative mortality is about 5%.

Complications of surgery include anastomotic leaks, fistulas, and strictures; bilious gastroesophageal reflux; and dumping syndrome. The burning chest pain of bile reflux after distal esophagectomy can be more annoying than the original symptom of dysphagia and may require subsequent Roux-en-Y jejunostomy for bile diversion. An interposed segment of small bowel or colon in the chest has a tenuous blood supply, and torsion, ischemia, or gangrene of the interposed bowel may result.

External beam radiation therapy: Radiation is usually used in combination with chemotherapy for patients who are poor candidates for curative surgery, including those with advanced disease. Radiation is contraindicated in patients with tracheoesophageal fistula because tumor shrinkage enlarges the fistula. Similarly, patients with vascular encasement by tumor may experience massive hemorrhage with tumor shrinkage. During the early stages of radiation therapy, edema may worsen esophageal obstruction, dysphagia, and odynophagia. This problem may require esophageal dilation or preradiation placement of a percutaneous gastrostomy feeding tube. Other adverse effects of radiation therapy include nausea, vomiting, anorexia, fatigue, esophagitis, excess esophageal mucus production, xerostomia, stricture, radiation pneumonitis, radiation pericarditis, myocarditis, and myelitis (spinal cord inflammation).

Chemotherapy: Tumors are poorly responsive to chemotherapy alone. Response rates (defined as ≥ 50% reduction in all measurable areas of tumor) vary from 10 to 40%, but responses generally are incomplete (minor shrinkage of tumor) and temporary. No drug is notably more effective than another.

Most commonly, cisplatin and 5-fluorouracil are used in combination. However, several other drugs, including mitomycin, doxorubicin, vindesine, bleomycin, and methotrexate, also are active against squamous cell carcinoma.

Palliation: Palliation is directed at reducing esophageal obstruction sufficiently to allow oral intake. Suffering caused by esophageal obstruction can be significant, with salivation and recurrent aspiration. Options include manual dilation procedures (bougienage), orally inserted stents, radiation therapy, laser photocoagulation, and photodynamic therapy. In some cases, cervical esophagostomy with feeding jejunostomy is required.

Relief provided by esophageal dilation rarely lasts more than a few days. Flexible metal mesh stents are more effective at maintaining esophageal patency. Some plastic-coated models can also be used to occlude tracheoesophageal fistulas, and some are available with a valve that prevents reflux when the stent must be placed near the lower esophageal sphincter.

Endoscopic laser therapy can palliate dysphagia by burning a central channel through the tumor and can be repeated if needed. Photodynamic therapy uses an injection of porfimer sodium, a hematoporphyrin

derivative that is taken up by tissues and acts as a photosensitizer. When activated by a laser beam directed on the tumor, this substance releases cytotoxic oxygen singlets that destroy tumor cells. Patients receiving this treatment must avoid sun exposure for 6 wk after treatment because the skin is also sensitized to light.

Supportive care: Nutritional support by enteral or parenteral supplementation enhances the tolerability and feasibility of all treatments. An endoscopically or surgically placed feeding tube provides a more distal route for feeding when the esophagus is obstructed.

Because nearly all cases of esophageal cancer are fatal, end-of-life care should always aim to control symptoms, especially pain and inability to swallow secretions (see also p. 3483). At some point, many patients need substantial doses of opioids. Patients should be advised to make end-of-life care decisions early in the course of disease and to record their wishes in an advance directive (see p. 3471).

Stomach Cancer

Etiology of stomach cancer is multifactorial, but *Helicobacter pylori* plays a significant role. Symptoms include early satiety, obstruction, and bleeding but tend to occur late in the disease. Diagnosis is by endoscopy, followed by CT and endoscopic ultrasound for staging. Treatment is mainly surgery; chemotherapy may provide a temporary response. Long-term survival is poor except for those with local disease.

Stomach cancer accounts for an estimated 21,000 cases and over 11,000 deaths in the US annually. Gastric adenocarcinoma accounts for 95% of malignant tumors of the stomach; less common are localized gastric lymphomas (see p. 1016) and leiomyosarcomas. Stomach cancer is the 2nd most common cancer worldwide, but the incidence varies widely; incidence is extremely high in Japan, China, Chile, and Iceland. In the US, incidence has declined in recent decades to the 7th most common cause of death from cancer. In the US, it is most common among blacks, Hispanics, and American Indians. Its incidence increases with age; > 75% of patients are > 50 yr.

Etiology

Helicobacter pylori infection is the cause of most stomach cancer. Autoimmune atrophic gastritis (see p. 133) and various genetic factors (see Gastrointestinal Stromal Tumors on p. 190) are also risk factors. Dietary factors are not proven causes.

Gastric polyps can be precursors of cancer. Inflammatory polyps may develop in patients taking NSAIDs, and fundic foveolar polyps are common among patients taking proton pump inhibitors. Adenomatous polyps, particularly multiple ones, although rare, are the most likely to develop cancer. Cancer is particularly likely if an adenomatous polyp is > 2 cm in diameter or has a villous histology. Because malignant transformation cannot be detected by inspection, all polyps seen at endoscopy should be removed. The incidence of stomach cancer is generally decreased in patients with duodenal ulcer.

Pathophysiology

Gastric adenocarcinomas can be classified by gross appearance:

- Protruding: The tumor is polypoid or fungating.
- Penetrating: The tumor is ulcerated.
- Superficial spreading: The tumor spreads along the mucosa or infiltrates superficially within the wall of the stomach.
- Linitis plastica: The tumor infiltrates the stomach wall with an associated fibrous reaction that causes a rigid "leather bottle" stomach.
- Miscellaneous: The tumor shows characteristics of ≥ 2 of the other types; this classification is the

largest.

Prognosis is better with protruding tumors than with spreading tumors because protruding tumors become symptomatic earlier.

Symptoms and Signs

Initial symptoms are nonspecific, often consisting of dyspepsia suggestive of peptic ulcer. Patients and physicians alike tend to dismiss symptoms or treat the patient for acid disease. Later, early satiety (fullness after ingesting a small amount of food) may occur if the cancer obstructs the pyloric region or if the stomach becomes nondistensible secondary to linitis plastica. Dysphagia may result if cancer in the cardiac region of the stomach obstructs the esophageal outlet. Loss of weight or strength, usually resulting from dietary restriction, is common. Massive hematemesis or melena is uncommon, but secondary anemia may follow occult blood loss. Occasionally, the first symptoms are caused by metastasis (eg, jaundice, ascites, fractures).

Physical findings may be unremarkable or limited to heme-positive stools. Late in the course, abnormalities include an epigastric mass; umbilical, left supraclavicular, or left axillary lymph nodes; hepatomegaly; and an ovarian or rectal mass. Pulmonary, CNS, and bone lesions may occur.

Diagnosis

• Endoscopy with biopsy

• Then CT and endoscopic ultrasound

Differential diagnosis commonly includes peptic ulcer and its complications.

Patients suspected of having stomach cancer should have endoscopy with multiple biopsies and brush cytology. Occasionally, a biopsy limited to the mucosa misses tumor tissue in the submucosa. X-rays, particularly double-contrast barium studies, may show lesions but rarely obviate the need for subsequent endoscopy.

Patients in whom cancer is identified require CT of the chest and abdomen to determine extent of tumor spread. If CT is negative for metastasis, endoscopic ultrasound should be done to determine the depth of the tumor and regional lymph node involvement. Findings guide therapy and help determine prognosis.

Basic blood tests, including CBC, electrolytes, and liver function tests, should be done to assess anemia, hydration, general condition, and possible liver metastases. Carcinoembryonic antigen (CEA) should be measured before and after surgery.

Screening: Screening with endoscopy is used in high-risk populations (eg, Japanese) but is not recommended in the US. Follow-up screening for recurrence in treated patients consists of endoscopy and CT of the chest, abdomen, and pelvis. If an elevated CEA dropped after surgery, follow-up should include CEA levels; a rise signifies recurrence.

Prognosis

Prognosis depends greatly on stage but overall is poor (5-yr survival: < 5 to 15%) because most patients present with advanced disease. If the tumor is limited to the mucosa or submucosa, 5-yr survival may be as high as 80%. For tumors involving local lymph nodes, survival is 20 to 40%. More widespread disease is almost always fatal within 1 yr. Gastric lymphomas have a better prognosis and are discussed in Ch. 118.

Treatment

• Surgical resection, sometimes combined with chemotherapy, radiation, or both

Treatment decisions depend on tumor staging and the patient's wishes (some may choose to forgo aggressive treatment—see p. 3471).

Curative surgery involves removal of most or all of the stomach and adjacent lymph nodes and is reasonable in patients with disease limited to the stomach and perhaps the regional lymph nodes (< 50% of patients). Adjuvant chemotherapy or combined chemotherapy and radiation therapy after surgery may be beneficial if the tumor is resectable.

Resection of locally advanced regional disease results in a 10-mo median survival (vs 3 to 4 mo without resection).

Metastasis or extensive nodal involvement precludes curative surgery, and at most, palliative procedures should be undertaken. However, the true extent of tumor spread often is not recognized until curative surgery is attempted. Palliative surgery typically consists of a gastroenterostomy to bypass a pyloric obstruction and should be done only if the patient's quality of life can be improved. In patients not undergoing surgery, combination chemotherapy regimens (5-fluorouracil, doxorubicin, mitomycin, cisplatin, or leucovorin in various combinations) may produce temporary response but little improvement in 5-yr survival. Radiation therapy is of limited benefit.

Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumors are tumors of the GI tract derived from mesenchymal precursor cells in the gut wall. They result from mutations of a growth factor receptor gene, *CKIT*. Some are caused by previous radiation therapy to the abdomen for other tumors.

Tumors are slow growing, and malignant potential varies from minimal to significant. Most (60 to 70%) occur in the stomach, 20 to 25% in the small bowel, and a small number in the esophagus, colon, and rectum. Average age at presentation is 50 to 60.

Symptoms vary with location but include bleeding, dyspepsia, and obstruction. Diagnosis is usually by endoscopy, with biopsy and endoscopic ultrasound for staging. Treatment is surgical removal. The role of radiation and chemotherapy is unclear, but the tyrosine kinase inhibitor imatinib has been beneficial.

Small-Bowel Tumors

Small-bowel tumors account for 1 to 5% of GI tumors (over 5000 cases in the US annually).

Benign tumors include leiomyomas, lipomas, neurofibromas, and fibromas. All may cause abdominal distention, pain, bleeding, diarrhea, and, if obstruction develops, vomiting. Polyps are not as common as in the colon.

Adenocarcinoma, a malignant tumor, is uncommon. Usually it arises in the duodenum or proximal jejunum and causes minimal symptoms. In patients with Crohn's disease, the tumors tend to occur distally and in bypassed or inflamed loops of bowel; adenocarcinoma occurs more often in Crohn's disease of the small bowel than in Crohn's disease of the colon.

Primary malignant **lymphoma** (see p. 1016) arising in the ileum may cause a long, rigid segment. Small-bowel lymphomas arise often in long-standing untreated celiac sprue.

Carcinoid tumors (see p. 907) occur most often in the small bowel, particularly the ileum, and the appendix, and in these locations are often malignant. Multiple tumors occur in 50% of cases. Of those > 2 cm in diameter, 80% have metastasized locally or to the liver by the time of operation. About 30% of small-bowel carcinoids cause obstruction, pain, bleeding, or carcinoid syndrome. Treatment is surgical resection; repeat operations may be required.

Kaposi's sarcoma (see p. 753), first described as a disease of elderly Jewish and Italian men, occurs in an aggressive form in Africans, transplant recipients, and AIDS patients, who have GI tract involvement 40 to 60% of the time. Lesions may occur anywhere in the GI tract but usually in the stomach, small bowel,

or distal colon. GI lesions usually are asymptomatic, but bleeding, diarrhea, proteinlosing enteropathy, and intussusception may occur. A second primary intestinal cancer occurs in ≤ 20% of patients; most often it is lymphocytic leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma, or adenocarcinoma of the GI tract. Treatment depends on the cell type and location and extent of the lesions.

Diagnosis

• Enteroclysis

• Sometimes push endoscopy or capsule video endoscopy

Enteroclysis (sometimes CT enteroclysis) is probably the most common study for mass lesions of the small bowel. Push endoscopy of the small bowel with an enteroscope may be used to visualize and biopsy tumors. Capsule video endoscopy can help identify small-bowel lesions, particularly bleeding sites; a swallowed capsule transmits 2 images/sec to an external recorder. The original capsule is not useful in the stomach or colon because it tumbles in these larger organs; a colon capsule camera with better optics and illumination is under development for use in these larger-diameter organs.

Treatment

• Surgical resection

Treatment is surgical resection. Electrocautery, thermal obliteration, or laser phototherapy at the time of enteroscopy or surgery may be an alternative to resection.

Polyps of the Colon and Rectum

An intestinal polyp is any mass of tissue that arises from the bowel wall and protrudes into the lumen. Most are asymptomatic except for minor bleeding, which is usually occult. The main concern is malignant transformation; most colon cancers arise in a previously benign adenomatous polyp. Diagnosis is by endoscopy. Treatment is endoscopic removal.

Polyps may be sessile or pedunculated and vary considerably in size. Incidence of polyps ranges from 7 to 50%; the higher figure includes very small polyps (usually hyperplastic polyps or adenomas) found at autopsy. Polyps, often multiple, occur most commonly in the rectum and sigmoid and decrease in frequency toward the cecum. Multiple polyps may represent familial adenomatous polyposis (see p. 192). About 25% of patients with cancer of the large bowel also have satellite adenomatous polyps.

Adenomatous (neoplastic) polyps are of greatest concern. Such lesions are classified histologically as tubular adenomas, tubulo-villous adenomas (villoglandular polyps), or villous adenomas. The likelihood of cancer in an adenomatous polyp at the time of discovery is related to size, histologic type, and degree of dysplasia; a 1.5-cm tubular adenoma has a 2% risk of containing a cancer vs a 35% risk in 3-cm villous adenomas. Serrated adenomas, a somewhat more aggressive type of adenoma, may develop from hyperplastic polyps.

Nonadenomatous (nonneoplastic) polyps include hyperplastic polyps, hamartomas, juvenile polyps, pseudopolyps, lipomas, leiomyomas, and other rarer tumors. Juvenile polyps occur in children, typically outgrow their blood supply, and autoamputate some time during or after puberty. Treatment is required only for uncontrollable bleeding or intussusception. Inflammatory polyps and pseudopolyps occur in chronic ulcerative colitis and in Crohn's disease of the colon. Multiple juvenile polyps (but not sporadic ones) convey an increased cancer risk. The specific number of polyps resulting in increased risk is not known.

Symptoms and Signs

Most polyps are asymptomatic. Rectal bleeding, usually occult and rarely massive, is the most frequent complaint. Cramps, abdominal pain, or obstruction may occur with a large lesion. Rectal polyps may be palpable by digital examination. Occasionally, a polyp on a long pedicle may prolapse through the anus.

Large villous adenomas may rarely cause watery diarrhea that may result in hypokalemia.

Diagnosis

• Colonoscopy

Diagnosis is usually made by colonoscopy. Barium enema, particularly double-contrast examination, is effective, but colonoscopy is preferred because polyps also may be removed during that procedure. Because rectal polyps are often multiple and may coexist with cancer, complete colonoscopy to the cecum is mandatory even if a distal lesion is found by flexible sigmoidoscopy.

Treatment

• Complete removal during colonoscopy

• Sometimes follow with surgical resection

• Follow-up surveillance colonoscopy

Polyps should be removed completely with a snare or electrosurgical biopsy forceps during total colonoscopy; complete excision is particularly important for large villous adenomas, which have a high potential for cancer. If colonoscopic removal is unsuccessful, laparotomy should be done.

Subsequent treatment depends on the histology of the polyp. If dysplastic epithelium does not invade the muscularis mucosa, the line of resection in the polyp's stalk is clear, and the lesion is well differentiated, endoscopic excision and close endoscopic follow-up should suffice. Patients with deeper invasion, an unclear resection line, or a poorly differentiated lesion should have segmental resection of the colon. Because invasion through the muscularis mucosa provides access to lymphatics and increases the potential for lymph node metastasis, such patients should have further evaluation (as in colon cancer —see p. 193).

The scheduling of follow-up examinations after polypectomy is controversial. Most authorities recommend total colonoscopy annually for 2 yr (or barium enema if total colonoscopy is impossible), with removal of newly discovered lesions. If 2 annual examinations are negative for new lesions, colonoscopy is recommended every 2 to 3 yr.

Prevention

Aspirin and COX-2 inhibitors may help prevent formation of new polyps in patients with polyps or colon cancer.

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is a hereditary disorder causing numerous colonic polyps and resulting in colon carcinoma by age 40. Patients are usually asymptomatic but may have heme-positive stool. Diagnosis is by colonoscopy and genetic testing. Treatment is colectomy.

FAP is an autosomal dominant disease in which ≥ 100 adenomatous polyps carpet the colon and rectum. The disorder occurs in 1 in 8,000 to 14,000 people. Polyps are present in 50% of patients by age 15, and 95% by 35. Cancer develops before age 40 in nearly all untreated patients.

Patients also can develop various extracolonic manifestations (previously termed Gardner's syndrome), both benign and malignant. Benign manifestations include desmoid tumors, osteomas of the skull or mandible, sebaceous cysts, and adenomas in other parts of the GI tract. Patients are at increased risk of cancer in the duodenum (5 to 11%), pancreas (2%), thyroid (2%), brain (medulloblastoma in < 1%), and liver (hepatoblastoma in 0.7% of children < 5).

Symptoms and Signs

Many patients are asymptomatic, but rectal bleeding, typically occult, occurs.

Diagnosis

• Colonoscopy

• Genetic testing of patient and 1st-degree relatives

• Offspring screened for hepatoblastoma

Diagnosis is made by finding > 100 polyps on colonoscopy. Diagnosed patients should have genetic testing to identify the specific mutation, which should then be sought in 1st-degree relatives. If genetic testing is unavailable, relatives should be screened with annual sigmoidoscopy beginning at age 12, reducing frequency with each decade. If no polyps are evident by age 50, screening frequency is then the same as for average-risk patients.

Children of parents with FAP should be screened for hepatoblastoma from birth to age 5 yr with annual serum fetoprotein levels and possibly liver ultrasound.

Treatment

• Colectomy

• Endoscopic surveillance of remainder of GI tract

• Perhaps aspirin or coxibs

Colectomy should be done at the time of diagnosis. Total proctocolectomy, either with ileostomy or mucosal proctectomy and ileoanal pouch, eliminates the risk of cancer. If subtotal colectomy (removal of most of the colon, leaving the rectum) with ileorectal anastomosis is done, the rectal remnant must be inspected every 3 to 6 mo; new polyps must be excised or fulgurated. Aspirin or coxibs may inhibit new polyp formation. If new ones appear too rapidly or prolifically to remove, excision of the rectum and permanent ileostomy are needed.

After colectomy, patients should have upper endoscopy every 6 mo to 4 yr, depending on the number of polyps (if any) in the stomach and duodenum. Annual physical examination of the thyroid, and possibly ultrasound, also is recommended.

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome is an autosomal dominant disease with multiple hamartomatous polyps in the stomach, small bowel, and colon along with distinctive pigmented skin lesions.

Patients are at a significantly increased risk of GI and non-GI cancers; possibly the genetic defect involves a tumor suppressor gene. GI cancers include those of the pancreas, small intestine, and colon. Non-GI cancers include those of the breast, lung, uterus, and ovaries.

The skin lesions are melanotic macules of the skin and mucous membranes, especially of the perioral region, lips and gums, hands, and feet. All but the buccal lesions tend to fade by puberty. Polyps may bleed and often cause obstruction or intussusception.

Diagnosis is suggested by the clinical picture. Genetic testing is not routinely available but should be considered. First-degree relatives should be evaluated and have routine surveillance for cancers, but there is no firm consensus on specific tests and intervals.

Colonic polyps larger than 1 cm typically are removed.

Colorectal Cancer

Colorectal cancer (CRC) is extremely common. Symptoms include blood in the stool or change in bowel habits. Screening is with fecal occult blood testing. Diagnosis is by colonoscopy. Treatment is surgical resection and chemotherapy for nodal involvement.

CRC accounts for an estimated 153,000 cases and 52,000 deaths in the US annually. In Western countries, the colon and rectum account for more new cases of cancer per year than any anatomic site except the lung. Incidence begins to rise at age 40 and peaks at age 60 to 75. Overall, 70% of cases occur in the rectum and sigmoid, and 95% are adenocarcinomas. Colon cancer is more common among women; rectal cancer is more common among men. Synchronous cancers (more than one) occur in 5% of patients.

Etiology

CRC most often occurs as transformation within adenomatous polyps. Serrated adenomas are particularly aggressive in their malignant transformation. About 80% of cases are sporadic, and 20% have an inheritable component. Predisposing factors include chronic ulcerative colitis and granulomatous colitis; the risk of cancer increases with the duration of these disorders.

Populations with a high incidence of CRC eat low-fiber diets that are high in animal protein, fat, and refined carbohydrates. Carcinogens may be ingested in the diet but are more likely produced by bacterial action on dietary substances or biliary or intestinal secretions. The exact mechanism is unknown.

CRC spreads by direct extension through the bowel wall, hematogenous metastasis, regional lymph node metastasis, perineural spread, and intraluminal metastasis.

Symptoms and Signs

Colorectal adenocarcinoma grows slowly, and a long interval elapses before it is large enough to cause symptoms. Symptoms depend on lesion location, type, extent, and complications.

The right colon has a large caliber, a thin wall, and its contents are liquid; thus, obstruction is a late event. Bleeding is usually occult. Fatigue and weakness caused by severe anemia may be the only complaints. Tumors sometimes grow large enough to be palpable through the abdominal wall before other symptoms appear.

The left colon has a smaller lumen, the feces are semisolid, and cancer tends to encircle the bowel, causing alternating constipation and increased stool frequency or diarrhea. Partial obstruction with colicky abdominal pain or complete obstruction may be the initial manifestation. The stool may be streaked or mixed with blood. Some patients present with symptoms of perforation, usually walled off (focal pain and tenderness), or rarely with diffuse peritonitis.

In rectal cancer, the most common initial symptom is bleeding with defecation. Whenever

[
Table 22-2. Staging Colorectal Cancer*]

rectal bleeding occurs, even with obvious hemorrhoids or known diverticular disease, coexisting cancer must be ruled out. Tenesmus or a sensation of incomplete evacuation may be present. Pain is common with perirectal involvement.

Some patients first present with symptoms and signs of metastatic disease (eg, hepatomegaly, ascites, supraclavicular lymph node enlargement).

Diagnosis

• Colonoscopy

Screening tests: Early diagnosis depends on routine examination, particularly fecal occult blood (FOB) testing. Cancer detected by this method tends to be at an earlier stage and hence more curable. For average-risk patients, FOB testing should be done annually after age 50, with flexible sigmoidoscopy every 5 yr. Some authorities recommend colonoscopy every 10 yr instead of sigmoidoscopy. Colonoscopy every 3 yr may be even better. Screening of patients with high-risk conditions (eg, ulcerative colitis) is discussed under the specific condition.

CT colonography (virtual colonoscopy) generates 3D and 2D images of the colon using multidetector row CT and a combination of oral contrast and gas distention of the colon. Viewing the high-resolution 3D images somewhat simulates the appearance of optical endoscopy, hence the name. It has some promise as a screening test for people who are unable or unwilling to undergo endoscopic colonoscopy but is less sensitive and highly interpreter dependent. It avoids the need for sedation but still requires thorough bowel preparation, and the gas distention may be uncomfortable. Additionally, unlike with optical colonoscopy, lesions cannot be biopsied during the diagnostic procedure.

Video capsule endoscopy of the colon has many technical problems and is not currently acceptable as a screening test.

Diagnostic tests: Patients with positive FOB tests require colonoscopy, as do those with lesions seen on sigmoidoscopy or imaging study. All lesions should be completely removed for histologic examination. If a lesion is sessile or not removable at colonoscopy, surgical excision should be strongly considered.

Barium enema x-ray, particularly a double-contrast study, can detect many lesions but is somewhat less accurate than colonoscopy and is not preferred as follow up to a positive FOB test.

Once cancer is diagnosed, patients should have abdominal CT, chest x-ray, and routine laboratory tests to seek metastatic disease and anemia and to evaluate overall condition.

Elevated serum carcinoembryonic antigen (CEA) levels are present in 70% of patients with CRC, but this test is not specific and therefore is not recommended for screening. However, if CEA is high preoperatively and low after removal of a colon tumor, monitoring CEA may help to detect recurrence earlier. CA 199 and CA 125 are other tumor markers that may be similarly used.

Prognosis

Prognosis depends greatly on stage (see Table 22-2). The 10-yr survival rate for cancer limited to the mucosa approaches 90%; with extension through the bowel wall, 70 to 80%; with positive lymph nodes, 30 to 50%; and with metastatic disease, < 20%.

Treatment

• Surgical resection, sometimes combined with chemotherapy, radiation, or both

Surgery: Surgery for cure can be attempted in the 70% of patients presenting without metastatic disease. Attempt to cure consists of wide resection of the tumor and its regional lymphatic drainage with reanastomosis of bowel segments. If there is ≤ 5 cm of normal bowel present between the lesion and the anal verge, an abdominoperineal resection is done, with permanent colostomy.

Resection of a limited number (1 to 3) of liver metastases is recommended in select nondebilitated patients as a subsequent procedure. Criteria include those whose primary tumor has been resected, whose liver metastases are in one hepatic lobe, and who have no extrahepatic metastases. Only a small number of patients with liver metastases meet these criteria, but 5-yr postoperative survival is 25%.

Adjuvant therapy: Chemotherapy (typically 5-fluorouracil and leucovorin) improves survival by 10 to 30% in colon cancer patients with positive lymph nodes. Rectal cancer patients with 1 to 4 positive lymph nodes benefit from combined radiation and chemotherapy; when > 4 positive lymph nodes are found,

combined modalities are less effective. Preoperative radiation therapy and chemotherapy to improve the resectability rate of rectal cancer or decrease the incidence of lymph node metastasis are gaining favor.

Follow-up: Postoperatively, colonoscopy should be done annually for 5 yr and every 3 yr thereafter if no polyps or tumors are found. If preoperative colonoscopy was incomplete because of an obstructing cancer, a "completion" colonoscopy should be done 3 mo after surgery.

Additional screening for recurrence should include history, physical examination, and laboratory tests (eg, CBC, liver function tests) every 3 mo for 3 yr and then every 6 mo for 2 yr. Imaging studies (CT or MRI) are often recommended at 1-yr intervals but are of uncertain benefit for routine follow up in the absence of abnormalities on examination or blood tests.

Palliation: When curative surgery is not possible or the patient is an unacceptable surgical risk, limited palliative surgery (eg, to relieve obstruction or resect a perforated area) may be indicated; median survival is 7 mo. Some obstructing tumors can be debulked by endoscopic laser treatment or electrocoagulation or held open by stents. Chemotherapy may shrink tumors and prolong life for several months.

Newer drugs used singly or in drug combinations include capecitabine (a 5-fluorouracil precursor), irinotecan, and oxaliplatin. Monoclonal antibodies such as bevacizumab, cetuximab, and panitumumab are also being used with some effectiveness. No regimen is clearly more effective for prolonging life in patients with metastatic CRC, although some have been shown to delay disease progression. Chemotherapy for advanced colon cancer should be managed by an experienced chemotherapist who has access to investigational drugs.

When metastases are confined to the liver, ambulatory hepatic artery infusion with floxuridine or radioactive microspheres via an implantable sc pump or an external pump worn on the belt may offer more benefit than systemic chemotherapy; however, these therapies are of uncertain benefit. When metastases are also extrahepatic, intrahepatic arterial chemotherapy offers no advantage over systemic chemotherapy.

Anorectal Cancer

The most common anorectal cancer is adenocarcinoma. Squamous cell (nonkeratinizing squamous cell or basaloid) carcinoma of the anorectum accounts for 3 to 5% of distal large-bowel cancers. Basal cell carcinoma, Bowen's disease (intradermal carcinoma), extramammary Paget's disease, cloacogenic carcinoma, and malignant melanoma are less common. Other tumors include lymphoma and various sarcomas. Metastasis occurs along the lymphatics of the rectum and into the inguinal lymph nodes.

Risk factors include infection with human papillomavirus (HPV), chronic fistulas, irradiated anal skin, leukoplakia, lymphogranuloma venereum, and condyloma acuminatum. Gay men practicing receptive anal intercourse are at increased risk. Patients with HPV infection may manifest dysplasia in slightly abnormal or normal-appearing anal epithelium (anal intraepithelial neoplasia—histologically graded I, II, or III). These changes are more common among HIV-infected patients, particularly gay men. Higher grades may progress to invasive carcinoma. It is unclear whether early recognition and eradication improve long-term outcome; hence, screening recommendations are unclear.

Wide local excision is often satisfactory treatment of perianal carcinomas. Combination chemotherapy and radiation therapy result in a high rate of cure when used for anal squamous and cloacogenic tumors. Abdominoperineal resection is indicated when radiation and chemotherapy do not result in complete regression of tumor and there are no metastases outside of the radiation field.

Hereditary Nonpolyposis Colorectal Carcinoma

Hereditary nonpolyposis colorectal carcinoma (HNPCC) is an autosomal dominant disorder responsible for 3 to 5% of cases of colorectal cancer (CRC). Symptoms, initial diagnosis, and treatment are similar to other forms of CRC. HNPCC is suspected by history and is confirmed by genetic testing. Patients also require surveillance for other cancer, particularly endometrial and

ovarian cancer.

Patients with one of several known mutations have a 70 to 80% lifetime risk of developing CRC. Compared to sporadic forms of colon cancer, HNPCC occurs at a younger age (mid 40s), and the lesion is more likely to be proximal to the splenic flexure. The precursor lesion is usually a single colonic adenoma, unlike the multiple adenomas present in patients with familial adenomatous polyposis (FAP), the other main hereditary form of CRC.

However, similar to FAP, numerous extracolonic manifestations occur. Nonmalignant disorders include cafe-au-lait spots, sebaceous gland tumors, and keratoacanthomas. Common associated cancers include endometrial and ovarian tumors (39% risk of endometrial and 9% risk of ovarian by age 70). Patients also have an elevated risk of cancer of the ureter, renal pelvis, stomach, biliary tree, and small bowel.

Symptoms and Signs

Symptoms and signs are similar to other forms of CRC, and diagnosis and management of the tumor itself are the same. The specific diagnosis of HNPCC is confirmed by genetic testing. However, deciding who to test is difficult because (unlike FAP) there is no typical clinical appearance. Thus, suspicion of HNPCC requires a detailed family history, which should be obtained in all younger patients identified with CRC.

Diagnosis

• Clinical criteria followed by testing for microsatellite instability (MSI)

• Genetic testing for confirmation

To meet the Amsterdam II criteria for HNPCC, all three of the following historical elements must be present:

• Three or more relatives with CRC or an HNPCC-associated cancer

• CRC involving at least two generations

• At least one case of CRC before age 50

Patients meeting these criteria should have their tumor tissue tested for MSI, a DNA abnormality. If MSI is present, genetic testing for specific HNPCC mutations is indicated. Other authorities use additional criteria (eg, Bethesda criteria) to initiate MSI testing. If MSI testing is not available locally, the patient should be referred to an appropriate center.

Patients with confirmed HNPCC require ongoing screening for other cancers. For endometrial cancer, annual endometrial aspiration or transvaginal ultrasound is recommended. For ovarian cancer, options include annual transvaginal ultrasound and serum CA 125 levels. Prophylactic hysterectomy and oophorectomy are also options. Urinalysis may be used to screen for renal tumors.

First-degree relatives of patients with HNPCC should have colonoscopy every 1 to 2 yr beginning in their 20s, and annually after age 40. Female 1st-degree relatives should be tested annually for endometrial and ovarian cancer. More distant blood relatives should have genetic testing; if results are negative, they should have colonoscopy at the frequency for average-risk patients.

Treatment

• Surgical resection

The most common treatment is resection of the index lesion with frequent surveillance for another colon cancer and any associated tumors in other organs. Because most HNPCC tumors occur proximal to the splenic flexure, subtotal colectomy, leaving the rectosigmoid intact, has been suggested as an alternative.

In either case, close follow up is needed.

Pancreatic Cancer

Pancreatic cancer, primarily ductal adenocarcinoma, accounts for an estimated 37,000 cases and 33,000 deaths in the US annually. Symptoms include weight loss, abdominal pain, and jaundice. Diagnosis is by CT. Treatment is surgical resection and adjuvant chemotherapy and radiation therapy. Prognosis is poor because disease is often advanced at the time of diagnosis.

Most pancreatic cancers are exocrine tumors that develop from ductal and acinar cells. Pancreatic endocrine tumors are discussed below.

Adenocarcinomas of the exocrine pancreas arise from duct cells 9 times more often than from acinar cells; 80% occur in the head of the gland. Adenocarcinomas appear at the mean age of 55 yr and occur 1.5 to 2 times more often in men. Prominent risk factors include smoking, a history of chronic pancreatitis, and possibly long-standing diabetes mellitus (primarily in women). Heredity plays some role. Alcohol and caffeine consumption do not seem to be risk factors.

Symptoms and Signs

Symptoms occur late. By diagnosis, 90% of patients have locally advanced tumors that have involved retroperitoneal structures, spread to regional lymph nodes, or metastasized to the liver or lung.

Most patients have severe upper abdominal pain, which usually radiates to the back. The pain may be relieved by bending forward or assuming the fetal position. Weight loss is common. Adenocarcinomas of the head of the pancreas cause obstructive jaundice (often causing pruritus) in 80 to 90% of patients. Cancer in the body and tail may cause splenic vein obstruction, resulting in splenomegaly, gastric and esophageal varices, and GI hemorrhage. The cancer causes diabetes in 25 to 50% of patients, leading to symptoms of glucose intolerance (eg, polyuria and polydipsia).

Diagnosis

• CT or magnetic resonance cholangiopancreatography (MRCP)

• CA 19-9 antigen to follow (not for screening)

The preferred tests are an abdominal helical CT or MRCP. If CT or MRCP shows apparent unresectable or metastatic disease, a percutaneous needle aspiration of an accessible lesion might be considered to obtain a tissue diagnosis. If CT shows a potentially resectable tumor or no tumor, MRCP or endoscopic ultrasound may be used to stage disease or detect small tumors not visible with CT. Patients with obstructive jaundice may have ERCP as the first diagnostic procedure.

Routine laboratory tests should be done. Elevation of alkaline phosphatase and bilirubin indicate bile duct obstruction or liver metastases. Pancreas-associated antigen CA 19-9 may be used to monitor patients diagnosed with pancreatic carcinoma and to screen those at high risk. However, this test is not sensitive or specific enough to be used for population screening. Elevated levels should drop with successful treatment; subsequent increases indicate progression. Amylase and lipase levels are usually normal.

Prognosis

Prognosis varies with stage but overall is poor (5-yr survival: < 2%), because many patients have advanced disease at the time of diagnosis.

Treatment

• Whipple procedure

• Adjuvant chemotherapy and radiation therapy

• Symptom control

About 80 to 90% of cancers are considered surgically unresectable at time of diagnosis because of metastases or invasion of major blood vessels. Depending on location of the tumor, the procedure of choice is most commonly a Whipple procedure (pancreatoduodenectomy). Adjuvant therapy with 5-fluorouracil (5-FU) and external beam radiation therapy is typically given, resulting in about 40% 2-yr and 25% 5-yr survival. This combination is also used for patients with localized but unresectable tumors and results in median survival of about 1 yr. Newer drugs (eg, gemcitabine, irinotecan, paclitaxel, oxaliplatin, carboplatin) may be more effective than 5-FU-based chemotherapy, but no drug, singly or in combination, is clearly superior in prolonging survival. Patients with hepatic or distant metastases may be offered chemotherapy as part of an investigational program, but the outlook is dismal with or without such treatment and some patients may choose to forego it.

If an unresectable tumor is found at operation and gastroduodenal or bile duct obstruction is present or pending, a double gastric and biliary bypass operation is usually done to relieve obstruction. In patients with inoperable lesions and jaundice, endoscopic placement of a bile duct stent relieves jaundice. However, surgical bypass should be considered in patients with unresectable lesions if life expectancy is > 6 to 7 mo because of complications associated with stents.

Symptomatic treatment: Ultimately, most patients experience pain and die. Thus, symptomatic treatment is as important as controlling disease. Appropriate end-of-life care should be discussed (see also p. 3480).

Patients with moderate to severe pain should receive an oral opioid in doses adequate to provide relief. Concern about addiction should not be a barrier to effective pain control. For chronic pain, long-acting preparations (eg, transdermal fentanyl, oxycodone, oxymorphone) are usually best. Percutaneous or operative splanchnic (celiac) block effectively controls pain in most patients. In cases of intolerable pain, opioids given sc or by IV, epidural, or intrathecal infusion provides additional relief.

If palliative surgery or endoscopic placement of a biliary stent fails to relieve pruritus secondary to obstructive jaundice, the patient can be managed with cholestyramine (4 g po once/day to qid). Phenobarbital 30 to 60 mg po tid to qid may be helpful.

Exocrine pancreatic insufficiency is treated with tablets of porcine pancreatic enzymes (pancrelipase). The patient should take enough to supply 16,000 to 20,000 lipase units before each meal or snack. If a meal is prolonged (as in a restaurant), some of the tablets should be taken during the meal. Optimal intraluminal pH for the enzymes is 8; thus, some clinicians give a proton pump inhibitor or H_2 blocker 2 times/day. Diabetes mellitus should be closely monitored and controlled.

Cystadenocarcinoma

Cystadenocarcinoma is a rare adenomatous pancreatic cancer that arises as a malignant degeneration of a mucous cystadenoma and manifests as upper abdominal pain and a palpable abdominal mass. Diagnosis is made by abdominal CT or MRI, which typically shows a cystic mass containing debris; the mass may be misinterpreted as necrotic adenocarcinoma or pancreatic pseudocyst. Unlike ductal adenocarcinoma, cystadenocarcinoma has a relatively good prognosis. Only 20% of patients have metastasis at the time of operation; complete excision of the tumor by distal or total pancreatectomy or by a Whipple procedure results in a 65% 5-yr survival.

Intraductal Papillary-Mucinous Tumor

Intraductal papillary-mucinous tumor (IPMT) is a rare cancer resulting in mucus hypersecretion and ductal obstruction. Histology may be benign, borderline, or malignant. Most (80%) occur in women and in the tail of the pancreas (66%).

Symptoms consist of pain and recurrent bouts of pancreatitis. Diagnosis is made by CT, sometimes along with endoscopic ultrasonography, magnetic resonance cholangiopancreatography, or ERCP. Benign and

malignant disease cannot be differentiated without surgical removal, which is the treatment of choice. With surgery, 5-yr survival is > 95% for benign or borderline cases, but 50 to 75% for malignant tumors.

Pancreatic Endocrine Tumors

Pancreatic endocrine tumors arise from islet and gastrin-producing cells and often produce many hormones. They have 2 general manifestations. Nonfunctioning tumors may cause obstructive symptoms of the biliary tract or duodenum, bleeding into the GI tract, or abdominal masses. Functioning tumors hypersecrete a particular hormone, causing various syndromes (see Table 22-3). These clinical syndromes can also occur in multiple endocrine neoplasia, in which tumors or hyperplasia affects two or more endocrine glands, usually the parathyroid, pituitary, thyroid, or adrenals (see p. 909).

Treatment for functioning and nonfunctioning tumors is surgical resection. If metastases preclude curative surgery, various antihormone treatments may be tried for functioning tumors. Because of tumor rarity, chemotherapy trials have not identified definitive treatment. However, streptozotocin has selective activity against pancreatic islet cells and is commonly used, either alone or in combination with 5-fluorouracil or doxorubicin. Some centers use chlorozotocin and interferon.

Insulinoma

An insulinoma is a rare pancreatic β-cell tumor that hypersecretes insulin. The main symptom is fasting hypoglycemia. Diagnosis is by a 48- or 72-h fast with measurement of glucose and insulin levels, followed by endoscopic ultrasound. Treatment is surgery when possible. Drugs that block insulin secretion (eg, diazoxide, octreotide, Ca channel blockers, β-blockers, phenytoin) are used for patients not responding to surgery.

Of all insulinomas, 80% are single and may be curatively resected if identified. Only 10% of insulinomas are malignant. Insulinoma occurs in 1/250,000 at a median age of 50 yr, except in multiple endocrine neoplasia (MEN) type I (about 10% of insulinomas), when it occurs in the 20s. Insulinomas associated with MEN type I are more likely to be multiple.

Surreptitious administration of exogenous insulin can cause episodic hypoglycemia mimicking insulinoma.

Symptoms and Signs

Hypoglycemia secondary to an insulinoma occurs during fasting. Symptoms are insidious and may mimic various psychiatric and

[**Table 22-3.** Pancreatic Endocrine Tumors]

neurologic disorders. CNS disturbances include headache, confusion, visual disturbances, motor weakness, palsy, ataxia, marked personality changes, and possible progression to loss of consciousness, seizures, and coma. Symptoms of sympathetic stimulation (faintness, weakness, tremulousness, palpitation, sweating, hunger, nervousness) are often present.

Diagnosis

• Insulin level

• Sometimes C-peptide or proinsulin levels

• Endoscopic ultrasound

Plasma glucose should be measured during symptoms. If hypoglycemia is present (glucose < 40 mg/dL [2.78 mmol/L]), an insulin level should be measured on a simultaneous sample. Hyperinsulinemia of > 6 μU/mL (42 pmol/L) suggests an insulin-mediated cause, as does a serum insulin to plasma glucose ratio > 0.3 (μU/mL)/(mg/dL).

Insulin is secreted as proinsulin, consisting of an α chain and β chain connected by a C peptide. Because pharmaceutical insulin consists only of the β chain, surreptitious insulin administration can be detected by measuring C-peptide and proinsulin levels. In patients with insulinoma, C peptide is ≥ 0.2 nmol/L and proinsulin is ≥ 5 pmol/L. These levels are normal or low in patients with surreptitious insulin administration.

Because many patients have no symptoms (and hence no hypoglycemia) at the time of evaluation, diagnosis requires admission to the hospital for a 48- or 72-h fast. Nearly all (98%) with insulinoma develop symptoms within 48 h of fasting; 70 to 80% within 24 h. Hypoglycemia as the cause of the symptoms is established by Whipple's triad: (1) Symptoms occur during the fast; (2) symptoms occur in the presence of hypoglycemia; and (3) ingestion of carbohydrates relieves the symptoms. Hormone levels are obtained as described above when the patient is having symptoms.

If Whipple's triad is not observed after prolonged fasting and the plasma glucose after an overnight fast is > 50 mg/dL (> 2.78 mmol/L), a C-peptide suppression test can be done. During insulin infusion (0.1 U/kg/h), patients with insulinoma fail to suppress C peptide to normal levels (≤ 1.2 ng/mL [≤ 0.40 nmol/L]).

Endoscopic ultrasonography has > 90% sensitivity and helps localize the tumor. PET also may be used. CT has not proved useful, and arteriography or selective portal and splenic vein catheterization is generally unnecessary.

Treatment

• Surgical resection

• Diazoxide or sometimes octreotide for hypoglycemia

Overall surgical cure rates approach 90%. A small, single insulinoma at or near the surface of the pancreas can usually be enucleated surgically. If a single large or deep adenoma is within the pancreatic body or tail, if there are multiple lesions of the body or tail (or both), or if no insulinoma is found (an unusual circumstance), a distal, subtotal pancreatectomy is done. In < 1% of cases, the insulinoma is ectopically located in peripancreatic sites of the duodenal wall or periduodenal area and can be found only by diligent search during surgery. Pancreatoduodenectomy (Whipple procedure) is done for resectable malignant insulinomas of the proximal pancreas. Total pancreatectomy is done if a previous subtotal pancreatectomy proves inadequate.

If hypoglycemia continues, diazoxide starting at 1.5 mg/kg po bid with a natriuretic can be used. Doses can be increased up to 4 mg/kg. A somatostatin analog, octreotide (100 to 500 µg sc bid to tid), is variably effective and should be considered for patients with continuing hypoglycemia refractory to diazoxide. Patients who respond may be converted to a long-acting octreotide formulation given as 20 to 30 mg IM once/mo. Patients using octreotide may also need to take supplemental pancreatic enzymes because octreotide suppresses pancreatic enzyme secretion. Other drugs that have modest and variable effect on insulin secretion include verapamil, diltiazem, and phenytoin.

If symptoms are not controlled, chemotherapy may be tried, but response is limited. Streptozotocin has a 30 to 40% response rate, and when combined with 5-fluorouracil, a 60% response rate lasting up to 2 yr. Other agents include doxorubicin, chlorozotocin, and interferon.

Zollinger-Ellison Syndrome

(Z-E Syndrome; Gastrinoma)

Zollinger-Ellison syndrome is caused by a gastrin-producing tumor usually located in the pancreas or the duodenal wall. Gastric acid hypersecretion and peptic ulceration result. Diagnosis is by measuring serum gastrin levels. Treatment is proton pump inhibitors and surgical removal.

Gastrinomas occur in the pancreas or duodenal wall 80 to 90% of the time. The remainder occur in the splenic hilum, mesentery, stomach, lymph node, or ovary. About 50% of patients have multiple tumors. Gastrinomas usually are small (< 1 cm in diameter) and grow slowly. About 50% are malignant. About 40 to 60% of patients with gastrinoma have multiple endocrine neoplasia (see p. 909).

Symptoms and Signs

Zollinger-Ellison syndrome typically manifests as aggressive peptic ulcer disease, with ulcers occurring in atypical locations (up to 25% are located distal to the duodenal bulb). However, as many as 25% do not have an ulcer at diagnosis. Typical ulcer symptoms and complications (eg, perforation, bleeding, obstruction) can occur. Diarrhea is the initial symptom in 25 to 40% of patients.

Diagnosis

• Serum gastrin level

• CT, scintigraphy, or PET to localize

The syndrome is suspected by history, particularly when symptoms are refractory to standard acid suppressant therapy.

The most reliable test is serum gastrin. All patients have levels > 150 pg/mL; markedly elevated levels of > 1000 pg/mL in a patient with compatible clinical features and gastric acid hypersecretion of > 15 mEq/h establish the diagnosis. However, moderate hypergastrinemia can occur with hypochlorhydric states (eg, pernicious anemia, chronic gastritis, use of proton pump inhibitors), in renal insufficiency with decreased clearance of gastrins, in massive intestinal resection, and in pheochromocytoma.

A secretin provocative test may be useful in patients with gastrin levels < 1000 pg/mL. An IV bolus of secretin 2 µg/kg is given with serial measurements of serum gastrin (10 and 1 min before, and 2, 5, 10, 15, 20, and 30 min after injection). The characteristic response in gastrinoma is an increase in gastrin levels, the opposite of what occurs in those with antral G-cell hyperplasia or typical peptic ulcer disease. Patients also should be evaluated for *Helicobacter pylori* infection, which commonly results in peptic ulceration and moderate excess gastrin secretion.

Once the diagnosis has been established, the tumor or tumors must be localized. The first test is abdominal CT or somatostatin receptor scintigraphy, which may identify the primary tumor and metastatic disease. PET or selective arteriography with magnification and subtraction is also helpful. If no signs of metastases are present and the primary is uncertain, endoscopic ultrasonography should be done. Selective arterial secretin injection is an alternative.

Prognosis

Five- and 10-yr survival is > 90% when an isolated tumor is removed surgically vs 43% at 5 yr and 25% at 10 yr with incomplete removal.

Treatment

• Acid suppression

• Surgical resection for localized disease

• Chemotherapy for metastatic disease

Acid suppression: Proton pump inhibitors are the drugs of choice: omeprazole or esomeprazole 40 mg po bid. The dose may be decreased gradually once symptoms resolve and acid output declines. A maintenance dose is needed; patients need to take these drugs indefinitely unless they undergo surgery.

Octreotide injections, 100 to 500 µg sc bid to tid, may also decrease gastric acid production and may be

palliative in patients not responding well to proton pump inhibitors. A long-acting form of octreotide can be used 20 to 30 mg IM once/mo.

Surgery: Surgical removal should be attempted in patients without apparent metastases. At surgery, duodenotomy and intraoperative endoscopic transillumination or ultrasound help localize tumors. Surgical cure is possible in 20% of patients if the gastrinoma is not part of a multiple endocrine neoplasia syndrome.

Chemotherapy: In patients with metastatic disease, streptozocin in combination with 5-fluorouracil or doxorubicin is the preferred chemotherapy for islet cell tumors. It may reduce tumor mass (in 50 to 60%) and serum gastrin levels and is a useful adjunct to omeprazole. Patients with metastatic disease are not cured by chemotherapy.

Vipoma

A vipoma is a non-β pancreatic islet cell tumor secreting vasoactive intestinal peptide (VIP), resulting in a syndrome of watery diarrhea, hypokalemia, and achlorhydria (WDHA syndrome). Diagnosis is by serum VIP levels. Tumor is localized with CT and endoscopic ultrasound. Treatment is surgical resection.

Of these tumors, 50 to 75% are malignant, and some may be quite large (7 cm) at diagnosis. In about 6%, vipoma occurs as part of multiple endocrine neoplasia (see p. 909).

Symptoms and Signs

The major symptoms are prolonged massive watery diarrhea (fasting stool volume > 750 to 1000 mL/day and nonfasting volumes of > 3000 mL/day) and symptoms of hypokalemia, acidosis, and dehydration. In half, diarrhea is constant; in the rest, diarrhea severity varies over time. About 33% have diarrhea < 1 yr before diagnosis, but 25% have diarrhea ≥ 5 yr before diagnosis. Lethargy, muscular weakness, nausea, vomiting, and crampy abdominal pain occur frequently. Flushing similar to the carcinoid syndrome occurs in 20% of patients during attacks of diarrhea.

Diagnosis

• Confirmation of secretory diarrhea

• Serum VIP levels

• Endoscopic ultrasonography, PET, or scintigraphy can localize

Diagnosis requires demonstration of secretory diarrhea (stool osmolality is close to plasma osmolality, and twice the sum of Na and K concentration in the stool accounts for all measured stool osmolality). Other causes of secretory diarrhea and, in particular, laxative abuse must be excluded (see p. 88). In such patients, serum VIP levels should be measured (ideally during a bout of diarrhea). Markedly elevated levels establish the diagnosis, but mild elevations may occur with short bowel syndrome and inflammatory diseases. Patients with elevated VIP levels should have tumor localization studies, such as endoscopic ultrasonography, PET, and octreotide scintigraphy or arteriography to localize metastases.

Electrolytes and CBC should be measured. Hyperglycemia and impaired glucose tolerance occur in ≤ 50% of patients. Hypercalcemia occurs in 50% of patients.

Treatment

• Fluid and electrolyte replacement

• Octreotide

• Surgical resection for localized disease

Initially, fluids and electrolytes must be replaced. Bicarbonate must be given to replace fecal loss and avoid acidosis. Because fecal losses of water and electrolytes increase as rehydration is achieved, continual IV replacement may become difficult.

Octreotide usually controls diarrhea, but large doses may be needed. Responders may benefit from a long-acting octreotide formulation given 20 to 30 mg IM once/mo. Patients using octreotide may also need to take supplemental pancreatic enzymes because octreotide suppresses pancreatic enzyme secretion.

Tumor resection is curative in 50% of patients with a localized tumor. In those with metastatic tumor, resection of all visible tumor may provide temporary relief of symptoms. The combination of streptozocin and doxorubicin may reduce diarrhea and tumor mass if objective response occurs (in 50 to 60%). Chemotherapy is not curative.

Glucagonoma

A glucagonoma is a pancreatic α-cell tumor that secretes glucagon, causing hyperglycemia and a characteristic skin rash. Diagnosis is by elevated glucagon levels and imaging studies. Tumor is localized with CT and endoscopic ultrasound. Treatment is surgical resection.

Glucagonomas are very rare but similar to other islet cell tumors in that the primary and metastatic lesions are slow-growing: 15-yr survival is common. Eighty percent of glucagonomas are malignant. The average age at symptom onset is 50 yr; 80% of patients are women. A few patients have multiple endocrine neoplasia type I.

Symptoms and Signs

Because glucagonomas produce glucagon, the symptoms are the same as those of diabetes. Frequently, weight loss, normochromic anemia, hypoaminoacidemia, and hypolipidemia are present, but the most distinctive clinical feature is a chronic eruption involving the extremities, often associated with a smooth, shiny, vermilion tongue and cheilitis. The exfoliating, brownish red, erythematous lesion with superficial necrolysis is termed necrolytic migratory erythema.

Diagnosis

• Serum glucagon level

• CT and endoscopic ultrasonography to localize

Most patients with glucagonoma have glucagon levels > 1000 pg/mL (normal < 200). However, moderate elevations occur in renal insufficiency, acute pancreatitis, severe stress, and fasting. Correlation with symptoms is required. Patients should have abdominal CT followed by endoscopic ultrasonography; MRI or PET may be used if CT is unrevealing.

Treatment

• Surgical resection for localized disease

• Chemotherapy for metastatic disease

• Octreotide to suppress glucagon production

Resection of the tumor alleviates all symptoms. Unresectable, metastatic, or recurrent tumors are treated with combination streptozocin and doxorubicin, which may decrease levels of circulating immunoreactive glucagon, lessen symptoms, and improve response rates (50%) but are unlikely to improve survival. Octreotide injections partially suppress glucagon production and relieve the erythema, but glucose tolerance may also decrease because octreotide decreases insulin secretion. Octreotide may quickly reverse anorexia and weight loss caused by the catabolic effect of glucagon excess. Patients who

respond may be converted to a long-acting octreotide formulation given 20 to 30 mg IM once/mo. Patients using octreotide may also need to take supplemental pancreatic enzymes because octreotide suppresses pancreatic enzyme secretion.

Locally applied, oral, or parenteral zinc may cause the erythema to disappear, but resolution may occur after simple hydration or IV administration of amino or fatty acids, suggesting that the erythema is not solely caused by zinc deficiency.

3 - Hepatic and Biliary Disorders

Chapter 23. Approach to the Patient With Liver Disease

Introduction

The liver is the most metabolically complex organ. Hepatocytes (liver parenchymal cells) perform the liver's metabolic functions:

• Formation and excretion of bile during bilirubin metabolism (see Sidebar 23-1)

• Regulation of carbohydrate homeostasis

• Lipid synthesis and secretion of plasma lipoproteins

• Control of cholesterol metabolism

• Formation of urea, serum albumin, clotting factors, enzymes, and numerous other proteins

• Metabolism or detoxification of drugs and other foreign substances

At the cellular level, portal triads consist of adjacent and parallel terminal branches of bile ducts, portal veins, and hepatic arteries that border the hepatocytes (see Fig. 23-1). Terminal branches of the hepatic veins are in the center of hepatic lobules. Because blood flows from the portal triads past the hepatocytes and drains via vein branches in the center of the lobule, the center of the lobule is the area most susceptible to ischemia.

Pathophysiology

Liver disorders can result from a wide variety of insults, including infections, drugs, toxins, ischemia, and autoimmune disorders. Occasionally, liver disorders occur postoperatively (see p. 223). Most liver disorders cause some degree of hepatocellular injury and necrosis, resulting in various abnormal laboratory test results and, sometimes, symptoms.

[**Fig. 23-1.** Organization of the liver.]

Symptoms may be due to liver disease itself (eg, jaundice due to acute hepatitis) or to complications of liver disease (eg, acute GI bleeding due to cirrhosis and portal hypertension).

Sidebar 23-1 Overview of Bilirubin Metabolism

The breakdown of heme produces bilirubin (an insoluble waste product) and other bile pigments. Bilirubin must be made water soluble to be excreted. This transformation occurs in 5 steps: formation, plasma transport, liver uptake, conjugation, and biliary excretion.

Formation: About 250 to 350 mg of unconjugated bilirubin forms daily; 70 to 80% derives from the breakdown of degenerating RBCs, and 20 to 30% (early-labeled bilirubin) derives primarily from other heme proteins in the bone marrow and liver. Hb is degraded to iron and biliverdin, which is converted to bilirubin.

Plasma transport: Unconjugated (indirect-reacting) bilirubin is not water soluble and so is transported in the plasma bound to albumin. It cannot pass through the glomerular membrane into the urine. Albumin binding weakens under certain conditions (eg, acidosis), and some substances (eg, salicylates, certain antibiotics) compete for the binding sites.

Liver uptake: The liver takes up bilirubin rapidly but does not take up the attached serum albumin.

Conjugation: Unconjugated bilirubin in the liver is conjugated to form mainly bilirubin diglucuronide, or conjugated (direct-reacting) bilirubin. This reaction, catalyzed by the microsomal enzyme glucuronyl transferase, renders the bilirubin water soluble.

Biliary excretion: Tiny canaliculi formed by adjacent hepatocytes progressively coalesce into ductules, interlobular bile ducts, and larger hepatic ducts. Outside the porta hepatis, the main hepatic duct joins the cystic duct from the gallbladder to form the common bile duct, which drains into the duodenum at the ampulla of Vater.

Conjugated bilirubin is secreted into the bile canaliculus with other bile constituents. In the intestine, bacteria metabolize bilirubin to form urobilinogen, much of which is further metabolized to stercobilins, which render the stool brown. In complete biliary obstruction, stools lose their normal color and become light gray (clay-colored stool). Some urobilinogen is reabsorbed, extracted by hepatocytes, and re-excreted in bile (enterohepatic circulation). A small amount is excreted in urine.

Because conjugated bilirubin is excreted in urine and unconjugated bilirubin is not, only conjugated hyperbilirubinemia (eg, due to hepatocellular or cholestatic jaundice) causes bilirubinuria.

Despite necrosis, the liver can regenerate itself. Even extensive patchy necrosis can resolve completely (eg, in acute viral hepatitis). Incomplete regeneration and fibrosis, however, may result from injury that bridges entire lobules or from less pronounced but ongoing damage.

Specific diseases preferentially affect certain hepatobiliary structures or functions (eg, acute viral hepatitis is primarily manifested by damage to hepatocytes or hepatocellular injury; primary biliary cirrhosis, by impairment of biliary secretion; and cryptogenic cirrhosis, by liver fibrosis and resultant portal venous hypertension). The part of the hepatobiliary system affected determines the symptoms, signs, and laboratory abnormalities (see also Ch. 24). Some disorders (eg, severe alcoholic liver disease) affect multiple liver structures, resulting in a combination of patterns of symptoms, signs, and laboratory abnormalities.

The prognosis of serious complications is worse in older adults, who are less able to recover from severe physiologic stresses and to tolerate toxic accumulations.

Evaluation

History: Various symptoms may develop, but few are specific for liver disorders:

- Common nonspecific symptoms include fatigue, anorexia, nausea, and, occasionally, vomiting, particularly in severe disorders.

- Loose, fatty stools (steatorrhea) can occur when cholestasis prevents sufficient bile from reaching the intestines. Patients with steatorrhea are at risk of deficiencies of fat-soluble vitamins (A, D, E, K). Common clinical consequences may include osteoporosis and bleeding.

- Fever can develop in viral or alcoholic hepatitis.

- Jaundice (see p. 212), occurring in both hepatocellular dysfunction and cholestatic disorders, is the most specific symptom. It is often accompanied by dark urine and light stools.

- Right upper quadrant pain due to liver disorders usually results from distention (eg, by passive venous congestion or tumor) or inflammation of the liver capsule.

- Erectile dysfunction and feminization develop; however, these symptoms may reflect the effects of alcohol more than liver disorders.

Family history, social history, and drug and substance use history should note risk factors for liver disorders (see

Table 23-1).

Physical examination: Abnormalities detectable on a physical examination usually do not develop until late in the course of the disease. Some common findings suggest a cause (see Table 23-2).

Ascites

Ascites is free fluid in the peritoneal cavity. The most common cause is portal hypertension. Symptoms usually result from abdominal distention. Diagnosis is based on physical examination and often ultrasonography or CT. Treatments include bed rest, dietary Na restriction, diuretics, and therapeutic paracentesis. Ascitic fluid can become infected (spontaneous bacterial peritonitis), often with pain and fever. Diagnosis of infection involves analysis and culture of ascitic fluid. Infection is treated with antibiotics.

[**Table 23-1.** Risk Factors for Liver Disorders]

Etiology

Ascites can result from chronic, but not acute, liver diseases.

Hepatic causes include the following:

• Portal hypertension (accounts for > 90% of hepatic cases), usually due to cirrhosis

• Chronic hepatitis

• Severe alcoholic hepatitis without cirrhosis

• Hepatic vein obstruction (Budd-Chiari syndrome)

Portal vein thrombosis does not usually cause ascites unless hepatocellular damage is also present.

Nonhepatic causes include the following:

• Generalized fluid retention associated with systemic diseases (eg, heart failure, nephrotic syndrome, severe hypoalbuminemia, constrictive pericarditis)

• Peritoneal disorders (eg, carcinomatous or infectious peritonitis, biliary leak due to surgery or another medical procedure)

• Less common causes, such as renal dialysis, pancreatitis, SLE, and endocrine disorders (eg, myxedema)

Pathophysiology

Mechanisms are complex and incompletely understood. Factors include altered Starling's forces in the portal vessels (low oncotic pressure due to hypoalbuminemia plus increased portal venous pressure), avid renal Na retention (urinary Na concentration is typically < 5 mEq/L), and possibly increased hepatic lymph formation.

Mechanisms that seem to contribute to renal Na retention include activation of the renin-angiotensin-aldosterone system; increased sympathetic tone; intrarenal shunting of blood away from the cortex; increased formation of nitric oxide; and altered formation or metabolism of ADH, kinins, prostaglandins, and atrial natriuretic factor. Vasodilation in the splanchnic arterial circulation may be a trigger, but the specific roles and interrelationships of these abnormalities remain uncertain.

Symptoms and Signs

Small amounts of ascitic fluid cause no symptoms. Moderate amounts cause increased abdominal girth and weight gain. Massive amounts may cause nonspecific diffuse abdominal pressure, but actual pain is uncommon and suggests another cause of acute abdominal pain (see p. 106). If ascites results in elevation of the diaphragm, dyspnea may occur. Symptoms of spontaneous bacterial peritonitis (SBP) may include new abdominal discomfort and fever.

Signs include shifting dullness on abdominal percussion and a fluid wave. Volumes < 1500 mL may not cause physical findings. Massive ascites causes tautness of the abdominal wall and flattening of the umbilicus. In liver diseases or peritoneal disorders, ascites is usually isolated or disproportionate to peripheral edema; in systemic diseases (eg, heart failure), the reverse is usually true.

Diagnosis

• Ultrasonography or CT unless physical findings make diagnosis obvious

• Often tests of ascitic fluid

Diagnosis may be based on physical examination if there is a large amount of fluid, but imaging tests are more sensitive. Ultrasonography and CT reveal much smaller volumes of fluid (100 to 200 mL) than does physical examination. SBP is suspected if a patient with ascites also has abdominal pain, fever, or unexplained deterioration.

Diagnostic paracentesis (see p. 99) should be done if any of the following occur:

• Ascites is newly diagnosed.

• Its cause is unknown.

• SBP is suspected.

[**Table 23-2.** Interpretation of Some Physical Findings]

About 50 to 100 mL of fluid is removed and analyzed for gross appearance, protein content, cell count and differential, cytology, culture, and, as clinically indicated, acid-fast stain, amylase, or both. In contrast to ascites due to inflammation or infection, ascites due to portal hypertension produces fluid that is clear and straw-colored, has a low protein concentration, a low PMN count (< 250 cells/µL), and, most reliably, a high serum-to-ascites albumin concentration gradient, which is the serum albumin concentration minus the ascitic albumin concentration. Gradients > 1.1 g/dL are relatively specific for ascites due to portal hypertension. In ascitic fluid, turbidity and a PMN count > 250 cells/µL indicate SBP, whereas bloody fluid can suggest a tumor or TB. The rare milky (chylous) ascites is most common with lymphoma.

Treatment

• Bed rest and dietary Na restriction

• Sometimes spironolactone, possibly plus furosemide

• Sometimes therapeutic paracentesis

Bed rest and dietary Na restriction (2000 mg/day) are the first and least risky treatments for ascites due to portal hypertension. Diuretics should be used if rigid Na restriction fails to initiate diuresis within a few days. Spironolactone is usually effective (in oral doses ranging from 50 mg once/day to 200 mg bid). A loop diuretic (eg, furosemide 20 to 160 mg po usually once/day or 20 to 80 mg po bid) should be added if spironolactone is insufficient. Because spironolactone can cause K retention and furosemide K depletion, the combination of these drugs often provides optimal diuresis with a lower risk of K abnormalities. Fluid restriction is indicated only for treatment of hyponatremia (serum Na < 120 mEq/L). Changes in body weight and urinary Na determinations reflect response to treatment. Weight loss of about 0.5 kg/day is

optimal because the ascitic compartment cannot be mobilized much more rapidly. More aggressive diuresis depletes fluid from the intravascular compartment, especially when peripheral edema is absent; this depletion may cause renal failure or electrolyte imbalance (eg, hypokalemia) that may precipitate portal-systemic encephalopathy. Inadequate dietary Na restriction is the usual cause of persistent ascites.

Therapeutic paracentesis is an alternative. Removal of 4 L/day is safe; many clinicians infuse IV salt-poor albumin (about 40 g/paracentesis) at about the same time to prevent intravascular volume depletion. Even single total paracentesis may be safe. Therapeutic paracentesis shortens the hospital stay with relatively little risk of electrolyte imbalance or renal failure; nevertheless, patients require ongoing diuretics and tend to reaccumulate fluid more rapidly than those treated without paracentesis.

Techniques for the autologous infusion of ascitic fluid (eg, the LeVeen peritoneovenous shunt) often cause complications and are generally no longer used. Transjugular intrahepatic portosystemic shunting (TIPS) can lower portal pressure and successfully treat ascites resistant to other treatments, but TIPS is invasive and may cause complications, including portal-systemic encephalopathy and worsening hepatocellular function.

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is infection of ascitic fluid without an apparent source. Manifestations may include fever, malaise, and symptoms of ascites and worsening hepatic failure. Diagnosis is by examination of ascitic fluid. Treatment is with cefotaxime or another antibiotic.

SBP is particularly common in cirrhotic ascites, especially among alcoholics. This infection can cause serious sequelae or death. The most common bacteria causing SBP are gram-negative *Escherichia coli* and *Klebsiella pneumoniae* and gram-positive *Streptococcus pneumoniae*; usually only a single organism is involved.

Symptoms and Signs

Patients have symptoms and signs of ascites. Discomfort is usually present; it typically is diffuse, constant, and mild to moderate in severity.

Signs of SBP may include fever, malaise, encephalopathy, worsening hepatic failure, and unexplained clinical deterioration. Peritoneal signs (eg, abdominal tenderness and rebound) are present but may be somewhat diminished by the presence of ascitic fluid.

Diagnosis

• Diagnostic paracentesis

Clinical diagnosis of SBP can be difficult; diagnosis requires a high index of suspicion and liberal use of diagnostic paracentesis, including culture. Transferring ascitic fluid to blood culture media before incubation increases the sensitivity of culture to almost 70%. PMN count of > 250 cells/µL is diagnostic of SBP. Blood cultures are also indicated. Because SBP usually results from a single organism, finding mixed flora on culture suggests a perforated abdominal viscus or contaminated specimen.

Treatment

• Cefotaxime or another antibiotic

If SBP is diagnosed, an antibiotic such as cefotaxime 2 g IV q 4 to 8 h (pending Gram stain and culture results) is given for at least 5 days and until ascitic fluid shows < 250 PMNs/µL. Antibiotics increase the chance of survival. Because SBP recurs within a year in up to 70% of patients, prophylactic antibiotics are indicated; quinolones (eg, norfloxacin 400 mg po once/day) are most widely used.

Antibiotic prophylaxis in ascitic patients with variceal hemorrhage decreases the risk of SBP.

Fatty Liver

(Hepatic Steatosis)

Fatty liver is excessive accumulation of lipid in hepatocytes, the most common liver response to injury.

Fatty liver develops for many reasons, involves many different biochemical mechanisms, and causes different types of liver damage. Clinically, it is most useful to distinguish fatty liver due to pregnancy or alcoholic liver disease (see p. 235) from that occurring in the absence of pregnancy and alcoholism (nonalcoholic fatty liver disease [NAFLD]). NAFLD includes simple fatty infiltration (a benign condition) and nonalcoholic steatohepatitis, a less common but more important variant.

(See also the American Gastroenterological Association's Medical Position Statement and Technical Review on nonalcoholic fatty liver disease.)

Nonalcoholic Steatohepatitis

Nonalcoholic steatohepatitis (NASH) is a syndrome that develops in patients who are not alcoholics; it causes liver damage that is histologically indistinguishable from alcoholic hepatitis. It develops most often in patients with at least one of the following risk factors: obesity, dyslipidemia, and glucose intolerance. Pathogenesis is poorly understood but seems to be linked to insulin resistance (eg, as in obesity or metabolic syndrome). Most patients are asymptomatic. Laboratory findings include elevations in aminotransferase levels. Biopsy is required to confirm the diagnosis. Treatment includes elimination of causes and risk factors.

NASH (sometimes called steatonecrosis) is diagnosed most often in patients between 40 yr and 60 yr but can occur in all age groups. Many affected patients have obesity, type 2 diabetes mellitus, or dyslipidemia.

Pathophysiology

Pathophysiology involves fat accumulation (steatosis), inflammation, and, variably, fibrosis. Steatosis results from hepatic triglyceride accumulation. Possible mechanisms for steatosis include reduced synthesis of very low density lipoprotein (VLDL) and increased hepatic triglyceride synthesis (possibly due to decreased oxidation of fatty acids or increased free fatty acids being delivered to the liver). Inflammation may result from lipid peroxidative damage to cell membranes. These changes can stimulate hepatic stellate cells, resulting in fibrosis. If advanced, NASH can cause cirrhosis and portal hypertension.

Symptoms and Signs

Most patients are asymptomatic. However, some have fatigue, malaise, or right upper quadrant abdominal discomfort. Hepatomegaly develops in about 75% of patients. Splenomegaly may develop if advanced hepatic fibrosis is present and is usually the first indication that portal hypertension has developed. Patients with cirrhosis due to NASH can be asymptomatic and may lack the usual signs of chronic liver disease.

Diagnosis

• Presence of risk factors

• Absence of hepatitis B and C and excessive alcohol intake

• Liver biopsy

The diagnosis should be suspected in patients with risk factors such as obesity, type 2 diabetes mellitus, or dyslipidemia and in patients with unexplained laboratory abnormalities suggesting liver disease. The

most common laboratory abnormalities are elevations in aminotransferase levels. Unlike in alcoholic liver disease, the ratio of AST/ALT in NASH is usually < 1. Alkaline phosphatase and γ-glutamyl transpeptidase (GGT) occasionally increase. Hyperbilirubinemia, prolongation of PT, and hypoalbuminemia are uncommon.

For diagnosis, strong evidence (such as a history corroborated by friends and relatives) that alcohol intake is not excessive (eg, is < 20 g/day) is needed. Serologic tests should show absence of hepatitis B and C infection (ie, hepatitis B surface antigen and hepatitis C virus antibody should be negative). Liver biopsy should reveal damage similar to that seen in alcoholic hepatitis, usually including large fat droplets (macrovesicular fatty infiltration). Indications for biopsy include unexplained signs of portal hypertension (including splenomegaly or cytopenia) and unexplained elevations in aminotransferase levels that persist for > 6 mo in a patient with diabetes, obesity, or dyslipidemia.

Imaging tests, including ultrasonography, CT, and particularly MRI, may identify hepatic steatosis. However, these tests cannot identify the inflammation typical of NASH and cannot differentiate NASH from other causes of hepatic steatosis.

Prognosis

Prognosis is controversial. Probably, most patients do not develop hepatic insufficiency or cirrhosis. However, some drugs (eg, cytotoxic drugs) and metabolic disorders are associated with acceleration of NASH. Prognosis is often good unless complications (eg, variceal hemorrhage) develop.

Treatment

• Elimination of causes and control of risk factors

The only widely accepted treatment goal is to eliminate potential causes and risk factors. Such a goal may include discontinuation of drugs or toxins, weight loss, and treatment for dyslipidemia or hyperglycemia. Preliminary evidence suggests that thiazolidinediones can help correct biochemical and histologic abnormalities in NASH. Many other treatments (eg, ursodeoxycholic acid, vitamin E, metronidazole, metformin, betaine, glucagon, glutamine infusion) have not been proved effective.

Jaundice

Jaundice is a yellowish discoloration of the skin and mucous membranes caused by hyperbilirubinemia. Jaundice becomes visible when the bilirubin level is about 2 to 3 mg/dL (34 to 51 µmol/L).

Pathophysiology

Most bilirubin is produced when Hb is broken down into unconjugated bilirubin (and other substances). Unconjugated bilirubin binds to albumin in the blood for transport to the liver, where it is taken up by hepatocytes and conjugated with glucuronic acid to make it water soluble. Conjugated bilirubin is excreted in bile into the duodenum. In the intestine, bacteria metabolize bilirubin to form urobilinogen. Some urobilinogen is eliminated in the feces, and some is reabsorbed, extracted by hepatocytes, reprocessed, and re-excreted in bile (enterohepatic circulation—see p. 205).

Mechanisms of hyperbilirubinemia: Hyperbilirubinemia may involve predominantly unconjugated or conjugated bilirubin.

Unconjugated hyperbilirubinemia is most often caused by ≥ 1 of the following:

• Increased production

• Decreased hepatic uptake

• Decreased conjugation

Conjugated hyperbilirubinemia is most often caused by ≥ 1 of the following:

• Dysfunction of hepatocytes (hepatocellular dysfunction)

• Slowing of bile egress from the liver (intrahepatic cholestasis)

• Obstruction of extrahepatic bile flow (extra-hepatic cholestasis)

Consequences: Outcome is determined primarily by the cause of jaundice and the presence and severity of hepatic dysfunction. Hepatic dysfunction can result in coagulopathy, encephalopathy, and portal hypertension (which can lead to GI bleeding).

Etiology

Although hyperbilirubinemia can be classified as predominantly unconjugated or conjugated, many hepatobiliary disorders cause both forms.

Many conditions (see
Table 23-3), including use of certain drugs (see
Table 23-4), can cause jaundice, but the most common causes overall are

• Inflammatory hepatitis (viral hepatitis, autoimmune hepatitis, toxic hepatic injury)

• Alcoholic liver disease

• Biliary obstruction

Evaluation

History: History of present illness should include onset and duration of jaundice. Hyperbilirubinemia can cause urine to darken before

[**Table 23-3.** Mechanisms and Some Causes of Jaundice in Adults]

jaundice is visible. Therefore, the onset of dark urine indicates onset of hyperbilirubinemia more accurately than onset of jaundice. Important associated symptoms include fever, prodromal symptoms (eg, fever, malaise, myalgias) before jaundice, urine and stool color, pruritus, steatorrhea, and abdominal pain (including location, severity, duration, and radiation). Important symptoms suggesting severe disease include nausea and vomiting, weight loss, and possible symptoms of coagulopathy (eg, easy bruising or bleeding, tarry or bloody stools).

Review of systems should seek symptoms of possible causes, including weight loss and abdominal pain (cancer); joint pain and swelling

[**Table 23-4.** Some Drugs and Toxins that Can Cause Jaundice]

(autoimmune or viral hepatitis, hemochromatosis, primary sclerosing cholangitis, sarcoidosis); and missed menses (pregnancy).

Past medical history should identify known causative disorders, such as hepatobiliary disease (eg, gallstones, hepatitis, cirrhosis); disorders that can cause hemolysis (eg, hemoglobinopathy, G6PD deficiency); and disorders associated with liver or biliary disease, including inflammatory bowel disease, infiltrative disorders (eg, amyloidosis, lymphoma, sarcoidosis, TB), and HIV infection or AIDS.

Drug history should include questions about use of drugs or exposure to toxins known to affect the liver (see Table 23-4) and about vaccination against hepatitis.

Surgical history should include questions about previous surgery on the biliary tract (a potential cause of strictures).

Social history should include questions about risk factors for hepatitis (see Table 23-5), amount and duration of alcohol use, injection drug use, and sexual history.

Family history should include questions about recurrent, mild jaundice in family members and diagnosed hereditary liver disorders. The patient's history of recreational drug and alcohol use should be corroborated by friends or family members when possible.

Physical examination: Vital signs are reviewed for fever and signs of systemic toxicity (eg, hypotension, tachycardia).

General appearance is noted, particularly for cachexia and lethargy.

Head and neck examination includes inspection of the sclerae and tongue for icterus and the eyes for Kayser-Fleischer rings. Mild jaundice is best seen by examining the sclerae in natural light; it is usually detectable when serum bilirubin reaches 2 to 2.5 mg/dL (34 to 43 µmol/L). Breath odor should be noted (eg, for fetor hepaticus).

The abdomen is inspected for collateral vasculature, ascites, and surgical scars. The liver is palpated for hepatomegaly, masses, nodularity, and tenderness. The spleen is palpated for splenomegaly. The abdomen is examined for umbilical hernia, shifting dullness, fluid wave, masses, and tenderness. The rectum is examined for gross or occult blood.

Men are checked for testicular atrophy and gynecomastia.

The upper extremities are examined for Dupuytren's contractures.

Neurologic examination includes mental status assessment and evaluation for asterixis.

The skin is examined for jaundice, palmar erythema, needle tracks, vascular spiders, excoriations, xanthomas (consistent with primary biliary cirrhosis), paucity of axillary and pubic hair, hyperpigmentation, ecchymoses, petechiae, and purpura.

Red flags: The following findings are of particular concern:

• Marked abdominal pain and tenderness

• Altered mental status

• GI bleeding (occult or gross)

• Ecchymoses, petechiae, or purpura

Interpretation of findings: Severity of illness is indicated mainly by the degree (if any) of hepatic dysfunction. Ascending cholangitis is a concern because it requires emergency treatment.

Severe hepatic dysfunction is indicated by encephalopathy (eg, mental status change, asterixis) or coagulopathy (eg, easy bleeding, purpura, tarry or heme-positive stool), particularly in patients with signs of portal hypertension

[**Table 23-5.** Some Risk Factors for Hepatitis]

(eg, abdominal collateral vasculature, ascites, splenomegaly). Massive upper GI bleeding suggests variceal bleeding due to portal hypertension (and possibly coagulopathy).

Ascending cholangitis is suggested by fever and marked, continuous right upper quadrant abdominal

pain; acute pancreatitis with biliary obstruction (eg, due to a common duct stone or pancreatic pseudocyst) may manifest similarly.

Cause of jaundice may be suggested by the following:

- Acute jaundice in the young and healthy suggests acute viral hepatitis, particularly when a viral prodrome, risk factors, or both are present; however, acetaminophen overdose is also common.
- Acute jaundice after acute drug or toxin exposure in healthy patients is likely due to that substance.
- A long history of heavy alcohol use suggests alcoholic liver disease, particularly when typical stigmata are present.
- A personal or family history of recurrent, mild jaundice without findings of hepatobiliary dysfunction suggests a hereditary disorder, usually Gilbert syndrome.
- Gradual onset of jaundice with pruritus, weight loss, and clay-colored stools suggests intrahepatic or extrahepatic cholestasis.
- Painless jaundice in elderly patients with weight loss and a mass but with minimal pruritus suggests biliary obstruction caused by cancer.

Other examination findings can also be helpful (see Table 23-6).

Testing: The following are done:

- Blood tests (bilirubin, aminotransferase, alkaline phosphatase)
- Usually imaging
- Sometimes biopsy or laparoscopy

Blood tests include measurement of total and direct bilirubin, aminotransferase, and alkaline phosphatase levels in all patients. Results help differentiate cholestasis from hepatocellular dysfunction (important because patients with cholestasis usually require imaging tests):

- Hepatocellular dysfunction: Marked aminotransferase elevation (> 500 U/L) and moderate alkaline phosphatase elevation (< 3 times normal)
- Cholestasis: Moderate aminotransferase elevation (< 200 U/L) and marked alkaline phosphatase elevation (> 3 times normal)
- Hyperbilirubinemia without hepatobiliary dysfunction: Mild hyperbilirubinemia (eg, < 3.5 mg/dL [< 59 µmol/L]) with normal aminotransferase and alkaline phosphatase levels

Also, patients with hepatocellular dysfunction or cholestasis have dark urine due to bilirubinuria because conjugated bilirubin is excreted in urine; unconjugated bilirubin is not. Bilirubin fractionation also differentiates conjugated from unconjugated forms. When aminotransferase and alkaline phosphatase levels are normal, fractionation of bilirubin can help suggest causes, such as Gilbert syndrome or hemolysis (unconjugated) vs Dubin-Johnson syndrome or Rotor's syndrome (conjugated).

Other blood tests are done based on clinical suspicion and initial test findings, as for the following:

- Signs of hepatic insufficiency (eg, encephalopathy, ascites, ecchymoses) or GI bleeding: Coagulation profile (PT/PTT)
- Hepatitis risk factors (see Table 23-5) or a hepatocellular mechanism suggested by blood test results:

Hepatitis viral and autoimmune serologic tests

- Fever, abdominal pain, and tenderness: CBC and, if patients appear ill, blood cultures

[**Table 23-6.** Findings Suggesting a Cause of Jaundice]

Suspicion of hemolysis can be confirmed by a peripheral blood smear.

Imaging is done if pain suggests extrahepatic obstruction or cholangitis or if blood test results suggest cholestasis.

Abdominal ultrasonography usually is done first; usually, it is highly accurate in detecting extrahepatic obstruction. CT and MRI are alternatives. Ultrasonography is usually more accurate for gallstones, and CT is more accurate for pancreatic lesions. All these tests can detect abnormalities in the biliary tree and focal liver lesions but are less accurate in detecting diffuse hepatocellular disorders (eg, hepatitis, cirrhosis).

If ultrasonography shows extrahepatic cholestasis, other tests may be necessary to determine the cause; usually, magnetic resonance cholangiopancreatography (MRCP) or ERCP is used. ERCP is more invasive but allows treatment of some obstructive lesions (eg, stone removal, stenting of strictures).

Liver biopsy is not commonly required but can help diagnose certain disorders (eg, disorders causing intrahepatic cholestasis, some kinds of hepatitis, some infiltrative disorders, Dubin-Johnson syndrome, hemochromatosis, Wilson's disease). Biopsy can also help when liver enzyme abnormalities are unexplained by other tests.

Laparoscopy (peritoneoscopy) allows direct inspection of the liver and gallbladder without the trauma of a full laparotomy. Unexplained cholestatic jaundice warrants laparoscopy occasionally and diagnostic laparotomy rarely.

Treatment

The cause and any complications are treated. Jaundice itself requires no treatment in adults (unlike in neonates—see p. 2788). Itching, if bothersome, may be relieved with cholestyramine 2 to 8 g po bid. However, cholestyramine is ineffective in patients with complete biliary obstruction.

Geriatrics Essentials

Symptoms may be attenuated or missed in the elderly; eg, abdominal pain may be mild or absent in acute viral hepatitis. A sleep disturbance or mild confusion resulting from portosystemic encephalopathy may be misattributed to dementia.

Key Points

- Acute jaundice, particularly with a viral prodrome, in the young and healthy suggests acute viral hepatitis.
- Painless jaundice in elderly patients with weight loss, an abdominal mass, and minimal pruritus suggests biliary obstruction caused by cancer.
- Aminotransferase levels of > 500 U/L and alkaline phosphatase elevation < 3 times normal suggest hepatocellular dysfunction.
- Aminotransferase levels of < 200 U/L and alkaline phosphatase elevation > 3 times normal suggest cholestasis.
- Significant hepatic dysfunction is indicated by altered mental status and coagulopathy.

Inborn Metabolic Disorders Causing Hyperbilirubinemia

Hereditary or inborn metabolic disorders may cause unconjugated or conjugated hyperbilirubinemia.

- Unconjugated hyperbilirubinemia: Gilbert syndrome, Crigler-Najjar syndrome, and primary shunt hyperbilirubinemia

- Conjugated hyperbilirubinemia: Dubin-Johnson syndrome and Rotor's syndrome

Gilbert Syndrome

Gilbert syndrome is a presumably lifelong disorder in which the only significant abnormality is asymptomatic, mild, unconjugated hyperbilirubinemia. It can be mistaken for chronic hepatitis or other liver disorders. Gilbert syndrome may affect as many as 5% of people. Although family members may be affected, a clear genetic pattern is difficult to establish.

Pathogenesis may involve complex defects in the liver's uptake of bilirubin. Glucuronyl transferase activity is low, though not as low as in Crigler-Najjar syndrome type II. In many patients, RBC destruction is also slightly accelerated, but this acceleration does not explain hyperbilirubinemia. Liver histology is normal.

Gilbert syndrome is most often detected in young adults serendipitously by finding an elevated bilirubin level, which usually fluctuates between 2 and 5 mg/dL (34 and 86 µmol/L) and tends to increase with fasting and other stresses.

Gilbert syndrome is differentiated from hepatitis by fractionation that shows predominantly unconjugated bilirubin, otherwise normal liver function test results, and absence of urinary bilirubin. It is differentiated from hemolysis by the absence of anemia and reticulocytosis. Treatment is unnecessary. Patients should be reassured that they do not have liver disease.

Crigler-Najjar Syndrome

This rare inherited disorder is caused by deficiency of the enzyme glucuronyl transferase. Patients with autosomal recessive type I (complete) disease have severe hyperbilirubinemia. They usually die of kernicterus by age 1 yr but may survive into adulthood. Treatment may include phototherapy and liver transplantation. Patients with autosomal dominant type II (partial) disease (which has variable penetrance) often have less severe hyperbilirubinemia (< 20 mg/dL [< 342 µmol/L]) and usually live into adulthood without neurologic damage. Phenobarbital 1.5 to 2 mg/kg po tid, which induces the partially deficient glucuronyl transferase, may be effective.

Primary Shunt Hyperbilirubinemia

This rare, familial, benign condition is characterized by overproduction of early-labeled bilirubin.

Dubin-Johnson Syndrome and Rotor's Syndrome

Dubin-Johnson syndrome and Rotor's syndrome cause conjugated hyperbilirubinemia, but without cholestasis, causing no symptoms or sequelae other than jaundice. In contrast to unconjugated hyperbilirubinemia in Gilbert syndrome (which also causes no other symptoms), bilirubin may appear in the urine. Aminotransferase and alkaline phosphatase levels are usually normal. Treatment is unnecessary.

Dubin-Johnson syndrome: This rare autosomal recessive disorder involves impaired excretion of bilirubin glucuronides. It is usually diagnosed by liver biopsy; the liver is deeply pigmented as a result of an intracellular melanin-like substance but is otherwise histologically normal.

Rotor's syndrome: This rare disorder is clinically similar to Dubin-Johnson syndrome, but the liver is not pigmented, and other subtle metabolic differences are present.

Portal Hypertension

Portal hypertension is caused most often by cirrhosis (in developed countries), schistosomiasis (in endemic areas), or hepatic vascular abnormalities. Consequences include esophageal varices and portal-systemic encephalopathy. Diagnosis is based on clinical criteria, often in conjunction with imaging tests and endoscopy. Treatment involves prevention of GI bleeding with endoscopy, drugs, or both and sometimes with portocaval shunting.

The portal vein, formed by the superior mesenteric and splenic veins, drains blood from the abdominal GI tract, spleen, and pancreas into the liver. Within reticuloendotheliumlined blood channels (sinusoids), blood from the terminal portal venules merges with hepatic arterial blood. Blood flows out of the sinusoids via the hepatic veins into the inferior vena cava.

Normal portal pressure is 5 to 10 mm Hg (7 to 14 cm H_2O), which exceeds inferior vena caval pressure by 4 to 5 mm Hg (portal venous gradient). Higher values are defined as portal hypertension.

Etiology

Portal hypertension results mainly from increased resistance to flow, which commonly arises from disease within the liver itself or uncommonly from blockage of the splenic or portal vein or impaired hepatic venous outflow (see Table 23-7). Increased flow volume is a rare cause, although it often contributes to portal hypertension in cirrhosis and in hematologic disorders that cause massive splenomegaly.

Pathophysiology

In cirrhosis, tissue fibrosis and regeneration increase resistance in the sinusoids and terminal portal venules. However, other potentially reversible factors contribute; they include contractility of sinusoidal lining cells, production of vasoactive substances (eg, endothelins, nitric oxide), various systemic mediators of arteriolar resistance, and possibly swelling of hepatocytes.

Over time, portal hypertension creates portal-systemic venous collaterals. They may slightly decrease portal vein pressure but can cause complications. Engorged serpentine submucosal vessels (varices) in the distal esophagus and sometimes in the gastric fundus can rupture, causing sudden, catastrophic GI bleeding. Bleeding rarely occurs unless the portal pressure gradient is > 12 mm Hg. Gastric mucosal vascular congestion (portal hypertensive gastropathy) can cause acute or chronic bleeding independent of varices. Visible abdominal wall collaterals are common; veins radiating from the umbilicus (caput medusae) are much rarer and indicate extensive flow in the umbilical and periumbilical veins.

[**Table 23-7.** Most Common Causes of Portal Hypertension]

Collaterals around the rectum can cause rectal varices that can bleed.

Portal-systemic collaterals shunt blood away from the liver. Thus, less blood reaches the liver when portal flow increases (diminished hepatic reserve). In addition, toxic substances from the intestine are shunted directly to the systemic circulation, contributing to portal-systemic encephalopathy (see p. 220). Venous congestion within visceral organs due to portal hypertension contributes to ascites via altered Starling's forces. Splenomegaly and hypersplenism (see p. 984) commonly occur as a result of increased splenic vein pressure. Thrombocytopenia, leukopenia, and, less commonly, hemolytic anemia may result.

Portal hypertension is often associated with a hyperdynamic circulation. Mechanisms are complex and seem to involve altered sympathetic tone, production of nitric oxide and other endogenous vasodilators, and enhanced activity of humoral factors (eg, glucagon).

Symptoms and Signs

Portal hypertension is asymptomatic; symptoms and signs result from its complications. The most dangerous is acute variceal bleeding (see p. 103). Patients typically present with sudden painless upper

GI bleeding, often massive. Bleeding from portal hypertensive gastropathy is often subacute or chronic. Ascites, splenomegaly, or portal-systemic encephalopathy may be present.

Diagnosis

• Usually, clinical evaluation

Portal hypertension is inferred in a patient with chronic liver disease by the presence of collateral circulation, splenomegaly, ascites, or portal-systemic encephalopathy. Proof requires direct portal pressure measurement by a transjugular catheter, which is invasive and usually not done. Imaging may help when cirrhosis is suspected. Ultrasonography or CT often reveals dilated intra-abdominal collaterals, and Doppler ultrasonography can determine portal vein patency and flow.

Esophagogastric varices and portal hypertensive gastropathy are best diagnosed by endoscopy, which may also identify predictors of esophagogastric variceal bleeding (eg, red markings on a varix).

Prognosis

Mortality during acute variceal hemorrhage may exceed 50%. Prognosis is predicted by the degree of hepatic reserve and the degree of bleeding. For survivors, the bleeding risk within the next 1 to 2 yr is 50 to 75%. Ongoing endoscopic or drug therapy lowers the bleeding risk but decreases long-term mortality only marginally. For treatment of acute bleeding, see pp. 102 and 104.

Treatment

• Ongoing endoscopic therapy and surveillance

• β-Blockers with or without isosorbide mononitrate

• Sometimes portal vein shunting

When possible, the underlying disorder is treated. Long-term treatment of esophagogastric varices that have bled is a series of endoscopic banding sessions to obliterate residual varices, then periodic surveillance endoscopy for recurrent varices.

Long-term drug therapy for varices that have bled involves β-blockers; these drugs lower portal pressure primarily by diminishing portal flow, although the effects vary. Propranolol (40 to 80 mg po bid) or nadolol (40 to 160 mg po once/day) is preferred, with dosage titrated to decrease heart rate by about 25%. Adding isosorbide mononitrate 10 to 20 mg po bid may further reduce portal pressure. Combined long-term endoscopic and drug therapy may be slightly more effective than either alone. Patients who do not adequately respond to either treatment should be considered for transjugular intrahepatic portosystemic shunting (TIPS) or, less frequently, a surgical portocaval shunt. TIPS creates a stent between the portal and hepatic venous circulation within the liver. Although TIPS may result in fewer immediate deaths than surgical shunting, particularly during acute bleeding, maintenance of patency may require repeat procedures because the stent may become stenosed or occluded over time. Long-term benefits are unknown. Liver transplantation may help some patients.

For patients with varices that have not yet bled, β-blockers lower the risk of bleeding.

For bleeding due to portal hypertensive gastropathy, drugs can be used to decrease portal pressure. A shunt should be considered if drugs are ineffective, but results may be less successful than for esophageal variceal bleeding.

Because it rarely causes clinical problems, hypersplenism requires no specific treatment, and splenectomy should be avoided.

Portal-Systemic Encephalopathy

Portal-systemic encephalopathy is a neuropsychiatric syndrome. It most often results from high gut protein or acute metabolic stress (eg, GI bleeding, infection, electrolyte abnormality) in a patient with portal-systemic shunting. Symptoms are mainly neuropsychiatric (eg, confusion, flapping tremor, coma). Diagnosis is based on clinical findings. Treatment usually is correction of the acute cause, restriction of dietary protein, and oral lactulose.

Portal-systemic encephalopathy better describes the pathophysiology than hepatic encephalopathy or hepatic coma, but all 3 terms are used interchangeably.

Etiology

Portal-systemic encephalopathy may occur in fulminant hepatitis caused by viruses, drugs, or toxins, but it more commonly occurs in cirrhosis or other chronic disorders when extensive portal-systemic collaterals have developed as a result of portal hypertension. Encephalopathy also follows portal-systemic anastomoses, such as surgically created anastomoses connecting the portal vein and vena cava (portacaval shunts, transjugular intrahepatic portosystemic shunting [TIPS]).

Precipitants: In patients with chronic liver disease, acute episodes of encephalopathy are usually precipitated by reversible causes. The most common are the following:

- Metabolic stress (eg, infection; electrolyte imbalance, especially hypokalemia; dehydration; use of diuretic drugs)

- Disorders that increase gut protein (eg, GI bleeding, high-protein diet)

- Nonspecific cerebral depressants (eg, alcohol, sedatives, analgesics)

Pathophysiology

In portal-systemic shunting, absorbed products that would otherwise be detoxified by the liver enter the systemic circulation, where they may be toxic to the brain, particularly the cerebral cortex. The substances causing brain toxicity are not precisely known. Ammonia, a product of protein digestion, is an important cause, but other factors (eg, alterations in cerebral benzodiazepine receptors and neurotransmission by γ-aminobutyric acid [GABA]) may also contribute. Aromatic amino acid levels in serum are usually high and branched-chain levels are low, but these levels probably do not cause encephalopathy.

Symptoms and Signs

Symptoms and signs of encephalopathy tend to develop in progressive stages (see Table 23-8).

Symptoms usually do not become apparent until brain function is moderately impaired. Constructional apraxia, in which patients cannot reproduce simple designs (eg, a star), develops early. Agitation and mania can develop but are uncommon. A characteristic flapping tremor (asterixis) is elicited when patients hold their arms outstretched with wrists dorsiflexed. Neurologic deficits are symmetric. Neurologic signs in coma usually reflect bilateral diffuse hemispheric dysfunction. Signs of brain stem dysfunction develop only in advanced coma, often during the hours or days before death. A musty, sweet breath odor (fetor hepaticus) can occur regardless of the stage of encephalopathy.

Diagnosis

- Clinical evaluation

- Often adjunctive testing with psychometric evaluation, ammonia level, EEG, or a combination

- Exclusion of other treatable disorders

[Table 23-8. Clinical Stages of Portal-Systemic Encephalopathy]

Diagnosis is ultimately based on clinical findings, but testing may help:

- Psychometric testing may reveal subtle neuropsychiatric deficits, which can help confirm early encephalopathy.
- Ammonia levels are usually done.
- An EEG usually shows diffuse slow-wave activity, even in mild cases, and may be sensitive but is not specific for early encephalopathy.

CSF examination is not routinely necessary; the only usual abnormality is mild protein elevation.

Other potentially reversible disorders that could cause similar manifestations (eg, infection, subdural hematoma, hypoglycemia, intoxication) should be ruled out. If portal-systemic encephalopathy is confirmed, the precipitating cause should be sought.

Prognosis

In chronic liver disease, correction of the precipitating cause usually causes encephalopathy to regress without permanent neurologic sequelae. Some patients, especially those with portacaval shunts or TIPS, require continuous therapy, and irreversible extrapyramidal signs or spastic paraparesis rarely develops. Coma (stage 4 encephalopathy) associated with fulminant hepatitis is fatal in up to 80% of patients despite intensive therapy; the combination of advanced chronic liver failure and portal-systemic encephalopathy is often fatal.

Treatment

- Treatment of the cause
- Bowel cleansing using oral lactulose or enemas
- Dietary protein restriction

Treating the cause usually reverses mild cases. Eliminating toxic enteric products is the other goal and is accomplished using several methods. The bowels should be cleared using enemas or, more often, oral lactulose syrup, which can be tube-fed to comatose patients. This synthetic disaccharide is an osmotic cathartic. It also lowers colonic pH, decreasing fecal ammonia production. The initial dosage, 30 to 45 mL po tid, should be adjusted to produce 2 or 3 soft stools daily. Dietary protein should be about 1.0 mg/kg/day, primarily from vegetable sources. Oral nonabsorbable antibiotics such as neomycin and rifaximin are effective for hepatic encephalopathy. Rifaximin is usually preferred because neomycin is an aminoglycoside, which can precipitate ototoxicity or nephrotoxicity.

Sedation deepens encephalopathy and should be avoided whenever possible. For coma caused by fulminant hepatitis, meticulous supportive and nursing care coupled with prevention and treatment of complications increase the chance of survival. High-dose corticosteroids, exchange transfusion, and other complex procedures designed to remove circulating toxins generally do not improve outcome. Patients deteriorating because of fulminant hepatic failure may be saved by liver transplantation.

Other potential therapies, including levodopa, bromocriptine, flumazenil, Na benzoate, infusions of branched-chain amino acids, keto-analogs of essential amino acids, and prostaglandins, have not proved effective. Complex plasma-filtering systems (artificial liver) show some promise but require much more study.

Systemic Abnormalities in Liver Disease

Liver disease often causes systemic symptoms and abnormalities (see Portal-Systemic Encephalopathy

on p. 220).

Circulatory Abnormalities

Hypotension in advanced liver failure may contribute to renal dysfunction. The pathogenesis of the hyperdynamic circulation (increased cardiac output and heart rate) and hypotension that develop in advanced liver failure or cirrhosis is poorly understood. However, peripheral arterial vasodilation probably contributes to both. Factors that may contribute in cirrhosis may include altered sympathetic tone, production of nitric oxide and other endogenous vasodilators, and enhanced activity of humoral factors (eg, glucagon).

For specific disorders of hepatic circulation (eg, Budd-Chiari syndrome), see Ch. 29.

Endocrine Abnormalities

Glucose intolerance, hyperinsulinism, insulin resistance, and hyperglucagonemia are often present in patients with cirrhosis; the elevated insulin levels reflect decreased hepatic degradation rather than increased secretion, whereas the opposite is true for hyperglucagonemia. Abnormal thyroid function tests may reflect altered hepatic handling of thyroid hormones and changes in plasma binding proteins rather than thyroid abnormalities.

Sexual effects are common. Chronic liver disease commonly impairs menstruation and fertility. Males with cirrhosis, especially alcoholics, often have both hypogonadism (including testicular atrophy, erectile dysfunction, decreased spermatogenesis) and feminization (gynecomastia, female habitus). The biochemical basis is not fully understood. Gonadotropin reserve of the hypothalamicpituitary axis is often blunted. Circulating testosterone levels are low, resulting mainly from decreased synthesis but also from increased peripheral conversion to estrogens. Levels of estrogens other than estradiol are usually increased, but the relationship between estrogens and feminization is complex. These changes are more prevalent in alcoholic liver disease than in cirrhosis of other etiologies, suggesting that alcohol, rather than liver disease, may be the cause. In fact, evidence indicates that alcohol itself is toxic to the testes.

Hematologic Abnormalities

Anemia is common among patients with liver disease. Contributing factors may include blood loss, folate (folic acid) deficiency, hemolysis, marrow suppression by alcohol, and a direct effect of chronic liver disease.

Leukopenia and **thrombocytopenia** often accompany splenomegaly in advanced portal hypertension.

Clotting and coagulation abnormalities are common and complex. Hepatocellular dysfunction and inadequate absorption of vitamin K may impair liver synthesis of clotting factors. An abnormal PT, depending on the severity of hepatocellular dysfunction, may respond to parenteral phytonadione (vitamin K_1) 5 to 10 mg once/day for 2 to 3 days. Thrombocytopenia, disseminated intravascular coagulation, and fibrinogen abnormalities also contribute to clotting disturbances in many patients.

Renal and Electrolyte Abnormalities

Renal and electrolyte abnormalities are common, especially among patients with ascites.

Hypokalemia may result from excess urinary K loss due to increased circulating aldosterone, renal retention of ammonium ion in exchange for K, secondary renal tubular acidosis, or diuretic therapy. Management consists of giving oral KCl supplements and withholding K-wasting diuretics.

Hyponatremia is common even though the kidneys may avidly retain Na (see Ascites on p. 206); it usually occurs with advanced hepatocellular disease and is difficult to correct. Relative water overload is more often responsible than total body Na depletion; K depletion may also contribute. Water restriction and K supplements may help; use of diuretics that increase free water clearance is controversial. Saline solution IV is indicated only if profound hyponatremia causes seizures or if total body Na depletion is

suspected; it should be avoided in patients with cirrhosis and fluid retention because it worsens ascites and only temporarily increases serum Na levels.

Advanced liver failure can alter acid-base balance, usually causing metabolic alkalosis. BUN levels are often low because of impaired liver synthesis; GI bleeding causes elevations because of an increased enteric load rather than renal impairment. When GI bleeding elevates BUN, normal creatinine values tend to confirm normal kidney function.

Renal failure in liver disease may reflect

• Rare disorders that directly affect both the kidneys and the liver (eg, carbon tetrachloride toxicity)

• Circulatory failure with decreased renal perfusion, with or without frank acute tubular necrosis

• Functional renal failure, often called hepatorenal syndrome

Hepatorenal syndrome: This syndrome consists of progressive oliguria and azotemia in the absence of structural damage to the kidney; it usually occurs in patients with fulminant hepatitis or advanced cirrhosis with ascites. Its unknown pathogenesis probably involves extreme vasodilation of the splanchnic arterial circulation, leading to decreased central arterial volume. Neural or humoral reductions in renocortical blood flow follow, resulting in a diminished glomerular filtration rate. Low urinary Na concentration and benign sediment usually distinguish it from tubular necrosis, but prerenal azotemia may be more difficult to distinguish; in equivocal cases, response to a volume load should be assessed.

Once established, renal failure due to hepatorenal syndrome is usually rapidly progressive and fatal (type 1 hepatorenal syndrome), although some cases are less severe, with stable low-grade renal insufficiency (type 2).

Liver transplantation is the only accepted treatment for type 1 hepatorenal syndrome; transjugular intrahepatic portosystemic shunting (TIPS) and vasoconstrictors show some promise, but more study is needed.

The Asymptomatic Patient With Abnormal Laboratory Test Results

Because aminotransferases and alkaline phosphatase are included in commonly done laboratory test panels, abnormalities are often detected in patients without symptoms or signs of liver disease. In such patients, the physician should obtain a history of exposure to possible liver toxins, including alcohol, prescription and nonprescription drugs, herbal teas and remedies, and occupational or other chemical exposures.

Aminotransferases: Mild isolated elevations of ALT or AST (< 2 times normal) may require only repeat testing; they resolve in about one third of cases. If abnormalities are present in other laboratory tests, are severe, or persist on subsequent testing, further evaluation is indicated as follows:

• Fatty liver should be considered; it can often be recognized clinically (see p. 211).

• Patients should be screened for hepatitis B and C (see p. 251).

• Patients > 40 should be screened for hemochromatosis (see p. 1032).

• Patients < 30 should be screened for Wilson's disease (see p. 51).

• Most patients, especially young or middle-aged women, should be screened for autoimmune disorders.

• Patients at risk should be screened for malaria and schistosomiasis.

If at this point the results are negative, screening for α_1-antitrypsin deficiency (see p. 1901) is indicated. If the entire evaluation reveals no cause, liver biopsy may be warranted.

Alkaline phosphatase: Isolated elevation of alkaline phosphatase levels in an asymptomatic patient requires confirmation of hepatic origin by showing elevation of 5´-nucleotidase or γ-glutamyl transpeptidase. If hepatic origin is confirmed, liver imaging, usually with ultrasonography or magnetic resonance cholangiopancreatography, is indicated. If no structural abnormality is found on imaging, intrahepatic cholestasis is possible and may be suggested by a history of exposure to drugs or toxins. Infiltrative diseases and liver metastases (eg, due to colon cancer) should also be considered. In women, antimitochondrial antibody should be obtained. Persistent unexplained elevations or suspicion of intrahepatic cholestasis warrants consideration of liver biopsy.

Postoperative Liver Dysfunction

Mild liver dysfunction sometimes occurs after major surgery even in the absence of preexisting liver disorders. This dysfunction usually results from hepatic ischemia or poorly understood effects of anesthesia. Patients with preexisting well-compensated liver disease (eg, cirrhosis with normal liver function) usually tolerate surgery well. However, surgery can increase the severity of some preexisting liver disorders; eg, laparotomy may precipitate acute liver failure in a patient with viral or alcoholic hepatitis.

Postoperative jaundice: Diagnosis of postoperative jaundice requires liver laboratory tests. Timing of symptoms also aids in diagnosis.

Multifactorial mixed hyperbilirubinemia is the most common reason for postoperative jaundice. It is caused by increased formation of bilirubin and decreased hepatic clearance. This disorder most often occurs after major surgery or trauma requiring multiple transfusions. Hemolysis, sepsis, resorption of hematomas, and blood transfusions can increase the bilirubin load; simultaneously, hypoxemia, hepatic ischemia, and other poorly understood factors impair hepatic function. This condition is usually maximal within a few days of operation. Hepatic insufficiency is rare, and hyperbilirubinemia typically resolves slowly but completely. Liver laboratory tests can often differentiate multifactorial mixed hyperbilirubinemia from hepatitis. In multifactorial mixed hyperbilirubinemia, severe hyperbilirubinemia with mild aminotransferase and alkaline phosphatase elevations are common. In hepatitis, aminotransferase levels are usually very high.

Postoperative hepatitis: Ischemic postoperative "hepatitis" results from insufficient liver perfusion, not inflammation. The cause is transient perioperative hypotension or hypoxia. Typically, aminotransferase levels increase rapidly (often > 1000 units/L), but bilirubin is only mildly elevated. Ischemic hepatitis is usually maximal within a few days of operation and resolves within a few days.

Halothane-related hepatitis can result from use of anesthetics containing halothane or related agents. It usually develops within 2 wk, is often preceded by fever, and is sometimes accompanied by a skin rash and eosinophilia.

True postoperative hepatitis is now rare. It used to result mainly from transmission of hepatitis C virus during blood transfusion.

Postoperative cholestasis: The most common cause of postoperative cholestasis is extrahepatic biliary obstruction due to intra-abdominal complications or drugs given postoperatively. Intrahepatic cholestasis occasionally develops after major surgery, especially after abdominal or cardiovascular procedures (benign postoperative intrahepatic cholestasis). The pathogenesis is unknown, but the condition usually resolves slowly and spontaneously. Occasionally, postoperative cholestasis results from acute acalculous cholecystitis or pancreatitis.

Chapter 24. Testing for Hepatic and Biliary Disorders

Introduction

Diagnosis of liver and biliary system disorders may include laboratory tests, imaging tests, and liver biopsy. Individual tests, particularly those of liver biochemistry and excretion, often have limited sensitivity and specificity. A combination of tests often best defines the cause and severity of disease. Useful algorithms (eg, Model of End-Stage Liver Disease [MELD], Child-Pugh score) have incorporated clinical and laboratory features to predict survival in patients with decompensated cirrhosis.

Laboratory Tests

Laboratory tests are generally effective for the following:

• Detecting hepatic dysfunction

• Assessing the severity of liver injury

• Monitoring the course of liver diseases and the response to treatment

• Refining the diagnosis

Many tests of liver biochemistry and excretory performance are called liver function tests. However, rather than assessing liver function, several of these tests measure liver enzymes that are released into the bloodstream (eg, release of aminotransferases from injured liver cells or of alkaline phosphatase due to cholestasis). Only certain tests actually assess liver function by evaluating hepatobiliary excretion (eg, bilirubin) or the liver's synthetic capability (eg, PT, usually reported as the INR; albumin).

The most useful laboratory tests to screen for liver disorders are serum aminotransferases (the most commonly used liver function tests), bilirubin, and alkaline phosphatase. Certain patterns of biochemical abnormalities help distinguish hepatocellular injury from impaired bile excretion (cholestasis—see Table 24-1). Tests that detect viral hepatitis, liver inflammation, or altered immunoregulation include hepatitis serologic tests (see p. 251) and measurement of immunoglobulins, antibodies, and autoantibodies.

A few laboratory tests are diagnostic by themselves; they include the following:

• IgM antibody to hepatitis A virus (anti-HAV) for acute hepatitis A

• Hepatitis B surface antigen (HBsAg) for hepatitis B

• Antibody to hepatitis C virus (anti-HCV) and HCV-RNA for hepatitis C

• Antimitochondrial antibody for primary biliary cirrhosis

• Serum ceruloplasmin (reduced) and urinary copper (elevated) for Wilson's disease

• Serum α_1-antitrypsin for α_1-antitrypsin deficiency

• α-Fetoprotein for hepatocellular carcinoma

Tests for Liver Injury

Aminotransferases: Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) leak from damaged cells; thus, these enzymes are sensitive indicators of liver injury. Markedly high values (> 500 IU/L; normal, ≤ 40 IU/L), which indicate acute hepatocellular necrosis or injury, usually result from the following:

• Acute viral hepatitis

• Toxin- or drug-induced hepatitis

• Ischemic hepatitis or hepatic infarction

High levels continue usually for days or, in viral hepatitis, for weeks. The degree of elevation may not reflect the extent of liver injury. Serial measurements better reflect severity and prognosis than does a single measurement. A fall to normal indicates recovery unless accompanied by an increase in bilirubin and in PT or INR (which indicates fulminant liver failure). Fulminant liver failure results in fewer liver cells that can leak enzymes.

Aminotransferase levels may also be markedly high in the following:

• Acute exacerbation of autoimmune hepatitis

• Reactivation of chronic hepatitis B

• Acute Budd-Chiari syndrome

• Acute fatty liver of pregnancy

• Passage of a common duct stone

Modest elevations (300 to 500 IU/L) persist in chronic liver disorders (eg, chronic hepatitis, alcoholic hepatitis) and in biliary obstruction, except when passage of a common duct stone can transiently result in markedly high levels, sometimes into the thousands.

Mild increases (< 300 IU/L) are nonspecific and often present in disorders such as

[**Table 24-1.** Common Patterns of Laboratory Test Abnormalities]

• Cirrhosis secondary to viral hepatitis

• Nonalcoholic fatty liver disease (NAFLD)

• Cholestatic liver disorders

• Hepatocellular cancer

Aminotransferases can be normal in certain liver disorders, such as

• Hemochromatosis

• Methotrexate- or amiodarone-induced liver injury

• Chronic hepatitis C

• NAFLD

Elevated ALT is somewhat specific for liver injury. Because AST is present in the heart, skeletal muscle, kidneys, and pancreas, elevated AST may reflect rhabdomyolysis or injury to one of these organs. In most liver disorders, the ratio of AST to ALT is < 1. However, in alcohol-related liver disease, the ratio is characteristically > 2 because pyridoxal-5´-phosphate is deficient in alcoholic patients; it is required for ALT synthesis but is less essential for AST synthesis. This deficiency also explains why elevations of ALT and AST are low (< 300 IU/L) in alcoholic patients.

Lactate dehydrogenase: LDH, commonly included in routine analysis, is present in many other tissues and is insensitive and nonspecific for hepatocellular injury. LDH is typically elevated in ischemic hepatitis and cancers that extensively infiltrate the liver.

Tests for Cholestasis

Bilirubin: Bilirubin, the pigment in bile, is produced from the breakdown of heme proteins, mostly from the heme moiety of hemoglobin in senescent RBCs. Unconjugated (free) bilirubin is insoluble in water and thus cannot be excreted in urine; most unconjugated bilirubin is bound to albumin in plasma. Bilirubin is conjugated in the liver with glucuronic acid to form the more water-soluble bilirubin diglucuronide. Conjugated bilirubin is then excreted through the biliary tract into the duodenum, where it is metabolized into urobilinogens (some of which are reabsorbed and resecreted into bile), then into orange-colored urobilins (most of which are eliminated in feces). These bile pigments give stool its typical color.

Hyperbilirubinemia results from one or more of the following:

• Increased bilirubin production

• Decreased liver uptake or conjugation

• Decreased biliary excretion (see p. 212)

Normally, total bilirubin is mostly unconjugated, with values of < 1.2 mg/dL (< 20 µmol/L). Fractionation measures the proportion of bilirubin that is conjugated (ie, direct, so-called because it is measured directly, without the need for solvents). Fractionation is most helpful for evaluating neonatal jaundice and for evaluating elevated bilirubin when other liver test results are normal, suggesting that hepatobiliary dysfunction is not the cause.

Unconjugated hyperbilirubinemia (indirect bilirubin fraction > 85%) reflects increased bilirubin production (eg, in hemolysis) or defective liver uptake or conjugation (eg, in Gilbert syndrome). Such increases in unconjugated bilirubin are usually < 5 times normal (to < 6 mg/dL [<100 µmol/L]) unless there is concurrent liver injury.

Conjugated hyperbilirubinemia (direct bilirubin fraction > 50%) results from decreased bile formation or excretion (cholestasis). When associated with other liver function test abnormalities, a high serum bilirubin indicates hepatocellular dysfunction. Serum bilirubin is somewhat insensitive for liver dysfunction. However, the development of severe hyperbilirubinemia in primary biliary cirrhosis, alcoholic hepatitis, and acute liver failure suggests a poor prognosis.

Bilirubinuria reflects the presence of conjugated bilirubin in urine; bilirubin spills into urine because blood levels are markedly elevated, indicating severe disease. Unconjugated bilirubin is water insoluble and bound to albumin and so cannot be excreted in urine. Bilirubinuria can be detected at the bedside with commercial urine test strips in acute viral hepatitis or other hepatobiliary disorders, even before jaundice appears. However, the diagnostic accuracy of such urine tests is limited. Results can be falsely negative when the urine specimen has been stored a long time, vitamin C has been ingested, or urine contains nitrates (eg, due to UTIs). Similarly, increases in urobilinogen are neither specific nor sensitive.

Alkaline phosphatase: Increased levels of this hepatocyte enzyme suggest cholestasis. Results may not be specific because alkaline phosphatase consists of several isoenzymes and has a widespread extrahepatic distribution (eg, in the placenta, the small intestine, WBCs, kidneys, and particularly bone).

Alkaline phosphatase levels increase to ≥ 4 times normal 1 to 2 days after onset of biliary obstruction, regardless of the site of obstruction. Levels may remain elevated for several days after the obstruction resolves because the half-life of alkaline phosphatase is about 7 days. Increases of up to 3 times normal occur in many liver disorders, including

• Hepatitis

• Cirrhosis

• Space-occupying lesions (eg, carcinoma)

• Infiltrative disorders (eg, amyloidosis, sarcoidosis, TB, metastases, abscesses)

• Syphilitic hepatitis (alkaline phosphatase may be disproportionately elevated compared with the modest changes in other liver tests)

Isolated elevations (ie, when other liver test results are normal) may accompany

• Focal liver lesions (eg, abscess, tumor)

• Partial or intermittent bile duct obstruction (eg, stone, stricture, cholangiocarcinoma)

• Syphilitic hepatitis

• Occasionally, infiltrative disorders

Isolated elevations also occur in the absence of any apparent liver or biliary disorder, as in the following:

• Some cancers without apparent liver involvement (eg, bronchogenic carcinoma, Hodgkin lymphoma, renal cell carcinoma)

• After ingestion of fatty meals (because of an enzyme produced in the small intestine)

• Pregnancy (because of an enzyme produced in the placenta)

• Children and adolescents who are still growing (because of bone growth)

• Chronic renal failure (because of an enzyme produced in the intestine and bone)

Levels of γ-glutamyl transpeptidase or 5´-nucleotidase, which are more specific to the liver, can differentiate hepatic from extrahepatic sources of alkaline phosphatase better than fractionation of alkaline phosphatase, which is technically difficult. Also, in otherwise asymptomatic elderly people, an increase in alkaline phosphatase usually originates in bone (eg, in Paget's disease) and does not require further investigation for liver injury.

5´-Nucleotidase: Increases in levels of this enzyme are as sensitive as alkaline phosphatase for detecting cholestasis and biliary obstruction but are more specific, almost always indicating hepatobiliary dysfunction. Because levels of alkaline phosphatase and 5´-nucleotidase do not always correlate, one can be normal while the other is increased.

γ-Glutamyl transpeptidase (GGT): Levels of this enzyme increase in hepatobiliary dysfunction, especially cholestasis, and correlate loosely with levels of alkaline phosphatase and 5´-nucleotidase. Levels do not increase because of bone lesions, during childhood, or during pregnancy. However, alcohol and certain drugs (eg, some anticonvulsants, warfarin) can induce hepatic microsomal (cytochrome P-450) enzymes, markedly increasing GGT and thus somewhat limiting its specificity.

Tests of Hepatic Synthetic Capacity

PT and INR: PT may be expressed in time (sec) or, preferably, as a ratio of the patient's measured PT to the laboratory's control value (INR—see p. 971). The INR is more accurate than PT for monitoring anticoagulation. PT or INR is a valuable measure of the liver's ability to synthesize fibrinogen and vitamin K-dependent clotting factors: factors II (prothrombin), V, VII, and X. Changes can occur rapidly because some of the involved clotting factors have short biologic half-lives (eg, 6 h for factor VII). Abnormalities indicate severe hepatocellular dysfunction, an ominous sign in acute liver disorders. In chronic liver disorders, an increasing PT or INR indicates progression to liver failure. The PT or INR does not increase

in mild hepatocellular dysfunction and is often normal in cirrhosis.

A prolonged PT and an abnormal INR can result from coagulation disorders such as a consumptive coagulopathy or vitamin K deficiency. Fat malabsorption, including cholestasis, can cause vitamin K deficiency. In chronic cholestasis, marked hepatocellular dysfunction can be ruled out if vitamin K replacement (10 mg sc) corrects PT by ≥ 30% within 24 h.

Serum proteins: Hepatocytes synthesize most serum proteins, including α- and β-globulins, albumin, and most clotting factors (but not factor VIII, produced by the vascular endothelium, or γ-globulin, produced by B cells). Hepatocytes also make proteins that aid in the diagnosis of specific disorders:

• α_1-Antitrypsin (absent in α_1-antitrypsin deficiency)

• Ceruloplasmin (reduced in Wilson's disease)

• Transferrin (saturated with iron in hemochromatosis)

• Ferritin (greatly increased in hemochromatosis)

These proteins usually increase in response to damage (eg, inflammation) to various tissues, so that elevations may not specifically reflect liver disorders.

Serum albumin commonly decreases in chronic liver disorders because of an increase in volume of distribution (eg, due to ascites), a decrease in hepatic synthesis, or both. Values < 3 g/dL (< 30 g/L) suggest decreased synthesis, caused by one of the following:

• Advanced cirrhosis (the most common cause)

• Alcoholism

• Chronic inflammation

• Protein undernutrition

Hypoalbuminemia can also result from excessive loss of albumin from the kidneys (ie, nephrotic syndrome), gut (eg, due to proteinlosing gastroenteropathies), or skin (eg, due to burns or exfoliative dermatitis).

Because albumin has a half-life of about 20 days, serum levels take weeks to increase or decrease.

Other Laboratory Tests

Ammonia: Nitrogen compounds that enter the colon (eg, ingested protein, secreted urea) are degraded by resident bacteria, liberating ammonia. The ammonia is then absorbed and transported via the portal vein to the liver. The healthy liver readily clears the ammonia from the portal vein and converts it to glutamine, which is metabolized by the kidneys into urea to be excreted. In patients with portal-systemic shunting, the diseased liver does not clear ammonia, which then enters the systemic circulation, possibly contributing to portal-systemic (hepatic) encephalopathy. Elevated ammonia levels occur in hepatic encephalopathy, but levels may be falsely low or high. In advanced liver disorders, the following may increase ammonia levels:

• High-protein meals

• GI bleeding

• Hypokalemia

• Metabolic alkalosis

- Certain drugs (eg, alcohol, barbiturates, diuretics, opioids, valproate)
- High-dose chemotherapy
- Parenteral nutrition
- Renal insufficiency
- Extreme muscle exertion and muscle wasting
- Salicylate intoxication
- Shock
- Ureterosigmoidostomy

UTI with a urease-producing organism (eg, *Proteus mirabilis*)

Because the degree of elevation in the ammonia level correlates poorly with severity of hepatic encephalopathy, this level has limited usefulness in monitoring therapy.

Serum immunoglobulins: In chronic liver disorders, serum immunoglobulins often increase. However, elevations are not specific and are usually not helpful clinically. Levels increase slightly in acute hepatitis, moderately in chronic active hepatitis, and markedly in autoimmune hepatitis. The pattern of immunoglobulin elevation adds little information, although different immunoglobulins are usually very high in different disorders:

- IgM in primary biliary cirrhosis
- IgA in alcoholic liver disease
- IgG in autoimmune hepatitis

Antimitochondrial antibodies: These heterogeneous antibodies are positive, usually in high titers, in > 95% of patients with primary biliary cirrhosis. They are also occasionally present in the following:

- Autoimmune hepatitis
- Drug-induced hepatitis
- Other autoimmune disorders, such as connective tissue disorders, myasthenia gravis, autoimmune thyroiditis, Addison's disease, and autoimmune hemolytic anemia

Antimitochondrial antibodies can help determine the cause of cholestasis because they are usually absent in extrahepatic biliary obstruction and primary sclerosing cholangitis.

Other antibodies: Other antibodies may help in diagnosis of the following:

- Autoimmune hepatitis: Smooth muscle antibodies against actin, antinuclear antibodies (ANA) that provide a homogeneous (diffuse) fluorescence, and antibodies to liver-kidney microsome type 1 (anti-LKM1) are often present.
- Primary biliary cirrhosis: Antimitochondrial antibody is key to the diagnosis.
- Primary sclerosing cholangitis: Perinuclear antineutrophil cytoplasmic antibodies (p-ANCA) can help raise the index of suspicion.

Isolated abnormalities of any of these antibodies are never diagnostic and do not elucidate pathogenesis.

α-Fetoprotein (AFP): AFP, a glycoprotein normally synthesized by the yolk sac in the embryo and then by the fetal liver, is elevated in neonates and hence the pregnant mother. AFP decreases rapidly during the first year of life, reaching adult values (normally, < 10 to 20 ng/mL or < 10 to 20 mg/L depending on the laboratory) by the age of 1 yr. An increase in AFP, no matter how small, should prompt consideration of primary hepatocellular carcinoma (HCC). Serum AFP generally correlates with tumor size, differentiation and metastatic involvement. Because small tumors may produce low levels of AFP, increasing values suggest the presence of HCC, especially when tumors are > 3 cm diameter. AFP also helps predict prognosis.

Mild AFP elevations also occur in acute and chronic hepatitis, probably reflecting liver regeneration; AFP can occasionally increase to 500 ng/mL in fulminant hepatitis. High AFP levels can occur in a few other disorders (eg, embryonic teratocarcinomas, hepatoblastomas in children, some hepatic metastases from GI tract cancers, some cholangiocarcinomas), but these circumstances are not common and usually can be differentiated based on clinical and histopathologic grounds.

Sensitivity, specificity, and peak levels of AFP in patients with HCC vary by population, reflecting differences in factors such as hepatitis prevalence and ethnicity. In areas with a relatively low prevalence of hepatitis (eg, North America and western Europe), AFP cutoff values of 20 ng/mL have a sensitivity of 39 to 64% and a specificity of 76 to 91%. However, not all HCCs produce AFP. Thus, AFP is not an ideal screening test but does have a role in detecting HCC. Levels exceeding normal (> 20 ng/mL), especially when increasing, strongly suggest HCC. In cirrhotic patients with a mass and a high value (eg, > 200 ng/mL), the predictive value is high. The combined use of AFP and ultrasonography currently provides the best surveillance.

Imaging Tests

Imaging is essential for accurately diagnosing biliary tract disorders and is important for detecting focal liver lesions (eg, abscess, tumor). It is limited in detecting and diagnosing diffuse hepatocellular disease (eg, hepatitis, cirrhosis).

Ultrasonography: Ultrasonography, traditionally done transabdominally and requiring a period of fasting, provides structural, but not functional, information. It is the least expensive, safest, and most sensitive technique for imaging the biliary system, especially the gallbladder. Ultrasonography is the procedure of choice for

• Screening for biliary tract abnormalities

• Evaluating the hepatobiliary tract in patients with right upper quadrant abdominal pain

• Differentiating intrahepatic from extrahepatic causes of jaundice

• Detecting liver masses

The kidneys, pancreas, and blood vessels are also often visible on hepatobiliary ultrasounds. Ultrasonography can measure spleen size and thus help diagnose splenomegaly, which suggests portal hypertension.

Use of endoscopic ultrasonography may further refine the approaches to hepatobiliary abnormalities.

Ultrasonography can be difficult in patients with intestinal gas or obesity and is operator-dependent. Endoscopic ultrasonography incorporates an ultrasound transducer into the tip of an endoscope and thus provides greater image resolution even when intestinal gas is present.

Gallstones cast intense echoes with distal acoustic shadowing that move with gravity. Transabdominal ultrasonography is extremely accurate (sensitivity > 95%) for gallstones > 2 mm in diameter. Endoscopic ultrasonography can detect stones as small as 0.5 mm (microlithiasis) in the gallbladder or biliary system.

Transabdominal and endoscopic ultrasonography can also identify biliary sludge (a mixture of particulate material and bile) as low-level echoes that layer in the dependent portion of the gallbladder without acoustic shadowing.

Cholecystitis typically causes

• A thickened gallbladder wall (> 3 mm)

• Pericholecystic fluid

• An impacted stone in the gallbladder neck

• Tenderness on palpation of the gallbladder with the ultrasound probe (ultrasonographic Murphy's sign)

Extrahepatic obstruction is indicated by dilated bile ducts. On transabdominal and endoscopic ultrasounds, bile ducts stand out as echo-free tubular structures. The diameter of the common duct is normally < 6 mm, increases slightly with age, and can reach 10 mm after cholecystectomy. Dilated ducts are virtually pathognomonic for extrahepatic obstruction in the appropriate clinical setting. Ultrasonography can miss early or intermittent obstruction that does not dilate the ducts. Transabdominal ultrasonography may not reveal the level or cause of biliary obstruction (eg, sensitivity for common duct stones is < 40%). Endoscopic ultrasonography has a better yield.

Focal liver lesions > 1 cm in diameter can usually be detected by transabdominal ultrasonography. In general, cysts are echo-free; solid lesions (eg, tumors, abscesses) tend to be echogenic. Carcinoma appears as a nonspecific solid mass. Ultrasonography has been used to screen for hepatocellular carcinoma in patients at high risk (eg, with chronic hepatitis B, cirrhosis, or hemochromatosis). Because ultrasonography can localize focal lesions, it can be used to guide aspiration and biopsy.

Diffuse disorders (eg, cirrhosis, sometimes fatty liver) can be detected with ultrasonography. Ultrasound elastography can measure liver stiffness as an index of hepatic fibrosis. In this procedure, the transducer emits a vibration that induces an elastic shear wave. The rate at which the wave is propagated through the liver is measured; liver stiffness speeds this propagation.

Doppler ultrasonography: This noninvasive method is used to assess direction of blood flow and patency of blood vessels around the liver, particularly the portal vein. Clinical uses include

• Detecting portal hypertension, (eg, indicated by significant collateral flow and the direction of flow)

• Assessing the patency of liver shunts (eg, surgical portocaval, percutaneous transhepatic)

• Evaluating portal vein patency before liver transplantation and detecting hepatic artery thrombosis after transplantation

• Detecting unusual vascular structures (eg, cavernous transformation of the portal vein)

• Assessing tumor vascularity before surgery

CT: CT is commonly used to identify hepatic masses, particularly small metastases, with an accuracy of about 80%. It is considered the most accurate imaging technique. CT with IV contrast is accurate for diagnosing cavernous hemangiomas of the liver as well as differentiating them from other abdominal masses. Neither obesity nor intestinal gas obscures CT images. CT can detect fatty liver and the increased hepatic density that occurs with iron overload. CT is less helpful than ultrasonography in identifying biliary obstruction but often provides the best assessment of the pancreas.

Cholescintigraphy: After patients fast, an IV technetium-labeled iminodiacetic compound (eg, hydroxy or diisopropyl iminodiacetic acid [HIDA or DISIDA]) is injected; these substances are taken up by the liver and excreted in bile, then enter the gallbladder.

In acute calculous cholecystitis, which is usually caused by impaction of a stone in the cystic duct, the gallbladder does not appear on a scintigraphic scan because the radionuclide cannot enter the gallbladder. Such nonvisualization is diagnostically quite accurate (except for false-positive results in some critically ill patients). However, cholescintigraphy is rarely needed clinically to diagnose acute cholecystitis.

If acalculous cholecystitis is suspected, the gallbladder is scanned before and after administration of cholecystokinin (used to initiate gallbladder contraction). The decrease in scintigraphic counts indicates the gallbladder ejection fraction. Reduced emptying, measured as the ejection fraction, suggests acalculous cholecystitis.

Cholescintigraphy also detects bile leaks (eg, after surgery or trauma) and anatomic abnormalities (eg, congenital choledochal cysts, choledochoenteric anastomoses). After cholecystectomy, cholescintigraphy can quantitate biliary drainage; biliary drainage helps identify sphincter of Oddi dysfunction.

Radionuclide liver scanning: Ultrasonography and CT have largely supplanted radionuclide scanning, which had been used to diagnose diffuse liver disorders and mass lesions of the liver. Radionuclide scanning shows the distribution of an injected radioactive tracer, usually technetium (^{99m}Tc sulfur colloid), which distributes uniformly within the normal liver. Space-occupying lesions > 4 cm, such as liver cysts, abscesses, metastases, and tumors, appear as defects. Diffuse liver disorders (eg, cirrhosis, hepatitis) decrease liver uptake of the tracer, with more appearing in the spleen and bone marrow. In hepatic vein obstruction (Budd-Chiari syndrome), liver uptake is decreased except in the caudate lobe because its drainage into the inferior vena cava is preserved.

Plain x-ray of the abdomen: Plain x-rays are not usually useful for diagnosis of hepatobiliary disorders. They are insensitive for gallstones unless the gallstones are calcified and large. Plain x-rays can detect a calcified (porcelain) gallbladder. Rarely, in gravely ill patients, x-rays show air in the biliary tree, which suggests emphysematous cholangitis.

MRI: MRI images blood vessels (without using contrast), ducts, and hepatic tissues. Its clinical uses are still evolving. MRI is superior to CT and ultrasonography for diagnosing diffuse liver disorders (eg, fatty liver, hemochromatosis) and for clarifying some focal defects (eg, hemangiomas). MRI also shows blood flow and therefore complements Doppler ultrasonography and CT angiography in the diagnosis of vascular abnormalities and in vascular mapping before liver transplantation.

Magnetic resonance cholangiopancreatography (MRCP) is more sensitive than CT or ultrasonography in diagnosing common bile duct abnormalities, particularly stones. Its images of the biliary system and pancreatic ducts are comparable to those obtained with ERCP and percutaneous transhepatic cholangiography, which are more invasive. Thus, MRCP is a useful screening tool when biliary obstruction is suspected and before therapeutic ERCP (eg, for simultaneous imaging and stone removal) is done.

ERCP: ERCP combines endoscopy through the second portion of the duodenum with contrast imaging of the biliary and pancreatic ducts. The papilla of Vater is cannulated through an endoscope placed in the descending duodenum, and the pancreatic and biliary ducts are then injected with a contrast agent.

ERCP provides detailed images of much of the upper GI tract and the periampullary area, biliary tract, and pancreas. ERCP can also be used to obtain tissue for biopsy. ERCP is the best test for diagnosis of ampullary cancers. ERCP is as accurate as endoscopic ultrasonography for diagnosis of common duct stones. Because it is invasive, ERCP is used more for treatment (including simultaneous diagnosis and treatment) than for diagnosis alone. ERCP is the procedure of choice for treating biliary and pancreatic obstructing lesions, as for

- Removal of bile duct stones
- Stenting of strictures (inflammatory or malignant)
- Sphincterotomy (eg, for sphincter of Oddi dysfunction)

Morbidity from a diagnostic ERCP with only injection of contrast material is about 1%. Adding sphincterotomy raises morbidity to 4 to 9% (mainly due to pancreatitis and bleeding). ERCP with manometry to measure sphincter of Oddi pressure causes pancreatitis in up to 25% of patients.

Percutaneous transhepatic cholangiography (PTC): With fluoroscopic or ultrasound guidance, the liver is punctured with a needle, the peripheral intrahepatic bile duct system is cannulated above the common hepatic duct, and a contrast agent is injected.

PTC is highly accurate in diagnosing biliary disorders and can be therapeutic (eg, decompression of the biliary system, insertion of an endoprosthesis). However, ERCP is usually preferred because PTC causes more complications (eg, sepsis, bleeding, bile leaks).

Operative cholangiography: A contrast agent is directly injected during laparotomy to image the bile duct system.

Operative cholangiography is indicated when jaundice occurs and noninvasive procedures are equivocal, suggesting common duct stones. The procedure can be followed by common duct exploration for removal of biliary stones. Technical difficulties have limited its use, particularly during laparoscopic cholecystectomy.

Liver Biopsy

Liver biopsy provides histologic information about liver structure and evidence of liver injury (type and degree, any fibrosis); this information can be essential not only to diagnosis but also to staging, prognosis, and management. Although only a small core of tissue is obtained, it is usually representative, even for focal lesions.

Liver biopsy is usually done percutaneously at the bedside or with ultrasound guidance. Ultrasound guidance is preferred because its complication rate is slightly lower and it provides opportunity to visualize the liver and target focal lesions.

Indications: Generally, biopsy is indicated for suspected liver abnormalities that are not identified by less invasive methods or that require histopathology for staging (see Table 24-2). Biopsy is especially valuable

[**Table 24-2.** Indications for Liver Biopsy*]

for detecting TB or other granulomatous infiltrations and for clarifying graft problems (ischemic injury, rejection, biliary tract disorders, viral hepatitis) after liver transplantation. Serial biopsies, commonly done over years, may be necessary to monitor disease progression.

Gross examination and histopathology are often definitive. Cytology (fine-needle aspiration), frozen section, and culture may be useful for selected patients. Metal content (eg, copper in suspected Wilson's disease, iron in hemochromatosis) can be measured in the biopsy specimen.

Limitations of liver biopsy include

• Sampling error

• Occasional errors or uncertainty in cases of cholestasis

• Need for a skilled histopathologist (some pathologists have little experience with needle specimens)

Contraindications: Absolute contraindications to liver biopsy include

• Patient's inability to remain still and to maintain brief expiration for the procedure

- Suspected vascular lesion (eg, hemangioma)

- Bleeding tendency (eg, INR > 1.2 despite receiving vitamin K, bleeding time > 10 min)

- Severe thrombocytopenia (< 50,000/mL)

Relative contraindications include profound anemia, peritonitis, marked ascites, high-grade biliary obstruction, and a subphrenic or right pleural infection or effusion. Nonetheless, percutaneous liver biopsy is sufficiently safe to be done on an outpatient basis. Mortality is 0.01%. Major complications (eg, intra-abdominal hemorrhage, bile peritonitis, lacerated liver) develop in about 2% of patients. Complications usually become evident within 3 to 4 h—the recommended period for monitoring patients.

Other routes: Transjugular venous biopsy of the liver is more invasive than the percutaneous route; it is reserved for patients with a severe coagulopathy. The procedure involves cannulating the right internal jugular vein and passing a catheter through the inferior vena cava into the hepatic vein. A fine needle is then advanced through the hepatic vein into the liver. Biopsy is successful in > 95% of patients. Complication rate is low; 0.2% bleed from puncture of the liver capsule.

Occasionally, liver biopsy is done during surgery (eg, laparoscopy); a larger, more targeted tissue sample can then be obtained.

Chapter 25. Drugs and the Liver

Introduction

Interaction between drugs and the liver can be categorized as follows:

• Effects of liver disease on drug metabolism

• Liver injury caused by drugs

• Effects of hepatic drug metabolism (eg, induction of hepatic enzymes, see p. 3177)

The number of possible interactions is vast.

Effects of Liver Disease on Drug Metabolism

Liver disease may have complex effects on drug clearance, biotransformation, and pharmacokinetics. Pathogenetic factors include alterations in intestinal absorption, plasma protein binding, hepatic extraction ratio, liver blood flow, portal-systemic shunting, biliary excretion, enterohepatic circulation, and renal clearance. Sometimes alterations increase levels of bioavailable drug, causing normal drug doses to have toxic effects. However, levels and effects for an individual drug are unpredictable and do not correlate well with the type of liver injury, its severity, or liver function test results. Thus, no general rules are available for modifying drug dosage in patients with liver disease.

Clinical effects can vary independent of drug bioavailability, especially in chronic liver disease; eg, cerebral sensitivity to opioids and sedatives is often enhanced in patients with chronic liver disease. Thus, seemingly small doses of these drugs given to cirrhotic patients may precipitate encephalopathy. The mechanism of this effect probably involves alterations in cerebral drug receptors.

Adverse drug reactions do not appear to be more likely in patients with advanced liver disease; however, such patients may tolerate any hepatic adverse effects of drugs less well.

Liver Injury Caused by Drugs

Many drugs (eg, statins) commonly cause asymptomatic elevation of hepatic enzymes (ALT, AST, alkaline phosphatase). However, clinically significant liver injury (eg, with jaundice, abdominal pain, or pruritus) or impaired liver function—ie, resulting in deficient protein synthesis (eg, with prolonged PT or with hypoalbuminemia)—is rare.

The term drug-induced liver injury (DILI) may be used to mean clinically significant liver injury or all (including asymptomatic) liver injury. DILI includes injury caused by medicinal herbs, plants, and nutritional supplements as well as drugs.

Pathophysiology

The pathophysiology of DILI varies depending on the drug (or other hepatotoxin) and, in many cases, is not entirely understood. Drug-induced injury mechanisms include covalent binding of the drug to cellular proteins resulting in immune injury, inhibition of cell metabolic pathways, blockage of cellular transport pumps, induction of apoptosis, and interference with mitochondrial function.

In general, the following are thought to increase risk of DILI:

• Age ≥ 18 yr

• Obesity

• Pregnancy

• Concomitant alcohol consumption

• Genetic polymorphisms (increasingly recognized)

Patterns of liver injury: DILI can be predictable (when injury usually occurs shortly after exposure and is dose-related) or unpredictable (when injury develops after a period of latency and has no relation to dose). Predictable DILI (commonly, acetaminophen-induced) is a common cause of acute jaundice and acute liver failure in the US. Unpredictable DILI is a rare cause of severe liver disease. Subclinical DILI may be underreported.

Biochemically, 3 types of liver injury are generally noted (see Table 25-1):

• **Hepatocellular:** Hepatocellular hepatotoxicity generally manifests as malaise and

[**Table 25-1.** Potentially Hepatotoxic Drugs]

right upper quadrant abdominal pain, associated with marked elevation in aminotransferase levels (ALT, AST, or both), which may be followed by hyperbilirubinemia in severe cases. Hyperbilirubinemia in this setting is known as hepatocellular jaundice and, according to Hy's law, is associated with mortality rates as high as 50%. If hepatocellular liver injury is accompanied by jaundice, impaired hepatic synthesis, and encephalopathy, chance of spontaneous recovery is low, and liver transplantation should be considered. This type of injury can result from drugs such as acetaminophen and isoniazid.

• **Cholestatic:** Cholestatic hepatotoxicity is characterized by development of pruritus and jaundice accompanied by marked elevation of serum alkaline phosphatase levels. Usually, this type of injury is less serious than severe hepatocellular syndromes, but recovery may be protracted. Substances known to lead to this type of injury include amoxicillin/clavulanate and chlorpromazine. Rarely, cholestatic hepatotoxicity leads to chronic liver disease and vanishing bile duct syndrome (progressive destruction of intrahepatic bile ducts).

• **Mixed:** In these clinical syndromes, neither aminotransferase nor alkaline phosphatase elevations are clearly predominant. Symptoms may also be mixed. Drugs such as phenytoin can cause this type of injury.

Diagnosis

• Identification of characteristic patterns of laboratory abnormalities

• Exclusion of other causes

Presentation varies widely, ranging from absent or nonspecific symptoms (eg, malaise, nausea, anorexia) to jaundice, impaired hepatic synthesis, and encephalopathy. Early recognition of DILI improves prognosis.

Identification of a potential hepatotoxin and a pattern of liver test abnormalities that is characteristic of the substance (its signature) make the diagnosis likely.

Because there is no confirmatory diagnostic test, other causes of liver disease, especially viral, biliary, alcoholic, autoimmune, and metabolic causes, need to be excluded. Drug rechallenge, although it can strengthen evidence for the diagnosis, should usually be avoided. Suspected cases of DILI should be reported to MedWatch (the FDA's adverse drug reaction monitoring program).

Treatment

• Early drug withdrawal

Management emphasizes drug withdrawal, which, if done early, usually results in recovery. In severe

cases, consultation with a specialist is indicated, especially if patients have hepatocellular jaundice and impaired liver function, because liver transplantation may be required. Antidotes for DILI are available for only a few hepatotoxins; such antidotes include *N*-acetylcysteine for acetaminophen toxicity and silymarin or penicillin for *Amanita phalloides* toxicity.

Prevention

Efforts to avoid DILI begin during the drug development process, although apparent safety in small preclinical trials does not ensure eventual safety of the drug after it is in widespread use. Postmarketing surveillance, although often voluntary in the US, can call attention to potentially hepatotoxic drugs. Routine monitoring of liver enzymes has not been shown to decrease the incidence of hepatotoxicity. Use of pharmacogenomics may allow tailoring of drug use and avoidance of potential toxicities in susceptible patients.

Chapter 26. Alcoholic Liver Disease

Alcohol consumption is high in most Western countries. In the US, > 10% of people abuse or are dependent on alcohol. The male:female ratio is about 2:1. Disorders that occur in alcohol abusers, often in sequence, include

• Fatty liver (in > 90%)

• Alcoholic hepatitis (in 10 to 35%)

• Cirrhosis (in 10 to 20%)

Hepatocellular carcinoma may also develop, especially in association with iron accumulation.

Risk Factors

The main causative factors in alcoholic liver disease are

• Quantity and duration of alcohol use (usually > 8 yr)

• Sex

• Genetic and metabolic traits

• Nutritional status

Quantity of alcohol: Among susceptible people, a linear correlation generally exists between the amount and duration of alcohol use and the development of liver disease.

Alcohol content is estimated to be the beverage volume (in mL) multiplied by its percentage of alcohol. For example, the alcohol content of 40 mL of an 80-proof (40% alcohol) beverage is 16 mL by volume. Each mL contains about 0.79 g of alcohol. Although values can vary, the percentage of alcohol averages 2 to 7% for most beers and 10 to 15% for most wines. Thus, a 12-oz glass of beer contains about 3 to 10 g of alcohol, and an 8-oz glass of wine contains about 10 to 15 g.

Risk increases markedly for men who drink > 40 g, particularly > 80 g, of alcohol/day for > 10 yr (eg, 3 to 6 cans of beer, 3 to 6 shots of hard liquor, 4 to 8 glasses of wine). For cirrhosis to develop, consumption must usually be > 80 g/day for > 10 yr. If consumption exceeds 230 g/day for 20 yr, risk of cirrhosis is about 50%. But only some chronic alcohol abusers develop liver disease. Thus, variations in alcohol intake do not fully explain variations in susceptibility, indicating that other factors are involved.

Sex: Women are more susceptible to alcoholic liver disease, even after adjustment for body size. Women require only 20 to 40 g of alcohol to be at risk—half of that for men. Risk in women may be increased because they have less alcohol dehydrogenase in their gastric mucosa; thus, first-pass oxidation of alcohol is decreased.

Genetic factors: Alcoholic liver disease often runs in families, suggesting genetic factors (eg, deficiency of cytoplasmic enzymes that eliminate alcohol).

Nutritional status: Undernutrition, particularly protein-energy undernutrition, increases susceptibility, as does a diet high in unsaturated fat and obesity.

Other factors: Other risk factors include iron accumulation in the liver (not necessarily related to iron intake) and concomitant hepatitis C.

Pathophysiology

Alcohol absorption and metabolism: Alcohol (ethanol) is readily absorbed from the stomach, but most

is absorbed from the small intestine. Alcohol cannot be stored. A small amount is degraded in transit through the gastric mucosa, but most is catabolized in the liver, primarily by alcohol dehydrogenase (ADH) but also by cytochrome P-450 2E1 (CYP2E1) and the microsomal enzyme oxidation system (MEOS).

Metabolism via the ADH pathway involves the following:

- ADH, a cytoplasmic enzyme, oxidizes alcohol into acetaldehyde. Genetic polymorphisms in ADH account for some individual differences in blood alcohol levels after the same alcohol intake but not in susceptibility to alcoholic liver disease.

- Acetaldehyde dehydrogenase (ALDH), a mitochondrial enzyme, then oxidizes acetaldehyde to acetate. Chronic alcohol consumption enhances acetate formation. Asians, who have lower levels of ALDH, are more susceptible to toxic acetaldehyde effects (eg, flushing); the effects are similar to those of disulfiram, which inhibits ALDH.

- These oxidative reactions generate hydrogen, which converts nicotinamide-adenine dinucleotide (NAD) to its reduced form (NADH), increasing the redox potential (NADH/NAD) in the liver.

- The increased redox potential inhibits fatty acid oxidation and gluconeogenesis, promoting fat accumulation in the liver.

Chronic alcoholism induces the MEOS (mainly in endoplasmic reticulum), increasing its activity. The main enzyme involved is CYP2E1. When induced, the MEOS pathway can account for 20% of alcohol metabolism. This pathway generates harmful reactive O_2 species, increasing oxidative stress and formation of O_2-free radicals.

Hepatic fat accumulation: Fat (triglycerides) accumulates throughout the hepatocytes for the following reasons:

- Export of fat from the liver is decreased because hepatic fatty acid oxidation and lipoprotein production decrease.

- Input of fat is increased because the decrease in hepatic fat export increases peripheral lipolysis and triglyceride synthesis, resulting in hyperlipidemia.

Hepatic fat accumulation may predispose to subsequent oxidative damage.

Endotoxins in the gut: Alcohol changes gut permeability, increasing absorption of endotoxins released by bacteria in the gut. In response to the endotoxins (which the impaired liver can no longer detoxify), liver macrophages (Kupffer cells) release free radicals, increasing oxidative damage.

Oxidative damage: Oxidative stress is increased by

- Liver hypermetabolism, caused by alcohol consumption

- Free radical-induced lipid peroxidative damage

- Reduction in protective antioxidants (eg, glutathione, vitamins A and E), caused by alcohol-related undernutrition

- Binding of alcohol oxidation products, such as acetaldehyde, to liver cell proteins, forming neoantigens and resulting in inflammation

- Accumulation of neutrophils and other WBCs, which are attracted by lipid peroxidative damage and neoantigens

- Inflammatory cytokines secreted by WBCs

Accumulation of hepatic iron, if present, aggravates oxidative damage. Iron can accumulate in alcoholic liver disease through ingestion of iron-containing fortified wines; most often, the iron accumulation is modest. This condition must be differentiated from hereditary hemochromatosis.

Resultant inflammation, cell death, and fibrosis: A vicious circle of worsening inflammation occurs: Cell necrosis and apoptosis result in hepatocyte loss, and subsequent attempts at regeneration result in fibrosis. Stellate (Ito) cells, which line blood channels (sinusoids) in the liver, proliferate and transform into myofibroblasts, producing an excess of type I collagen and extracellular matrix. As a result, the sinusoids narrow, limiting blood flow. Fibrosis narrows the terminal hepatic venules, compromising hepatic perfusion and thus contributing to portal hypertension. Extensive fibrosis is associated with an attempt at regeneration, resulting in liver nodules. This process culminates in cirrhosis.

Pathology

Fatty liver, alcoholic hepatitis, and cirrhosis are often considered separate, progressive manifestations of alcoholic liver disease. However, their features often overlap.

Fatty liver (steatosis) is the initial and most common consequence of excessive alcohol consumption. Fatty liver is potentially reversible. Macrovesicular fat accumulates as large droplets of triglyceride and displaces the hepatocyte nucleus, most markedly in perivenular hepatocytes. The liver enlarges.

Alcoholic hepatitis (steatohepatitis) is a combination of fatty liver, diffuse liver inflammation, and liver necrosis (often focal)—all in various degrees of severity. The damaged hepatocytes are swollen with a granular cytoplasm (balloon degeneration) or contain fibrillar protein in the cytoplasm (Mallory or alcoholic hyaline bodies). Severely damaged hepatocytes become necrotic. Sinusoids and terminal hepatic venules are narrowed. Cirrhosis may also be present.

Alcoholic cirrhosis is advanced liver disease characterized by extensive fibrosis that disrupts the normal liver architecture. The amount of fat present varies. Alcoholic hepatitis may coexist. The feeble compensatory attempt at hepatic regeneration produces relatively small nodules (micronodular cirrhosis). As a result, the liver usually shrinks. In time, even with abstinence, fibrosis forms broad bands, separating liver tissue into large nodules (macronodular cirrhosis—see p. 241).

Symptoms and Signs

Symptoms usually become apparent in patients during their 30s or 40s; severe problems appear about a decade later.

Fatty liver is often asymptomatic. In one third of patients, the liver is enlarged and smooth, but it is not usually tender.

Alcoholic hepatitis ranges from mild and reversible to life threatening. Most patients with moderate disease are undernourished and present with fatigue, fever, jaundice, right upper quadrant pain, tender hepatomegaly, and sometimes a hepatic bruit. About 40% deteriorate soon after hospitalization, with consequences ranging from mild (eg, increasing jaundice) to severe (eg, ascites, portal-systemic encephalopathy, variceal bleeding, liver failure with hypoglycemia, coagulopathy). Other manifestations of cirrhosis may be present.

Cirrhosis, if compensated, may be asymptomatic. The liver is usually small; when the liver is enlarged, fatty liver or hepatoma should be considered. Symptoms range from those of alcoholic hepatitis to the complications of end-stage liver disease, such as portal hypertension (often with esophageal varices and upper GI bleeding, splenomegaly, ascites, and portal-systemic encephalopathy). Portal hypertension may lead to intrapulmonary arteriovenous shunting with hypoxemia (hepatopulmonary syndrome), which may cause cyanosis and nail clubbing. Acute renal failure secondary to progressively decreasing renal blood flow (hepatorenal syndrome) may develop. Hepatocellular carcinoma develops in 10 to 15% of patients with alcoholic cirrhosis.

Chronic alcoholism, rather than liver disease, causes Dupuytren's contracture of the palmar fascia,

vascular spiders, and peripheral neuropathy. In men, chronic alcoholism causes signs of hypogonadism and feminization (eg, smooth skin, lack of male-pattern baldness, gynecomastia, testicular atrophy, changes in pubic hair). Undernutrition may lead to multiple vitamin deficiencies (eg, of folate and thiamin), enlarged parotid glands, and white nails. In alcoholics, Wernicke's encephalopathy and Korsakoff's psychosis result mainly from thiamin deficiency. Hepatitis C occurs in > 25% of alcoholics; this combination markedly worsens the progression of liver disease.

Rarely, patients with fatty liver or cirrhosis present with Zieve's syndrome (hyperlipidemia, hemolytic anemia, and jaundice).

Diagnosis

• Confirmed history of alcohol use

• Liver function tests and CBC

• Sometimes liver biopsy

Alcohol is suspected as the cause of liver disease in any patient who chronically consumes excess alcohol, particularly > 80 g/day. History should be confirmed by family members. Patients can be screened for alcoholism using the CAGE questionnaire (need to *C*ut down, *A*nnoyed by criticism, *G*uilty about drinking, and need for a morning *E*ye-opener). There is no specific test for alcoholic liver disease, but if the diagnosis is suspected, liver function tests (PT; serum bilirubin, aminotransferase, and albumin levels) and CBC are done to detect signs of liver injury and anemia.

Elevations of aminotransferases are moderate (< 300 IU/L) and do not reflect the extent of liver damage. The ratio of AST to ALT is ≥ 2. The basis for low ALT is a dietary deficiency of pyridoxal phosphate (vitamin B_6), which is needed for ALT to function. Its effect on AST is less pronounced. Serum γ-glutamyl transpeptidase (GGT) increases, more because ethanol induces this enzyme than because patients have cholestasis or liver injury or use other drugs. Serum albumin may be low, usually reflecting undernutrition but occasionally reflecting otherwise obvious liver failure with deficient synthesis. Macrocytosis with an MCV > 100 fL reflects the direct effect of alcohol on bone marrow as well as macrocytic anemia resulting from folate deficiency, which is common among undernourished alcoholics. Indexes of the severity of liver disease are

• Serum bilirubin, which represents secretory function

• PT or INR, which reflects synthetic ability

Thrombocytopenia can result from the direct toxic effects of alcohol on bone marrow or from splenomegaly, which accompanies portal hypertension. Neutrophilic leukocytosis may result from alcoholic hepatitis, although coexisting infection (particularly pneumonia and spontaneous bacterial peritonitis) should also be suspected.

Imaging tests are not routinely needed for diagnosis. If done for other reasons, abdominal ultrasonography or CT may suggest fatty liver or show evidence of splenomegaly, portal hypertension, or ascites. Ultrasound elastrography measures liver stiffness and thus detects advanced fibrosis. This valuable adjunct can obviate the need for liver biopsy to check for cirrhosis and help assess prognosis. Its exact role is under study.

If abnormalities suggest alcoholic liver disease, screening tests for other treatable forms of liver disease, especially viral hepatitis, should be done. Because features of fatty liver, alcoholic hepatitis, and cirrhosis overlap, describing the precise findings is more useful than assigning patients to a specific category, which can only be determined by liver biopsy.

Not all experts agree on the indications for liver biopsy. Proposed indications include the following:

• Unclear clinical diagnosis (eg, equivocal clinical and laboratory findings, unexplained persistent

elevations of aminotransferase levels)

• Clinical suspicion of > 1 cause of liver disease (eg, alcohol plus viral hepatitis)

• Desire for a precise prediction of prognosis

Liver biopsy confirms liver disease, helps identify excessive alcohol use as the likely cause, and establishes the stage of liver injury. If iron accumulation is observed, measurement of the iron content and genetic testing can eliminate hereditary hemochromatosis (see p. 1032) as the cause.

For stable patients with cirrhosis, α-fetoprotein measurement and liver ultrasonography should be done to screen for hepatocellular carcinoma (see p. 265).

Prognosis

Prognosis is determined by the degree of hepatic fibrosis and inflammation. Fatty liver and alcoholic hepatitis without fibrosis are reversible if alcohol is avoided. With abstinence, fatty liver completely resolves within 6 wk. Fibrosis and cirrhosis are irreversible.

Certain biopsy findings (eg, neutrophils, perivenular fibrosis) indicate a worse prognosis. Proposed quantitative indexes to predict severity and mortality use primarily laboratory features of liver failure such as prothrombin time, creatinine (for hepatorenal syndrome) and bilirubin levels. The Maddrey discriminant function is calculated from the formula:

$$4.6 \times (\text{PT} - \text{control PT}) + \text{serum bilirubin}$$

For this formula, bilirubin level is measured in mg/dL (converted from bilirubin in µmol/L by dividing by 17). A value of > 32 is associated with a high short-term mortality rate (eg, after 1 mo, 35% without encephalopathy and 45% with encephalopathy). Other indexes include the Model for End-Stage Liver Disease (MELD), Glasgow alcoholic hepatitis score, and Lille model.

Once cirrhosis and its complications (eg, ascites, bleeding) develop, the 5-yr survival rate is about 50%; survival is higher in patients who abstain and lower in patients who continue drinking.

Coexisting iron accumulation or chronic hepatitis C increases risk of hepatocellular carcinoma.

Treatment

• Abstinence

• Supportive care

• Corticosteroids and enteral nutrition for severe alcoholic hepatitis

• Sometimes transplantation

Restricting alcohol intake: Abstinence is the mainstay of treatment; it prevents further damage from alcoholic liver disease and thus prolongs life. Because compliance is problematic, a compassionate team approach is essential. Behavioral and psychosocial interventions can help motivated patients; they include rehabilitation programs and support groups (see p. 1521), brief interventions by primary care physicians, and therapies that explore and clarify the motivation to abstain (motivational enhancement therapy).

Drugs, if used, should only supplement other interventions. Opioid antagonists (naltrexone or nalmefene) and drugs that modulate γ-aminobutyric acid receptors (baclofen or acamprosate) appear to have a short-

term benefit by reducing the craving and withdrawal symptoms. Disulfiram inhibits aldehyde dehydrogenase, allowing acetaldehyde to accumulate; thus, drinking alcohol within 12 h of taking disulfiram causes flushing and has other unpleasant effects. However, disulfiram has not been shown to promote abstinence and consequently is recommended only for certain patients.

Supportive care: General management emphasizes supportive care. A nutritious diet and vitamin supplements (especially B vitamins) are important during the first few days of abstinence. Alcohol withdrawal requires use of benzodiazepines (eg, diazepam). In patients with advanced alcoholic liver disease, excessive sedation can precipitate hepatic encephalopathy and thus must be avoided.

Severe acute alcoholic hepatitis commonly requires hospitalization, often in an intensive care unit, to facilitate enteral feeding (which can help manage nutritional deficiencies) and to manage specific complications (eg, infection, bleeding from esophageal varices, specific nutritional deficiencies, Wernicke's encephalopathy, Korsakoff's psychosis, electrolyte abnormalities, portal hypertension, ascites, portal-systemic encephalopathy—see elsewhere in THE MANUAL).

Specific treatment: Corticosteroids (eg, prednisolone 40 mg/day po for 4 wk, followed by tapered doses improve outcome in patients who have severe acute alcoholic hepatitis and who do not have infection, GI bleeding, renal failure, or pancreatitis.

Other than corticosteroids and enteral feeding, few specific treatments are clearly established. Antioxidants (eg, *S*-adenosyl-L-methionine, phosphatidylcholine, metadoxine) show promise in ameliorating liver injury during early cirrhosis but require further study. Therapies directed at cytokines, particularly tumor necrosis factor-α (TNF-α), and aiming to reduce inflammation have had mixed results in small trials. Pentoxifylline, a phosphodiesterase inhibitor that inhibits TNF-α synthesis, has some benefit. In contrast, when biologic agents that inhibit TNF-α (eg, infliximab, etanercept) are used, risk of infection outweighs benefit. Drugs given to decrease fibrosis (eg, colchicine, penicillamine) and drugs given to normalize the hypermetabolic state of the alcoholic liver (eg, propylthiouracil) have no proven benefit. Antioxidant remedies, such as silymarin (milk thistle) and vitamins A and E, are ineffective.

Liver transplantation can be considered if disease is severe. With transplantation, 5-yr survival rates are comparable to those for nonalcoholic liver disease—as high as 80% in patients without active liver disease and 50% in those with acute alcoholic hepatitis. Because up to 50% of patients resume drinking after transplantation, most programs require 6 mo of abstinence before transplantation is done.

Chapter 27. Fibrosis and Cirrhosis

Introduction

In hepatic fibrosis, excessive connective tissue accumulates in the liver; this tissue represents scarring in response to chronic, repeated liver cell injury. Commonly, fibrosis progresses, disrupting hepatic architecture and eventually function, as regenerating hepatocytes attempt to replace and repair damaged tissue. When such disruption is widespread, cirrhosis is diagnosed. To develop, cirrhosis usually requires > 6 mo of liver disease but can occur more rapidly (eg, during infancy with biliary atresia, after liver transplantation for severe liver disease secondary to chronic hepatitis B or C).

Fibrosis

Hepatic fibrosis is overly exuberant wound healing in which excessive connective tissue builds up in the liver. The extracellular matrix is overproduced, degraded deficiently, or both. The trigger is chronic injury, especially if there is an inflammatory component. Fibrosis itself causes no symptoms but can lead to portal hypertension (the scarring distorts blood flow through the liver) or cirrhosis (the scarring results in disruption of normal hepatic architecture and liver dysfunction). Diagnosis is based on liver biopsy. Treatment involves correcting the underlying condition when possible.

Various types of chronic liver injury can cause fibrosis (see Table 27-1). Self-limited, acute liver injury (eg, acute viral hepatitis A), even when fulminant, does not necessarily distort the scaffolding architecture and hence does not cause fibrosis, despite loss of hepatocytes. In its initial stages, hepatic fibrosis can regress if the cause is reversible (eg, with viral clearance). After months or years of chronic or repeated injury, fibrosis becomes permanent. Fibrosis develops even more rapidly in mechanical biliary obstruction.

Pathophysiology

Activation of the hepatic perivascular stellate cells (Ito cells, which store fat) initiates fibrosis. These and adjacent cells proliferate, becoming contractile cells termed myofibroblasts. These cells produce excessive amounts of abnormal matrix (consisting of collagen, other glycoproteins, and glycans) and matricellular proteins. Kupffer cells (resident macrophages), injured hepatocytes, platelets, and leukocytes aggregate. As a result, reactive O_2 species and inflammatory mediators (eg, platelet-derived growth factor, transforming growth factors, and connective tissue growth factor) are released. Thus, stellate cell activation results in abnormal extracellular matrix, both in quantity and composition.

Myofibroblasts, stimulated by endothelin-1, contribute to increased portal vein resistance and increase the density of the abnormal matrix. Fibrous tracts join branches of afferent portal veins and efferent hepatic veins, bypassing the hepatocytes and limiting their blood supply. Hence, fibrosis contributes both to hepatocyte ischemia (causing hepatocellular dysfunction) and portal hypertension. The

[**Table 27-1.** Disorders and Drugs that Can Cause Hepatic Fibrosis]

extent of the ischemia and portal hypertension determines how the liver is affected. For example, congenital hepatic fibrosis affects portal vein branches, largely sparing the parenchyma. The result is portal hypertension with sparing of hepatocellular function.

Symptoms and Signs

Hepatic fibrosis itself does not cause symptoms. Symptoms may develop secondary to the primary disorder or to portal hypertension. Portal hypertension with splenomegaly is often asymptomatic unless complications, such as variceal GI bleeding, ascites, or portal-systemic encephalopathy, develop. Eventually, cirrhosis supervenes.

Diagnosis

• Biopsy

Hepatic fibrosis is suspected in patients who have an underlying disorder or take a drug that could cause fibrosis or who have unexplained abnormalities in liver function or enzymes. Noninvasive tests (eg, serologic markers) are under study but are not yet ready for routine clinical use. Imaging tests such as ultrasonography, CT, and MRI may detect findings associated with fibrosis (eg, portal hypertension, splenomegaly, cirrhosis) but are not sensitive to parenchymal fibrosis itself. Liver biopsy is currently the only means of detecting hepatic fibrosis. Biopsy is indicated to clarify the diagnosis (eg, nonalcoholic steatohepatitis, primary biliary cirrhosis) and stage its progress (eg, in chronic hepatitis C to determine whether fibrosis is present or whether it has progressed to cirrhosis).

Treatment

• Treatment of cause

Because fibrosis represents a response to hepatic damage, primary treatment should focus on the cause (removing the basis of the liver injury). Such treatment may include eliminating HBC or HCV in chronic viral hepatitis, abstaining from alcohol in alcoholic liver disease, removing heavy metals such as iron in hemochromatosis or copper in Wilson's disease, and decompressing bile ducts in biliary obstruction.

Treatments aimed at reversing the fibrosis are usually too toxic for long-term use (eg, corticosteroids, penicillamine) or have no proven efficacy (eg, colchicine). Other antifibrotic treatments are under study. Simultaneous use of multiple antifibrotic drugs may eventually prove most beneficial.

Cirrhosis

Cirrhosis is a late stage of hepatic fibrosis that has resulted in widespread distortion of normal hepatic architecture. Cirrhosis is characterized by regenerative nodules surrounded by dense fibrotic tissue. Symptoms may not develop for years and are often nonspecific (eg, anorexia, fatigue, weight loss). Late manifestations include portal hypertension, ascites, and, when decompensation occurs, liver failure. Diagnosis often requires liver biopsy. Cirrhosis is usually considered irreversible. Treatment is supportive.

Cirrhosis is a leading cause of death worldwide. The causes of cirrhosis are the same as those of fibrosis (see Table 27-1). In developed countries, most cases result from chronic alcohol abuse or chronic hepatitis C. In parts of Asia and Africa, cirrhosis often results from chronic hepatitis B. Cirrhosis of unknown etiology (cryptogenic cirrhosis) is becoming less common as many specific causes (eg, chronic hepatitis C, steatohepatitis) are identified. Injury to the bile ducts also can result in cirrhosis, as occurs in mechanical bile duct obstruction, primary biliary cirrhosis (see p. 244), and primary sclerosing cholangitis (see p. 278).

Pathophysiology

There are 2 primary factors:

• Hepatic fibrosis

• Regenerating liver cells

In response to injury and loss, growth regulators induce hepatocellular hyperplasia (producing regenerating nodules) and arterial growth (angiogenesis). Among the growth regulators are cytokines and hepatic growth factors (eg, epithelial growth factor, hepatocyte growth factor, transforming growth factor-α, tumor necrosis factor). Insulin, glucagon, and patterns of intrahepatic blood flow determine how and where nodules develop.

Angiogenesis produces new vessels within the fibrous sheath that surrounds nodules. These vessels connect the hepatic artery and portal vein to hepatic venules, restoring the intrahepatic circulatory

pathways. Such interconnecting vessels provide relatively low-volume, high-pressure venous drainage that cannot accommodate as much blood volume as normal. As a result, portal vein pressure increases. Such distortions in blood flow contribute to portal hypertension, which increases because the regenerating nodules compress hepatic venules.

The progression rate from fibrosis to cirrhosis and the morphology of cirrhosis vary from person to person. Presumably, the reason for such variation is the extent of exposure to the injurious stimulus and the individual's response.

Complications: Portal hypertension (see p. 218) is the most common serious complication; it can manifest as GI bleeding from esophageal, gastric, or rectal varices or portal hypertensive gastropathy. Portal hypertension can be massive. Cirrhosis can cause other cardiovascular complications. Vasodilation and intrapulmonary right-to-left shunting and ventilation/perfusion mismatch can result in hypoxia (hepatopulmonary syndrome). A cardiac myopathy can also accompany cirrhosis.

Ascites can develop, with a risk of spontaneous bacterial peritonitis. Splenic congestion with hypersplenism may occur, resulting in splenomegaly, platelet sequestration, and consequent cytopenia.

Progressive loss of hepatic architecture impairs function, leading to hepatic insufficiency; it manifests as coagulopathy, renal failure (hepatorenal syndrome—see p. 223), and hepatic encephalopathy. Hepatocytes secrete less bile, contributing to cholestasis and jaundice. Less bile in the intestine causes malabsorption of dietary fat (triglycerides) and fat-soluble vitamins. Malabsorption of vitamin D may contribute to osteoporosis. Undernutrition is common. It may result from anorexia with reduced food intake or, in patients with alcoholic liver disease, from malabsorption due to pancreatic insufficiency.

Blood disorders are common. Anemia results from hypersplenism, chronic GI bleeding, folate deficiency (particularly in patients with alcoholism), and hemolysis. Clotting may be impaired because of coagulopathy or thrombocytopenia. Coagulopathy results from impaired hepatic synthesis of the factors necessary for clotting, malabsorption of vitamin K due to impaired bile secretion into the duodenum, or both. Thrombocytopenia may be caused by hypersplenism (platelet sequestration), alcohol excess (directly inhibiting the bone marrow), or both. Pancytopenia also occurs with alcoholism.

Hepatocellular carcinoma frequently complicates cirrhosis, particularly cirrhosis resulting from chronic hepatitis B and C viruses, hemochromatosis, alcohol-related liver disease, $\alpha_1$antitrypsin deficiency, or glycogen storage disease.

Histopathology: Cirrhosis is characterized by regenerating nodules and fibrosis. Incompletely formed liver nodules, nodules without fibrosis (nodular regenerative hyperplasia), and congenital hepatic fibrosis (ie, widespread fibrosis without regenerating nodules) are not true cirrhosis.

Cirrhosis can be micronodular or macronodular. Micronodular cirrhosis is characterized by uniformly small nodules (< 3 mm in diameter) and thick regular bands of connective tissue. Typically, nodules lack lobular organization; terminal (central) hepatic venules and portal triads are distorted. With time, macronodular cirrhosis often develops. The nodules vary in size (3 mm to 5 cm in diameter) and have some rather normal lobular organization of portal triads and terminal hepatic venules. Broad fibrous bands of varying thickness surround the large nodules. Collapse of the normal hepatic architecture is suggested by the concentration of portal triads within the fibrous scars. Mixed cirrhosis (incomplete septal cirrhosis) combines elements of micronodular and macronodular cirrhosis. Differentiation between these morphologic types of cirrhosis has limited clinical value.

Symptoms and Signs

Cirrhosis may be asymptomatic for years. One third of patients never develop symptoms. Often, the first symptoms are nonspecific; they include generalized fatigue (due to cytokine release), anorexia, malaise, and weight loss (see Table 27-2). The liver is typically palpable and firm, with a blunt edge, but is sometimes small and difficult to palpate. Nodules usually are not palpable.

Clinical signs that suggest a chronic liver disorder or chronic alcohol use but are not specific for cirrhosis include muscle wasting, palmar erythema, parotid gland enlargement, white nails, clubbing, Dupuytren's contracture, spider angiomas (< 10 may be normal), gynecomastia, axillary hair loss, testicular atrophy, and peripheral neuropathy.

Once complications of cirrhosis develop, decompensation inexorably ensues.

Diagnosis

• Liver function tests, coagulation tests, CBC, and serologic tests for viral cause

• Sometimes biopsy

• Identification of cause based on clinical evaluation and selective testing

General approach: Cirrhosis is suspected in patients with manifestations of any of its complications (see Table 27-2), particularly portal hypertension or ascites. Early cirrhosis should be considered in patients with nonspecific

[**Table 27-2.** Common Symptoms and Signs Due to Complications of Cirrhosis]

symptoms or characteristic laboratory abnormalities detected incidentally during laboratory testing, particularly in patients who have a disorder or take a drug that might cause fibrosis.

Testing seeks to detect cirrhosis and any complications and to determine its cause.

Laboratory tests: Diagnostic testing begins with liver function tests, coagulation tests, CBC, and serologic tests for viral causes (eg, hepatitis B and C). Laboratory tests alone may increase suspicion for cirrhosis but cannot confirm or exclude it. Liver biopsy becomes necessary if a clear diagnosis would lead to better management and outcome.

Test results may be normal or may indicate nonspecific abnormalities due to complications of cirrhosis or alcoholism. ALT and AST levels are often modestly elevated. Alkaline phosphatase and γ-glutamyl transpeptidase (GGT) are often normal; elevated levels indicate cholestasis or biliary obstruction. Bilirubin is usually normal but increases when cirrhosis progresses, particularly in primary biliary cirrhosis (see p. 244). Decreased serum albumin and a prolonged PT directly reflect impaired hepatic synthesis —usually an end-stage event. Albumin can also be low when nutrition is poor. Serum globulin increases in cirrhosis and in most liver disorders with an inflammatory component. Anemia is common and usually normocytic with a high RBC distribution width. Anemia is often multifactorial; contributing factors may include chronic GI bleeding (usually causing microcytic anemia), folate nutritional deficiency (causing macrocytic anemia, especially in alcohol abuse), hemolysis, and hypersplenism. CBC may detect leukopenia, thrombocytopenia, or pancytopenia.

Diagnostic imaging: Imaging tests are not highly sensitive or specific for the diagnosis of cirrhosis by themselves, but they can often detect its complications. In advanced cirrhosis, ultrasonography shows a small, nodular liver. Ultrasonography also detects portal hypertension and ascites.

CT can detect a nodular texture, but it has no advantage over ultrasonography. Radionuclide liver scans using technetium-99m sulfur colloid may show irregular liver uptake and increased spleen and bone marrow uptake. MRI is more expensive than other imaging tests and has little advantage.

Identification of the cause: Determining the specific cause of cirrhosis requires key clinical information from the history and examination, as well as selective testing. Alcohol is the likely cause in patients with a documented history of alcoholism and clinical findings such as gynecomastia, spider angiomas (telangiectasia), and testicular atrophy plus laboratory confirmation of liver damage (AST elevated more than ALT) and liver enzyme induction (a greatly increased GGT). Fever, tender hepatomegaly, and jaundice suggest the presence of alcoholic hepatitis.

Detecting hepatitis B surface antigen (HBsAg) and IgG antibodies to hepatitis B (IgG anti-HBc) confirms chronic hepatitis B. Identifying serum antibody to hepatitis C (anti-HCV) and HCV-RNA points to hepatitis C.

If common causes such as alcohol or viral hepatitis are not confirmed, other less common causes are sought:

- Presence of antimitochondrial antibodies (in 95%) suggests primary biliary cirrhosis.
- Strictures and dilations of the intrahepatic and extrahepatic bile ducts seen on magnetic resonance cholangiopancreatography (MRCP) suggest primary sclerosing cholangitis.
- Increased serum Fe and transferrin and possibly results of genetic testing suggest hemochromatosis.
- Decreased serum ceruloplasmin and characteristic copper test results suggest Wilson's disease.
- Hypergammaglobulinemia and presence of autoantibodies (eg, antinuclear or anti-smooth muscle antibodies) indicate autoimmune hepatitis.

Liver biopsy: If clinical criteria and noninvasive testing are inconclusive, liver biopsy is usually done. Its sensitivity approaches 100%. Nonalcoholic steatohepatitis (NASH), often associated with obesity, diabetes, or the metabolic syndrome, may be evident on ultrasound scans but requires liver biopsy for confirmation. In obvious cases of cirrhosis with a marked coagulopathy, portal hypertension, ascites, and liver failure, biopsy is not required when results would not change management.

Monitoring: Patients with cirrhosis, particularly if due to chronic viral hepatitis B or C or hemochromatosis, should be screened for hepatocellular carcinoma (eg, measuring α-fetoprotein levels and ultrasonography every 6 to 12 mo—see p. 266).

Prognosis

Prognosis is often unpredictable. It depends on factors such as etiology, severity, presence of complications, comorbid conditions, host factors, and effectiveness of therapy. Patients who continue to drink alcohol, even small amounts, have a very poor prognosis. The Child-Turcotte-Pugh scoring system uses clinical and laboratory information to stratify disease severity, surgical risk, and overall prognosis (see Tables 27-3 and 27-4).

Treatment

- Supportive care

In general, treatment is supportive and includes stopping injurious drugs, providing nutrition (including supplemental vitamins), and treating the underlying disorders and complications. Doses of drugs metabolized in the liver should be reduced. All alcohol and hepatotoxic substances must be avoided. Withdrawal symptoms during hospitalization should be anticipated in patients who have cirrhosis and have continued to abuse alcohol.

Patients with varices need therapy to prevent bleeding (see p. 219). Liver transplantation is indicated for end-stage liver failure in suitable candidates.

Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is an autoimmune liver disorder characterized by the progressive destruction of intrahepatic bile ducts, leading to cholestasis, cirrhosis, and liver failure. Patients usually are asymptomatic at presentation but may experience fatigue or have symptoms of cholestasis (eg, pruritus, steatorrhea) or cirrhosis (eg, portal hypertension,

ascites). Laboratory tests reveal cholestasis, increased IgM, and, characteristically, antimitochondrial antibodies in the serum. Liver biopsy may be necessary for diagnosis and staging. Treatment includes ursodeoxycholic acid, cholestyramine (for pruritus),

[**Table 27-3.** Child-Turcotte-Pugh Scoring System]

[**Table 27-4.** Interpretation of the Child-Turcotte-Pugh Scoring System]

supplementary fat-soluble vitamins, and, ultimately for advanced disease, liver transplantation.

Etiology

PBC is the most common liver disease associated with chronic cholestasis in adults. Most (95%) cases occur in women aged 35 to 70. PBC also clusters in families. A genetic predisposition, perhaps involving the X chromosome, probably contributes. There may be an inherited abnormality of immune regulation. An autoimmune mechanism has been implicated; antibodies to antigens located on the inner mitochondrial membranes occur in > 95% of cases. These antimitochondrial antibodies (AMAs), the serologic hallmarks of PBC, are not cytotoxic and are not involved in bile duct damage. PBC is associated with other autoimmune disorders, such as RA, systemic sclerosis, Sjogren's syndrome, CREST syndrome, autoimmune thyroiditis, and renal tubular acidosis.

T cells attack the small bile ducts. CD4 and CD8 T lymphocytes directly target biliary epithelial cells. The trigger for the immunologic attack on bile ducts is unknown. Exposure to foreign antigens, such as an infectious (bacterial or viral) or toxic agent, may be the instigating event. These foreign antigens might be structurally similar to endogenous proteins (molecular mimicry); then the subsequent immunologic reaction would be autoimmune and self-perpetuating. Destruction and loss of bile ducts lead to impaired bile formation and secretion (cholestasis). Retained toxic materials such as bile acids then cause further damage, particularly to hepatocytes. Chronic cholestasis thus leads to liver cell inflammation and scarring in the periportal areas. Eventually, hepatic inflammation decreases as hepatic fibrosis progresses to cirrhosis.

Autoimmune cholangitis is sometimes considered to be a separate disorder. It is characterized by autoantibodies, such as antinuclear antibodies (ANAs), anti-smooth muscle antibodies, or both and has a clinical course and response to treatment that are similar to PBC. However, in autoimmune cholangitis, AMAs are absent.

Symptoms and Signs

About half of patients present without symptoms. Symptoms or signs may develop during any stage of the disease and may include fatigue or reflect cholestasis (and the resulting fat malabsorption, which may lead to vitamin deficiencies and osteoporosis), hepatocellular dysfunction, or cirrhosis.

Symptoms usually develop insidiously. Pruritus, fatigue, and dry mouth and eyes are the initial symptoms in > 50% of patients and can precede other symptoms by months or years. Other initial manifestations include right upper quadrant discomfort (10%); an enlarged, firm, nontender liver (25%); splenomegaly (15%); hyperpigmentation (25%); xanthelasmas (10%); and jaundice (10%). Eventually, all the features and complications of cirrhosis occur. Peripheral neuropathy and other autoimmune disorders associated with PBC may also develop.

Diagnosis

• Liver function tests

• Antimitochondrial antibodies

• Ultrasonography and often MRCP

• Liver biopsy

In asymptomatic patients, PBC is detected incidentally when liver function tests detect abnormalities, typically elevated levels of alkaline phosphatase and γ-glutamyl transpeptidase (GGT). PBC is suspected in middle-aged women with classic symptoms (eg, unexplained pruritus, fatigue, right upper quadrant discomfort, jaundice) or laboratory results suggesting cholestatic liver disease: elevated alkaline phosphatase and GGT but minimally abnormal aminotransferases (ALT, AST). Serum bilirubin is usually normal in the early stages; elevation indicates disease progression and a worsening prognosis.

If PBC is suspected, liver function tests and tests to measure serum IgM (increased in PBC) and AMA should be done. ELISA tests are 95% sensitive and 98% specific for PBC; false-positive results can occur in autoimmune hepatitis (type 1). Other autoantibodies (eg, ANAs, anti-smooth muscle antibodies, rheumatoid factor) may be present. Extrahepatic biliary obstruction should be ruled out. Ultrasonography is often done first, but ultimately MRCP and sometimes ERCP are necessary. Unless life expectancy is short or there is a contraindication, liver biopsy is usually done. Liver biopsy confirms the diagnosis; it may detect pathognomonic bile duct lesions, even in early stages. As PBC progresses, it becomes morphologically indistinguishable from other forms of cirrhosis. Liver biopsy also helps stage PBC, which has 4 histologic stages:

• Stage 1: Inflammation, abnormal connective tissue, or both, confined to the portal areas

• Stage 2: Inflammation, fibrosis, or both, confined to the portal and periportal areas

• Stage 3: Bridging fibrosis

• Stage 4: Cirrhosis

Autoimmune cholangitis is diagnosed when AMAs are absent in a patient who otherwise would be diagnosed with PBC.

Prognosis

Usually, PBC progresses to terminal stages over 15 to 20 yr, although the rate of progression varies. PBC may not diminish quality of life for many years. Patients who present without symptoms tend to develop symptoms over 2 to 7 yr but may not do so for 10 to 15 yr. Once symptoms develop, median life expectancy is 10 yr. Predictors of rapid progression include the following:

• Rapid worsening of symptoms

• Advanced histologic changes

• Older patient age

• Presence of edema

• Presence of associated autoimmune disorders

• Abnormalities in bilirubin, albumin, PT, or INR

The prognosis is ominous when pruritus disappears, xanthomas shrink, jaundice develops, and serum cholesterol decreases.

Treatment

• Arresting or reversing liver damage

• Treating complications (chronic cholestasis and liver failure)

• Eventually, doing liver transplantation

All alcohol use and hepatotoxic drugs should be stopped. Ursodeoxycholic acid (15 mg/kg po once/day) decreases liver damage, prolongs survival, and delays the need for liver transplantation. About 20% of patients do not have biochemical improvement after ≥ 4 mo; they may have advanced disease and require liver transplantation in a few years. Other drugs proposed to decrease liver damage have not improved overall clinical outcomes or are controversial.

Pruritus may be controlled with cholestyramine 6 to 8 g po bid. This anionic-binding drug binds bile salts and thus may aggravate fat malabsorption. If cholestyramine is taken long-term, supplements of fat-soluble vitamins should be considered. Cholestyramine can decrease absorption of ursodeoxycholic acid, so these drugs should not be given simultaneously.

Some patients with pruritus respond to ursodeoxycholic acid and ultraviolet light; others may warrant a trial of rifampin or an opioid antagonist, such as naltrexone. Patients with fat malabsorption due to bile salt deficiency should be treated with vitamins A, D, E, and K. For osteoporosis, weight-bearing exercises, bisphosphonates, or raloxifene may be needed in addition to Ca and vitamin D supplements. In later stages, portal hypertension (see p. 218) or complications of cirrhosis (see p. 241) require treatment.

Liver transplantation has excellent results. The general indication is decompensated liver disease (uncontrolled variceal bleeding, refractory ascites, intractable pruritus, and hepatic encephalopathy). Survival rates after liver transplantation are > 90% at 1 yr, > 80% at 5 yr, and > 65% at 10 yr. AMAs tend to persist after transplantation. PBC recurs in 15% of patients in the first few years and in > 30% by 10 yr. So far, recurrent PBC after liver transplantation has a benign course. Cirrhosis rarely occurs.

Chapter 28. Hepatitis

Introduction

Hepatitis is an inflammation of the liver characterized by diffuse or patchy necrosis. Major causes are specific hepatitis viruses, alcohol, and drugs. Less common causes include other viral infections (eg, infectious mononucleosis, yellow fever, cytomegalovirus infection) and leptospirosis. Parasitic infections (eg, schistosomiasis, malaria, amebiasis), pyogenic infections, and abscesses that affect the liver are not considered hepatitis. Liver involvement with TB and other granulomatous infiltrations is sometimes called granulomatous hepatitis, but the clinical, biochemical, and histologic features differ from those of diffuse hepatitis.

Various systemic infections and other illnesses may produce small focal areas of hepatic inflammation or necrosis. This nonspecific reactive hepatitis can cause minor liver function abnormalities but is usually asymptomatic.

Some types of infectious and noninfectious liver inflammation are summarized (see Table 28-1).

Acute Viral Hepatitis

Acute viral hepatitis is diffuse liver inflammation caused by specific hepatotropic viruses that have diverse modes of transmission and epidemiologies. A nonspecific viral prodrome is followed by anorexia, nausea, and often fever or right upper quadrant pain. Jaundice often develops, typically as other symptoms begin to resolve. Most cases resolve spontaneously, but some progress to chronic hepatitis. Occasionally, acute viral hepatitis progresses to acute hepatic failure (fulminant hepatitis). Diagnosis is by liver function tests and serologic tests to identify the virus. Good hygiene can prevent acute viral hepatitis. Depending on the specific virus, preexposure and postexposure prophylaxis may be possible using vaccines or serum globulins. Treatment is usually supportive.

(See also Neonatal Hepatitis B Virus Infection on p. 2825.)

Acute viral hepatitis is a common, worldwide disease that has different causes; each type shares clinical, biochemical, and morphologic features. Liver infections caused by nonhepatitis viruses (eg, Epstein-Barr virus, yellow fever virus, cytomegalovirus) generally are not termed acute viral hepatitis.

Etiology

At least 5 specific viruses appear to be responsible (see Table 28-2). Other unidentified viruses probably also cause acute viral hepatitis.

Hepatitis A virus (HAV): HAV is a single-stranded RNA picornavirus. It is the most common cause of acute viral hepatitis and is particularly common among children and young adults. In some countries, > 75% of adults have been exposed. HAV spreads primarily by fecal-oral contact and thus may occur in areas of poor hygiene. Waterborne and food-borne epidemics occur, especially in underdeveloped countries. Eating contaminated raw shellfish is sometimes responsible. Sporadic cases are also common, usually as a result of person-to-person contact. Fecal shedding of the virus occurs before symptoms develop and usually ceases a few days after symptoms begin; thus, infectivity often has already ceased when hepatitis becomes clinically evident. HAV has no known chronic carrier state and does not cause chronic hepatitis or cirrhosis.

Hepatitis B virus (HBV): HBV is the most thoroughly characterized and complex hepatitis virus. The infective particle consists of a viral core plus an outer surface coat. The core contains circular double-stranded DNA and DNA polymerase, and it replicates within the nuclei of infected hepatocytes. A surface coat is added in the cytoplasm and, for unknown reasons, is produced in great excess.

HBV is the 2nd most common cause of acute viral hepatitis. Prior unrecognized infection is common but is

much less widespread than that with HAV. HBV is often transmitted parenterally, typically by contaminated blood or blood products. Routine screening of donor blood for hepatitis B surface antigen (HBsAg) has nearly eliminated the previously common posttransfusion transmission, but transmission through needles shared by drug users remains common. Risk of HBV is increased for patients in renal dialysis and oncology units and for hospital personnel in contact with blood. The virus may be spread through contact with other body fluids (eg, between sex partners, both heterosexual and homosexual; in closed institutions, such as mental health institutions and prisons), but infectivity is far lower than that of HAV, and the means of transmission is often unknown. The role of insect bites in transmission is unclear. Many cases of acute hepatitis B occur sporadically without a known source.

HBV, for unknown reasons, is sometimes associated with several primarily extrahepatic disorders, including polyarteritis nodosa, other connective tissue diseases, membranous glomerulonephritis, and essential mixed cryoglobulinemia. The pathogenic role of HBV in these disorders is unclear, but autoimmune mechanisms are suggested.

Chronic HBV carriers provide a worldwide reservoir of infection. Prevalence varies widely according to several factors, including geography (eg, < 0.5% in North America and northern Europe, > 10% in some regions of the Far East). Vertical transmission from mother to infant is common (see p. 2644).

[**Table 28-1.** Selected Diseases or Organisms Associated with Liver Inflammation]

Hepatitis C virus (HCV): HCV is a single-stranded RNA flavivirus. Six major HCV subtypes exist with varying amino acid sequences (genotypes); these subtypes vary geographically and in virulence and response to therapy. HCV can also alter its amino acid pattern over time in an infected person, producing quasispecies.

Infection is most commonly transmitted through blood, primarily when parenteral drug users share needles, but also through tattoos or body piercing. Sexual transmission and vertical transmission from mother to infant are relatively rare. Transmission through blood transfusion has become very rare since the advent of screening tests for donated blood. Some sporadic cases occur in patients without apparent risk factors. HCV prevalence varies with geography and other risk factors.

HCV infection sometimes occurs simultaneously with specific systemic disorders, including essential mixed cryoglobulinemia, porphyria cutanea tarda (about 60 to 80% of porphyria patients have HCV infection, but only a few patients infected with HCV develop porphyria), and glomerulonephritis; the mechanisms are uncertain. In addition, up to 20% of patients with alcoholic liver disease harbor HCV. The reasons for this high association are unclear because concomitant alcohol and drug use accounts for only a portion of cases. In these patients, HCV and alcohol act synergistically to exacerbate liver damage.

Hepatitis D virus (HDV): HDV, or delta agent, is a defective RNA virus that can replicate only in the presence of HBV. It occurs uncommonly as a co-infection with acute hepatitis B or as a superinfection in chronic hepatitis B. Infected hepatocytes contain delta particles coated with HBsAg. Prevalence of HDV varies widely geographically, with endemic pockets in several countries. Parenteral drug users are at relatively high risk, but HDV (unlike HBV) has not widely permeated the homosexual community.

Hepatitis E virus (HEV): HEV is an enterically transmitted RNA virus. Outbreaks of acute HEV infection, often waterborne and linked to fecal contamination of the water supply, have occurred in China, India, Mexico, Pakistan, Peru, Russia, and central and northern Africa. These outbreaks have epidemiologic characteristics similar to HAV epidemics. Sporadic cases also occur. No outbreaks have occurred in the US or in Western Europe. Like HAV, HEV does not cause chronic hepatitis or cirrhosis, and there is no chronic carrier state.

Symptoms and Signs

General: Acute infection tends to develop in predictable phases. Infection begins with an incubation period (see Table 28-2), during which the virus multiplies and spreads without symptoms. The prodromal, or pre-icteric, phase follows, causing nonspecific symptoms, such as profound anorexia, malaise, nausea and vomiting, and often fever or right upper quadrant abdominal pain. Urticaria and arthralgias

occasionally occur, especially in HBV infection. After 3 to 10 days, the urine darkens, followed by jaundice (the icteric phase). Systemic symptoms often regress, and the patient feels better despite worsening jaundice. During the icteric phase, the liver is usually enlarged and tender, but the edge of the liver remains soft and smooth. Mild splenomegaly occurs in 15 to 20% of patients. Jaundice usually peaks within 1 to 2 wk and then fades during a 2- to 4-wk recovery phase. Appetite usually returns after the first week. Acute viral hepatitis usually resolves spontaneously 4 to 8 wk after symptom onset.

Sometimes anicteric hepatitis, a minor flulike illness without jaundice, is the only manifestation. It occurs more often than icteric hepatitis in patients with HCV infection and in children with HAV infection.

Recrudescent hepatitis occurs in a few patients and is characterized by recurrent manifestations during the recovery phase. Manifestations of cholestasis may develop during the icteric phase (called cholestatic hepatitis) but usually resolve. When they persist, they cause prolonged jaundice, elevated alkaline phosphatase, and pruritus, despite general regression of inflammation.

Virus-specific: HAV often does not cause jaundice and may not cause any symptoms. It almost invariably resolves after the acute infection, although there can be early recrudescence.

HBV causes a wide spectrum of liver diseases, from a subclinical carrier state to severe or fulminant acute hepatitis, particularly in the elderly, in whom mortality can reach 10 to 15%. Five to 10% of all patients with HBV develop chronic hepatitis or become inactive carriers. Cirrhosis can develop. Hepatocellular carcinoma can ultimately develop in chronic HBV infection, even without being preceded by cirrhosis.

HCV may be asymptomatic during the acute infection. Its severity often fluctuates, sometimes with recrudescent hepatitis and

[**Table 28-2.** Characteristics of Hepatitis Viruses]

roller-coaster aminotransferase levels for many years or even decades. HCV has the highest rate of chronicity (about 75%). The resultant chronic hepatitis is usually asymptomatic or benign but progresses to cirrhosis in 20 to 30% of patients; cirrhosis often takes decades to appear. Hepatocellular carcinoma can result from HCV-induced cirrhosis but results only rarely from chronic infection without cirrhosis (unlike in HBV infection).

Acute HDV infection typically manifests as unusually severe acute HBV infection (co-infection), an acute exacerbation in chronic HBV carriers (superinfection), or a relatively aggressive course of chronic HBV infection.

HEV may be severe, especially in pregnant women.

Diagnosis

- Liver function tests (AST and ALT elevated out of proportion to alkaline phosphatase, usually with hyperbilirubinemia)

- Viral serologic testing

- PT measurement

Initial diagnosis: Acute hepatitis must first be differentiated from other disorders that cause similar symptoms. In the prodromal phase, hepatitis mimics various nonspecific viral illnesses and is difficult to diagnose. Anicteric patients suspected of having hepatitis based on risk factors are tested initially with nonspecific liver function tests, including aminotransferases, bilirubin, and alkaline phosphatase. Usually, acute hepatitis is suspected only during the icteric phase. Thus, acute hepatitis should be differentiated from other disorders causing jaundice (see
Fig. 28-1 and p. 212).

Acute hepatitis can usually be differentiated from other causes of jaundice by its marked elevations of AST and ALT (typically ≥ 400 IU/L). ALT is typically higher than AST, but absolute levels correlate poorly with clinical severity. Values increase early in the prodromal phase, peak before jaundice is maximal, and fall slowly during the recovery phase. Urinary bilirubin usually precedes jaundice. Hyperbilirubinemia in acute viral hepatitis varies in severity, and fractionation has no clinical value. Alkaline phosphatase is usually only moderately elevated; marked elevation suggests extrahepatic cholestasis and prompts imaging tests (eg, ultrasonography). Liver biopsy generally is not needed unless the diagnosis is uncertain. If laboratory results suggest acute hepatitis, particularly if ALT and AST are > 1000 IU/L, PT is measured. Manifestations of portal-systemic encephalopathy, bleeding diathesis, or prolongation of INR suggest fulminant hepatitis (see p. 254).

If acute hepatitis is suspected, efforts are next directed toward identifying its cause. A history of exposure may provide the only clue of drug-induced or toxic hepatitis. The history should also elicit risk factors for viral hepatitis. Prodromal sore throat and diffuse adenopathy suggest infectious mononucleosis rather than viral hepatitis. Alcoholic hepatitis is suggested by a history of drinking, more gradual onset of symptoms, and presence of vascular spiders or signs of chronic alcohol use or chronic liver disease (see also p. 235); aminotransferase levels rarely exceed 300 IU/L, even in severe cases. Also, unlike in viral hepatitis, AST is typically higher than ALT, although this difference by itself does not reliably differentiate the two. In uncertain cases, liver biopsy usually distinguishes alcoholic from viral hepatitis.

Serology: In patients with findings suggesting acute viral hepatitis, the following studies are done to screen for hepatitis viruses A, B, and C:

• IgM antibody to HAV (IgM anti-HAV)

• HBsAg

• IgM antibody to hepatitis B core (IgM anti-HBc)

• Antibody to HCV (anti-HCV)

If any are positive, further serologic testing may be necessary to differentiate acute from past or chronic infection (see Tables 28-3, 28-4, and 28-5). If serology suggests hepatitis B, testing for hepatitis B e antigen (HBeAg) and antibody to hepatitis B e antigen (anti-HBe) is usually done to help determine the prognosis and to guide antiviral therapy. If serologically confirmed HBV is severe, anti-HDV is measured. If the patient has recently traveled to an endemic area, IgM anti-HEV should be measured if the test is available.

HAV is present in serum only during acute infection and cannot be detected by clinically available tests. IgM antibody typically develops early in the infection and peaks about 1 to 2 wk after the development of jaundice. It diminishes within several weeks, followed by the development of protective IgG antibody (IgG anti-HAV), which persists usually for life. Thus, IgM antibody is a marker of acute infection, whereas IgG anti-HAV indicates only previous exposure to HAV and immunity to recurrent infection.

HBV has at least 3 distinct antigen-antibody systems that can be tested: HBsAg, hepatitis B core antigen (HBcAg), and HBeAg. HBV-DNA can also be tested. HBV surface coat can be detected in serum as HBsAg. HBsAg characteristically appears during the incubation period, usually 1 to 6 wk before clinical or biochemical

[**Fig. 28-1.** Simplified diagnostic approach to possible acute viral hepatitis.]

illness develops, and implies infectivity of the blood. It disappears during convalescence. However, HBsAg is occasionally transient. The corresponding protective antibody (anti-HBs) appears weeks or months later, after clinical recovery, and usually persists for life; thus, its detection indicates past HBV infection and relative immunity. In 5 to 10% of patients, HBsAg persists and antibodies do not develop; these patients become asymptomatic carriers of the virus or develop chronic hepatitis.

HBcAg reflects the viral core. It is detectable in infected liver cells but not in serum except by special techniques. Antibody to HBcAg (anti-HBc) generally appears at the onset of clinical illness; thereafter, titers gradually diminish, usually over years or life. Its presence with anti-HBs indicates recovery from previous HBV infection. Anti-HBc is also present in chronic HBsAg carriers, who do not mount an anti-HBs response. In acute infection, anti-HBc is mainly of the IgM class, whereas in chronic infection, IgG anti-HBc predominates. IgM anti-HBc is a sensitive marker of acute HBV infection and occasionally is the only marker of recent infection, reflecting a window between disappearance of HBsAg and appearance of anti-HBs.

HBeAg is a protein derived from the viral core (not to be confused with hepatitis E virus).

[Table 28-3. Hepatitis A Serology]

Present only in HBsAg-positive serum, HBeAg tends to suggest more active viral replication and greater infectivity. In contrast, presence of the corresponding antibody (anti-HBe) suggests lower infectivity. Thus, e antigen markers are more helpful in prognosis than in diagnosis. Chronic liver disease develops more often among patients with HBeAg and less often among patients with anti-HBe.

In patients with active HBV infection, HBV-DNA can be detected in the serum with special testing, although this testing is not routinely available.

In **HCV**, serum antibody to HCV (anti-HCV) almost always implies active infection; it is not protective. Anti-HCV usually appears within 2 wk of acute infection but is sometimes delayed; however, HCV-RNA is positive. In a small proportion of patients, anti-HCV merely reflects prior exposure with clearance of the virus rather than active infection. In such cases, ALT and AST levels are usually normal. In unclear cases, HCV-RNA is measured.

[Table 28-4. Hepatitis B Serology*]

[Table 28-5. Hepatitis C Serology]

In **HDV**, anti-HDV implies active infection. It may not be detectable until weeks after the acute illness.

In **HEV**, the test for IgM anti-HEV is not routinely available. In a patient with endemic exposure and compatible clinical findings, anti-HEV suggests acute HEV infection.

Biopsy: Biopsy is usually unnecessary but, if done, usually reveals similar histopathology regardless of the specific virus: patchy cell dropout, acidophilic hepatocellular necrosis, mononuclear inflammatory infiltrate, histologic evidence of regeneration, and preservation of the reticulin framework. HBV can occasionally be diagnosed based on the presence of ground-glass hepatocytes (caused by HBsAg-packed cytoplasm) and using special immunologic stains for the viral components. However, these findings are unusual in acute HBV and are much more common in chronic HBV infection. HCV causation can sometimes be inferred from subtle morphologic clues. Liver biopsy may help predict prognosis in acute hepatitis but is rarely done solely for this purpose. Complete histologic recovery occurs unless extensive necrosis bridges entire acini (bridging necrosis). Most patients with bridging necrosis recover fully. However, some cases progress to chronic hepatitis.

Treatment

• Supportive care

• Occasionally postexposure prophylaxis

No treatments attenuate acute viral hepatitis except, occasionally, postexposure immunoprophylaxis. Alcohol should be avoided because it can increase liver damage. Restrictions on diet or activity, including commonly prescribed bed rest, have no scientific basis. Most patients may safely return to work after jaundice resolves, even if AST or ALT levels are slightly elevated. For cholestatic hepatitis,

cholestyramine 8 g po once/day or bid can relieve itching. Viral hepatitis should be reported to the local or state health department.

Prevention

Because treatments have limited efficacy, prevention of viral hepatitis is very important. Good personal hygiene helps prevent transmission, particularly fecal-oral transmission, as occurs with HAV and HEV. Blood and other body fluids (eg, saliva, semen) of patients with acute HBV and HCV and stool of patients with HAV are considered infectious. Barrier protection is recommended, but isolation of patients does little to prevent spread of HAV and is of no value in HBV or HCV infection. Posttransfusion infection is minimized by avoiding unnecessary transfusions and screening all donors for HBsAg and anti-HCV. Screening has decreased the incidence of posttransfusion hepatitis, probably to about 1/100,000 units of blood component transfused.

Immunoprophylaxis can involve active immunization using vaccines and passive immunization.

HAV: Preexposure HAV prophylaxis should be provided for travelers to highly endemic areas. It should also be considered for military personnel, day-care center employees, diagnostic laboratory workers, and, because they have an increased risk of fulminant hepatitis from HAV, patients with chronic liver disorders (including chronic hepatitis C). Several vaccines against HAV are available, each with different doses and schedules; they are safe, provide protection within about 4 wk, and provide prolonged protection (probably for > 20 yr).

Standard immune globulin, formerly immune serum globulin, prevents or decreases the severity of HAV infection and should be given to family members and close contacts of patients for postexposure prophylaxis; 0.02 mL/kg IM is generally recommended, but some experts advise 0.06 mL/kg (3 to 5 mL for adults).

HBV: Vaccination in endemic areas has dramatically reduced local prevalence. Pre-exposure immunization has long been recommended for people at high risk. However, selective vaccination of high-risk groups in the US and other nonendemic areas has not substantially decreased the incidence of HBV; thus, vaccination is now recommended for all US residents < 18 beginning at birth. Universal worldwide vaccination is desirable but is too expensive to be feasible.

Two recombinant vaccines are available; both are safe, even during pregnancy. Three IM deltoid injections are given: at baseline, at 1 mo, and at 6 mo. Children are given lower doses, and immunosuppressed patients and patients receiving hemodialysis are given higher doses.

After vaccination, levels of anti-HBs remain protective for 5 yr in 80 to 90% of immunocompetent recipients and for 10 yr in 60 to 80%. Booster doses of vaccine are recommended for patients receiving hemodialysis and immunosuppressed patients whose anti-HBs is < 10 mIU/mL.

HBV postexposure immunoprophylaxis combines vaccination with hepatitis B immune globulin (HBIG), a product with high titers of anti-HBs. HBIG probably does not prevent infection but prevents or attenuates clinical illness. For infants born to HBsAg-positive mothers, an initial dose of vaccine plus 0.5 mL of HBIG is given IM in the thigh immediately after birth. For anyone having sexual contact with an HBsAg-positive person or percutaneous or mucous membrane exposure to HBsAg-positive blood, 0.06 mL/kg of HBIG is given IM within days, along with vaccine. Any previously vaccinated patient sustaining a percutaneous HBsAg-positive exposure is tested for anti-HBs; if titers are < 10 mIU/mL, a booster dose of vaccine is given.

HCV, HDV, and HEV: A vaccine is now available for hepatitis E; it appears to have about 95% efficacy in preventing symptomatic infection in males and is safe. Efficacy in other groups, duration of protection, and efficacy in preventing asymptomatic infection are unknown. No product exists for immunoprophylaxis of HCV or HDV. However, prevention of HBV prevents HDV. The propensity of HCV for changing its genome hampers vaccine development.

Fulminant Hepatitis

Fulminant hepatitis is a rare syndrome of massive necrosis of liver parenchyma and a decrease in liver size (acute yellow atrophy) that usually occurs after infection with certain hepatitis viruses, exposure to toxic agents, or drug-induced injury.

HBV is sometimes responsible, and up to 50% of cases of fulminant hepatitis B involve HDV coinfection. Fulminant hepatitis with HAV is rare but may be more likely in people with preexisting liver disorders. The role of HCV remains uncertain.

Patients rapidly deteriorate because portal-systemic encephalopathy develops, often followed by coma within hours or a few days, sometimes with cerebral edema. Bleeding commonly results from hepatic failure or disseminated intravascular coagulation, and functional renal failure (hepatorenal syndrome —see p. 223) may develop. Increasing PT, portal-systemic encephalopathy, and particularly renal failure are ominous.

Meticulous nursing care and aggressive treatment of complications improve the outcome. However, emergency liver transplantation provides the best hope for survival. Survival in adults is uncommon without transplantation; children tend to do better. Patients who survive usually recover fully.

Chronic Hepatitis

Chronic hepatitis is hepatitis that lasts > 6 mo. Common causes include hepatitis B and C viruses, autoimmune mechanisms (autoimmune hepatitis), and drugs. Many patients have no history of acute hepatitis, and the first indication is discovery of asymptomatic aminotransferase elevations. Some patients present with cirrhosis or its complications (eg, portal hypertension). Biopsy is necessary to confirm the diagnosis and to grade and stage the disease. Treatment is directed toward complications and the underlying condition (eg, corticosteroids for autoimmune hepatitis, antiviral therapy for viral hepatitis). Liver transplantation is often indicated for end-stage disease.

Etiology

Hepatitis lasting > 6 mo is generally defined as chronic, although this duration is arbitrary. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are frequent causes of chronic hepatitis; 5 to 10% of cases of HBV infection, with or without hepatitis D virus (HDV) co-infection, and about 75% of cases of HCV infection become chronic. Hepatitis A and E viruses are not causes. Although the mechanism of chronicity is uncertain, liver injury is mostly determined by the patient's immune reaction to the infection.

Many cases are idiopathic. A high proportion of idiopathic cases have prominent features of immune-mediated hepatocellular injury (autoimmune hepatitis), including the following:

- The presence of serologic immune markers
- An association with histocompatibility haplotypes common in autoimmune disorders (eg, HLA-B1, HLA-B8, HLA-DR3, HLA-DR4)
- A predominance of T lymphocytes and plasma cells in liver histologic lesions
- Complex in vitro defects in cellular immunity and immunoregulatory functions
- An association with other autoimmune disorders (eg, RA, autoimmune hemolytic anemia, proliferative glomerulonephritis)
- A response to therapy with corticosteroids or immunosuppressants

Sometimes chronic hepatitis has features of both autoimmune hepatitis and another chronic liver disorder (eg, primary biliary cirrhosis, chronic viral hepatitis). These conditions are called overlap syndromes.

Many drugs, including isoniazid, methyldopa, nitrofurantoin, and, rarely, acetaminophen, can cause chronic hepatitis. The mechanism varies with the drug and may involve altered immune responses, cytotoxic intermediate metabolites, or genetically determined metabolic defects.

Other causes of chronic hepatitis include alcoholic hepatitis and nonalcoholic steatohepatitis. Less often, chronic hepatitis results from α_1-antitrypsin deficiency or Wilson's disease.

Cases were once classified histologically as chronic persistent, chronic lobular, or chronic active hepatitis. A more useful recent classification system specifies the etiology, the intensity of histologic inflammation and necrosis (grade), and the degree of histologic fibrosis (stage). Inflammation and necrosis are potentially reversible; fibrosis generally is not.

Symptoms and Signs

Clinical features vary widely. About one third of cases develop after acute hepatitis, but most develop insidiously de novo. Many patients are asymptomatic, especially in chronic HCV infection. However, malaise, anorexia, and fatigue are common, sometimes with low-grade fever and nonspecific upper abdominal discomfort. Jaundice is usually absent. Often, particularly with HCV, the first findings are signs of chronic liver disease (eg, splenomegaly, spider nevi, palmar erythema). A few patients with chronic hepatitis develop manifestations of cholestasis. In the autoimmune variant, especially in young women, manifestations may involve virtually any body system and can include acne, amenorrhea, arthralgia, ulcerative colitis, pulmonary fibrosis, thyroiditis, nephritis, and hemolytic anemia.

Chronic HCV is occasionally associated with lichen planus, mucocutaneous vasculitis, glomerulonephritis, porphyria cutanea tarda, and perhaps non-Hodgkin B-cell lymphoma. About 1% of patients develop symptomatic cryoglobulinemia with fatigue, myalgias, arthralgias, neuropathy, glomerulonephritis, and skin rashes (urticaria, purpura, or leukocytoclastic vasculitis); asymptomatic cryoglobulinemia is more common.

Diagnosis

• Liver function test results compatible with hepatitis

• Viral serologic tests

• Possibly autoantibodies, immunoglobulins, α_1-antitrypsin level, and other tests

• Usually biopsy

• Serum albumin and PT

The diagnosis is suspected in patients with suggestive symptoms and signs, incidentally noted elevations in aminotransferase levels, or previously diagnosed acute hepatitis. Liver function tests are needed if not previously done and include serum ALT, AST, alkaline phosphatase, and bilirubin. Aminotransferase elevations are the most characteristic laboratory abnormalities. Although levels can vary, they are typically 100 to 500 IU/L. ALT is usually higher than AST. Amino-transferase levels can be normal during chronic hepatitis if the disease is quiescent, particularly with HCV. Alkaline phosphatase is usually normal or only slightly elevated but is occasionally markedly high. Bilirubin is usually normal unless the disease is severe or advanced. However, abnormalities in these laboratory tests are not specific and can result from other disorders, such as alcoholic liver disease, recrudescent acute viral hepatitis, and primary biliary cirrhosis.

If laboratory results are compatible with hepatitis, viral serologic tests are done to exclude HBV and HCV (see Tables 28-4 and 28-5). Unless these tests indicate viral etiology, further testing is required. The first tests done include autoantibodies, immunoglobulins, and α_1-antitrypsin level. Children and young adults are screened for Wilson's disease with a ceruloplasmin level. Marked elevations in serum immunoglobulins suggest chronic autoimmune hepatitis but are not conclusive. Autoimmune hepatitis is normally diagnosed based on the presence of antinuclear (ANA), anti-smooth muscle, or anti-liver/kidney

microsomal type 1 (anti-LKM1) antibodies at titers of 1:80 (in adults) or 1:20 (in children).

Unlike in acute hepatitis, biopsy is necessary. Mild cases may have only minor hepatocellular necrosis and inflammatory cell infiltration, usually in portal regions, with normal acinar architecture and little or no fibrosis. Such cases rarely develop into clinically important liver disease or cirrhosis. In more severe cases, biopsy typically shows periportal necrosis with mononuclear cell infiltrates (piecemeal necrosis) accompanied by variable periportal fibrosis and bile duct proliferation. The acinar architecture may be distorted by zones of collapse and fibrosis, and frank cirrhosis sometimes coexists with signs of ongoing hepatitis. Biopsy is also used to grade and stage the disease.

In most cases, the specific cause of chronic hepatitis cannot be discerned via biopsy alone, although cases caused by HBV can be distinguished by the presence of ground-glass hepatocytes and special stains for HBV components. Autoimmune cases usually have a more pronounced infiltration by lymphocytes and plasma cells. In patients with histologic but not serologic criteria for chronic autoimmune hepatitis, variant autoimmune hepatitis is diagnosed; many have overlap syndromes.

Serum albumin and PT should be measured to determine severity; hepatic insufficiency is suggested by low serum albumin or prolonged PT. If symptoms or signs of cryoglobulinemia develop during chronic hepatitis, particularly with HCV, cryoglobulin levels and rheumatoid factor should be measured; high levels of rheumatoid factor and low levels of complement suggest cryoglobulinemia.

Patients with chronic HBV infection should be screened annually for hepatocellular cancer with ultrasonography and serum α-fetoprotein measurement, although the cost-effectiveness of this practice is debated. Patients with chronic HCV infection should be similarly screened only if cirrhosis is present.

Prognosis

Prognosis is highly variable. Chronic hepatitis caused by a drug often regresses completely when the offending drug is withdrawn. Without treatment, cases caused by HBV can resolve (uncommon), progress rapidly, or progress slowly to cirrhosis over decades. Resolution often begins with a transient increase in disease severity and results in seroconversion from hepatitis B e antigen (HBeAg) to antibody to hepatitis B e antigen (anti-HBe). Co-infection with HDV causes the most severe form of chronic HBV infection; without treatment, cirrhosis develops in up to 70% of patients. Untreated chronic hepatitis due to HCV produces cirrhosis in 20 to 30% of patients, although development may take decades. Chronic autoimmune hepatitis usually responds to therapy but sometimes causes progressive fibrosis and eventual cirrhosis.

Chronic HBV infection increases the risk of hepatocellular cancer. The risk is also increased in chronic HCV infection, but only if cirrhosis has already developed (see p. 265).

Treatment

• Supportive care

• Treatment of cause (eg, corticosteroids for autoimmune hepatitis, antivirals for HBV, interferons for HCV)

Treatment goals include management of complications (eg, ascites, encephalopathy) and treatment of the cause. Drugs that cause hepatitis should be stopped. Underlying disorders, such as Wilson's disease, should be treated. In chronic hepatitis due to HBV, prophylaxis for contacts of patients may be helpful (see p. 254); corticosteroids and immunosuppressive drugs should be avoided because they enhance viral replication. No prophylactic measures are required for contacts of patients with HCV infection.

Autoimmune hepatitis: Corticosteroids, with or without azathioprine, prolong survival. Prednisone is usually started at 30 to 40 mg po once/day, then tapered to the lowest dose that maintains aminotransferases at normal or near-normal levels. Some experts give concomitant azathioprine 1 to 1.5 mg/kg po once/day; others add azathioprine only if low-dose prednisone fails to maintain suppression. Most patients require long-term, low-dose maintenance treatment. Liver transplantation may be required for end-stage disease.

HBV: Antiviral treatment is indicated for patients with elevated aminotransferase levels, clinical or biopsy evidence of progressive disease, or both. The goal is to eliminate HBV-DNA. Treatment may need to be continued indefinitely and thus may be very expensive; stopping treatment prematurely can lead to relapse, which may be severe. However, treatment may be stopped if HBeAg converts to anti-HBe or if tests for HBsAg become negative. Drug resistance is also a concern. Six antiviral drugs—entecavir, adefovir, lamivudine, interferon-α (INF-α), pegylated INF-α2a (peginterferon-α2a), and telbivudine—are available (see
Table 28-6).

First-line treatment is usually with an oral antiviral drug, such as entecavir (a nucleoside analogue) or adefovir (a nucleotide analogue). Combination therapy has not proved superior to monotherapy.

Entecavir appears to have higher antiviral potency than other commonly used drugs. Resistance to entecavir is uncommon, but the drug has not been in widespread clinical use for very long. Dosage is 0.5 mg po once/day; however, patients who have previously taken

[**Table 28-6.** Comparison of Drugs Commonly Used to Treat Chronic Viral Hepatitis B*]

a nucleoside analogue should take 1 mg po once/day. Dose reduction is required in patients with renal insufficiency. Serious adverse effects appear to be uncommon so far, although the drug can induce tumors in animals.

Adefovir is also relatively potent. Dosage is 10 mg po once/day. Adefovir may cause renal dysfunction, so serum creatinine level must be measured periodically and the dose reduced if necessary.

Alternatively, lamivudine (a nucleoside analogue) 100 mg po once/day is given. It has few adverse effects, which is one of its advantages over other antiviral drugs used to treat chronic HBV infection. INF-α (usually IFN-α2b), formerly first-line treatment, can be used. Dosage is 5 million IU sc once/day or 10 million IU sc 3 times/wk for 4 mo. In about 40% of patients, this regimen eliminates HBV-DNA and causes seroconversion to anti-HBe; a successful response is usually presaged by a temporary increase in aminotransferase levels. The drug must be given by injection and is often poorly tolerated. The first 1 or 2 doses cause an influenza-like syndrome. Later, fatigue, malaise, depression, bone marrow suppression, and, rarely, bacterial infections or autoimmune disorders can occur. In patients with advanced cirrhosis, IFN-α can precipitate hepatic failure and is therefore contraindicated. Other contraindications include renal failure, immunosuppression, solid organ transplantation, cytopenia, and substance abuse. In a few patients, treatment must be stopped because of intolerable adverse effects. The drug should be given cautiously or not at all to patients with ongoing substance abuse or a major psychiatric disorder.

Pegylated IFN-α2 can also be given. Dosage is 180 µg sc once/wk. Adverse effects are similar to those of INF-α but may be less severe.

Telbivudine is a new drug that has greater efficacy than lamivudine but has high rates of resistance.

Liver transplantation should be considered for end-stage liver disease caused by HBV, but the infection aggressively attacks the graft, and prognosis is less favorable than when liver transplantation is done for other indications. Long-term posttransplantation therapy with lamivudine improves the outcome.

HCV: For chronic hepatitis due to HCV, treatment is indicated if aminotransferase levels are elevated and biopsy shows active inflammatory disease with evolving fibrosis. Treatment aims to permanently eliminate HCV-RNA (sustained response), which is associated with permanent normalization of aminotransferase and cessation of histologic progression.

Combination therapy with pegylated IFN-α plus ribavirin has the best results. Pegylated IFN-α2b 1.5 µg/kg sc once/wk and pegylated IFN-α2a 180 µg sc once/wk have comparable results. Ribavirin 500 to 600 mg po bid is usually given, although 400 mg bid may be sufficient for viral genotypes 2 and 3.

HCV genotype and viral load are determined before treatment because results influence treatment.

Genotype 1 is the most common type but is relatively resistant to treatment. Combination therapy is given for 1 yr; a sustained response rate of about 45 to 50% overall occurs. Results are more favorable in patients with early disease and less favorable in those who already have cirrhosis. HCV viral load should be measured at 3 mo and treatment stopped if RNA has not declined by at least 2 log levels compared with pretreatment values.

Less common genotypes 2 and 3 respond more favorably. Combination therapy is required for only 6 mo and gives an overall sustained response rate of about 75%. Longer treatment does not improve the results.

Adverse effects of pegylated IFN are similar to those of IFN-α but may be less severe; contraindications are also similar (see above).

Ribavirin is usually well tolerated but commonly causes anemia due to hemolysis; dosage should be decreased if hemoglobin falls to < 10 g/dL. Ribavirin is teratogenic for both men and women, necessitating contraception until 6 mo after completion of treatment. Patients who cannot tolerate ribavirin should be given pegylated IFN-α, but results are not as good as with combination treatment. Ribavirin monotherapy is of no value.

In most adult transplantation centers, advanced cirrhosis due to HCV is now the most common indication for liver transplantation. Although HCV recurs in the graft, the course is usually indolent, and long-term survival rates are relatively high.

Chapter 29. Vascular Disorders of the Liver

Introduction

The liver has a dual blood supply. The portal vein (which is rich in nutrients and relatively high in O_2) provides two thirds of blood flow to the liver. The hepatic artery (which is O_2-rich) supplies the rest. The hepatic veins drain the liver into the inferior vena cava. When portal vein blood flow increases, hepatic artery flow decreases and vice versa (the hepatic arterial buffer response). This dual, reciprocally compensatory blood supply provides some protection from hepatic ischemia in healthy people.

Despite its dual blood supply, the liver, a metabolically active organ, can be injured by

- **Ischemia:** Ischemia results from reduced blood flow, reduced O_2 delivery, increased metabolic activity, or all three.

- **Insufficient venous drainage:** The cause may be focal or diffuse obstruction. Manifestations of focal venous obstruction depend on the location. Diffuse venous congestion causes congestive hepatopathy. Reduced venous outflow from the liver (originating in the hepatic veins or within the liver itself, usually from cirrhosis) results in portal hypertension.

- **Specific vascular lesions:** The hepatic artery, hepatic vein, or portal vein may be involved. In peliosis hepatis, the vascular lesion occurs in the sinusoids (microvascular anastomoses between the portal and hepatic veins).

Hepatic Ischemia

Diffuse ischemia can cause ischemic hepatitis; focal ischemia can cause hepatic infarction or ischemic cholangiopathy. Hepatic infarction results from hepatic artery disorders.

Ischemic Hepatitis

(Acute Hepatic Infarction; Hypoxic Hepatitis; Shock Liver)

Ischemic hepatitis is diffuse liver damage due to an inadequate blood or O_2 supply.

Causes are most often systemic:

- Impaired hepatic perfusion (eg, due to heart failure or acute hypotension)

- Hypoxemia (eg, due to respiratory failure or carbon monoxide toxicity)

- Increased metabolic demand (eg, due to sepsis)

Focal lesions of the hepatic vasculature are less common causes. Ischemic hepatitis may develop when hepatic artery thrombosis occurs during liver transplantation or when a sickle cell crisis is associated with portal vein thrombosis (thus compromising the dual blood supply to the liver). Centrizonal necrosis develops without liver inflammation (ie, not a true hepatitis).

Symptoms may include nausea, vomiting, and tender hepatomegaly.

Diagnosis

- Clinical evaluation and liver function tests

- Doppler ultrasonography, MRI, or arteriography

Ischemic hepatitis is suspected in patients who have risk factors and laboratory abnormalities:

• Serum aminotransferase increases dramatically (eg, to 1000 to 3000 IU/L).

• LDH increases within hours of ischemia (unlike acute viral hepatitis).

• Serum bilirubin increases modestly, only to ≤ 4 times its normal level.

• PT/INR increases.

Diagnostic imaging helps define the cause: Doppler ultrasonography, MRI, or arteriography can identify an obstructed hepatic artery or portal vein thrombosis.

Treatment

• Hepatic reperfusion

Treatment is directed at the cause, aiming to restore hepatic perfusion, particularly by improving cardiac output and reversing any hemodynamic instability.

If perfusion is restored, aminotransferase decreases over 1 to 2 wk. In most cases, liver function is fully restored. Fulminant liver failure, although uncommon, can occur in patients with preexisting cirrhosis.

Ischemic Cholangiopathy

Ischemic cholangiopathy is focal damage to the biliary tree due to disrupted flow from the hepatic artery via the peribiliary arterial plexus.

Common causes of ischemic cholangiopathy include vascular injury during orthotopic liver transplantation or laparoscopic cholecystectomy, graft-rejection injury, chemoembolization, radiation therapy, and thrombosis resulting from hypercoagulability disorders. Bile duct injury (ischemic necrosis) results, causing cholestasis, cholangitis, or biliary strictures (often multiple).

Symptoms (eg, pruritus, dark urine, pale stools), laboratory tests, and imaging studies indicate cholestasis.

The diagnosis is suspected when cholestasis is evident in patients at risk, particularly after liver transplantation. Ultrasonography is the 1st-line diagnostic imaging test for cholestasis, but most patients require magnetic resonance cholangiopancreatography, ERCP, or both to rule out other causes such as cholelithiasis or cholangiocarcinoma.

Treatment is directed at the cause. After liver transplantation, such treatment includes antirejection therapy and possible retransplantation. Biliary strictures warrant endoscopic balloon dilation and stenting.

Congestive Hepatopathy

(Passive Hepatic Congestion)

Congestive hepatopathy is diffuse venous congestion within the liver that results from right-sided heart failure (usually due to a cardiomyopathy, tricuspid regurgitation, mitral insufficiency, cor pulmonale, or constrictive pericarditis).

Moderate or severe right-sided heart failure increases central venous pressure, which is transmitted to the liver via the inferior vena cava and hepatic veins. Chronic congestion leads to atrophy of hepatocytes, distention of sinusoids, and centrizonal fibrosis, which, if severe, progresses to cirrhosis (cardiac cirrhosis). The basis for liver cell death is probably sinusoidal thrombosis that propagates to the central veins and branches of the portal vein, causing ischemia.

Most patients are asymptomatic. However, moderate congestion causes right upper quadrant discomfort

(due to stretching of the liver capsule) and tender hepatomegaly. Severe congestion leads to massive hepatomegaly and jaundice. Ascites may result from the transmitted central venous hypertension; infrequently, splenomegaly results. With transmitted central venous hypertension, the hepatojugular reflex is present, unlike in hepatic congestion due to Budd-Chiari syndrome.

Diagnosis

• Clinical evaluation

Congestive hepatopathy is suspected in patients who have right-sided heart failure, jaundice, and tender hepatomegaly. Liver biochemistries are modestly abnormal: unconjugated hyperbilirubinemia (total bilirubin < 3 mg/dL), elevated (usually < 2 to 3 fold) aminotransferases, and prolonged PT/INR. Any ascitic fluid has a high albumin content (> 25 g/L) and serum ascites/albumin gradient. (≥ 1.1). Because the laboratory abnormalities are nonspecific, recognition of congestive hepatopathy is ultimately clinical. The liver disorder is more important as an index of the severity of heart failure than as a diagnosis by itself.

Treatment

Treatment is directed at the underlying heart failure.

Hepatic Artery Disorders

The hepatic artery may be occluded. Uncommonly, aneurysms develop.

Hepatic Artery Occlusion

Causes of hepatic artery occlusion include thrombosis (eg, due to hypercoagulability disorders, severe arteriosclerosis, or vasculitis), emboli (eg, due to endocarditis, tumors, therapeutic embolization, or chemoembolization), iatrogenic causes (eg, ligation during surgery), vasculitis (via nonthrombotic mechanisms), structural arterial abnormalities (eg, hepatic artery aneurysm), eclampsia, cocaine use, and sickle cell crisis. Usually, the result is an hepatic infarct. In patients with a liver transplant or preexisting portal vein thrombosis, hepatic artery thrombosis causes ischemic hepatitis (see p. 259). Because of the liver's dual blood supply, the liver is somewhat resistant to ischemic hepatitis and infarction.

Hepatic artery occlusion does not elicit symptoms without hepatic infarction or ischemic hepatitis. Hepatic infarction may be asymptomatic or cause right upper quadrant pain, fever, nausea, vomiting, and jaundice. Leukocytosis and a high aminotransferase level are common.

Diagnosis

• Vascular imaging

Diagnosis of hepatic artery occlusion is confirmed by imaging with Doppler ultrasonography, usually followed by angiography. The choice between CT angiography, magnetic resonance angiography, and celiac arteriography largely depends on availability and expertise. CT may detect a wedge-shaped area of low attenuation.

Treatment

Treatment is directed at the cause.

Aneurysms

Aneurysms of the hepatic artery are uncommon. They tend to be saccular and multiple. Causes include infection, arteriosclerosis, trauma, and vasculitis. Untreated aneurysms may cause death by rupturing into the common bile duct (causing hemobilia), peritoneum (causing peritonitis), or adjacent hollow viscera. Hemobilia may cause jaundice, upper GI bleeding, and abdominal pain in the right upper quadrant.

Diagnosis is suspected if typical symptoms occur or if imaging tests detect an aneurysm. Doppler ultrasonography, followed by contrast CT, is required for confirmation.

Treatment is embolization or surgical ligation.

Hepatic Vein Disorders

Obstruction of hepatic venous outflow can occur in extrahepatic vessels (Budd-Chiari syndrome) or intrahepatic vessels (veno-occlusive disease) but often occurs in both. Obstruction results in congestion of the sinusoids, hepatomegaly, portal hypertension, reduced portal blood flow, ascites, and splenomegaly.

Budd-Chiari Syndrome

Budd-Chiari syndrome is obstruction of hepatic venous outflow that originates anywhere from the small hepatic veins inside the liver to the inferior vena cava and right atrium. Manifestations range from no symptoms to fulminant liver failure. Diagnosis is based on ultrasonography. Treatment includes supportive medical therapy and measures to establish and maintain venous patency, such as thrombolysis, decompression with shunts, and long-term anticoagulation.

Etiology

In the Western world, the most common cause is a clot obstructing the hepatic veins and the adjacent inferior vena cava. Clots commonly result from the following:

- Thrombotic conditions (eg, protein C or S deficiency, antiphospholipid syndrome, antithrombin III deficiency, factor V Leiden mutation, pregnancy, oral contraceptive use)
- Hematologic disorders (eg, myeloproliferative disorders such as polycythemia and paroxysmal nocturnal hemoglobinopathy)
- Inflammatory bowel disease
- Connective tissue disorders
- Trauma
- Infection (eg, hydatid cyst, amebiasis)
- Tumor invasion of the hepatic vein (eg, hepatocellular or renal cell carcinoma)

Sometimes Budd-Chiari syndrome begins during pregnancy and unmasks a previously asymptomatic hypercoagulability disorder.

The cause of obstruction is often unknown. In Asia and South Africa, the basic defect is often a membranous obstruction (webs) of the inferior vena cava above the liver, likely representing recanalization of a prior thrombus in adults or a developmental flaw (eg, venous stenosis) in children. This type of obstruction is called obliterative hepatocavopathy.

Budd-Chiari syndrome usually develops over weeks or months. When it does, cirrhosis and portal hypertension tend to develop.

Symptoms and Signs

Manifestations range from none (asymptomatic) to fulminant liver failure or cirrhosis. Symptoms vary depending on whether the obstruction occurs acutely or over time.

Acute obstruction (in about 20%) causes fatigue, right upper quadrant pain, nausea, vomiting, mild

jaundice, tender hepatomegaly, and ascites. It typically occurs during pregnancy. Fulminant liver failure with encephalopathy is rare. Aminotransferase levels are quite high

Chronic outflow obstruction (developing over weeks to months) may be rather asymptomatic in some patients until it progresses or may cause fatigue, abdominal pain, and hepatomegaly. Lower-extremity edema and ascites may result from venous obstruction, even in the absence of cirrhosis. Cirrhosis may develop, leading to variceal bleeding, massive ascites, splenomegaly, hepatopulmonary syndrome (see p. 1988), or a combination. Complete obstruction of the inferior vena cava causes edema of the abdominal wall and legs plus visibly tortuous superficial abdominal veins from the pelvis to the costal margin.

Diagnosis

• Clinical evaluation and liver function tests

• Vascular imaging

Budd-Chiari syndrome is suspected in patients with

• Hepatomegaly, ascites, liver failure, or cirrhosis when there is no obvious cause (eg, alcohol abuse, hepatitis) or when the cause is unexplained

• Abnormal liver function test results and risk factors for thrombosis

Liver function tests are usually abnormal; the pattern is variable and nonspecific. Imaging usually begins with abdominal Doppler ultrasonography, which can show the direction of blood flow and the site of obstruction. Magnetic resonance angiography and CT are useful if ultrasonography is not diagnostic. Conventional angiography (venography with pressure measurements and arteriography) is necessary if therapeutic or surgical intervention is planned. Liver biopsy is done occasionally to diagnose the acute stages and determine whether cirrhosis has developed.

Prognosis

Without treatment, most patients with complete venous obstruction die of liver failure within 3 yr. For patients with incomplete obstruction, the course varies.

Treatment

• Supportive care

• Restoration and maintenance of adequate venous outflow

Treatment varies according to its onset (acute vs chronic) and severity (fulminant liver failure vs decompensated cirrhosis vs stable or asymptomatic). The cornerstones of management are

• Giving supportive therapy directed at complications (eg, ascites, liver failure, esophageal varices)

• Decompressing the congested liver (ie, maintaining venous outflow)

• Preventing propagation of the clot

Aggressive interventions (eg, thrombolysis, stents) are used when the disease is acute (eg, within 4 wk and in the absence of cirrhosis). Thrombolysis can dissolve acute clots, allowing recanalization and so relieving hepatic congestion. Radiologic procedures have a major role using angioplasty, stenting, and portosytemic shunts. For caval webs or hepatic venous stenosis, decompression via percutaneous transluminal balloon angioplasty with intraluminal stents can maintain hepatic outflow. When dilation of a hepatic outflow narrowing is not technically feasible, transjugular intrahepatic portosystemic shunting (TIPS) and various surgical shunts can provide decompression by diversion into the systemic circulation. Portosystemic shunts are generally not used if hepatic encephalopathy is present; such shunts worsen

liver function. Further, shunts tend to thrombose, especially when associated with hematologic disorders.

Long-term anticoagulation is often necessary to prevent recurrence. Liver transplantation may be lifesaving in patients with fulminant disease or decompensated cirrhosis.

Veno-Occlusive Disease

(Sinusoidal Obstruction Syndrome)

Hepatic veno-occlusive disease is caused by endothelial injury, leading to nonthrombotic occlusion of the terminal hepatic venules and hepatic sinusoids, rather than of the hepatic veins or inferior vena cava (as in Budd-Chiari syndrome).

Venous congestion causes portal hypertension and ischemic necrosis (which leads to cirrhosis).

Common causes include

• Irradiation

• Graft-vs-host disease resulting from bone marrow or hematopoietic cell transplantation

• Pyrrolizidine alkaloids in crotalaria and senecio plants (eg, medicinal bush teas) and other herbs (eg, comfrey)

• Other hepatotoxins (eg, dimethylnitrosamine, aflatoxin, azathioprine, some anticancer drugs)

Initial manifestations include sudden jaundice, ascites, and tender, smooth hepatomegaly. Onset is within the first 3 wk of transplantation in bone marrow or hematopoietic cell recipients, who either recover spontaneously within a few weeks (or sometimes, with mild cases, after an increase in immunosuppressant therapy) or die of fulminant liver failure. Other patients have recurrent ascites, portal hypertension, splenomegaly, and, eventually, cirrhosis.

Diagnosis

• Clinical evaluation and liver function tests

• Ultrasonography

• Sometimes invasive tests (eg, liver biopsy, measurement of portal-hepatic venous pressure gradient)

The diagnosis is suspected in patients with unexplained clinical or laboratory evidence of liver disease, particularly in those with known risk factors, such as bone marrow or hematopoietic cell transplantation. Laboratory results are nonspecific: elevated aminotransferase and conjugated bilirubin levels. PT/INR becomes abnormal when disease is severe. Ultrasonography shows retrograde flow in the portal vein. If the diagnosis is unclear, invasive tests become necessary—eg, liver biopsy or measurement of the portal-hepatic venous pressure gradient (a pressure gradient > 10 mm Hg suggests veno-occlusive disease). Measuring the pressure across the liver entails inserting a catheter percutaneously into a hepatic vein and then wedging it into the liver. This wedged pressure reflects portal vein pressure. (An exception is portal vein thrombosis; in this case, the pressure is normal despite portal hypertension.)

Treatment

• Supportive care

• Treatment of cause

• For progressive disease, transjugular intrahepatic portosystemic shunting or transplantation

Ursodeoxycholic acid helps prevent graft-vs-host disease in bone marrow or hematopoietic cell transplant recipients. Management includes withdrawing the causative agent (such as herbal teas) and providing supportive therapy. Most patients have mild to moderate disease and do quite well. Those that progress may require transjugular intrahepatic portosystemic shunting (TIPS) for relief of portal hypertension. However, in 25%, veno-occlusive disease is severe, accompanied by fulminant liver failure. Liver transplantation is a last resort.

Portal Vein Disorders

Nearly all portal vein disorders obstruct portal vein blood flow and cause portal hypertension (see p. 218). Obstruction can be

- Extrahepatic—portal vein thrombosis due to a hypercoagulable state, vessel wall lesion (eg, pylephlebitis, omphalitis), an adjacent lesion (eg, pancreatitis, tumor), or congenital atresia of the portal vein

- Intrahepatic (eg, microvascular portal vein obstruction as in schistosomiasis, primary biliary cirrhosis, sarcoidosis, noncirrhotic portal hypertension)

Portal Vein Thrombosis

Portal vein thrombosis causes portal hypertension and consequent GI bleeding from varices, usually in the lower esophagus or stomach. Diagnosis is based on ultrasonography. Treatment involves control of variceal bleeding (usually with endoscopic banding, IV octreotide, or both), prevention of recurrence using β-blockers and sometimes surgical shunts and thrombolysis for acute thrombosis.

Etiology

Common causes vary by age group (see Table 29-1).

Symptoms and Signs

Acute portal vein thrombosis is commonly asymptomatic unless associated with another event, such as pancreatitis (the cause), or another complication, such as mesenteric venous thrombosis. Most often, clinical features—splenomegaly (especially in children) and variceal hemorrhage—develop chronically secondary to portal hypertension. Ascites is uncommon (10%) in postsinusoidal portal hypertension. Ascites may be precipitated when cirrhosis is also present or when serum albumin (and thus oncotic pressure) deceases after high-volume fluid resuscitation for a major GI bleed.

Diagnosis

- Clinical evaluation and liver function tests

- Doppler ultrasonography

Portal vein thrombosis is suspected in patients with the following:

- Manifestations of portal hypertension without cirrhosis

- Mild abnormalities in liver function or enzymes plus risk factors such as neonatal umbilical infection, childhood appendicitis, or a hypercoagulability disorder

Doppler ultrasonography is usually diagnostic, showing diminished or absent portal vein flow and sometimes the thrombus. Difficult cases may require MRI or CT with contrast. Angiography may be required to guide shunt surgery.

[Table 29-1. Common Causes of Portal Vein Thrombosis*]

Treatment

• For some acute cases, thrombolysis

• Long-term anticoagulation

• Management of portal hypertension and its complications

In acute cases, thrombolysis is sometimes successful, best reserved for recent occlusion, particularly in hypercoagulable states. Anticoagulation does not lyse clots but has some value for long-term prevention in hypercoagulable states despite the risk of variceal bleeding. In neonates and children, treatment is directed at the cause (eg, omphalitis, appendicitis). Otherwise, management is directed at the portal hypertension and its complications (see p. 218); treatment can include octreotide IV (a synthetic analog of somatostatin) and endoscopic banding to control variceal bleeding and nonselective β-blockers to prevent rebleeding. These therapies have decreased the use of surgical shunts (eg, mesocaval, splenorenal), which can become occluded and have an operative mortality rate of 5 to 50%. Transjugular intrahepatic portosytemic shunting (TIPS) is not recommended. TIPS requires monitoring (including frequent angiography) to assess patency, may become blocked, and may not adequately decompress the liver.

Peliosis Hepatis

Peliosis hepatis is typically an asymptomatic disorder in which multiple blood-filled cystic spaces develop randomly in the liver.

Measuring a few millimeters to about 3 cm in diameter, the cysts of peliosis hepatis often lack a cell lining and are surrounded by hepatocytes. Some have an endothelial cell lining, accompanied by dilated hepatic sinusoids. The cause is probably damage to the sinusoidal lining cells. Peliosis hepatis is associated with use of hormones (eg, anabolic steroids, oral contraceptives, glucocorticoids), tamoxifen, vinyl chloride, vitamin A, and, particularly in kidney transplant recipients, azathioprine.

Peliosis hepatis is usually asymptomatic, but occasionally cysts rupture, resulting in hemorrhage and sometimes causing death. Some patients develop overt liver disease, characterized by jaundice, hepatomegaly, and liver failure.

Mild cases may be detected incidentally during imaging tests done because liver function test results are slightly abnormal or for other reasons. Ultrasonography or CT can detect cysts.

Chapter 30. Liver Masses and Granulomas

Introduction

Liver masses include cysts, benign tumors, primary liver cancers, and metastatic liver cancer. Certain drugs and disorders can result in granuloma formation in the liver.

Hepatic Cysts

Isolated cysts are commonly detected incidentally on abdominal ultrasonography or CT. These cysts are usually asymptomatic and have no clinical significance. The rare congenital polycystic liver is commonly associated with polycystic disease of the kidneys (see p. 2385) and other organs. It causes progressive nodular hepatomegaly (sometimes massive) in adults. Nevertheless, hepatocellular function is remarkably well preserved, and portal hypertension rarely develops.

Other hepatic cysts include the following:

- Hydatid (echinococcal) cysts (see p. 1362)
- Caroli's disease, which is rare, autosomal recessive, and characterized by segmental cystic dilation of intrahepatic bile ducts (often becoming symptomatic in adulthood, with stone formation, cholangitis, and sometimes cholangiocarcinoma)
- True cystic tumors (rare)

Benign Liver Tumors

Benign liver tumors are relatively common. Most are asymptomatic, but some cause hepatomegaly, right upper quadrant discomfort, or intraperitoneal hemorrhage. Most are detected incidentally on ultrasound or other scans. Liver function tests are usually normal or only slightly abnormal. Diagnosis is usually possible with imaging tests but may require biopsy. Treatment is needed only in a few specific circumstances.

Hepatocellular adenoma: Hepatocellular adenoma is the most important benign tumor to recognize. It occurs primarily in women of childbearing age, particularly those taking oral contraceptives, possibly via estrogen's effects. Most adenomas are asymptomatic, but large ones may cause right upper quadrant discomfort. Rarely, adenomas manifest as peritonitis and shock due to rupture and intraperitoneal hemorrhage. Rarely, they become malignant.

Diagnosis is often suspected based on ultrasound or CT results, but biopsy is sometimes needed for confirmation.

Adenomas due to contraceptive use often regress if the contraceptive is stopped. If the adenoma does not regress or if it is subcapsular or > 5 cm, surgical resection is often recommended.

Focal nodular hyperplasia: This localized hamartoma may resemble macronodular cirrhosis histologically. Diagnosis is usually based on MRI or CT with contrast, but biopsy may be necessary. Treatment is rarely needed.

Hemangiomas: Hemangiomas are usually small and asymptomatic; they occur in 1 to 5% of adults. These tumors often have a characteristic highly vascular appearance. Rupture is rare, even when tumors are large. Hemangiomas are found incidentally during ultrasonography, CT, or MRI. Treatment is usually not indicated.

In infants, hemangiomas often regress spontaneously by age 2 yr. However, large hemangiomas occasionally cause arteriovenous shunting sufficient to cause heart failure and sometimes consumption coagulopathy. In these cases, treatment may include high-dose corticosteroids, sometimes diuretics and digoxin to improve heart function, interferon-α (given sc), surgical removal, selective hepatic artery

embolization, and, rarely, liver transplantation.

Other benign tumors: Lipomas (usually asymptomatic) and localized fibrous tumors (eg, fibromas) rarely occur in the liver.

Benign bile duct adenomas are rare, inconsequential, and usually detected incidentally. They are sometimes mistaken for metastatic cancer.

Primary Liver Cancer

Primary liver cancer is usually hepatocellular carcinoma. The first manifestations of liver cancer are usually nonspecific, delaying the diagnosis. Prognosis is usually poor.

Hepatocellular Carcinoma

Hepatocellular carcinoma (hepatoma) usually occurs in patients with cirrhosis and is common in areas where infection with hepatitis B and C viruses is prevalent. Symptoms and signs are usually nonspecific. Diagnosis is based on α-fetoprotein (AFP) levels, imaging tests, and sometimes liver biopsy. Screening with periodic AFP measurement and ultrasonography is sometimes recommended for high-risk patients. Prognosis is poor when cancer is advanced, but for small tumors that are confined to the liver, ablative therapies are palliative and surgical resection or liver transplantation is sometimes curative.

Hepatocellular carcinoma is the most common type of primary liver cancer and results in about 14,000 deaths annually in the US. However, it is more common outside the US, particularly in East Asia and sub-Saharan Africa; incidence generally parallels geographic prevalence of chronic hepatitis B virus (HBV) infection.

Etiology

Hepatocellular carcinoma is usually a complication of cirrhosis.

The presence of HBV increases risk of hepatocellular carcinoma by > 100-fold among HBV carriers. Incorporation of HBV-DNA into the host's genome may initiate malignant transformation, even in the absence of chronic hepatitis or cirrhosis.

Other disorders that cause hepatocellular carcinoma include cirrhosis due to chronic hepatitis C virus (HCV) infection, hemochromatosis, and alcoholic cirrhosis. Patients with cirrhosis due to other conditions are also at increased risk.

Environmental carcinogens may play a role; eg, ingestion of food contaminated with fungal aflatoxins is believed to contribute to the high incidence of hepatocellular carcinoma in subtropical regions.

Symptoms and Signs

Most commonly, previously stable patients with cirrhosis present with abdominal pain, weight loss, right upper quadrant mass, and unexplained deterioration. Fever may occur. In a few patients, the first manifestation of hepatocellular carcinoma is bloody ascites, shock, or peritonitis, caused by hemorrhage of the tumor. Occasionally, a hepatic friction rub or bruit develops.

Occasionally, systemic metabolic complications, including hypoglycemia, erythrocytosis, hypercalcemia, and hyperlipidemia, occur. These complications may manifest clinically.

Diagnosis

• α-Fetoprotein (AFP) measurement

• Imaging (CT, ultrasonography, or MRI)

Diagnosis is based on AFP measurement and an imaging test. In adults, AFP signifies dedifferentiation of hepatocytes, which most often indicates hepatocellular carcinoma; 40 to 65% of patients with the cancer have high AFP levels (> 400 µg/L). High levels are otherwise rare, except in teratocarcinoma of the testis, a much less common tumor. Lower values are less specific and can occur with hepatocellular regeneration (eg, in hepatitis). Other blood tests, such as AFP-L3 (an AFP isoform) and des-γ-carboxyprothrombin, are being studied as markers to be used for early detection of hepatocellular carcinoma.

Depending on local preferences and capabilities, the first imaging test may be contrast-enhanced CT, ultrasonography, or MRI. Hepatic arteriography is occasionally helpful in equivocal cases and can be used to outline the vascular anatomy when ablation or surgery is planned.

If imaging shows characteristic findings and AFP is elevated, the diagnosis is clear. Liver biopsy, often guided by ultrasonography or CT, is sometimes indicated for definitive diagnosis.

Staging: If a hepatocellular carcinoma is diagnosed, evaluation usually includes chest CT without contrast, imaging of the portal vein (if not already done) by MRI or CT with contrast to exclude thrombosis, and sometimes bone scanning.

Hepatocellular carcinoma is staged based on the following (American Cancer Society classification system—see Table 30-1):

• T: How many primary tumors, how big they are, and whether the cancer has spread to adjacent organs

• N: Whether the cancer has spread to nearby lymph nodes

• M: Whether the cancer has metastasized to other organs of the body

Numbers (0 to 4) are added after T, N, and M to indicate increasing severity. The letter X means no assessment is possible.

Screening: An increasing number of hepatocellular carcinomas are being detected through screening programs. Screening patients with cirrhosis is reasonable, although this measure is controversial and has not been shown to reduce mortality. One common screening method is AFP measurement and ultrasonography every 6 or 12 mo. Many experts advise screening patients with longstanding hepatitis B even when cirrhosis is absent.

Treatment

• Transplantation if tumors are small and few

[**Table 30-1.** Staging Hepatocellular Carcinoma*]

For single tumors < 5 cm or ≤ 3 tumors ≤ 3 cm that are limited to the liver, liver transplantation results in as good a prognosis as liver transplantation done for noncancerous disorders. Alternatively, surgical resection may be done; however, the cancer usually recurs.

Ablative treatments (eg, hepatic arterial chemoembolization, intratumoral ethanol injection, cryoablation, radiofrequency ablation) provide palliation and slow tumor growth; they are used when patients are awaiting liver transplantation.

If the tumor is large (> 5 cm), is multifocal, has invaded the portal vein, or is metastatic (ie, stage III or higher), prognosis is much less favorable (eg, 5-yr survival rates of about 5% or less). Radiation therapy is usually ineffective. Some newer chemotherapeutic regimens are promising.

Prevention

Use of vaccine against HBV eventually decreases the incidence, especially in endemic areas. Preventing the development of cirrhosis of any cause (eg, via treatment of chronic hepatitis C, early detection of hemochromatosis, management of alcoholism) can also have a significant effect.

Other Primary Liver Cancers

Other primary liver cancers are uncommon or rare. Diagnosis usually requires biopsy. Prognosis is typically poor. Some cancers, if localized, can be resected. With resection or liver transplantation, survival may be prolonged.

Fibrolamellar carcinoma: This distinct variant of hepatocellular carcinoma has a characteristic morphology of malignant hepatocytes enmeshed in lamellar fibrous tissue. It usually occurs in young adults and has no association with preexisting cirrhosis, HBV, HCV, or other known risk factors. AFP levels are rarely elevated. Prognosis is better than that for hepatocellular carcinoma, and many patients survive several years after tumor resection.

Cholangiocarcinoma: This tumor originates in the biliary epithelium. It is common in China, where underlying infestation with liver flukes is believed to contribute. Elsewhere, it is less common than hepatocellular carcinoma; histologically, the two may overlap. Primary sclerosing cholangitis greatly increases risk of cholangiocarcinoma.

Hepatoblastoma: Although rare, hepatoblastoma is one of the most common primary liver cancers in infants, particularly those with a family history of familial adenomatous polyposis (see p. 192). It can also develop in children. Some patients with hepatoblastoma present with precocious puberty caused by ectopic gonadotropin production, but the cancer is usually detected because of deteriorating general health and a right upper quadrant mass. An elevated AFP level and abnormal imaging test results may help in the diagnosis.

Angiosarcoma: This rare cancer is associated with specific chemical carcinogens, including industrial vinyl chloride.

Metastatic Liver Cancer

Liver metastases are common in many types of cancer, especially those of the GI tract, breast, lung, and pancreas. The first symptoms of metastases are usually nonspecific (eg, weight loss, right upper quadrant discomfort); they are sometimes the first symptoms of the primary cancer. Liver metastases are suspected in patients with weight loss and hepatomegaly or with primary tumors likely to spread to the liver. Diagnosis is usually supported by an imaging test, most often ultrasonography, spiral CT with contrast, or MRI with contrast. Treatment usually involves palliative chemotherapy.

Metastatic liver cancer is more common than primary liver cancer and is sometimes the initial clinical manifestation of cancer originating in the GI tract, breast, lung, or pancreas.

Symptoms and Signs

Early liver metastases may be asymptomatic. Nonspecific symptoms of cancer (eg, weight loss, anorexia, fever) often develop first. The liver may be enlarged, hard, or tender; massive hepatomegaly with easily palpable nodules signifies advanced disease. Hepatic bruits and pleuritic-type pain with an overlying friction rub are uncommon but characteristic. Splenomegaly is occasionally present, especially when the primary cancer is pancreatic. Concomitant peritoneal tumor seeding may produce ascites, but jaundice is usually absent or mild initially unless a tumor causes biliary obstruction.

In the terminal stages, progressive jaundice and hepatic encephalopathy presage death.

Diagnosis

• CT with contrast or MRI with contrast

• Sometimes biopsy

Liver metastases are suspected in patients with weight loss and hepatomegaly or with primary tumors likely to spread to the liver. If metastases are suspected, liver function tests are often done, but results are usually not specific for the diagnosis. Alkaline phosphatase, γ-glutamyl transpeptidase, and sometimes LDH typically increase earlier or to a greater degree than do other test results; aminotransferase levels vary. Imaging tests have good sensitivity and specificity. Ultrasonography is usually helpful, but CT with contrast or MRI with contrast is often more accurate.

Liver biopsy guided by imaging provides the definitive diagnosis and is done if other tests are equivocal or if histologic information (eg, cell type of the liver metastasis) may help determine the treatment plan.

Treatment

Treatment depends on the extent of metastasis. With solitary or very few metastases due to colorectal cancer, surgical resection may prolong survival. Depending on characteristics of the primary tumor, systemic chemotherapy may shrink tumors and prolong life but is not curative; hepatic intra-arterial chemotherapy sometimes has the same effect but with fewer or milder systemic adverse effects.

Radiation therapy to the liver occasionally alleviates severe pain due to advanced metastases but does not prolong life. Extensive disease is fatal and is best managed by palliation for the patient and support for the family (see p. 3480).

Hematologic Cancers and the Liver

The liver is commonly involved in advanced leukemia and related blood disorders. Liver biopsy is not needed. In hepatic lymphoma, especially Hodgkin lymphoma, the extent of liver involvement determines staging and treatment but may be difficult to assess. Hepatomegaly and abnormal liver function tests may reflect a systemic reaction to Hodgkin lymphoma rather than spread to the liver, and biopsy often shows nonspecific focal mononuclear infiltrates or granulomas of uncertain significance. Treatment is directed at the hematologic cancer.

Hepatic Granulomas

Hepatic granulomas have numerous causes and are usually asymptomatic. However, the underlying disorder may cause extrahepatic manifestations, hepatic inflammation, fibrosis, portal hypertension, or a combination. Diagnosis is based on liver biopsy, but biopsy is necessary only if a treatable underlying disorder (eg, infection) is suspected or if other liver disorders need to be ruled out. Treatment depends on the underlying disorder.

Hepatic granulomas, although sometimes insignificant, more often reflect clinically relevant disease. The term granulomatous hepatitis is often used to describe the condition, but the disorder is not true hepatitis, and the presence of granulomas does not imply hepatocellular inflammation.

Etiology

Hepatic granulomas have many causes (see Table 30-2.); drugs and systemic disorders (often infections) are more common causes than primary liver disorders. Infections must be identified because they require specific treatments. TB and schistosomiasis are the most common infectious causes worldwide; fungal and viral causes are less common. Sarcoidosis is the most common noninfectious cause; the liver is involved in about two thirds of patients, and occasionally, clinical manifestations of sarcoidosis are predominantly hepatic.

Granulomas are much less common in primary liver disorders; primary biliary cirrhosis is the only important cause. Small granulomas occasionally occur in other liver disorders but are not clinically significant.

Idiopathic granulomatous hepatitis is a rare syndrome of hepatic granulomas with recurrent fever, myalgias, fatigue, and other systemic symptoms, which often occur intermittently for years. Some experts believe it is a variant of sarcoidosis.

Pathophysiology

A granuloma is a localized collection of chronic inflammatory cells with epithelioid cells and giant multinucleated cells. Caseation necrosis or foreign body tissue (eg, schistosome eggs) may be present. Most granulomas occur in the parenchyma, but in primary biliary cirrhosis, granulomas may occur in the hepatic triads.

Granuloma formation is incompletely understood. Granulomas may develop in response to poorly soluble exogenous or endogenous irritants. Immunologic mechanisms are involved.

Hepatic granulomas rarely affect hepatocellular function. However, when granulomas are part of a broader inflammatory reaction involving the liver (eg, drug reactions, infectious mononucleosis), hepatocellular dysfunction is present. Sometimes inflammation causes progressive hepatic fibrosis and portal hypertension, typically with schistosomiasis and occasionally with extensive sarcoidal infiltration.

Symptoms and Signs

Granulomas themselves are typically asymptomatic; even extensive infiltration usually causes only minor hepatomegaly and little or no jaundice. Symptoms, if they occur, reflect the underlying condition (eg, constitutional symptoms in infections, hepatosplenomegaly in schistosomiasis).

[Table 30-2. Causes of Hepatic Granulomas]

Diagnosis

• Liver function tests

• Imaging

• Biopsy

Hepatic granulomas are suspected in patients with

• Conditions that commonly cause granulomas

• Unexplained hepatic masses found during imaging tests

• Occasionally, when an imaging test is done to evaluate asymptomatic elevations in liver enzymes, particularly alkaline phosphatase

When granulomas are suspected, liver function tests are usually done, but results are nonspecific and are rarely helpful in diagnosis. Alkaline phosphatase (and γ-glutamyltransferase) is often mildly elevated but occasionally may be markedly elevated. Other test results may be normal or abnormal, reflecting additional hepatic damage (eg, widespread hepatic inflammation due to a drug reaction). Usually, imaging tests, such as ultrasonography, CT, or MRI, are not diagnostic; they may show calcification (if granulomas are long-standing) or filling defects, particularly with confluent lesions.

Diagnosis is based on liver biopsy. However, biopsy is usually indicated only to diagnose treatable causes (eg, infections) or to rule out nongranulomatous disorders (eg, chronic viral hepatitis). Biopsy sometimes detects evidence of the specific cause (eg, schistosome eggs, caseation of TB, fungal organisms). However, other tests (eg, cultures, skin tests, laboratory tests, imaging tests, other tissue specimens) are often needed.

In patients with constitutional or other symptoms suggesting infection (eg, FUO), specific measures are taken to increase the diagnostic sensitivity of biopsy for infections; eg, a portion of the fresh biopsy specimen is sent for culture, or special stains for acid-fast bacilli, fungi, and other organisms are used. Often, cause cannot be established.

Prognosis

Hepatic granulomas caused by drugs or infection regress completely after treatment. Sarcoid granulomas may disappear spontaneously or persist for years, usually without causing clinically important liver disease. Progressive fibrosis and portal hypertension (sarcoidal cirrhosis) rarely develop.

In schistosomiasis, progressive portal scarring (pipestem fibrosis) is typical; liver function is usually preserved, but marked splenomegaly and variceal hemorrhage can occur.

Treatment

• Treatment of cause

Treatment is directed at the underlying disorder. When the cause is unknown, treatment is usually withheld, and follow-up with periodic liver function tests is instituted. However, if symptoms of TB (eg, prolonged fever) and deteriorating health occur, empiric antituberculous therapy may be justified.

Corticosteroids may benefit patients with progressive hepatic sarcoidosis, although whether these drugs prevent hepatic fibrosis is unclear. However, corticosteroids are not indicated for most patients with sarcoidosis and are warranted only if TB and other infections can be excluded confidently.

Chapter 31. Gallbladder and Bile Duct Disorders

Introduction

The liver produces about 500 to 600 mL of bile each day. Bile is isosmotic with plasma and consists primarily of water and electrolytes but also organic compounds: bile salts, phospholipids (mostly lecithin), cholesterol, bilirubin, and other endogenously produced or ingested compounds, such as proteins that regulate GI function and drugs or their metabolites. Bilirubin is a degradation product of heme compounds from worn-out RBCs and is the pigment that gives bile its yellow-green color.

Bile salts (bile acids) are the major organic component in bile. The liver uses active transport to secrete bile salts into the canaliculus, the cleft between adjacent hepatocytes. Canalicular transport is the rate-limiting step in bile formation. Once secreted, bile salts draw other bile components (particularly Na^+ and water) into the canaliculus by osmosis. Bile salts are also biologic detergents that enable the body to excrete cholesterol and potentially toxic compounds (eg, bilirubin, drug metabolites). The function of bile salts in the duodenum is to solubilize ingested fat and fat-soluble vitamins, facilitating their digestion and absorption. From the liver, bile flows from the intrahepatic collecting system into the right or left hepatic duct, then into the common hepatic duct.

During fasting, about 75% of the bile secreted passes from the common hepatic duct into the gallbladder via the cystic duct. The rest flows directly into the common bile duct (formed by the junction of the common hepatic and cystic ducts) into the duodenum. During fasting, the gallbladder absorbs up to 90% of bile water, concentrating and storing bile.

Bile empties from the gallbladder into the common bile duct. The common bile duct joins with the pancreatic duct to form the ampulla of Vater, which empties into the duodenum. Before joining the pancreatic duct, the common bile duct tapers to a diameter of ≤ 0.6 cm.

The sphincter of Oddi, which surrounds both the pancreatic duct and the common bile duct, includes a sphincter for each duct. Bile does not normally flow retrograde into the pancreatic duct. These sphincters are highly sensitive to cholecystokinin and other gut hormones (eg, gastrin-releasing peptide) and to alterations in cholinergic tone (eg, by anticholinergic drugs).

Eating releases gut hormones and stimulates cholinergic nerves, causing the gallbladder to contract and the sphincter of Oddi to relax. As a result, the gallbladder empties 50 to 75% of its contents into the duodenum. Conversely, during fasting, an increase in sphincter tone facilitates gallbladder filling.

Bile salts are poorly absorbed by passive diffusion in the proximal small bowel; most intestinal bile salts reach the terminal ileum, which actively absorbs 90% into the portal venous circulation. Returned to the liver, bile salts are efficiently extracted, promptly modified (eg, conjugated if they arrive in the free form), and secreted back into bile. Bile salts circulate through this pathway from liver to gut to liver—the enterohepatic circulation—10 to 12 times/day.

Cholelithiasis

Cholelithiasis is the presence of one or more calculi (gallstones) in the gallbladder. In developed countries, about 10% of adults and 20% of people > 65 yr have gallstones. Gallstones tend to be asymptomatic. The most common symptom is biliary colic; gallstones do not cause dyspepsia or fatty food intolerance. More serious complications include cholecystitis; biliary tract obstruction (from stones in the bile ducts or choledocholithiasis), sometimes with infection (cholangitis); and gallstone pancreatitis. Diagnosis is usually by ultrasonography. If cholelithiasis causes symptoms or complications, cholecystectomy is necessary.

Risk factors for gallstones include female sex, obesity, increased age, American Indian ethnicity, a Western diet, and a family history. Most disorders of the biliary tract result from gallstones.

Pathophysiology

Biliary sludge is often a precursor of gallstones. It consists of Ca bilirubinate (a polymer of bilirubin), cholesterol microcrystals, and mucin. Sludge develops during gallbladder stasis, as occurs during pregnancy or use of TPN. Most sludge is asymptomatic and disappears when the primary condition resolves. Alternatively, sludge can evolve into gallstones or migrate into the biliary tract, obstructing the ducts and leading to biliary colic, cholangitis, or pancreatitis.

There are several types of gallstones.

Cholesterol stones account for > 85% of gallstones in the Western world. For cholesterol gallstones to form, the following is required:

- Bile must be supersaturated with cholesterol. Normally, water-insoluble cholesterol is made water soluble by combining with bile salts and lecithin to form mixed micelles. Supersaturation of bile with cholesterol most commonly results from excessive cholesterol secretion (as occurs in obesity or diabetes) but may result from a decrease in bile salt secretion (eg, in cystic fibrosis because of bile salt malabsorption) or in lecithin secretion (eg, in a rare genetic disorder that causes a form of progressive intrahepatic familial cholestasis).

- The excess cholesterol must precipitate from solution as solid microcrystals. Such precipitation in the gallbladder is accelerated by mucin, a glycoprotein, or other proteins in bile.

- The microcrystals must aggregate and grow. This process is facilitated by the binding effect of mucin forming a scaffold and by retention of microcrystals in the gallbladder with impaired contractility due to excess cholesterol in bile.

Black pigment stones are small, hard gallstones composed of Ca bilirubinate and inorganic Ca salts (eg, Ca carbonate, Ca phosphate). Factors that accelerate stone development include alcoholic liver disease, chronic hemolysis, and older age.

Brown pigment stones are soft and greasy, consisting of bilirubinate and fatty acids (Ca palmitate or stearate). They form during infection, inflammation, and parasitic infestation (eg, liver flukes in Asia).

Gallstones grow at about 1 to 2 mm/yr, taking 5 to 20 yr before becoming large enough to cause problems. Most gallstones form within the gallbladder, but brown pigment stones form in the ducts. Gallstones may migrate to the bile duct after cholecystectomy or, particularly in the case of brown pigment stones, develop behind strictures as a result of stasis and infection.

Symptoms and Signs

About 80% of people with gallstones are asymptomatic. The remainder have symptoms ranging from biliary-type pain (biliary colic) to cholecystitis to life-threatening cholangitis. Biliary colic is the most common symptom.

Stones occasionally traverse the cystic duct without causing symptoms. However, most gallstone migration leads to cystic duct obstruction, which, even if transient, causes biliary colic. Biliary colic characteristically begins in the right upper quadrant but may occur elsewhere in the abdomen. It is often poorly localized, particularly in diabetics and the elderly. The pain may radiate into the back or down the arm. Episodes begin suddenly, become intense within 15 min to 1 h, remain at a steady intensity (not colicky) for up to 12 h (usually < 6 h), and then gradually disappear over 30 to 90 min, leaving a dull ache. The pain is usually severe enough to send patients to the emergency department for relief. Nausea and some vomiting are common, but fever and chills do not occur unless cholecystitis has developed. Mild right upper quadrant or epigastric tenderness may be present; peritoneal findings are absent. Between episodes, patients feel well.

Although biliary-type pain can follow a heavy meal, fatty food is not a specific precipitating factor. Nonspecific GI symptoms, such as gas, bloating, and nausea, have been inaccurately ascribed to gallbladder disease. These symptoms are common, having about equal prevalence in cholelithiasis,

peptic ulcer disease, and functional GI disorders.

Little correlation exists between the severity and frequency of biliary colic and pathologic changes in the gallbladder. Biliary colic can occur in the absence of cholecystitis. If colic lasts > 12 h, particularly if it is accompanied by vomiting or fever, acute cholecystitis or pancreatitis is likely.

Diagnosis

• Ultrasonography

Gallstones are suspected in patients with biliary colic. Abdominal ultrasonography is the method of choice for detecting gallbladder stones; sensitivity and specificity are 95%. Ultrasonography also accurately detects sludge. CT, MRI (see p. 230), and oral cholecystography (rarely available now, although quite accurate) are alternatives. Endoscopic ultrasonography accurately detects small gallstones (< 3 mm) and may be needed if other tests are equivocal. Laboratory tests usually are not helpful; typically, results are normal unless complications develop. Asymptomatic gallstones and biliary sludge are often detected incidentally when imaging, usually ultrasonography, is done for other reasons. About 10 to 15% of gallstones are calcified and visible on plain x-rays.

Prognosis

Patients with asymptomatic gallstones become symptomatic at a rate of about 2%/yr. The symptom that develops most commonly is biliary colic rather than a major biliary complication. Once biliary symptoms begin, they are likely to recur; pain returns in 20 to 40% of patients/yr, and about 1 to 2% of patients/yr develop complications such as cholecystitis, choledocholithiasis, cholangitis, and gallstone pancreatitis.

Treatment

• Laparoscopic cholecystectomy for symptomatic stones

• Expectant for asymptomatic stones; sometimes stone dissolution

Most asymptomatic patients decide that the discomfort, expense, and risk of elective surgery are not worth removing an organ that may never cause clinical illness. However, if symptoms occur, gallbladder removal (cholecystectomy) is indicated because pain is likely to recur and serious complications can develop.

Surgery: Surgery can be done with an open or laparoscopic technique.

Open cholecystectomy, which involves a large abdominal incision and direct exploration, is safe and effective. Its overall mortality rate is about 0.1% when done electively during a period free of complications.

Laparoscopic cholecystectomy is the treatment of choice. Using video endoscopy and instrumentation through small abdominal incisions, the procedure is less invasive than open cholecystectomy. The result is a much shorter convalescence, decreased postoperative discomfort, improved cosmetic results, yet no increase in morbidity or mortality. Laparoscopic cholecystectomy is converted to an open procedure in 2 to 5% of patients, usually because biliary anatomy cannot be identified or a complication cannot be managed. Older age typically increases the risks of any type of surgery.

Cholecystectomy effectively prevents future biliary colic but is less effective for preventing atypical symptoms such as dyspepsia. Cholecystectomy does not result in nutritional problems or a need for dietary limitations. Some patients develop diarrhea, often because bile salt malabsorption in the ileum is unmasked. Prophylactic cholecystectomy is warranted in asymptomatic patients with cholelithiasis only if they have large gallstones (> 3 cm) or a calcified gallbladder (porcelain gallbladder); these conditions increase the risk of gallbladder carcinoma.

Stone dissolution: For patients who decline surgery or who are at high surgical risk (eg, because of

concomitant medical disorders or advanced age), gallbladder stones can sometimes be dissolved by ingesting bile acids orally for many months. The best candidates for this treatment are those with small, radiolucent stones (more likely to be composed of cholesterol) in a functioning nonobstructed gallbladder (indicated by normal filling detected during cholescintigraphy or oral cholecystography or by absence of stones in the neck).

Ursodeoxycholic acid 8 to 10 mg/kg/day po dissolves 80% of tiny stones < 0.5 cm in diameter within 6 mo. For larger stones (the majority), the success rate is much lower, even with higher doses of ursodeoxycholic acid. Further, after successful dissolution, stones recur in 50% within 5 yr. Most patients are thus not candidates and prefer laparoscopic cholecystectomy. However, ursodeoxycholic acid can help prevent stone formation in morbidly obese patients who are losing weight rapidly after bariatric surgery or while on a very low calorie diet.

Stone fragmentation (extracorporeal shock wave lithotripsy) to assist stone dissolution and clearance is now unavailable.

Cholecystitis

Cholecystitis, which is inflammation of the gallbladder, can be acute or chronic.

Acute Cholecystitis

Acute cholecystitis is inflammation of the gallbladder that develops over hours, usually because a gallstone obstructs the cystic duct. Symptoms include right upper quadrant pain and tenderness, sometimes accompanied by fever, chills, nausea, and vomiting. Abdominal ultrasonography detects the gallstone and sometimes the associated inflammation. Treatment usually involves antibiotics and cholecystectomy.

Acute cholecystitis is the most common complication of cholelithiasis. Conversely, ≥ 95% of patients with acute cholecystitis have cholelithiasis. When a stone becomes impacted in the cystic duct and persistently obstructs it, acute inflammation results. Bile stasis triggers release of inflammatory enzymes (eg, phospholipase A, which converts lecithin to lysolecithin, which then may mediate inflammation). The damaged mucosa secretes more fluid into the gallbladder lumen than it absorbs. The resulting distention further releases inflammatory mediators (eg, prostaglandins), worsening mucosal damage and causing ischemia, all of which perpetuate inflammation. Bacterial infection can supervene. The vicious circle of fluid secretion and inflammation, when unchecked, leads to necrosis and perforation. If acute inflammation resolves, the gallbladder becomes fibrotic and contracted and does not concentrate bile or empty normally—features of chronic cholecystitis.

Acute acalculous cholecystitis: Acalculous cholecystitis is cholecystitis without stones. It accounts for 5 to 10% of cholecystectomies done for acute cholecystitis. Risk factors include the following:

• Critical illness (eg, major surgery, burns, sepsis, or trauma)

• Prolonged fasting or TPN (both predispose to bile stasis)

• Shock

• Immune deficiency

• Vasculitis (eg, SLE, polyarteritis nodosa)

The mechanism probably involves inflammatory mediators released because of ischemia, infection, or bile stasis. Sometimes an infecting organism can be identified (eg, *Salmonella* sp or cytomegalovirus in immunodeficient patients). In young children, acute acalculous cholecystitis tends to follow a febrile illness without an identifiable infecting organism.

Symptoms and Signs

Most patients have had prior attacks of biliary colic or acute cholecystitis. The pain of cholecystitis is similar in quality and location to biliary colic but lasts longer (ie, > 6 h) and is more severe. Vomiting is common, as is right subcostal tenderness. Within a few hours, Murphy's sign (deep inspiration exacerbates the pain during palpation of the right upper quadrant and halts inspiration) develops along with involuntary guarding of upper abdominal muscles on the right side. Fever, usually low grade, is common.

In the elderly, the first or only symptoms may be systemic and nonspecific (eg, anorexia, vomiting, malaise, weakness, fever). Sometimes fever does not develop.

Acute cholecystitis begins to subside in 2 to 3 days and resolves within 1 wk in 85% of patients.

Complications: Without treatment, 10% of patients develop localized perforation, and 1% develop free perforation and peritonitis. Increasing abdominal pain, high fever, and rigors with rebound tenderness or ileus suggest empyema (pus in the gallbladder), gangrene, or perforation. When acute cholecystitis is accompanied by jaundice or cholestasis, partial common duct obstruction is likely, usually due to stones or inflammation. Other complications include the following:

• Mirizzi's syndrome: Rarely, a gallstone becomes impacted in the cystic duct or Hartman's pouch and compresses and obstructs the common bile duct, causing cholestasis.

• Gallstone pancreatitis: Gallstones pass from the gallbladder into the biliary tract and block the pancreatic duct.

• Cholecystoenteric fistula: Infrequently, a large stone erodes the gallbladder wall, creating a fistula into the small bowel (or elsewhere in the abdominal cavity); the stone may pass freely or obstruct the small bowel (gallstone ileus).

Acute acalculous cholecystitis: The symptoms are similar to those of acute cholecystitis with gallstones but may be difficult to identify because patients tend to be severely ill (eg, ICU setting) and may be unable to communicate clearly. Abdominal distention or unexplained fever may be the only clue. Untreated, the disease can rapidly progress to gallbladder gangrene and perforation, leading to sepsis, shock, and peritonitis; mortality approaches 65%.

Diagnosis

• Ultrasonography

• Cholescintigraphy if ultrasonography results are equivocal or if acalculous cholecystitis is suspected

Acute cholecystitis is suspected based on symptoms and signs.

Transabdominal ultrasonography is the best test to detect gallstones. The test may also elicit local abdominal tenderness over the gallbladder (ultrasonographic Murphy's sign). Pericholecystic fluid or thickening of the gallbladder wall indicates acute inflammation.

Cholescintigraphy is useful when results are equivocal; failure of the radionuclide to fill the gallbladder suggests an obstructed cystic duct (ie, an impacted stone). False-positive results may be due to the following:

• A critical illness

• Receiving TPN and no oral foods (because gallbladder stasis prevents filling)

• Severe liver disease (because the liver does not secrete the radionuclide)

• Previous sphincterotomy (which facilitates exit into the duodenum rather than the gallbladder)

Morphine provocation, which increases tone in the sphincter of Oddi and enhances filling, helps eliminate false-positive results.

Abdominal CT identifies complications such as gallbladder perforation or pancreatitis.

Laboratory tests are done but are not diagnostic. Leukocytosis with a left shift is common. In uncomplicated acute cholecystitis, liver function tests are normal or only slightly elevated. Mild cholestatic abnormalities (bilirubin up to 4 mg/dL and mildly elevated alkaline phosphatase) are common, probably indicating inflammatory mediators affecting the liver rather than mechanical obstruction. More marked increases, especially if lipase (amylase is less specific) is elevated > 2-fold, suggest bile duct obstruction. Passage of a stone through the biliary tract increases aminotransferases (ALT, AST).

Acute acalculous cholecystitis: Acute acalculous cholecystitis is suggested if a patient has no gallstones but has ultrasonographic Murphy's sign or a thickened gallbladder wall and pericholecystic fluid. A distended gallbladder, biliary sludge, and a thickened gallbladder wall without pericholecystic fluid (due to low albumin or ascites) may result simply from a critical illness. CT identifies extrabiliary abnormalities. Cholescintigraphy is more helpful; failure of a radionuclide to fill may indicate edematous cystic duct obstruction. Giving morphine helps eliminate a false-positive result due to gallbladder stasis.

Treatment

• Supportive care (hydration, analgesics, antibiotics)

• Cholecystectomy

Management includes hospital admission, IV fluids, and analgesia with an NSAID (ketorolac) or an opioid. Nothing is given orally, and nasogastric suction is instituted if vomiting or an ileus is present. Parenteral antibiotics are usually initiated to treat possible infection, but evidence of benefit is lacking. Empiric coverage, directed at gram-negative enteric organisms, involves IV regimens such as ceftriaxone 2 g q 24 h plus metronidazole 500 mg q 8 h, piperacillin/tazobactam 4 g q 6 h, or ticarcillin/clavulanate 4 g q 6 h.

Cholecystectomy cures acute cholecystitis and relieves biliary pain. Early cholecystectomy is generally preferred, best done during the first 24 to 48 h in the following situations:

• The diagnosis is clear and patients are at low surgical risk.

• Patients are elderly or have diabetes and are thus at higher risk of infectious complications.

• Patients have empyema, gangrene, perforation, or acalculous cholecystitis.

Surgery may be delayed when patients have an underlying severe chronic disorder (eg, cardiopulmonary) that increases the surgical risks. In such patients, cholecystectomy is deferred until medical therapy stabilizes the comorbid disorders or until cholecystitis resolves. If cholecystitis resolves, cholecystectomy may be done ≥ 6 wk later. Delayed surgery carries the risk of recurrent biliary complications. Percutaneous cholecystostomy is an alternative to cholecystectomy for patients at very high surgical risk, such as the elderly, those with acalculous cholecystitis, and those in an ICU because of burns, trauma, or respiratory failure.

Chronic Cholecystitis

Chronic cholecystitis is long-standing gallbladder inflammation almost always due to gallstones.

Chronic cholecystitis almost always results from gallstones and prior episodes of acute cholecystitis (even if mild). Damage ranges from a modest infiltrate of chronic inflammatory cells to a fibrotic, shrunken gallbladder. Extensive calcification due to fibrosis is called porcelain gallbladder.

Symptoms and Signs

Gallstones intermittently obstruct the cystic duct and so cause recurrent biliary colic. Such episodes of pain are not necessarily accompanied by overt gallbladder inflammation; the extent of inflammation does not correlate with the intensity or frequency of biliary colic. Upper abdominal tenderness may be present, but usually fever is not. Fever suggests acute cholecystitis. Once episodes begin, they are likely to recur.

Diagnosis

• Ultrasonography

Chronic cholecystitis is suspected in patients with recurrent biliary colic plus gallstones. Ultrasonography or another imaging test usually shows gallstones and sometimes a shrunken, fibrotic gallbladder. The diagnosis is made in patients with a history of recurrent biliary colic and evidence of gallstones on ultrasonography. Cholescintigraphy may show nonvisualization of the gallbladder but is less accurate.

Treatment

Laparoscopic cholecystectomy is indicated to prevent symptom recurrence and further biliary complications. This procedure is particularly valid for the porcelain gallbladder associated with gallbladder carcinoma.

Acalculous Biliary Pain

Acalculous biliary pain is biliary colic without gallstones, resulting from structural or functional disorders; it is sometimes treated with laparoscopic cholecystectomy.

Biliary colic can occur in the absence of gallstones, particularly in young women. Acalculous biliary pain accounts for up to 15% of laparoscopic cholecystectomies. Common causes of such biliary pain include the following:

• Microscopic stones—not detected by routine abdominal ultrasonography

• Abnormal gallbladder emptying

• An overly sensitive biliary tract

• Sphincter of Oddi dysfunction

• Hypersensitivity of the adjacent duodenum

• Possibly gallstones that have spontaneously passed

Some patients eventually develop other functional GI disorders.

Diagnosis

Acalculous biliary pain is suspected in patients with biliary colic when diagnostic imaging cannot detect gallstones. Imaging should include ultrasonography and, where available, endoscopic ultrasonography (for small stones < 1 cm). Abnormal laboratory tests may reveal evidence of a biliary tract abnormality (eg, elevated alkaline phosphatase, bilirubin, ALT, or AST) or a pancreatic abnormality (eg, elevated lipase) during an episode of acute pain. Cholescintigraphy with cholecystokinin infusion measures gallbladder emptying (ejection fraction); potentially interfering drugs such as Ca channel blockers, opioids, and anticholinergics should not be used. ERCP with biliary manometry detects sphincter of Oddi dysfunction. The best diagnostic approach remains problematic.

Treatment

Laparoscopic cholecystectomy improves outcomes for patients with microscopic stones and possibly

abnormal gallbladder motility. The role of laparoscopic cholecystectomy or endoscopic sphincterotomy remains problematic. Drug therapies have no proven benefit.

Postcholecystectomy Syndrome

Postcholecystectomy syndrome is occurrence of abdominal symptoms after cholecystectomy.

Postcholecystectomy syndrome occurs in 5 to 40% of patients. It refers to presumed gallbladder symptoms that continue or that develop after cholecystectomy or to other symptoms that result from cholecystectomy. Removal of the gallbladder, the storage organ for bile, normally has few consequences on biliary tract function or pressures. In about 10%, biliary colic appears to result from functional or structural abnormalities of the sphincter of Oddi, resulting in altered biliary pressures or heightened sensitivity.

The most common symptoms are dyspepsia or otherwise nonspecific symptoms rather than true biliary colic. Papillary stenosis, which is rare, is fibrotic narrowing around the sphincter, perhaps caused by trauma and inflammation due to pancreatitis, instrumentation (eg, ERCP), or prior passage of a stone. Other causes include a retained bile duct stone, pancreatitis, and gastroesophageal reflux.

Diagnosis

• ERCP with biliary manometry or biliary nuclear scanning

• Exclusion of extrabiliary pain

Patients with postcholecystectomy pain should be evaluated as indicated for extra-biliary as well as biliary causes. If the pain suggests biliary colic, alkaline phosphatase, bilirubin, ALT, amylase, and lipase should be measured, and ERCP with biliary manometry or biliary nuclear scanning should be done. Elevated liver enzymes suggest sphincter of Oddi dysfunction; elevated amylase and lipase suggest dysfunction of the sphincter's pancreatic portion.

Dysfunction is best detected by biliary manometry done during ERCP, although ERCP has a risk of inducing pancreatitis. Manometry shows increased pressure in the biliary tract when pain is reproduced. A slowed hepatic hilum-duodenal transit time on a scan also suggests sphincter of Oddi dysfunction. Diagnosis of papillary stenosis is based on a clear-cut history of recurrent episodes of biliary pain and abnormal liver (or pancreatic) enzyme tests.

Treatment

Endoscopic sphincterotomy can relieve recurrent pain due to sphincter of Oddi dysfunction, especially if due to papillary stenosis. It is controversial for patients who have postcholecystectomy pain and no objective abnormalities.

Choledocholithiasis and Cholangitis

Choledocholithiasis is the presence of stones in bile ducts; the stones can form in the gallbladder or in the ducts themselves. These stones cause biliary colic, biliary obstruction, gallstone pancreatitis, or cholangitis (bile duct infection and inflammation). Cholangitis, in turn, can lead to strictures, stasis, and choledocholithiasis. Diagnosis usually requires visualization by magnetic resonance cholangiopancreatography or ERCP. Early endoscopic or surgical decompression is indicated.

Stones may be described as

• Primary stones (usually brown pigment stones), which form in the bile ducts

• Secondary stones (usually cholesterol), which form in the gallbladder but migrate to the bile ducts

• Residual stones, which are missed at the time of cholecystectomy (evident < 3 yr later)

• Recurrent stones, which develop in the ducts > 3 yr after surgery

In developed countries, > 85% of common duct stones are secondary; affected patients have additional stones located in the gallbladder. Up to 10% of patients with symptomatic gallstones also have associated common bile duct stones. After cholecystectomy, brown pigment stones may result from stasis (eg, due to a postoperative stricture) and the subsequent infection. The proportion of ductal stones that are pigmented increases with time after cholecystectomy.

Bile duct stones may pass into the duodenum asymptomatically. Biliary colic occurs when the ducts become partially obstructed. More complete obstruction causes duct dilation, jaundice, and, eventually, cholangitis (a bacterial infection). Stones that obstruct the

[
Table 31-1. Causes of Bile Duct Obstruction]

ampulla of Vater can cause gallstone pancreatitis. Some patients (usually the elderly) present with biliary obstruction due to stones that have caused no symptoms previously.

In **acute cholangitis,** bile duct obstruction allows bacteria to ascend from the duodenum. Most (85%) cases result from common bile duct stones, but bile duct obstruction can result from tumors or other conditions (see Table 31-1). Common infecting organisms include gram-negative bacteria (eg, *Escherichia coli, Klebsiella* sp, *Enterobacter* sp); less common are gram-positive bacteria (eg, *Enterococcus* sp) and mixed anaerobes (eg, *Bacteroides* sp, *Clostridia* sp). Symptoms include abdominal pain, jaundice, and fever or chills (Charcot's triad). The abdomen is tender, and often the liver is tender and enlarged (often containing abscesses). Confusion and hypotension predict about a 50% mortality rate and high morbidity.

Recurrent pyogenic cholangitis (Oriental cholangiohepatitis, hepatolithiasis) is characterized by intrahepatic brown pigment stone formation. This disorder occurs in Southeast Asia. It consists of sludge and bacterial debris in the bile ducts. Undernutrition and parasitic infestation (eg, *Clonorchis sinensis*, *Opisthorchis viverrini*) increase susceptibility. Parasitic infestation can cause obstructive jaundice with intrahepatic ductal inflammation, proximal stasis, stone formation, and cholangitis. Repeating cycles of obstruction, infection, and inflammation lead to bile duct strictures and biliary cirrhosis. The extrahepatic ducts tend to be dilated, but the intrahepatic ducts appear straight because of periductal fibrosis.

In AIDS-related cholangiopathy or cholangitis, direct cholangiography may show abnormalities similar to those in primary sclerosing cholangitis or papillary stenosis (ie, multiple strictures and dilations involving the intrahepatic and extrahepatic bile ducts). Etiology is probably infection, most likely with cytomegalovirus, *Cryptosporidium* sp, or microsporidia.

Diagnosis

• Liver function tests

• Ultrasonography

Common duct stones should be suspected in patients with jaundice and biliary colic. Fever and leukocytosis further suggest acute cholangitis. Elevated levels of bilirubin, alkaline phosphatase, ALT, and γ-glutamyltransferase are consistent with extrahepatic obstruction, suggesting stones, particularly in patients with features of acute cholecystitis or cholangitis.

Ultrasonography may show stones in the gallbladder and occasionally in the common duct (less accurate). The common duct is dilated (> 6 mm in diameter if the gallbladder is intact; > 10 mm after a cholecystectomy). If the ducts are not dilated early in the presentation (eg, first day), stones have probably passed. If doubt exists, magnetic resonance cholangiopancreatography (MRCP) is highly accurate for retained stones. ERCP is done if MRCP is equivocal; it can be therapeutic as well as

diagnostic. CT, though less accurate than ultrasonography, can detect liver abscesses.

For suspected acute cholangitis, CBC and blood cultures are essential. Leukocytosis is common, and aminotransferases may reach 1000 IU/L, suggesting acute hepatic necrosis, often due to microabscesses. Blood cultures guide antibiotic choice.

Treatment

• ERCP and sphincterotomy

If biliary obstruction is suspected, ERCP and sphincterotomy are necessary to remove the stone. Success rate exceeds 90%; up to 7% of patients have complications (eg, bleeding pancreatitis, infection with fibrosis and subsequent duct stricture). Laparoscopic cholecystectomy, which is not as well suited for operative cholangiography or common duct exploration, can be done electively following ERCP and sphincterotomy. Mortality and morbidity after open cholecystectomy with common duct exploration are higher. In patients at high risk of complications with cholecystectomy (eg, the elderly), sphincterotomy alone is an alternative.

Acute cholangitis is an emergency requiring aggressive supportive care and urgent removal of the stones, endoscopically or surgically. Antibiotics are given, similar to those used for acute cholecystitis (see p. 274) An alternative regimen for very ill patients is imipenem and ciprofloxacin, plus metronidazole to cover anaerobes.

For recurrent pyogenic cholangitis, management aims to provide supportive care (eg, broad-spectrum antibiotics), eradicate any parasites, and mechanically clear the ducts of stones and debris endoscopically (via ERCP) or surgically.

Sclerosing Cholangitis

Sclerosing cholangitis refers to chronic cholestatic syndromes characterized by patchy inflammation, fibrosis, and strictures of the intrahepatic and extrahepatic bile ducts. Progression obliterates the bile ducts and leads to cirrhosis, liver failure, and sometimes cholangiocarcinoma.

Sclerosing cholangitis may be primary (with no known cause) or secondary due to immune deficiencies (congenital in children, acquired in adults as AIDS cholangiopathy) often associated with superimposed infections (eg, cytomegalovirus, *Cryptosporidium*), histiocytosis X, or use of drugs (eg, intraarterial floxuridine). Both primary and secondary sclerosing cholangitis cause similar inflammatory and fibrosing lesions scarring the bile ducts. Other causes of bile duct strictures are choledocholithiasis, postoperative biliary stricture, ischemic bile duct injury (during liver transplantation), congenital biliary abnormalities, cholangiocarcinoma, and parasitic infestations.

Diagnosis of biliary strictures and dilations requires imaging techniques such as ultrasonography and cholangiography. Treatment focuses on relieving biliary obstruction (eg, dilating and stenting strictures) and, when possible, eradicating responsible organisms or treating the cause (eg, HIV).

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC), the most common form of sclerosing cholangitis, has no known cause. However, 80% of patients have inflammatory bowel disease, most often ulcerative colitis. Other associated conditions include connective tissue disorders, alloimmune disorders, and immunodeficiency syndromes, sometimes complicated by opportunistic infections. Fatigue and pruritus develop insidiously and progressively. Diagnosis is by cholangiography (magnetic resonance cholangiopancreatography or ERCP). Liver transplantation is indicated for advanced disease.

Most (70%) patients with PSC are men. Mean age at diagnosis is 40 yr.

Etiology

Although the cause is unknown, PSC is associated with inflammatory bowel disease, which is present in 80% of patients. About 5% of patients with ulcerative colitis and about 1% with Crohn's disease develop PSC. This association and the presence of several autoantibodies (eg, anti-smooth muscle and perinuclear antineutrophilic antibodies [pANCA]) suggest immune-mediated mechanisms. T cells appear to be involved in the destruction of the bile ducts, implying disordered cellular immunity. A genetic predisposition is suggested by a tendency for the disorder to develop in multiple family members and a higher frequency in people with HLAB8 and HLADR3, which are often correlated with autoimmune disorders. An unknown trigger (eg, bacterial infection, ischemic duct injury) probably causes PSC to develop in genetically predisposed people.

Symptoms and Signs

Onset is usually insidious, with progressive fatigue and then pruritus. Jaundice tends to develop later. About 10 to 15% of patients present with repeated episodes of right upper quadrant pain and fever, possibly due to ascending bacterial cholangitis. Steatorrhea and deficiencies of fat-soluble vitamins can develop. Persistent jaundice harbingers advanced disease. Symptomatic gallstones and choledocholithiasis tend to develop in about 75% of patients. Some patients, asymptomatic until late in the course, first present with hepatosplenomegaly or cirrhosis. PSC tends to slowly and inexorably progress. The terminal phase involves decompensated cirrhosis, portal hypertension, ascites, and liver failure. The time from diagnosis to liver failure is about 12 yr.

Despite the association between PSC and inflammatory bowel disease, the two diseases tend to run separate courses. Ulcerative colitis may appear years before PSC yet tends to have a milder course when associated with PSC. Similarly, total colectomy does not change the course of PSC. The presence of both diseases increases the risk of colorectal carcinoma, regardless of whether a liver transplantation has been done for PSC. Cholangiocarcinoma develops in 10 to 15% of patients.

Diagnosis

• Magnetic resonance cholangiopancreatography (MRCP)

PSC is suspected in patients with unexplained abnormalities in liver biochemical tests, particularly in those with inflammatory bowel disease. A cholestatic pattern is typical: elevated alkaline phosphatase and γ-glutamyltransferase (GGT) rather than aminotransferases. Gamma globulin and IgM levels tend to be increased. Anti-smooth muscle antibodies and pANCA are usually positive. Antimitochondrial antibody, positive in primary biliary cirrhosis, is characteristically negative.

Imaging of the hepatobiliary system begins with ultrasonography to exclude extrahepatic biliary obstruction. Although ultrasonography or CT can show ductal dilation, diagnosis requires cholangiography to show multiple strictures and dilations in the intrahepatic and extrahepatic bile ducts. Imaging should begin with MRCP. ERCP is usually a 2nd choice because it is invasive. Liver biopsy is generally not required for diagnosis; when done, it shows bile duct proliferation, periductal fibrosis, inflammation, and loss of bile ducts. With disease progression, periductal fibrosis extends from the portal regions and eventually leads to secondary biliary cirrhosis.

Measurement of serum tumor markers and ERCP surveillance with brush cytology should be done regularly to check for cholangiocarcinoma.

Treatment

• Supportive care

• ERCP dilation for major (dominant) strictures

• Transplantation for recurrent bacterial cholangitis or complications of end-stage liver disease

Asymptomatic patients usually require only monitoring (eg, physical examination and liver biochemical tests twice/yr). Ursodeoxycholic acid (up to 15 mg/kg/day reduces itching and improve biochemical markers but not survival. Chronic cholestasis (see p. 212) and cirrhosis require supportive treatment. Episodes of bacterial cholangitis warrant antibiotics and therapeutic ERCP, as needed. If a single stricture appears to be the major cause of obstruction (a dominant stricture, found in about 20% of patients), ERCP dilation (with brush cytology to check for tumors) and stenting can relieve symptoms.

Liver transplantation is the only treatment that improves life expectancy in patients with PSC and offers a cure. Recurrent bacterial cholangitis or complications of end-stage liver disease (eg, intractable ascites, portal-systemic encephalopathy, bleeding esophageal varices) are reasonable indications for liver transplantation.

AIDS Cholangiopathy

AIDS cholangiopathy is biliary obstruction secondary to biliary tract strictures caused by various opportunistic infections.

Before the advent of highly active antiretroviral therapy, cholangiopathy occurred in 25% of patients with AIDS, especially in those with a low CD4 count (< 100/µL). The most common pathogen is *Cryptosporidium parvum*. Others include cytomegalovirus, microsporidia, and *Cyclospora* sp. Papillary stenosis or intrahepatic or extrahepatic sclerosing cholangitis develops in most patients. Over half have both.

Common symptoms include right upper quadrant and epigastric pain and diarrhea. A few patients have fever and jaundice. Severe pain usually indicates papillary stenosis. Milder pain suggests sclerosing cholangitis. The diarrhea reflects small-bowel infection, often cryptosporidiosis.

Diagnosis

• Usually ERCP and ultrasonography

ERCP provides the diagnosis, identification of the causal organism by small-bowel biopsy, and a therapeutic opportunity to relieve strictures. Ultrasonography is noninvasive and very accurate (> 95%). CT and magnetic resonance cholangiopancreatography likely have supportive roles.

Liver biochemistry is consistent with cholestasis, especially a high alkaline phosphatase level.

Treatment

• Endoscopic procedures

Endoscopic sphincterotomy can markedly relieve pain, jaundice, and cholangitis in patients with papillary stenosis. Isolated or dominant strictures can be stented endoscopically. Although the cause is an infectious agent, antimicrobial therapy alone does not relieve the biliary tract damage or its sequelae. Because of its use in primary sclerosing cholangitis, ursodeoxycholic acid may have a role in treating intrahepatic ductal sclerosis and cholestasis.

Tumors of the Gallbladder and Bile Ducts

Gallbladder and bile duct tumors can cause extrahepatic biliary obstruction. Symptoms may be absent but often are constitutional or reflect biliary obstruction. Diagnosis is based on ultrasonography plus CT cholangiography or magnetic resonance cholangiopancreatography. Prognosis is grim. Mechanical bile drainage can often relieve pruritus, recurrent sepsis, and pain due to biliary obstruction.

Cholangiocarcinomas and other bile duct tumors are rare (1 to 2/100,000 people) but are usually malignant. Cholangiocarcinomas occur predominantly in the extrahepatic bile ducts: 60 to 70% in the perihilar region (Klatskin tumors), about 25% in the distal ducts, and the rest in the liver. Risk factors

include primary sclerosing cholangitis, older age, infestation with liver flukes, and a choledochal cyst.

Gallbladder carcinoma is uncommon (2.5/100,000). It is more common among American Indians, patients with large gallstones (> 3 cm), and those with extensive gallbladder calcification due to chronic cholecystitis (porcelain gallbladder). Nearly all (70 to 90%) patients also have gallstones. Median survival is 3 mo. Cure is possible when cancer is found early (eg, incidentally at cholecystectomy).

Gallbladder polyps are usually asymptomatic benign mucosal projections that develop in the lumen of the gallbladder. Most are < 10 mm in diameter and composed of cholesterol ester and triglycerides; the presence of such polyps is called cholesterolosis. They are found in about 5% of people during ultrasonography. Other, much less common benign polyps include adenomas (causing adenomyomatosis) and inflammatory polyps. Small gallbladder polyps are incidental findings that do not require treatment.

Symptoms and Signs

Most patients with cholangiocarcinomas present with pruritus and painless obstructive jaundice, typically at age 50 to 70 yr. Early perihilar tumors may cause only vague abdominal pain, anorexia, and weight loss. Other features include acholic stool, a palpable mass, hepatomegaly, or a distended gallbladder (Courvoisier's sign, with distal cholangiocarcinoma). Pain may resemble that of biliary colic (reflecting biliary obstruction) or may be constant and progressive. Sepsis (acute cholangitis), though unusual, may be induced by ERCP.

Manifestations of gallbladder carcinoma may range from incidental findings at cholecystectomy done for biliary pain to cholelithiasis to advanced disease with constant pain, weight loss, and an abdominal mass or obstructive jaundice.

Most gallbladder polyps cause no symptoms.

Diagnosis

Cholangiocarcinomas are suspected when extrahepatic biliary obstruction is unexplained. Laboratory test results reflect the degree of cholestasis. In patients with primary sclerosing cholangitis, serum carcinoembryonic antigen (CEA) and cancer antigen (CA) 19-9 levels are used for surveillance to detect the development of cholangiocarcinoma. Diagnosis is based on ultrasonography (or endoscopic ultrasonography) and CT cholangiography or magnetic resonance cholangiopancreatography. When these methods are inconclusive, ERCP with percutaneous transhepatic cholangiography (PTC) becomes necessary. ERCP not only detects the tumor but also, with brushings, can provide a tissue diagnosis, sometimes making ultrasonography- or CT-guided needle biopsy unnecessary. Contrast-enhanced CT assists in staging.

Gallbladder carcinomas are better defined by CT than by ultrasonography. Open laparotomy is necessary to determine disease extent, which guides treatment.

Treatment

• For cholangiocarcinomas, stenting (or another bypass procedure) or occasionally resection

For cholangiocarcinoma, stenting or surgically bypassing the obstruction relieves pruritus, jaundice, and perhaps fatigue.

Hilar cholangiocarcinomas with CT evidence of spread are stented via PTC or ERCP. Distal duct cholangiocarcinomas are stented endoscopically with ERCP. If cholangiocarcinoma appears localized, surgical exploration determines resectability by hilar resection or pancreaticoduodenectomy. However, successful resection is uncommon.

Liver transplantation is not indicated because of the high recurrence rate. Effectiveness of adjuvant chemotherapy and radiation therapy for cholangiocarcinomas is unproved as yet.

Many gallbladder carcinomas are treated symptomatically.

4 - Musculoskeletal and Connective Tissue Disorders

Chapter 32. Approach to the Patient With Joint Disease

Introduction

Some musculoskeletal disorders affect primarily the joints, causing arthritis. Others affect primarily the bones (eg, fractures, Paget's disease, tumors), muscles or other extra-articular soft tissues (eg, fibromyalgia), or periarticular soft tissues (eg, polymyalgia rheumatica, bursitis, tendinitis, sprain). Arthritis has myriad possible causes, including infection, autoimmune disorders, crystal-induced inflammation, and noninflammatory tissue degeneration (eg, osteoarthritis). Arthritis may affect single joints (monarthritis) or multiple joints (polyarthritis) in a symmetric or asymmetric manner. Joints may suffer fractures or sprains (see elsewhere in THE MANUAL).

History

The clinician should focus on systemic and extra-articular symptoms as well as joint symptoms. Many symptoms, including fever, chills, malaise, weight loss, Raynaud's syndrome, mucocutaneous symptoms (eg, rash, eye irritation or pain, photosensitivity), and GI or cardiopulmonary symptoms, can be associated with various joint disorders.

Pain is the most common symptom of joint disorders. The history should address the character, location, severity, factors that aggravate or relieve pain, and time frame (new-onset or recurrent). The clinician must determine whether pain is worse when first moving a joint or after prolonged use and whether it is present upon waking or develops during the day. Usually, pain originating from superficial structures is better localized than pain originating from deeper structures. Pain originating in small distal joints tends to be better localized than pain originating in large proximal joints. Joint pain can be referred from extra-articular structures or from other joints. Arthritis often causes aching pain, whereas neuropathies often cause burning pain.

Stiffness may mean weakness, fatigue, or fixed limitation of motion to patients. The clinician must separate the inability to move a joint from reluctance to move a joint because of pain. Characteristics of stiffness may suggest a cause, as in the following:

- Discomfort that occurs with motion when attempting to move a joint after a period of rest occurs in rheumatic disease. Duration of stiffness after beginning joint motion reflects its severity.

- The theater sign (stiffness upon standing that necessitates walking slowly after sitting for several hours) is common in osteoarthritis.

- Stiffness is more severe and prolonged in inflammatory joint disorders.

- Morning stiffness in peripheral joints that lasts > 1 h can be an important early symptom of RA (see Table 32-1).

- In the low back, morning stiffness that lasts > 1 h may reflect spondylitis.

Fatigue is a desire to rest that reflects exhaustion. It differs from weakness, inability to move, and reluctance to move due to pain with movement.

Instability (buckling of a joint) may suggest weakness of the ligaments or other structures that stabilize the joint, which are assessed by stress testing. Buckling occurs most often in the knee and most often results from an internal joint derangement.

Physical Examination

Each involved joint should be inspected and palpated, and the range of motion should be estimated. With polyarticular disease, certain nonarticular signs (eg, fever, wasting, rash) may reflect systemic disorders.

The rest position of joints is noted, along with any erythema, swelling, deformity, and skin abrasions or punctures. Involved joints are compared with their uninvolved opposites or with those of the examiner.

Joints are gently palpated, noting the presence and location of tenderness, warmth, and swelling. Determining whether tenderness is present along the joint line or over tendon insertions or bursae is particularly important. Soft masses, bulges, or tissues that fill normal concavities or spaces (representing joint effusion or synovial proliferation) are noted. Palpation of

[**Table 32-1.** Distinguishing Inflammatory vs Noninflammatory Features in Joint Disease by Features]

swollen joints can sometimes differentiate among joint effusion, synovial thickening, and capsular or bony enlargement. Small joints (eg, the acromioclavicular, tibiofibular, radioulnar) can be the source of pain that was initially believed to arise from a nearby major joint. Bony enlargement (often due to osteophytes) is noted.

Active range of motion (the maximum range through which the patient can move the joint) is measured first, using a goniometer; limitation may reflect weakness, pain, or stiffness as well as mechanical abnormalities. Then passive range of motion (the maximum range through which the examiner can move the joint) is assessed; passive limitation generally reflects mechanical abnormalities (eg, scarring, swelling, deformities) rather than weakness or pain. Active and passive movement of an inflamed joint (eg, due to infection or gout) may be very painful.

Patterns of joint involvement should be noted. Symmetric involvement of multiple joints is common in systemic diseases (eg, RA); monarticular (involving one joint) or asymmetric oligoarticular (involving ≤ 4) joint involvement is more common in osteoarthritis and psoriatic arthritis. Small peripheral joints are commonly affected in RA, and the larger joints and spine are affected more in spondyloarthropathies. However, a pattern of involvement may not be apparent in early disease.

Crepitus, a palpable or audible grinding produced by motion, is noted. It may be caused by roughened articular cartilage or by tendons; crepitus-causing motions should be determined and may suggest which structures are involved.

Specific features should be sought at each joint.

Elbow: Synovial swelling and thickening caused by joint disease occur in the lateral aspect between the radial head and olecranon, causing a bulge. Full 180° extension of the joint should be attempted. Although full extension is possible with nonarthritic or extra-articular problems such as tendinitis, its loss is an early change in arthritis. The area around the joint is examined for swellings. Rheumatoid nodules are firm, occurring especially along the extensor surface of the forearm. Tophi are sometimes visible under the skin as cream-colored aggregates and indicate gout. Swelling of the olecranon bursa occurs over the tip of the olecranon, is cystic, and does not limit joint motion; infection, trauma, gout, and RA are possible causes. Epitrochlear nodes occur above the medial epicondyle; they can result from inflammation in the hand but can also suggest sarcoidosis or lymphoma.

Shoulder: Because pain can be referred to areas around the shoulder, shoulder palpation should include the glenohumeral, acromioclavicular, and sternoclavicular joints, the coracoid process, clavicle, acromion process, subacromial bursa, biceps tendon, and greater and lesser tuberosities of the humerus, as well as the neck. Glenohumeral joint effusions may cause a bulge between the coracoid process and the humeral head. Possible causes include RA, osteoarthritis, septic arthritis, Milwaukee shoulder (see p. 355), and other arthropathies.

Limited motion, weakness, pain, and other disturbances of mobility caused by rotator cuff impairment can be quickly identified by having the patient attempt to abduct and raise both arms above the head and then to slowly lower them. Muscle atrophy and neurologic abnormalities should be sought.

Knee: At the knee, gross deformities such as swelling (eg, joint effusion, popliteal cysts), quadriceps muscle atrophy, and joint instability may be obvious when the patient stands and walks. With the patient

supine, the examiner should palpate the knee, identifying the patella, femoral condyles, tibial tuberosity, tibial plateau, fibular head, medial and lateral joint lines, popliteal fossa, and quadriceps and patellar tendons. The medial and lateral joint lines correspond to locations of the medial and lateral menisci and can be located by palpation while slowly flexing and extending the knee. Tender extra-articular bursae such as the anserine bursa below the medial joint line should be differentiated from true intra-articular disturbances.

Detection of small knee effusions is often difficult and is best accomplished using the bulge sign. The knee is fully extended and the leg slightly externally rotated while the patient is supine with muscles relaxed. The medial aspect of the knee is stroked to express any fluid away from this area. Placement of one hand on the suprapatellar pouch and gentle stroking or pressing on the lateral aspect of the knee can create a fluid wave or bulge, visible medially when an effusion is present. Larger effusions can be identified visually or by balloting the patella. Joint effusion can result from many joint diseases, including RA, osteoarthritis, gout, and trauma.

Full 180° extension of the knee is attempted to detect flexion contractures. The patella is tested for free, painless motion.

Hip: Examination begins with gait evaluation. A limp is common in patients with significant hip arthritis. It may be caused by pain, leg shortening, flexion contracture, muscle weakness, or knee problems. Loss of internal rotation (often the earliest change in hip osteoarthritis or any hip synovitis), flexion, extension, or abduction can usually be demonstrated. Placement of one hand on the patient's iliac crest detects pelvic movement that might be mistaken for hip movement. Flexion contracture can be identified by attempting leg extension with the opposite hip maximally flexed to stabilize the pelvis. Tenderness over the femoral greater trochanter suggests bursitis (which is extra-articular) rather than an intra-articular disorder. Pain with passive range of motion (assessed by internal and external rotation with the patient supine and the hip and knee flexed to 90°) suggests intra-articular origin. However, patients may have simultaneous intra-articular and extra-articular disorders.

Other: Hand examination is discussed elsewhere (see p. 385 and Polyarticular Joint Pain on p. 292). Foot and ankle examination is discussed in Ch. 44. Examination of the neck and back is discussed on p. 379.

Testing

Laboratory testing and imaging studies often provide less information than do the history and physical examination. While some testing may be warranted in some patients, extensive testing is often not.

Blood tests: Some tests, although not specific, can be helpful in supporting the possibility of certain systemic rheumatic diseases, as for the following:

- Antinuclear antibodies (ANA) and complement in SLE
- Rheumatoid factor and anticitrullinated peptide (CCP) in RA
- HLA-B27 in spondyloarthropathy (occasionally useful)
- Antineutrophil cytoplasmic antibodies (ANCA) in certain vasculitides (occasionally useful)

Tests such as WBC count, ESR, and C-reactive protein may help determine the likelihood that arthritis is inflammatory due to infectious or other systemic disorders, but these tests are not highly specific or sensitive. For example, an elevated ESR or C-reactive protein level suggests inflammation or may be due to aging or a large number of nonarticular inflammatory conditions (eg, infection, cancer). Also, such markers may not be elevated in all inflammatory disorders.

Imaging studies: Imaging studies are often unnecessary. Plain x-rays in particular reveal mainly bony abnormalities, and most joint disorders do not affect bone primarily. However, imaging may help in the initial evaluation of relatively localized, unexplained persistent or severe joint and particularly spine

abnormalities; they may reveal primary or metastatic tumors, osteomyelitis, bone infarctions, periarticular calcifications (as in calcific tendinitis), or other changes in deep structures that may escape physical examination. If chronic RA, gout, or osteoarthritis is suspected, erosions, cysts, and joint space narrowing with osteophytes may be visible. In pseudogout, Ca pyrophosphate deposition may be visible in intra-articular cartilage.

For musculoskeletal imaging, plain x-rays may be obtained first, but they are often less sensitive, particularly during early disease, than MRI, CT, or ultrasonography. MRI is the most accurate study for fractures not visible on plain x-rays, particularly in the hip and pelvis, and for soft tissues and internal derangements of the knee. CT is useful if MRI is contraindicated or unavailable. Ultrasonography, arthrography, and bone scanning may help in certain conditions, as can biopsy of bone, synovium, or other tissues.

Arthrocentesis: Arthrocentesis is the process of puncturing the joint with a needle to withdraw fluid. If there is an effusion and arthrocentesis is done correctly, fluid can generally be withdrawn. Examination of synovial fluid is the most accurate way to exclude infection, diagnose crystal-induced arthritis, and otherwise determine the cause of joint effusions. It is indicated in all patients with severe or unexplained monarticular joint effusions and in patients with unexplained polyarticular effusions.

Arthrocentesis is done using strictly sterile technique. Infection or other rash over the site used to enter the joint is a contraindication. Preparations for collecting samples should be made before doing the procedure. Local anesthesia, with lidocaine or difluoroethane spray, is often used. Many joints are punctured on the extensor surface to avoid nerves, arteries, and veins, which are usually on the joint's flexor surface. A 20-gauge needle can be used for most larger joints. Smaller joints of the upper and lower extremities are probably easier to access using a 22- or 23-gage needle. As much fluid as is possible should be removed. Specific anatomic landmarks are used (see
Figs. 32-1,
32-2, and
32-3).

Metacarpophalangeal joints, metatarsophalangeal joints, and interphalangeal joints of the hands and feet are punctured similarly to each other, using a 22- or 23-gauge needle. The needle is inserted dorsally, to either side of the extensor tendon. Distraction of the joint is sometimes useful to open the joint space and allow easier access.

[**Fig. 32-1.** Arthrocentesis of the shoulder.]

Synovial fluid examination: At the bedside, gross characteristics of the fluid are assessed, such as its color, turbidity, and viscosity. Viscosity can be assessed using the string sign. The length of a viscous string of joint fluid dropped from the syringe is normally > 3 cm. Inflammation decreases viscosity, shortening the length of the string.

Gross characteristics allow many effusions to be tentatively classified as noninflammatory, inflammatory, or infectious (see
Table 32-2). Effusions can also be hemorrhagic. Each type of effusion suggests certain joint diseases (see
Table 32-3). So-called noninflammatory effusions are actually mildly inflammatory but tend to suggest diseases such as osteoarthritis, in which inflammation is not severe.

Laboratory tests commonly done on joint fluid include cell count, leukocyte differential, Gram stain and culture (if infection is a concern—see p. 365), and wet drop examination for cells and crystals. However, the exact tests often depend on which diagnoses are suspected.

Microscopic examination of a wet drop preparation of synovial fluid for crystals (only a single drop of fluid from a joint is needed), using polarized light, is essential for definitive diagnosis of gout, pseudogout, and other crystal-induced arthritides (see p. 349). A polarizer over the light source and another polarizer between the specimen and the examiner's eye allow visualization of crystals with a shiny white birefringence. Compensated polarized light is provided by inserting a first-order red plate, as is found in

commercially available microscopes. The effects of a compensator can be reproduced by placing 2 strips of clear adhesive tape on a glass slide and placing this slide over the lower polarizer. Such a homemade system should be tested against a commercial polarizing microscope. The most common crystals seen are those diagnostic of gout (monosodium urate, negatively birefringent needle-shaped crystals) and pseudogout (Ca pyrophosphate, positively birefringent square-ended crystals). If crystals appear atypical in a wet drop, several less common crystals (cholesterol, liquid lipid crystals, oxalate, cryoglobulins) or artifacts (eg, depot corticosteroid crystals) should be considered.

Other synovial fluid findings that occasionally make or suggest a specific diagnosis include the following:

• Specific organisms (identifiable by Gram or acid-fast stain)

• Marrow spicules or fat globules (caused by fracture)

• Reiter's cells (monocytes on Wright's-stained smears that have phagocytized PMNs), which appear most often in reactive arthritis

• Amyloid fragments (identifiable by Congo red stain)

• Sickled RBCs (caused by sickle cell hemoglobinopathies)

[Fig. 32-2. Arthrocentesis of the elbow.]

[Table 32-2. Classification of Synovial Effusions]

Monarticular Joint Pain

Monarticular pain may originate from the joint itself or surrounding structures. There may be pain (arthralgia) or also inflammation (arthritis) with redness, warmth, and swelling. Pain may occur only with use, suggesting a mechanical problem (eg, osteoarthritis, tendinitis), or also at rest, suggesting inflammation (eg, crystal disease, septic arthritis). There may or may not be fluid within the joint (effusion). Prompt assessment is essential to exclude infection. It is important to remember that acute monarticular arthritis is sometimes the initial manifestation of some types of polyarticular arthritis (eg, psoriatic arthritis, RA).

Pathophysiology

Monarticular pain may originate

• Within a joint (intra-articular)

• Around a joint (periarticular)

Intra-articular disorders may be inflammatory (eg, infectious, rheumatoid, crystal deposition arthritis) or noninflammatory (eg, osteoarthritis, internal derangement).

Periarticular disorders include bursitis and tendinitis.

Crystal-induced arthritis is usually caused by monosodium urate crystals (gout) or Ca pyrophosphate dihydrate crystals (pseudogout).

Etiology

At all ages, injury is the most common cause of acute monarticular joint pain; history of trauma is usually obvious.

[Fig. 32-3. Arthrocentesis of the knee.]

[**Table 32-3.** Differential Diagnosis Based on Synovial Fluid Classification*†]

Among young adults, the most common nontraumatic causes are the following:

• Disseminated gonococcal infection

• Periarticular syndromes

Among older adults, the most common nontraumatic causes are the following:

• Osteoarthritis

• Crystal-induced disease (gout or pseudogout)

• Periarticular syndromes

The most dangerous cause at any age is acute infectious arthritis, because it requires acute operative intervention (saline washout of the joint) and antibiotics to minimize permanent damage to the joint and to prevent sepsis and death.

At all ages, rare causes include adjacent osteomyelitis, avascular necrosis, pigmented villonodular synovitis, hemarthrosis (eg, in hemophilia or coagulopathies), and tumors (see Table 32-4).

Evaluation

Acute monarticular joint pain requires especially rapid diagnosis because some of its causes, particularly infectious (septic) arthritis and crystal-induced arthritis, require rapid treatment.

[**Table 32-4.** Some Causes of Monarticular Joint Pain]

Evaluation should determine whether the joint or periarticular structures are the cause of symptoms and whether there is inflammation. If inflammation is present or the diagnosis is unclear, symptoms and signs of polyarticular and systemic disorders should be sought and all joints should be examined.

History: History of present illness should focus on the acuity of onset (eg, abrupt, gradual), whether the problem is new or recurrent, and whether other joints have caused pain in the past. Also, temporal patterns (eg, diurnal variation, persistent vs intermittent), exacerbating and mitigating factors (eg, cold weather, activity), and any recent or past trauma to the joint should be noted. Patients should be specifically asked about unprotected sexual contact (possible gonococcal infection), tick bites, and residence in or travel to an area where Lyme disease is endemic.

Review of systems should seek symptoms of causative disorders, including fever (infection), urethritis (gonococcal arthritis), and previous unexplained illness with rash (Lyme arthritis).

Past medical history should identify known joint disorders (particularly gout, osteoarthritis) and any known conditions that may cause monarticular joint pain (eg, coagulopathy, bursitis, tendinitis, hemoglobinopathy). Drug history should be reviewed for any use of anticoagulants or diuretics and for chronic corticosteroid use. A family history should also be obtained.

Physical examination: Vital signs are reviewed for fever. Examination of the head, neck, and skin should note any signs of conjunctivitis, psoriatic plaques, mucosal lesions, ecchymoses, or malar rash. Genital examination should note any discharge or other findings consistent with sexually transmitted diseases.

Joints are inspected for deformities, erythema, and swelling. Range of motion is assayed, first actively and then passively; any crepitus on joint motion is noted.

Palpation is done to detect warmth, identify any effusion, and localize the area of tenderness. Of particular importance is whether the tenderness is directly over the joint line or adjacent to it (helping to differentiate an intra-articular from a periarticular disorder). Sometimes, compression of the joint without flexing or extending it (eg, pushing on the end of the great toe for patients with pain in the 1st metatarsophalangeal joint), sometimes with slight rotation, also helps differentiate intra-articular from periarticular disorders; this maneuver is not particularly painful for patients with tendinitis or bursitis but is quite painful for those with arthritis. If the patient can tolerate it, the joint is stressed with various maneuvers to identify disruption of cartilage or ligaments (eg, in the knee, valgus and varus tests, anterior and posterior drawer tests, Lachman's test, and McMurray's test). Comparison with the contralateral unaffected joint often helps detect more subtle changes.

Large effusions in the knee are typically readily apparent. The examiner can check for minor knee effusions by pushing the suprapatellar pouch inferiorly and then pressing medially on the lateral side of the patella on an extended knee. This maneuver causes swelling to appear on the medial side.

Periarticular structures also should be examined to look for discrete soft swelling at the site of a bursa (bursitis), point tenderness at the insertion of a tendon (tendinitis), and point tenderness over a tendon with fine crepitus (tenosynovitis).

Red flags: The following findings are of particular concern:

• Erythema, warmth, effusion, and decreased range of motion

• Fever

• Acute-onset joint pain in a sexually active young adult

• Skin breaks with cellulitis adjacent to the affected joint

• Underlying bleeding disorder, hemoglobinopathy, or anticoagulation

• Extra-articular or systemic symptoms

Interpretation of findings: Antecedent trauma suggests a fracture, meniscal tear, or hemarthrosis. In the absence of trauma, history and physical examination may suggest a cause, but testing is often necessary to rule out serious causes.

Acuteness of onset is a very important feature. Severe joint pain that develops over hours suggests crystal-induced arthritis or, less often, infectious arthritis. A previous attack of crystal-induced arthritis with development of similar symptoms suggests recurrence. Gradual onset of pain is typical of RA or noninfectious arthritis but can result from certain infectious arthritides (eg, mycobacterial, fungal).

Pain during rest and on initiating activity suggests inflammatory arthritis, whereas pain worsened by movement and relieved by rest suggests mechanical disorders (eg, osteoarthritis).

Pain worse with active than with passive joint motion may indicate tendinitis or bursitis; intra-articular inflammation generally restricts active and passive range of joint motion severely.

Increased warmth and erythema suggest inflammation, but erythema is often absent during inflammation. Tenderness or swelling at only one side of a joint, or away from the joint line, suggests an extra-articular origin (eg, in ligaments, tendons, or bursae); findings on several aspects of the joint suggest an intra-articular cause.

Although gout can involve many different single joints or combinations of joints, acute, painful monarticular arthritis of the metatarsophalangeal joint of a great toe (podagra) is especially suggestive.

The presence of systemic findings can help narrow the diagnosis. Urethritis can suggest gonococcal infection (although gonococcal arthritis often develops in patients without symptoms of urethritis). Fever is

indicative of septic joint, crystal-induced arthropathy, or osteomyelitis. Symptoms indicating dermatologic, cardiac, or pulmonary involvement suggest diseases that are more commonly associated with polyarticular joint pain.

Testing: Joint aspiration (arthrocentesis) should be done in patients with an effusion or other signs of inflammation (eg, erythema, warmth, fever). Studies of the joint fluid should include WBC count with differential (to determine whether the effusion is bloody or inflammatory), Gram stain and cultures, and microscopic examination for crystals. Finding crystals in synovial fluid confirms crystal-induced arthritis but does not rule out coexisting infection. A noninflammatory synovial fluid (eg, < 2000/µL WBCs or < 75% neutrophils) should lead to consideration of osteoarthritis, soft-tissue injury, or viral infection.

X-rays usually are done unless the cause is clearly a flare-up of a known disorder (eg, gout) or is a clinically obvious bursitis or tendinitis, which can often be diagnosed without further testing.

Other imaging tests (eg, CT, MRI, bone scan) are adjunctive and are done depending on what diagnoses are being considered (see Table 32-4).

Blood tests (eg, ESR, antinuclear antibodies, rheumatoid factor, anticyclic citrullinated peptide [CCP] antibody, HLA-B27 testing) may help support an early diagnosis of a noninfectious inflammatory arthritis.

Treatment

Overall treatment is directed at the underlying disorder.

Joint inflammation is usually treated symptomatically with NSAIDs. Pain without inflammation is usually more safely treated with acetaminophen. Joint immobilization with a splint or sling can sometimes relieve pain. Heat therapy may relieve muscle spasm around joints. Cold therapy may be analgesic in inflammatory joint diseases.

Physical therapy after the acute symptoms have lessened is useful to maintain range of motion and strengthen surrounding muscles.

Key Points

- Atraumatic joint pain should prompt consideration of degenerative disease, crystal-induced arthropathy, infection, or cancer.
- Arthrocentesis is mandatory to rule out infection in a joint that is red, warm, and swollen.
- Disseminated gonococcal infection is the most common cause of acute nontraumatic monarthritis in young adults, whereas osteoarthritis is the most common cause in older adults.
- Crystals in synovial fluid confirm crystal-induced arthritis but do not rule out coexisting infection.
- Joint pain that is still unexplained after arthrocentesis and x-ray should be evaluated with MRI to rule out uncommon etiologies (eg, occult fracture, avascular necrosis, pigmented villonodular synovitis).

Polyarticular Joint Pain

Joints may simply be painful (arthralgia) or also inflamed (arthritis), with redness, warmth, and swelling. Pain may occur only with use or also at rest, and there may or may not be fluid within the joint (effusion).

A useful initial distinction is whether pain is present in one joint (monarticular) or multiple joints (polyarticular). When multiple joints are affected, different terms can be used:

- Arthritis involving ≤ 4 joints, particularly when it occurs in an asymmetric fashion, is oligoarticular or pauciarticular arthritis.

• Arthritis involving > 4 joints, usually in a symmetric fashion, is polyarticular arthritis.

Pathophysiology

Polyarticular arthralgia can originate from arthritis or from extra-articular disorders (eg, polymyalgia rheumatica, fibromyalgia). Pain caused by intra-articular disorders may be secondary to an inflammatory arthritis (eg, infection, RA, crystal deposition) or a noninflammatory process (eg, osteoarthritis).

Inflammatory arthritis may involve peripheral joints only (eg, hands, knees, feet) or both peripheral and axial joints (eg, sacroiliac, apophyseal, discovertebral, costovertebral).

Etiology

Peripheral oligoarticular and polyarticular arthritis have specific, likely causes (see Table 32-5); the presence or absence of axial involvement helps limit possibilities. However, in many patients, arthritis is often transient and resolves without diagnosis or may not fulfill the criteria for any defined rheumatic disease.

Acute polyarticular arthritis is most often due to the following:

• Infection (usually viral)

• Flare of a rheumatic disease

[**Table 32-5.** Some Causes of Polyarticular Joint Pain]

Chronic polyarticular arthritis in adults is most often due to the following:

• RA (inflammatory)

• Osteoarthritis (noninflammatory)

Chronic polyarticular arthritis in children is most often due to the following:

• Juvenile idiopathic arthritis

Evaluation

Evaluation should determine whether the joints or periarticular structures are the cause of symptoms and whether there is inflammation or effusion. If inflammation is present or the diagnosis is unclear, symptoms and signs of systemic disorders should be sought.

History: History of present illness should identify the acuity of onset (eg, abrupt, gradual), temporal patterns (eg, diurnal variation, persistent vs intermittent), chronicity (eg, acute vs longstanding), and exacerbating factors (eg, cold weather, activity). Patients should be specifically asked about unprotected sexual contact (possible gonococcal infection) and tick bites or residence in a Lyme-endemic area.

Review of systems should seek symptoms and signs of causative disorders (see Tables 32-5 and 32-6).

[**Table 32-6.** Some Suggestive Findings in Polyarticular Joint Pain]

Past medical history and family history should identify known rheumatic disorders and other conditions capable of causing joint symptoms (see Table 32-5).

Physical examination: Vital signs are reviewed for fever.

Examination of the head, neck, and skin should note any signs of conjunctivitis, iritis, mucosal lesions,

sinonasal abnormalities, lymphadenopathy, ecchymoses, skin ulcers, psoriatic plaques, purpura, or malar rash.

Cardiopulmonary examination should note any signs of acute inflammatory disease or serositis (eg, murmur, pericardial rub, muffled heart sounds, bibasilar dullness consistent with pleural effusion).

Genital examination should note any discharge, ulcers, or other findings consistent with sexually transmitted diseases.

Musculoskeletal examination should note muscular point tenderness associated with fibromyalgia. Joint examination begins with inspection for deformities, erythema, swelling, or effusion and then proceeds to palpation and estimation of pain and crepitus with active and passive range of motion. Comparison with the contralateral unaffected joint often helps detect more subtle changes. Examination should note whether the distribution of affected joints is symmetric.

Periarticular structures also should be examined for discrete, soft swelling at the site of a bursa (bursitis), point tenderness at the insertion of a tendon (tendinitis), and point tenderness over a tendon with fine crepitus (tenosynovitis).

Red flags: The following findings are of particular concern:

• Hot, swollen, red joints

• Any extra-articular symptoms (eg, fever, rash, plaques, ulcers, conjunctivitis, iritis, murmur, purpura)

Interpretation of findings: An important initial element is whether pain originates in the joints, spine, or both or in other structures such as bones, tendons, bursae, muscles, other soft-tissue structures, or nerves. Pain that worsens with active rather than passive joint motion may indicate tendinitis or bursitis; intra-articular inflammation generally restricts active and passive range of joint motion severely. Tenderness or swelling at only one side of a joint, or away from the joint line, suggests an extra-articular origin (eg, in ligaments, tendons, or bursae); findings on several aspects of the joint suggest an intra-articular cause. Pain that is diffuse and described inconsistently or vaguely may result from fibromyalgia or functional disorders.

If the joints, spine, or both are involved, differentiating inflammatory from noninflammatory disorders may help. Clinical findings of prominent morning stiffness, nontraumatic joint swelling, and fever or weight loss are suggestive of an inflammatory disorder, but testing is often helpful.

Examination of the hand joints may yield other clues (see Table 32-6) and may help differentiate osteoarthritis from RA (see
Table 32-7).

Back pain with arthritis suggests ankylosing spondylitis a reactive or psoriatic arthritis, or fibromyalgia.

[**Table 32-7.** Differential Features of the Hand in RA and Osteoarthritis]

Testing: The following tests are of particular importance:

• Arthrocentesis

• Serologic testing

• Usually ESR

Arthrocentesis is mandatory in most patients with a new effusion and can help rule out infection and crystal arthropathy as well as distinguish between an inflammatory and noninflammatory process. Other tests may be needed to identify specific disorders (see Table 32-5).

If the specific diagnosis cannot be established clinically and if determining whether arthritis is inflammatory may help determine the diagnosis, ESR and C-reactive protein may be done. A low ESR makes inflammatory causes (eg, rheumatic disease, gout, infection, vasculitis) less likely but does not rule them out. Elevated results argue more strongly for inflammation, but they are very nonspecific, particularly in older adults.

Once a diagnosis of a systemic disease is thought to be most likely, supportive serologic testing for antinuclear antibodies, double-stranded DNA, rheumatoid factor, anticyclic citrullinated peptide, and antineutrophil cytoplasmic antibodies may assist in making the diagnosis.

Treatment

The underlying disorder is treated. Systemic diseases may require either immunosuppression or antibiotics as determined by the diagnosis. Joint inflammation is usually treated symptomatically with NSAIDs. Pain without inflammation is usually more safely treated with acetaminophen. Joint immobilization with a splint or sling can sometimes relieve pain. Heat therapy may relieve muscle spasm around joints, and cold therapy may be analgesic in inflammatory joint diseases. For cases of chronic arthritis, continued physical activity is encouraged.

Geriatrics Essentials

Osteoarthritis is by far the most common cause of arthritis in older people. RA most commonly begins between ages 30 and 40, but in up to one third of patients, it develops after the age of 60. Because paraneoplastic phenomena also can cause inflammatory polyarthritis, cancer should be considered in older adults in whom new-onset RA is suspected.

Key Points

- The differential diagnosis of polyarticular joint pain can be narrowed by considering how many joints are affected, whether inflammation is present, and whether any extra-articular signs are present.
- Chronic arthritis is most often caused by juvenile idiopathic arthritis in children and osteoarthritis and RA in adults.
- Acute polyarticular arthritis is most often due to infection, gout, or a flare of rheumatic disease.
- Arthrocentesis is mandatory in most cases of a new effusion and can help rule out infection and crystal-induced arthropathy as well as distinguish between an inflammatory and noninflammatory process.

Chapter 33. Autoimmune Rheumatic Disorders

Introduction

Autoimmune rheumatic disorders include eosinophilic fasciitis, mixed connective tissue disease, polymyositis and dermatomyositis, relapsing polychondritis, Sjogren's syndrome, SLE, and systemic sclerosis. RA and the spondyloarthropathies and their variants (see Ch. 35) are also immune mediated. The triggers and precise pathophysiology remain unknown for all these disorders, although many aspects of pathogenesis are becoming clearer. Patients with most autoimmune rheumatic disorders are at increased risk of atherosclerosis.

Eosinophilic Fasciitis

Eosinophilic fasciitis (EF) is an uncommon disorder characterized by symmetric and painful inflammation, swelling, and induration of the arms and legs. Diagnosis is by biopsy of skin and fascia. Treatment is with corticosteroids.

The cause of EF is unknown. The disorder occurs mostly in middle-aged men but can occur in women and children.

Symptoms and Signs

The disease often begins after strenuous physical activity (eg, chopping wood). The initial features are pain, swelling, and inflammation of the skin and subcutaneous tissues, followed by induration, creating a characteristic orange-peel configuration most evident over the anterior surfaces of the extremities. The face and trunk are occasionally involved. Restriction of arm and leg movement usually develops insidiously. Contractures commonly evolve, secondary to induration and thickening of the fascia, but the process may also involve tendons, synovial membranes, and muscle. Typically, EF does not involve the fingers and toes (acral areas). Muscle strength is unimpaired, but myalgia and arthritis may occur. Carpal tunnel syndrome may also occur.

Fatigue and weight loss are common. Rarely, aplastic anemia, thrombocytopenia, and lymphoproliferative processes develop.

Diagnosis

• Biopsy

EF should be suspected in patients with typical symptoms. The cutaneous manifestations may suggest systemic sclerosis; however, patients with systemic sclerosis usually also have Raynaud's syndrome, acral involvement, telangiectasia, and visceral changes (eg, esophageal dysmotility). All of these are absent in EF.

Diagnosis is confirmed by en bloc biopsy, which should be deep enough to include fascia and adjacent muscle fibers. Characteristic findings are inflammation of the fascia, with or without eosinophils.

Blood tests are not diagnostic, but CBC shows eosinophilia (in early active disease), and serum protein electrophoresis shows polyclonal hypergammaglobulinemia. CBC should be done in all patients because the presence of eosinophilia helps in the diagnosis. Autoantibodies are usually absent. MRI, although not specific, can show thickened fascia, the increased signal intensity in the superficial muscle fibers correlating with the inflammation.

Prognosis

Although the long-term outcome varies, EF is often self-limited and uncomplicated.

Treatment

• Oral prednisone

Most patients respond rapidly to high doses of prednisone (40 to 60 mg po once/day followed by gradual reduction to 5 to 10 mg/day as soon as the fascitis resolves). Continued low doses may be required for 2 to 5 yr. Some patients require longer courses and possibly other drugs (eg, hydroxychloroquine, cyclosporine). NSAIDs and H_2 blockers (eg, cimetidine) also have been used to treat EF.

Monitoring with CBCs is advised because of the occasional hematologic complications.

Mixed Connective Tissue Disease

Mixed connective tissue disease (MCTD) is an uncommon, specifically defined, overlap syndrome characterized by clinical features of SLE, systemic sclerosis, and polymyositis with very high titers of circulating antinuclear antibody to a ribonucleoprotein antigen. Hand swelling, Raynaud's syndrome, polyarthralgia, inflammatory myopathy, esophageal hypomotility, and pulmonary dysfunction are common. Diagnosis is by the combination of clinical features, antibodies to ribonucleoprotein, and absence of antibodies specific for other autoimmune diseases. Treatment varies with disease severity and organ involvement but usually includes corticosteroids and sometimes additional immunosuppressants.

MCTD occurs worldwide and in all races, with a peak incidence in the teens and 20s. About 80% of people who have this disease are women. The cause is unknown. In some patients, the disorder evolves into classic systemic sclerosis or SLE.

Symptoms and Signs

Raynaud's syndrome may precede other manifestations by years. Frequently, the first manifestations resemble early SLE, systemic sclerosis, polymyositis, dermatomyositis, or even RA. Whatever the initial manifestation, limited disease tends to progress and become widespread, and the clinical pattern changes over time.

The most frequent finding is swelling of the hands that eventually causes a sausage-like appearance of the fingers. Skin findings include lupus or dermatomyositis-like rashes. Diffuse systemic sclerosis-like skin changes and ischemic necrosis or ulceration of the fingertips may occasionally develop.

Almost all patients have polyarthralgias, and 75% have frank arthritis. Often the arthritis is nondeforming, but erosive changes and deformities similar to those in RA (eg, boutonniere and swan-neck deformities) may be present. Proximal muscle weakness with or without tenderness is common.

Renal disease occurs in about 10% and is often mild but occasionally causes morbidity or mortality. Sometimes pulmonary involvement is the most serious complication. Heart failure can occur. Sjogren's syndrome may develop. A trigeminal sensory neuropathy develops more frequently in MCTD than in other systemic autoimmune diseases. It may be the presenting feature and is considered the most frequent CNS manifestation.

Diagnosis

• Testing for antinuclear antibodies (ANA), extractable nuclear antigen (ENA), and ribonucleoprotein (RNP)

• Organ involvement determined as clinically indicated

MCTD should be suspected when additional overlapping features are present in patients appearing to have SLE, systemic sclerosis, polymyositis, or RA.

Tests for ANA and antibody to ENA and RNP antigen are done first. If results of these tests are compatible with MCTD (eg, RNP antibodies very high, positive ANA), tests for rheumatoid factors, anti Jo-1 (anti-histidyl t-RNA synthetase), antibodies to the ribonuclease-resistant Smith (Sm) component of ENA,

and double-stranded DNA are done to exclude other possible diagnoses.

Further evaluation depends on symptoms and signs; manifestations of myositis, renal involvement, or pulmonary involvement prompt tests of those organs (eg, CK, MRI, electromyogram, or muscle biopsy for diagnosis of myositis).

Almost all patients have high titers (often > 1:1000) of fluorescent ANA that produce a speckled pattern. Antibodies to ENA are usually present at very high titers (> 1:100,000). Antibody to RNP is present, whereas antibody to the ribonuclease-resistant Sm component of ENA is absent.

Rheumatoid factors are frequently positive, and titers are often high. The ESR is frequently elevated.

Prognosis

The overall 10-yr survival rate is 80%, but prognosis depends largely on which manifestations predominate. Patients with features of systemic sclerosis and polymyositis have a worse prognosis. Patients are at increased risk of atherosclerosis. Causes of death include pulmonary hypertension, renal failure, MI, colonic perforation, disseminated infection, and cerebral hemorrhage. Some patients have sustained remissions for many years without treatment.

Treatment

• NSAIDs or antimalarials for mild disease

• Corticosteroids for moderate to severe disease

• Sometimes other immunosuppressants

General management and initial drug therapy are tailored to the specific clinical problem and are similar to those of SLE. Most patients with moderate or severe disease respond to corticosteroids, particularly if treated early. Mild disease is often controlled by NSAIDs, antimalarials, or sometimes low-dose corticosteroids. Severe major organ involvement usually requires higher doses of corticosteroids (eg, prednisone 1 mg/kg po once/day) and additional immunosuppressants. If patients develop features of myositis or systemic sclerosis, treatment is as for those diseases.

All patients should be closely monitored for atherosclerosis. Patients on long-term corticosteroid therapy should receive osteoporosis prophylaxis.

Polymyositis and Dermatomyositis

Polymyositis and dermatomyositis are uncommon systemic rheumatic disorders characterized by inflammatory and degenerative changes in the muscles (polymyositis) or in the skin and muscles (dermatomyositis). The most specific skin signs are Gottron's papules over the knuckles and a periorbital heliotropic rash. Manifestations include symmetric weakness, some tenderness, and later atrophy, principally of the proximal limb girdle muscles. Complications can include visceral involvement and cancer. Diagnosis is by clinical findings and abnormalities on muscle tests, which may include muscle enzymes, MRI, electromyography, and muscle biopsy. Treatment is with corticosteroids, sometimes combined with immunosuppressants or IV immune globulin.

The female:male ratio is 2:1. These disorders may appear at any age but occur most commonly from age 40 to 60 or, in children, from age 5 to 15.

Etiology

The cause seems to be an autoimmune reaction to muscle tissue in genetically susceptible people. Familial clustering occurs, and HLA subtypes DR3, DR52, DR6 seem to be the genetic predisposition. Possible inciting events include viral myositis and underlying cancer. Picornavirus-like structures have

been found in muscle cells, but their significance is not known, and viruses can trigger similar disorders in animals. The association of cancer with dermatomyositis (much less so with polymyositis) suggests that a tumor may incite myositis as the result of an autoimmune reaction against a common antigen in muscle and tumor.

Pathophysiology

Pathologic changes in both disorders include cellular damage and atrophy, with variable degrees of inflammation. Muscles in the hands, feet, and face are affected less than other skeletal muscles. Involvement of visceral muscles in the pharynx and upper esophagus and occasionally the heart, stomach, or intestines can impair the functions of those organs. High blood levels of myoglobin from rhabdomyolysis can damage the kidneys. Inflammation may occur in joints and lungs, especially in patients with antisynthetase antibodies.

Dermatomyositis is characterized by immune complex deposition in the vessels and is considered a complement-mediated vasculopathy. In contrast, the main pathophysiologic abnormality in polymyositis is direct T cell-mediated muscle injury.

Classification

Myositis has been divided into several subtypes:

- Primary idiopathic polymyositis can occur at any age and does not involve the skin.
- Primary idiopathic dermatomyositis is similar to primary idiopathic polymyositis but also involves the skin.
- Polymyositis or dermatomyositis associated with cancer can occur at any age but is most common among older adults; the cancer can develop up to 2 yr before or after the myositis.
- Childhood dermatomyositis can be associated with systemic vasculitis.
- Polymyositis or dermatomyositis can occur with an associated disorder such as progressive systemic sclerosis, mixed connective tissue disease, RA, SLE, or sarcoidosis.

Inclusion body myositis is a separate disorder that has clinical manifestations similar to chronic idiopathic polymyositis; however, it develops at an older age, frequently involves distal muscles (eg, hand and feet muscles), has a longer duration, responds poorly to therapy, and has a different histologic appearance.

Symptoms and Signs

Onset of polymyositis may be acute (particularly in children) or insidious (particularly in adults). Polyarthralgias, Raynaud's syndrome, dysphagia, pulmonary symptoms, and constitutional complaints (notably fever, fatigue, and weight loss) may also occur.

Muscle weakness may progress over weeks to months. However, it takes destruction of 50% of muscle fibers to cause symptomatic weakness (ie, muscle weakness indicates advanced myositis). Patients may have difficulty raising their arms above their shoulders, climbing steps, or rising from a sitting position. Patients may become wheelchair-bound or bedridden because of weakness of pelvic and shoulder girdle muscles. The flexors of the neck may be severely affected, causing an inability to raise the head from the pillow. Involvement of pharyngeal and upper esophageal muscles may impair swallowing and predispose to aspiration. Muscles of the hands, feet, and face escape involvement. Limb contractures may eventually develop.

Joint manifestations include polyarthralgia or polyarthritis, often with swelling, effusions, and other characteristics of nondeforming arthritis, which occur in about 30% of patients. However, joint manifestations tend to be mild. They occur more often in a subset with Jo-1 or other antisynthetase antibodies.

Visceral involvement (except that of the pharynx and upper esophagus) is less common in polymyositis than in some other rheumatic disorders (eg, SLE, systemic sclerosis). Occasionally, and especially in patients with antisynthetase antibodies, interstitial pneumonitis (manifested by dyspnea and cough) is the most prominent manifestation. Cardiac arrhythmias (including conduction disturbances and abnormal systolic time intervals) can occur but are often asymptomatic. GI symptoms, more common among children with associated vasculitis, may include hematemesis, melena, and ischemic bowel perforation.

Skin changes, which occur in dermatomyositis, tend to be dusky and erythematous. Periorbital edema with a purplish appearance (heliotrope rash) is specific for dermatomyositis. The rash may be slightly elevated and smooth or scaly; it may appear on the forehead, V of the neck and shoulders, chest and back, forearms and lower legs, elbows and knees, medial malleoli, and radiodorsal aspects of the proximal interphalangeal and metacarpophalangeal joints (Gottron's papules—also a relatively specific finding). The base and sides of the fingernails may be hyperemic or thickened. Desquamating dermatitis with splitting of the skin may evolve over the radial aspects of the fingers. The primary skin lesions frequently fade completely but may be followed by secondary changes (eg, brownish pigmentation, atrophy, scarring, vitiligo). Subcutaneous calcification may occur, particularly in children.

Diagnosis

• Clinical criteria

• Muscle biopsy (definitive)

Polymyositis should be suspected in patients with proximal muscle weakness with or without muscle tenderness. Dermatomyositis should be suspected in patients with a heliotropic rash or Gottron's papules, even without polymyositis, and in patients with symptoms of polymyositis and any skin findings compatible with dermatomyositis. Polymyositis and dermatomyositis share certain clinical findings with systemic sclerosis or, less frequently, with SLE or vasculitis. Establishing the diagnosis requires as many as possible of the following 5 criteria:

• Proximal muscle weakness

• Characteristic rash

• Elevated serum muscle enzymes (CK, or if this is not elevated, aminotransferases or aldolase)

• Characteristic electromyographic or MRI abnormalities

• Muscle biopsy changes (the definitive test)

Muscle biopsy excludes some similar conditions such as inclusion body myositis and postviral rhabdomyolysis. Biopsy findings can be variable, but chronic inflammation and muscle degeneration and regeneration are typical. A definite diagnosis made by muscle biopsy is recommended before treatment of polymyositis to exclude other muscle disorders. To increase the sensitivity of the biopsy results, the biopsy sample should be obtained from a muscle that has one or more of the following characteristics:

• Weakness on clinical examination

• Inflammation identified on MRI

• Contralateral pair of a muscle shown to be abnormal on electromyography

Laboratory studies can increase or decrease suspicion for the disorder, assess its severity, identify overlaps, and help detect complications. Autoantibodies should be tested. Antinuclear antibodies are positive in up to 80% of patients. Detailed testing of the antinuclear antibodies (ANA), when present, is important in identifying other overlap syndromes, most often those with another autoimmune disorder. About 30% of patients have myositis-specific autoantibodies: antibodies to aminoacyl-tRNA synthetases (anti-synthetase antibodies), including anti-Jo-1; antibodies to signal recognition particle (SRP—anti-SRP

antibodies); and antibodies to Mi-2, a nuclear helicase. The relationship between these autoantibodies and disease pathogenesis remains unclear, although antibody to Jo-1 is a significant marker for fibrosing alveolitis, pulmonary fibrosis, arthritis, and Raynaud's syndrome.

Periodic measurement of CK is helpful in monitoring treatment. However, in patients with widespread muscle atrophy, levels are occasionally normal despite chronic, active myositis. Muscle biopsy, MRI, or high CK levels can often differentiate a relapse of polymyositis from corticosteroid-induced myopathy. Aldolase is a less specific marker for muscle injury than CK.

Cancer screening is recommended by some authorities for any adult who has dermatomyositis or for patients ≥ 60 yr who have polymyositis because these patients often have unsuspected cancers. Screening should include a physical examination that includes breast, pelvis, and rectum (with occult blood testing); CBC; biochemical profile; mammogram; carcinoembryonic antigen; urinalysis; chest x-ray; and any other tests appropriate based on patient's age. Additional investigation should be based on history and physical examination findings. Some authorities recommend CT of the chest, abdomen, and pelvis. Younger patients without symptoms of cancer need not undergo screening.

Prognosis

Long remissions (even apparent recovery) occur in up to 50% of treated patients within 5 yr, more often in children. Relapse, however, may still occur at any time. Overall 5-yr survival rate is 75% and is higher in children. Death in adults is preceded by severe and progressive muscle weakness, dysphagia, undernutrition, aspiration pneumonia, or respiratory failure with superimposed pulmonary infection. Polymyositis tends to be more severe and resistant to treatment in patients with cardiac or pulmonary involvement. Death in children may be a result of bowel vasculitis. Cancer, if present, generally determines the overall prognosis.

Treatment

• Corticosteroids

• Sometimes immunosuppressants (eg, methotrexate, azathioprine, cyclosporine, IV immune globulin)

Physical activities should be modestly curtailed until the inflammation subsides. Corticosteroids are the drugs of choice initially. For acute disease, adults receive prednisone ≥ 40 to 60 mg po once/day. Serial measurements of CK provide the best early guide of therapeutic effectiveness, falling toward or reaching normal in most patients in 6 to 12 wk, followed by improved muscle strength. Once enzyme levels have returned to normal, prednisone can be gradually reduced. If muscle enzyme levels rise, the dose is increased. Patients who seem to recover can have treatment gradually withdrawn with close monitoring, but most adults require chronic maintenance with prednisone (up to 10 to 15 mg/day). Children require initial doses of prednisone of 30 to 60 mg/m^2 once/day. In children, it may be possible to stop prednisone after ≥ 1 yr of remission.

Occasionally, patients treated chronically with high-dose corticosteroids become increasingly weak because of a superimposed corticosteroid myopathy.

If a patient does not to respond to corticosteroids, depends on a high to moderate dose of corticosteroids, or develops a corticosteroid myopathy or another complication that necessitates stopping or decreasing prednisone, immunosuppressants (eg, methotrexate, azathioprine, cyclosporine, IV immune globulin) should be tried. Some patients have received only methotrexate (generally in higher doses than used for RA) for ≥ 5 yr. IV immune globulins can be effective in some patients refractory to drug treatment, but the prohibitive cost has precluded comparative trials. Some clinicians combine prednisone with an immunosuppressant. Other possible emerging therapies include anti-tumor necrosis factor (TNF) agents and rituximab.

Myositis associated with tumors, metastatic disease, or inclusion body myositis usually is more refractory to corticosteroids. Cancer-associated myositis may remit if the tumor is removed.

People with an autoimmune disorder are at higher risk of atherosclerosis and should be closely monitored. Patients on long-term corticosteroid therapy should receive osteoporosis prophylaxis.

Relapsing Polychondritis

Relapsing polychondritis is an episodic, inflammatory, and destructive disorder involving primarily cartilage of the ear and nose but also potentially affecting the eyes, tracheobronchial tree, heart valves, kidneys, joints, skin, and blood vessels. Diagnosis is by a combination of clinical, laboratory, imaging, and sometimes biopsy findings. Treatment usually requires prednisone and other immunosuppressants.

Relapsing polychondritis affects men and women equally; onset typically is in middle age. An association with RA, systemic vasculitis, SLE, and other connective tissue disorders suggests an autoimmune etiology.

Symptoms and Signs

Acute pain, erythema, and swelling most commonly affect the pinna cartilage. Nasal cartilage inflammation is the next most common, followed by arthritis that varies from arthralgias to symmetric or asymmetric nondeforming arthritis involving large and small joints, with a predilection for the costochondral joints. The next most common manifestations, in decreasing order of frequency, are inflammation of the eye (eg, conjunctivitis, scleritis, iritis, keratitis, chorioretinitis); cartilaginous tissue of the larynx, trachea, or bronchi (causing hoarseness, cough, and tenderness over the laryngeal cartilage); internal ear; cardiovascular system (eg, aortic regurgitation, mitral regurgitation, pericarditis, myocarditis, aortic aneurysms, aortitis); kidney; and skin. Bouts of acute inflammation heal over weeks to months, with recurrences over several years. Various rashes can develop.

Advanced disease can lead to destruction of supporting cartilage, causing floppy ears; saddle nose; pectus excavatum; and visual, auditory, and vestibular abnormalities. Tracheal narrowing can lead to dyspnea, pneumonia, or even tracheal collapse. Coexisting systemic vasculitis (leukocytoclastic vasculitis or polyarteritis nodosa), myelodysplastic syndrome, or cancer is possible.

Diagnosis

• Clinical criteria

• Sometimes biopsy

Diagnosis is established if the patient develops at least 3 of the following:

• Bilateral chondritis of the external ears

• Inflammatory polyarthritis

• Nasal chondritis

• Ocular inflammation

• Respiratory tract chondritis

• Auditory or vestibular dysfunction

Biopsy of involved cartilage, most often the pinna, is helpful if clinical diagnosis is not clear-cut.

Laboratory tests are done. They are not specific but may help to exclude other disorders. Synovial fluid analysis reveals mild inflammatory changes that are nonspecific but help to rule out an infectious process. Blood tests may show normocytic-normochromic anemia, leukocytosis, elevated ESR or γ-globulin levels, and occasionally positive rheumatoid factor, antinuclear antibodies (ANA), or, in up to 25%, antineutrophil

cytoplasmic antibodies (ANCA). Abnormal renal function may indicate an associated vasculitis. A positive c-ANCA test (ANCA that are reactive mainly to proteinase-3) suggests Wegener's granulomatosis, which can cause similar findings (see p. 329).

The upper and lower airways should be evaluated, including complete spirometric testing and chest CT, when the diagnosis is made.

Prognosis

Mortality after 5 yr is 30%, from collapse of laryngeal and tracheal structures or from cardiovascular complications such as large-vessel aneurysm, cardiac valvular insufficiency, or systemic vasculitis.

Treatment

- NSAIDs or dapsone for mild ear disease
- Corticosteroids
- Sometimes methotrexate or other immunosuppressants (eg, cyclosporine, cyclophosphamide, azathioprine)

Mild recurrent ear disease may respond to NSAIDs in anti-inflammatory doses, or dapsone (50 to 100 mg po once/day). However, most patients are treated with prednisone 30 to 60 mg po once/day, with tapering of the dose as soon as there is a clinical response. Some patients require chronic use. In such patients, methotrexate 7.5 to 20 mg po once/wk can reduce the requirement for corticosteroids. Very severe cases may require other immunosuppressants, such as cyclosporine, cyclophosphamide, or azathioprine (see p. 337). None of these therapies has been tested in controlled trials or has been shown to decrease mortality. If tracheal narrowing causes stridor, a tracheostomy or stent may be needed. More extensive tracheobronchial collapse may require tracheal reconstruction. Eye disease may sometimes be recalcitrant to treatment, especially when involving the sclera, and carries a poor prognosis.

All patients should be closely monitored for atherosclerosis given the risk of premature atherosclerosis in systemic vasculitides. Patients on long-term corticosteroid therapy should receive osteoporosis prophylaxis.

Sjogren's Syndrome

Sjogren's syndrome (SS) is a relatively common chronic, autoimmune, systemic, inflammatory disorder of unknown cause. It is characterized by dryness of the mouth, eyes, and other mucous membranes due to lymphocytic infiltration of the exocrine gland and secondary gland dysfunction. Sjogren's syndrome can affect various exocrine glands or other organs. Diagnosis is by specific criteria relating to eye, mouth, and salivary gland involvement, autoantibodies, and (occasionally) histopathology. Treatment is symptomatic.

SS occurs most frequently among middle-aged women. SS is classified as primary when there is no other associated disease. In about 30% of patients with autoimmune disorders such as RA, SLE, systemic sclerosis, mixed connective tissue disease, Hashimoto's thyroiditis, primary biliary cirrhosis, or chronic autoimmune hepatitis, SS develops and, in such cases, is classified as secondary. Genetic associations have been found (eg, HLADR3 antigens in whites with primary SS).

Pathophysiology

Salivary, lacrimal, and other exocrine glands become infiltrated with CD4+ T cells and with some B cells. The T cells produce inflammatory cytokines (eg, IL-2, interferon-γ). Salivary duct cells also produce cytokines, eventually damaging the secretory ducts. Atrophy of the secretory epithelium of the lacrimal glands causes desiccation of the cornea and conjunctiva (keratoconjunctivitis sicca—see p. 592). Lymphocytic infiltration and intraductal cellular proliferation in the parotid gland cause luminal narrowing and in some cases formation of compact cellular structures termed myoepithelial islands; atrophy of the

gland can result. Dryness and GI mucosal or submucosal atrophy and diffuse infiltration by plasma cells and lymphocytes may cause symptoms (eg, dysphagia).

Symptoms and Signs

Glandular manifestations: SS often affects the eyes or mouth initially and sometimes exclusively. Dry eyes can cause irritation and photosensitivity. In advanced cases, the cornea is severely damaged, epithelial strands hang from the corneal surface (keratitis filiformis), and vision can be impaired. Diminished saliva (xerostomia) results in difficulty chewing and swallowing, secondary *Candida* infection, tooth decay, and calculi in the salivary ducts. Taste and smell may be diminished. Dryness may also develop in the skin and in mucous membranes of the nose, throat, larynx, bronchi, vulva, and vagina. Dryness of the respiratory tract may cause cough. Alopecia may occur. Parotid glands enlarge in 33% of patients and are usually firm, smooth, and mildly tender. Chronic salivary gland enlargement is rarely painful unless there is obstruction or infection.

Extraglandular manifestations: Joint disease in SS is typically nonerosive and nondeforming. Arthralgias occur in about 50% of patients. Arthritis occurs in about 33% of patients and is similar in distribution to RA but is not erosive.

Other common extraglandular manifestations include generalized lymphadenopathy, Raynaud's syndrome, parenchymal lung involvement (which is common but infrequently serious), and vasculitis. Vasculitis can occasionally affect the peripheral nerves (causing peripheral polyneuropathy or mononeuritis multiplex) or CNS or cause rashes (including purpura) and glomerulonephritis. Kidney involvement can cause renal tubular acidosis, impaired concentrating ability, kidney stones, or interstitial nephritis. Pseudolymphoma, malignant lymphoma, or Waldenstrom's macroglobulinemia can develop; patients develop non-Hodgkin lymphoma at 40 times the normal rate. Chronic hepatobiliary disease and pancreatitis (exocrine pancreatic tissue is similar to that of salivary glands) may also occur.

Diagnosis

• Eye symptoms, oral symptoms, and eye and salivary gland testing

• Autoantibodies

• Sometimes salivary gland biopsy

SS should be suspected in patients with gritty or dry eyes or dry mouth, enlarged salivary glands, peripheral neuropathy, purpura, or unexplained renal tubular acidosis. Such patients should receive diagnostic tests that can include evaluation of the eyes and salivary glands and serologic tests. Different criteria have been proposed for classification of SS. The latest modifications to the American-European classification criteria for SS were proposed in 2002. These criteria were not developed for use in routine clinical practice, and not every patient who receives a clinical diagnosis of SS fulfills the proposed criteria (usually > 3 of 6 manifestations). The 6 manifestations are eye symptoms, oral symptoms, positive eye tests, salivary gland involvement, autoantibodies, and histopathology.

Eye symptoms are ≥ 3 mo of either dry eyes or use of tear substitutes ≥ 3 times/day; slit-lamp examination may also confirm dry eyes.

Oral symptoms are > 3 mo of daily dry mouth sensation, daily use of liquids to aid in swallowing, or swollen salivary glands.

Eye signs include evaluation by Schirmer's test, which measures the quantity of tears secreted in 5 min after irritation from a filter paper strip placed under each lower eyelid. A young person normally moistens 15 mm of each paper strip. Most people with SS moisten < 5 mm, although about 15% of test results are false-positive and 15% are false-negative. Ocular staining with an eyedrop of rose bengal or lissamine green solution is highly specific. Slit-lamp examination showing a fluorescein tear breakup in < 10 sec is also suggestive.

Salivary gland involvement can be confirmed by abnormally low saliva production (≤ 1.5 mL/15 min) as measured by salivary flow, sialography, or salivary scintiscanning, although these tests are used less often.

Autoantibodies (serologic criteria) have limited sensitivity and specificity. They include antibodies to Ro (SS-A autoantibodies—see Systemic Lupus Erythematosus on p. 305) or to nuclear antigens (termed La or SS-B autoantibodies), antinuclear antibodies, or an elevated level of antibodies against γ-globulin. Rheumatoid factor is present in > 70% of patients. ESR is elevated in 70%, 33% have anemia, and up to 25% have leukopenia.

Histopathology is assessed by biopsy of minor salivary glands in the buccal mucosa. Salivary gland biopsy is usually reserved for patients in whom the diagnosis cannot be established by autoantibody testing or when a major organ is involved. Histopathologic involvement is confirmed if labial minor salivary glands show multiple large foci of lymphocytes with atrophy of acinar tissue.

Most common causes of dry eyes and dry mouth (sicca symptoms) are aging and drugs, but when parotid enlargement occurs in addition to sicca symptoms, diseases such as hepatitis C, HIV, bulimia, and sarcoidosis should be differentiated from SS.

Prognosis

SS is chronic, and death may occasionally result from pulmonary infection and, rarely, from renal failure or lymphoma. Associated systemic autoimmune disorders may dictate prognosis.

Treatment

• Symptomatic treatment for sicca symptoms

• Avoidance of aggravating factors

• Occasionally oral corticosteroids or cyclophosphamide

SS should be initially managed by topical therapy of dry eyes and dry mouth. Other systemic manifestations of SS should be treated depending on the severity and the involved organ. Recognition of therapies for other conditions that can exacerbate dryness complaints is crucial. Hydroxychloroquine 200 to 400 mg po once/day is usually given to halt the progression of the disease and for the treatment of arthralgias.

Dry eyes should be treated with lubricating eye preparations (initially drops such as hypromellose or methylcellulose and an OTC ointment at bedtime). Other treatments include drainage (punctal) duct closure and topical cyclosporine. Skin and vaginal dryness can be treated with lubricants.

Mouth dryness may be avoided by sipping fluids throughout the day, chewing sugarless gum, and using a saliva substitute containing carboxymethylcellulose as a mouthwash. Drugs that decrease salivary secretion (eg, antihistamines, antidepressants, other anticholinergics) should be avoided. Fastidious oral hygiene and regular dental visits are essential. Stones must be promptly removed, preserving viable salivary tissue. The pain of suddenly enlarged salivary glands is generally best treated with warm compresses and analgesics. Pilocarpine 5 mg po tid to qid or cevimeline HCl 30 mg po tid can stimulate salivary production but should be avoided in patients with bronchospasm and closed-angle glaucoma.

Aggressive systemic treatment is occasionally indicated. It is usually reserved for patients with associated diseases (eg, severe vasculitis or visceral involvement); corticosteroids (eg, prednisone 1 mg/kg po once/day) or cyclophosphamide 5 mg/kg po once/day may be used.

Systemic Lupus Erythematosus

(Disseminated Lupus Erythematosus)

Systemic lupus erythematosus (SLE) is a chronic, multisystem, inflammatory disorder of autoimmune etiology, occurring predominantly in young women. Common manifestations may include arthralgias and arthritis; malar and other skin rashes; pleuritis or pericarditis; renal or CNS involvement; and hematologic cytopenias. Diagnosis requires clinical and serologic criteria. Treatment of severe ongoing active disease requires corticosteroids, often hydroxychloroquine, and sometimes immunosuppressants.

Of all cases, 70 to 90% occur in women (usually of child-bearing age). SLE is more common among blacks and Asians than whites. It can affect patients of any age, including neonates. Increased awareness of mild forms has resulted in a worldwide rise in reported cases. In some countries, the prevalence of SLE rivals that of RA. SLE may be precipitated by currently unknown environmental triggers that cause autoimmune reactions in genetically predisposed people. Some drugs (eg, hydralazine, procainamide, isoniazid) cause a reversible lupus-like syndrome.

Symptoms and Signs

Clinical findings vary greatly. SLE may develop abruptly with fever or insidiously over months or years with episodes of arthralgias and malaise. Vascular headaches, epilepsy, or psychoses may be initial findings. Manifestations referable to any organ system may appear. Periodic exacerbations (flares) may occur.

Joint manifestations: Joint symptoms, ranging from intermittent arthralgias to acute polyarthritis, occur in about 90% of patients and may precede other manifestations by years. Most lupus polyarthritis is nondestructive and nondeforming. However, in long-standing disease, deformities without bone erosions may develop (eg, the metacarpophalangeal and interphalangeal joints may rarely develop ulnar drift or swan-neck deformities without bony or cartilaginous erosions [Jaccoud's arthritis]).

Skin and mucous membrane manifestations (see also p. 309): Skin lesions include malar butterfly erythema (flat or raised) that generally spares the nasolabial folds. The absence of papules and pustules helps distinguish SLE from rosacea. A variety of other erythematous, firm, maculopapular lesions can occur elsewhere, including exposed areas of the face and neck, upper chest, and elbows. Skin blistering and ulceration are rare, although recurrent ulcers on mucous membranes (particularly the central portion of the hard palate near the junction of the hard and soft palate, the buccal and gum mucosa, and the anterior nasal septum) are common. Generalized or focal alopecia is common during active phases of SLE. Panniculitis can cause subcutaneous nodular lesions. Vasculitic skin lesions may include mottled erythema on the palms and fingers, periungual erythema, nail-fold infarcts, urticaria, and palpable purpura. Petechiae may develop secondary to thrombocytopenia. Photosensitivity occurs in most patients.

Cardiopulmonary manifestations: Cardiopulmonary symptoms commonly include recurrent pleurisy, with or without pleural effusion. Pneumonitis is rare, although minor impairments in pulmonary function are common. Severe pulmonary hemorrhage occasionally occurs. Prognosis has traditionally been poor but seems to be improving, possibly because of better early, aggressive, critical care. Other complications include pulmonary emboli, pulmonary hypertension, and shrinking lung syndrome. Cardiac complications include pericarditis (most commonly), pericardial effusion, and myocarditis. Serious, rare complications are coronary artery vasculitis, valvular involvement, and Libman-Sacks endocarditis. Accelerated atherosclerosis is an increasing cause of morbidity and mortality. Congenital heart block can develop in neonates.

Adenopathy and splenic manifestations: Generalized adenopathy is common, particularly among children, young adults, and blacks. Splenomegaly occurs in 10% of patients. The spleen may develop periarterial fibrosis.

Neurologic manifestations: Neurologic symptoms can result from involvement of any part of the central or peripheral nervous system or meninges. Mild cognitive impairment is common. There may also be headaches, personality changes, ischemic stroke, subarachnoid hemorrhage, seizures, psychoses, organic brain syndrome, aseptic meningitis, peripheral neuropathies, transverse myelitis, or cerebellar dysfunction.

Renal manifestations: Renal involvement can develop at any time and may be the only manifestation of SLE. It may be benign and asymptomatic or progressive and fatal. Renal lesions can range in severity from a focal, usually benign, glomerulitis to a diffuse, potentially fatal, membranoproliferative glomerulonephritis. Common manifestations include proteinuria (most often), an abnormal urinary sediment manifested by RBC casts and leukocytes, hypertension, and edema.

Obstetric manifestations: Obstetric manifestations include early and late fetal loss. In patients with antiphospholipid antibodies, the risk of recurrent miscarriages is increased. Pregnancy can be successful (see p. 2636), particularly after 6 to 12 mo of remission, but SLE flares are common during pregnancy. Pregnancy should be timed for when disease is in remission. During pregnancy, the patient should be monitored closely for any disease flare or thrombotic events by a multidisciplinary team that includes a rheumatologist, an obstetrician who specializes in high-risk pregnancies, and a hematologist.

Hematologic manifestations: Hematologic manifestations include anemia (often autoimmune hemolytic), leukopenia (usually lymphopenia, with < 1500 cells/µL,), and thrombocytopenia (sometimes life-threatening autoimmune thrombocytopenia). Recurrent arterial or venous thrombosis, thrombocytopenia, and a high probability of obstetric complications occur in patients with antiphospholipid antibodies. Thromboses probably account for many of the complications of SLE, including obstetric complications.

GI manifestations: GI manifestations can result from bowel vasculitis or impaired bowel motility. In addition, pancreatitis can result from SLE or from its treatment with corticosteroids or azathioprine. Manifestations may include abdominal pain from serositis, nausea, vomiting, manifestations of bowel perforation, and pseudo-obstruction. SLE rarely causes parenchymal liver disease.

Diagnosis

• Clinical criteria

• Cytopenias

• Autoantibodies

SLE should be suspected in patients, particularly young women, with any of the symptoms and signs. However, early-stage SLE can mimic other connective (or nonconnective) tissue disorders, including RA if arthritic symptoms predominate. Mixed connective tissue disease can mimic SLE but also may involve features of systemic sclerosis, rheumatoid-like polyarthritis, and polymyositis or dermatomyositis. Infections (eg, bacterial endocarditis, histoplasmosis) can mimic SLE and may develop as a result of treatment-caused immunosuppression. Disorders such as sarcoidosis and paraneoplastic syndromes can also mimic SLE.

Laboratory testing differentiates SLE from other connective tissue disorders. Routine testing should include the following:

• Antinuclear antibodies (ANA)

• CBC

• Urinalysis

• Chemistry profile including renal and liver enzymes

The diagnosis is especially likely if ≥ 4 of the criteria in Table 33-1 are present at any time but is still possible if < 4 criteria are present. If the diagnosis is suspected but not established, additional testing for autoantibodies can be useful. Establishing the diagnosis may require repeated evaluations over months or years.

Fluorescent ANA: The fluorescent test for ANA is the best screen for SLE; positive ANA tests (usually in high titer: > 1:80) occur in > 98%. However, positive ANA tests can also occur in RA, other connective tissue disorders, cancers, and even in the general population. The false-positive rate varies from about 3% for ANA titers of 1:320 to about 30% for ANA titers of 1:40 among healthy controls. Drugs such as hydralazine, procainamide, and tumor necrosis factor (TNF)-α antagonists can produce positive ANA results as well as a lupus-like syndrome; the ANA eventually becomes negative if the drug is stopped. Positive ANA should prompt more specific testing such as anti-double-stranded DNA antibodies; high titers are highly specific for SLE but occur in only 25 to 30% of people with SLE.

Other ANA and anticytoplasmic antibodies: The ANA test is very sensitive, but it is not specific for SLE; thus, evidence of other autoantibodies is needed to establish the diagnosis. They include Ro [SSA], La [SSB], Smith [Sm], ribonucleoprotein [RNP], and double-stranded DNA. Ro is predominantly cytoplasmic; anti-Ro antibodies are occasionally present in ANA-negative SLE patients presenting with chronic cutaneous lupus. Anti-Ro is the causal antibody for neonatal lupus and congenital heart block. Anti-Sm is highly specific for SLE but, like anti-double-stranded DNA, is not sensitive. Anti-RNP occurs in patients with SLE, mixed connective tissue disease, and occasionally other systemic autoimmune disorders and systemic sclerosis.

[Table 33-1. Criteria for the Classification of SLE*]

Other blood tests: Leukopenia (usually lymphopenia) is common. Hemolytic anemia may occur. Thrombocytopenia in SLE may be difficult or impossible to differentiate from idiopathic thrombocytopenic purpura except that patients have other features of SLE. False-positive serologic tests for syphilis occur in 5 to 10% of SLE patients. These test results may be associated with the lupus anticoagulant and a prolonged PTT. Abnormal values in one or more of these assays suggest the presence of antiphospholipid antibodies (eg, anticardiolipin antibodies), which should then be measured directly by enzyme-linked immunosorbent assay (ELISA). Antiphospholipid antibodies are associated with arterial or venous thrombosis, thrombocytopenia, and, during pregnancy, spontaneous abortion or late fetal death but may be present in asymptomatic patients.

Other tests help monitor disease severity and determine the need for treatment. Serum complement levels (C3, C4) are often depressed in active disease and are usually lowest in patients with active nephritis. ESR is elevated frequently during active disease. C-reactive protein levels are not necessarily elevated.

Renal involvement: Screening for renal involvement begins with urinalysis. RBC and WBC casts suggest active nephritis. Urinalysis should be done at regular intervals, even for patients in apparent remission, because kidney disease may be asymptomatic. Renal biopsy is usually not necessary for diagnosis of SLE or to confirm renal involvement but is helpful in evaluating the status of renal disease (ie, active inflammation vs postinflammatory scarring) and guide therapy. Patients with chronic renal insufficiency and mostly sclerotic glomeruli are not likely to benefit from aggressive immunosuppressive therapy.

Prognosis

The course is usually chronic, relapsing, and unpredictable. Remissions may last for years. If the initial acute phase is controlled, even if very severe (eg, with cerebral thrombosis or severe nephritis), the long-term prognosis is usually good. The 10-yr survival in most developed countries is > 95%. Improved prognosis is in part due to earlier diagnosis and more effective therapies. More severe disease requires more toxic therapies, which increase risk of mortality. Examples of such complications include infection from immunosuppression or osteoporosis from long-term corticosteroid use. Increased risk of coronary artery disease can contribute to premature death.

Treatment

• NSAIDs and often antimalarials for mild disease

• Corticosteroids and often immunosuppressants for severe disease

To simplify therapy, SLE should be classified as mild (eg, fever, arthritis, pleurisy, pericarditis, headache, rash) or severe (eg, hemolytic anemia, thrombocytopenic purpura, massive pleural and pericardial involvement, significant renal damage, acute vasculitis of the extremities or GI tract, florid CNS involvement).

Mild or remittent disease: Little or no therapy may be needed. Arthralgias are usually controlled with NSAIDs. Antimalarials help, particularly when joint and skin manifestations are prominent. Hydroxychloroquine 200 mg po once/day or bid reduces the frequency of SLE flares. Alternatives include chloroquine 250 mg po once/day and quinacrine 50 to 100 mg po once/day. Hydroxychloroquine can rarely cause retinal toxicity. The eyes should be examined at 12-mo intervals.

Severe disease: Corticosteroids are first-line therapy. A combination of prednisone and immunosuppressants is recommended in active, serious CNS lupus, vasculitis especially affecting viscera or nerves, or active lupus nephritis. Prednisone is usually given in doses of 40 to 60 mg po once/day, but the dose may vary according to the manifestation of SLE. Oral azathioprine 1 to 2.5 mg/kg once/day or oral cyclophosphamide 1 to 4 mg/kg once/day can be used as an immunosuppressant. For renal involvement, cyclophosphamide is usually given in intermittent IV pulses instead of daily oral doses; eg, about 500 mg to 1 g/m^2 IV (together with mesna and fluid loading to protect the bladder) monthly for 6 mo and then once q 3 mo for 18 mo (less frequently if there is renal or hematologic toxicity—see Table 33-2).

In CNS lupus or other critical crises, methylprednisolone 1 g by slow (1-h) IV infusion on 3 successive days is often the initial treatment, followed by IV cyclophosphamide, as mentioned previously. Mycophenolate mofetil is an alternative to cyclophosphamide therapy for patients with active kidney disease who have preserved kidney function. IgG 400 mg/kg IV once/day for 5 consecutive days may be useful for refractory thrombocytopenia. Patients

[**Table 33-2.** Protocol for Chemotherapy with Cyclophosphamide and IV Mesna]

with end-stage renal disease can undergo kidney transplantation, as an alternative to dialysis, with a successful outcome, especially if their disease has been in remission.

Improvement of severe SLE often takes 4 to 12 wk. Thrombosis or embolism of cerebral, pulmonary, or placental vessels requires short-term treatment with heparin and longer treatment with warfarin, if the diagnosis of antiphospholipid syndrome is confirmed. The target INR is usually 3.

Suppressive therapy: For most patients, the risk of flares can be decreased without prolonged high-dose corticosteroids. Chronic disease should be treated with the lowest dose of corticosteroids and other drugs that control inflammation (eg, antimalarials, low-dose immunosuppressants). Treatment should be guided by clinical features primarily, although anti-double-stranded DNA antibody titers or serum complement levels may be followed. Other pertinent blood and urine tests may be used to assess specific organ involvement. Anti-double-stranded DNA antibody titers or serum complement levels may not parallel nonrenal disease flares. If a patient needs long-term high-dose corticosteroids, alternative oral immunosuppressants should be considered. Ca, vitamin D, and bisphosphonate therapy should be considered in patients taking corticosteroids long term.

Focal complications and coexisting medical conditions: All patients should be closely monitored for atherosclerosis. Long-term anticoagulation is vital in patients with antiphospholipid antibodies and recurrent thrombosis (see p. 2228).

If a pregnant patient has antiphospholipid antibodies, thrombotic complications can be limited with corticosteroids (prednisone ≤ 30 mg po once/day), low-dose aspirin, or anticoagulation with heparin. Daily heparin given subcutaneously with or without one baby aspirin throughout the 2nd and 3rd trimesters may be the most successful prophylactic measure.

Variant Forms of Lupus

Discoid lupus erythematosus (DLE): DLE, also sometimes called chronic cutaneous lupus

erythematosus, is a set of skin changes that can occur as part of lupus, with or without systemic involvement. Skin lesions begin as erythematous plaques and progress to atrophic scars. They cluster in light-exposed areas of the skin, such as the face, scalp, and ears. Untreated, lesions extend and develop central atrophy and scarring. There may be widespread scarring alopecia. Mucous membrane involvement may be prominent, especially in the mouth.

Patients presenting with typical discoid lesions should be evaluated for SLE. Antibodies against double-stranded DNA are almost invariably absent in DLE. Although it does not differentiate DLE from SLE, biopsy can rule out other disorders (eg, lymphoma or sarcoidosis). Biopsy should be done from the active margin of a skin lesion.

Early treatment can prevent permanent atrophy. Exposure to sunlight or ultraviolet light should be minimized (eg, using potent sunscreens when outdoors). Topical corticosteroid ointments (particularly for dry skin) or creams (less greasy than ointments) tid to qid (eg, triamcinolone acetonide 0.1 or 0.5%, fluocinolone 0.025 or 0.2%, flurandrenolide 0.05%, betamethasone valerate 0.1%, and, particularly betamethasone dipropionate 0.05%) usually cause involution of small lesions; they should not be used excessively or on the face (where they cause skin atrophy). Resistant lesions can be covered with plastic tape coated with flurandrenolide. Alternatively, intradermal injection with triamcinolone acetonide 0.1% suspension (< 0.1 mL per site) may resolve lesions, but secondary atrophy frequently follows. Antimalarials (eg, hydroxychloroquine 200 mg po once/day or bid) can help, including for facial lesions. In resistant cases, combinations (eg, hydroxychloroquine 200 mg/day plus quinacrine 50 to 100 mg po once/day) may be required for months to years.

Subacute cutaneous lupus erythematosus (SCLE): SCLE is a variant form of SLE in which skin involvement is prominent. Patients with SCLE develop extensive recurring rashes. Annular or papulosquamous lesions may develop on the face, arms, and trunk. Lesions are usually photosensitive and can develop hypopigmentation but rarely scar. Arthritis and fatigue are common in SCLE, but neurologic and renal manifestations are not. Patients may be ANA-positive or ANA-negative. Most have antibodies to Ro (SSA). Infants whose mothers have Ro antibodies may have congenital SCLE or congenital heart block. SCLE should be treated similarly to SLE.

Systemic Sclerosis

(Scleroderma)

Systemic sclerosis (SSc) is a rare chronic disease of unknown cause characterized by diffuse fibrosis, degenerative changes, and vascular abnormalities in the skin, joints, and internal organs (especially the esophagus, lower GI tract, lungs, heart, and kidneys). Common symptoms include Raynaud's syndrome, polyarthralgia, dysphagia, heartburn, and swelling and eventually skin tightening and contractures of the fingers. Lung, heart, and kidney involvement accounts for most deaths. Diagnosis is clinical, but laboratory tests help with confirmation. Specific treatment is difficult, and emphasis is often on treatment of complications.

SSc is about 4 times more common among women than men. It is most common among people aged 20 to 50 and is rare in children. SSc can develop as part of mixed connective tissue disease.

Etiology

Immunologic mechanisms and heredity (certain HLA subtypes) play a role in etiology. SSc-like syndromes can result from exposure to vinyl chloride, bleomycin, pentazocine, epoxy and aromatic hydrocarbons, contaminated rapeseed oil, or L-tryptophan.

Pathophysiology

Pathophysiology involves vascular damage and activation of fibroblasts; collagen and other extracellular proteins in various tissues are overproduced.

In SSc, the skin develops more compact collagen fibers in the reticular dermis, epidermal thinning, loss of

rete pegs, and atrophy of dermal appendages. T cells may accumulate, and extensive fibrosis in the dermal and subcutaneous layers develops. In the nail folds, capillary loops dilate and some microvascular loops are lost. In the extremities, chronic inflammation and fibrosis of the synovial membrane and surfaces and periarticular soft tissues occur.

Esophageal motility becomes impaired, and the lower esophageal sphincter becomes incompetent; gastroesophageal reflux and secondary strictures can develop. The intestinal muscularis mucosa degenerates, leading to pseudodiverticula in the colon and ileum. Interstitial and peribronchial fibrosis or intimal hyperplasia of small pulmonary arteries can develop; if long-standing, pulmonary hypertension can result. Diffuse myocardial fibrosis or cardiac conduction abnormalities occur. Intimal hyperplasia of interlobular and arcuate arteries can develop within the kidneys, causing renal ischemia and hypertension.

SSc varies in severity and progression, ranging from generalized skin thickening with rapidly progressive and often fatal visceral involvement (SSc with diffuse scleroderma) to isolated skin involvement (often just the fingers and face) and slow progression (often several decades) before visceral disease develops. The latter form is termed limited cutaneous scleroderma or CREST syndrome (calcinosis cutis, Raynaud's syndrome, esophageal dysmotility, sclerodactyly, telangiectasias). In addition, SSc can overlap with other autoimmune rheumatic disorders—eg, sclerodermatomyositis (tight skin and muscle weakness indistinguishable from polymyositis) and mixed connective tissue disease.

Symptoms and Signs

The most common initial symptoms and signs are Raynaud's syndrome and insidious swelling of the distal extremities with gradual thickening of the skin of the fingers. Polyarthralgia is also prominent. GI disturbances (eg, heartburn, dysphagia) or respiratory complaints (eg, dyspnea) are occasionally the first manifestations.

Skin and nail manifestations: Swelling of the skin is usually symmetric and progresses to induration. It may be confined to the fingers (sclerodactyly) and hands, or it may affect most or all of the body. The skin eventually becomes taut, shiny, and hypopigmented or hyperpigmented; the face becomes masklike; and telangiectases may appear on the fingers, chest, face, lips, and tongue. Subcutaneous calcifications may develop, usually on the fingertips (pulps) and over bony eminences. Trophic ulcers are common, especially on the fingertips, overlying the finger joints, or over calcinotic nodules. Abnormal capillary and microvascular loops in the nails can be seen with an ophthalmoscope or dissecting microscope.

Joint manifestations: Polyarthralgias or mild arthritis can be prominent. Flexion contractures may develop in the fingers, wrists, and elbows. Friction rubs may develop over the joints, tendon sheaths, and large bursae.

GI manifestations: Esophageal dysfunction is the most frequent visceral disturbance and occurs in most patients. Dysphagia (usually retrosternal) usually develops first. Acid reflux can cause heartburn and stricture. Barrett's esophagus occurs in one third of patients and predisposes to complications (eg, stricture, adenocarcinoma). Hypomotility of the small bowel causes anaerobic bacterial overgrowth that can lead to malabsorption. Air may penetrate the damaged bowel wall and be visible on x-rays (pneumatosis intestinalis). Leakage of bowel contents into the peritoneal cavity can cause peritonitis. Distinctive wide-mouthed diverticula can develop in the colon. Biliary cirrhosis may develop in patients with CREST syndrome.

Cardiopulmonary manifestations: Lung involvement generally progresses indolently, with substantial individual variability, but is a common cause of death. Lung fibrosis can impair gas exchange, leading to exertional dyspnea and restrictive disease with eventual respiratory failure. Acute alveolitis (potentially responsive to therapy) can develop. Esophageal dysfunction can lead to aspiration pneumonia. Pulmonary hypertension may develop, as can heart failure, both of which are poor prognostic findings. Pericarditis with effusion or pleurisy can occur. Cardiac arrhythmias are common.

Renal manifestations: Severe, often sudden renal disease (renal crisis) may occur, most commonly in the first 4 to 5 yr and in patients with diffuse scleroderma. It is usually heralded by sudden, severe

hypertension.

Diagnosis

• Clinical evaluation

• Usually antinuclear antibodies (ANA), Scl-70 (topoisomerase I), and anticentromere antibodies

SSc should be considered in patients with Raynaud's syndrome, typical musculoskeletal or skin manifestations, or unexplained dysphagia, malabsorption, pulmonary fibrosis, pulmonary hypertension, cardiomyopathies, or conduction disturbances. Diagnosis can be obvious in patients with combinations of classic manifestations, such as Raynaud's syndrome, dysphagia, and tight skin. However, in some patients, the diagnosis cannot be made clinically, and confirmatory laboratory tests can increase the probability of disease but do not rule it out.

Serum ANA and Scl-70 antibody should be obtained. ANA are present in ≥ 90%, often with an antinucleolar pattern. Antibody to centromeric protein (anticentromere antibody) occurs in the serum of a high proportion of patients with CREST syndrome and is detectable on the ANA. Scl-70 antigen is a DNA-binding protein sensitive to nucleases. Patients with diffuse scleroderma are more likely than those with CREST to have anti-Scl-70 antibodies. Rheumatoid factor also is positive in one third of patients.

If lung involvement is suspected, pulmonary function testing, chest CT, and echocardiography can begin to define its severity. Acute alveolitis is often detected by high-resolution chest CT.

Prognosis

The course depends on the type of SSc but is often unpredictable. Typically, progression is slow. Overall 10-yr survival is about 65%. Most patients with diffuse skin disease eventually develop visceral complications, which are the usual causes of death. Prognosis is poor if cardiac, pulmonary, or renal manifestations are present early. Heart failure may be intractable. Ventricular ectopy, even if asymptomatic, increases the risk of sudden death. Acute renal insufficiency, if untreated, progresses rapidly and causes death within months. Patients with CREST syndrome may have disease that is limited and nonprogressive for long periods; visceral changes (eg, pulmonary hypertension caused by vascular disease of the lung, a peculiar form of biliary cirrhosis) eventually develop, but the course is often remarkably benign.

Treatment

• Treatment directed at symptoms and dysfunctional organs

No drug significantly influences the natural course of SSc overall, but various drugs are of value in treating specific symptoms or organ systems. NSAIDs can help arthritis. Corticosteroids may be helpful if there is overt myositis or mixed connective tissue disease but may predispose to renal crisis. Penicillamine, long used for treatment of skin thickening, has not shown clear efficacy in recent trials.

Various immunosuppressants, including methotrexate, azathioprine, and cyclophosphamide, may help pulmonary alveolitis. Successful lung transplantation has been reported. Epoprostenol (prostacyclin) and bosentan may be helpful for pulmonary hypertension. Ca channel blockers, such as nifedipine 20 mg po tid or as an extended-release formulation, or angiotensin receptor blockers, such as losartan 50 mg po once/day, may help Raynaud's syndrome. Patients should dress warmly. IV infusions of prostaglandin E1 (alprostadil) or epoprostenol or sympathetic blockers can be used for digital ischemia. Reflux esophagitis is relieved by frequent small feedings, high-dose proton pump inhibitors, and sleeping with the head of the bed elevated. Esophageal strictures may require periodic dilation; gastroesophageal reflux may possibly require gastroplasty. Tetracycline 500 mg po bid or another broad-spectrum antibiotic can suppress overgrowth of intestinal flora and may alleviate malabsorption symptoms. Physiotherapy may help preserve muscle strength but is ineffective in preventing joint contractures. No treatment affects calcinosis.

For acute renal crisis, prompt treatment with an ACE inhibitor can dramatically prolong survival. Blood pressure is usually, but not always, controlled. The mortality rate of renal crisis remains high. If end-stage renal disease develops, it may be reversible, but dialysis and transplantation may be necessary.

Chapter 34. Vasculitis

Introduction

Vasculitis is inflammation of blood vessels, often with ischemia, necrosis, and occlusive changes. It can affect any blood vessel—arteries, arterioles, veins, venules, or capillaries. Most damage results when inflammation narrows vessels and causes tissue necrosis. Clinical manifestations of specific vasculitic disorders are diverse and depend on the size of the involved vessels and the organs affected by ischemia.

Etiology

Vasculitis may be primary or secondary. Primary vasculitis results from an inflammatory response that targets the vessel walls and has no known cause. Secondary vasculitis may be triggered by an infection, a drug, or a toxin or may occur as part of another inflammatory disorder or cancer.

Pathophysiology

Histologic description of an affected vessel should include the following:

- A description of vessel wall damage
- The nature of the inflammatory infiltrate in the vessel wall (eg, granulomatous, nongranulomatous, leukocytoclastic vasculitis)
- A description of healing responses (eg, intimal hypertrophy, fibrosis)

Certain features (eg, predominant inflammatory cells, location of inflammation) suggest particular vasculitic processes and may aid in the diagnosis (see Table 34-1). For example, in many acute lesions, the predominant inflammatory cells are PMNs; in chronic lesions, lymphocytes predominate.

Inflammation may be segmental or involve the entire vessel. At sites of inflammation, varying degrees of cellular inflammation and necrosis or scarring occur in one or more layers

[**Table 34-1.** Histologic Clues to Diagnosis of Vasculitic Disorders]

[
Table 34-2. Classification of Vasculitic Disorders]

of the vessel wall. Inflammation in the media of a muscular artery tends to destroy the internal elastic lamina.

Leukocytoclastic vasculitis is a histopathologic term used to describe findings in small-vessel vasculitis. It refers to breakdown of inflammatory cells that leaves small nuclear fragments (nuclear debris) in and around the vessels. Inflammation is transmural, rarely necrotizing, and nongranulomatous. PMNs predominate early; later, lymphocytes predominate. Resolution of the inflammation tends to result in fibrosis and intimal hypertrophy. Intimal hypertrophy or secondary clot formation can narrow the arterial lumen and accounts for tissue ischemia or necrosis.

Classification

Vasculitic disorders can be classified according to the size of the predominant vessel affected (see Table 34-2). However, there is often substantial overlap.

Symptoms and Signs

Size of the affected vessels helps determine clinical presentation (see Table 34-2).

Regardless of the size of the vessels involved, patients can present with symptoms and signs of systemic inflammation (eg, fever, night sweats, fatigue, anorexia, weight loss, arthralgias, arthritis). Some manifestations are life- or organ-threatening and require immediate treatment. They include alveolar hemorrhage, rapidly progressive glomerulonephritis, mesenteric ischemia, orbital pseudotumor threatening the optic nerve (in Wegener's granulomatosis), and vision loss in patients with giant cell arteritis.

Diagnosis

• Clinical evaluation

• Antineutrophil cytoplasmic antibodies (ANCA) tests

• Biopsy

• Angiography

Systemic vasculitis is suspected in patients with the following:

• Symptoms or signs characteristic of vasculitis (eg, mononeuritis multiplex, leukocytoclastic vasculitis)

• Ischemic manifestations (eg, ischemic stroke, limb claudication, mesenteric ischemia) out of proportion to a patient's risk factors for atherosclerosis

• Unexplained combinations of symptoms in more than one organ system that are compatible with vasculitis (eg, hypertension, myalgias), particularly when symptoms of a systemic illness are present

Primary vasculitic disorders are diagnosed based on the presence of characteristic symptoms, physical findings, compatible laboratory test results, and exclusion of other causes (ie, secondary vasculitis). Histologic examination is done whenever possible and may point to a particular vasculitic disorder (see Table 34-1).

Routine laboratory tests are done. Most results are nonspecific but can help support the diagnosis. Tests usually include CBC, ESR or C-reactive protein, serum albumin and total protein, and tests for ANCA. Often, patients present with elevated ESR or C-reactive protein, anemia due to chronic inflammation, elevated platelets, and low serum albumin and total protein. Freshly voided urine must be tested for RBCs, RBC casts, and protein to identify renal involvement. Serum creatinine levels should be checked and monitored. Leukopenia and thrombocytopenia are uncommon.

Detection of ANCA may support the diagnosis of Wegener's granulomatosis, Churg-Strauss syndrome, or microscopic polyangiitis. Standardized tests for ANCA include immunofluorescence staining and enzyme-linked immunosorbent assay (ELISA). Immunofluorescence staining of ethanol-fixed neutrophils can detect the cytoplasmic pattern of cANCA or the perinuclear pattern of pANCA. Then solid-phase ELISA is used to check for antibodies specific for the major autoantigens: proteinase-3 (PR3), which correlates with the cANCA staining pattern, or myeloperoxidase (MPO), which correlates with the pANCA staining pattern. Because false-positives occur, ANCA should be measured only when one of these vasculitic disorders is clinically suspected.

Other useful laboratory tests include hepatitis B and C serologic testing, testing for the presence of cryoglobulins, and complement levels to diagnose viral or cryoglobulinemic vasculitis. Further testing is determined by clinical findings. A chest x-ray should be done to check for infiltrates, but high-resolution noncontrast CT of the chest may be needed to check for subtle findings, such as small nodules or cavities. Bilateral diffuse infiltrates suggest possible alveolar hemorrhage, which requires immediate diagnosis and treatment. Other imaging tests may be required. For example, magnetic resonance angiography of large blood vessels and the aorta is useful for diagnosis and monitoring when such vessels appear affected. If symptoms suggest mononeuritis multiplex, electromyography is done.

Because vasculitic disorders are rare and treatment may have severe adverse effects, tissue biopsy is done to confirm the diagnosis whenever possible. Usually, clinical findings suggest the best site for biopsy. For example, if clinical and electromyographic findings suggest mononeuritis multiplex with dysfunction of a specific peripheral nerve, tissue around arteries supplying the nerve is biopsied. Usually, biopsies of unaffected tissue are much less likely to provide positive results.

Because vasculitis is often segmental or focal, biopsy may not show inflammation even when a vessel is affected. Sampling from multiple areas or long segments of a vessel may increase diagnostic sensitivity.

Treatment

- Corticosteroids and cyclophosphamide to induce remission of life- or organ-threatening disorders

- Tapering or elimination of corticosteroids and substitution of methotrexate or azathioprine to maintain remission

Treatment depends on the etiology and extent and severity of disease. For secondary vasculitic disorders, removing the cause (eg, infection, drug, cancer) can help.

For primary vasculitic disorders, treatment aims to induce and maintain remission. Remission is induced by using cytotoxic immunosuppressants and high-dose corticosteroids, usually for 3 to 6 mo, until remission occurs or disease activity is acceptably reduced. Adjusting treatment to maintain remission usually takes longer, on average > 1 or 2 yr. During this period, the goal is to eliminate corticosteroids or reduce their dose and to use less potent immunosuppressants as long as needed.

Induction of remission: For less severe forms of vasculitis, low doses of corticosteroids and less potent immunosuppressants (eg, methotrexate, azathioprine, mycophenolate mofetil) may be used.

Severe, rapidly progressive and life- or organ-threatening vasculitis (eg, causing alveolar hemorrhage, rapidly progressive glomerulonephritis, or mesenteric ischemia) is a medical emergency requiring hospital admission and immediate treatment. Treatment consists of the following:

- **Corticosteroids:** High-dose corticosteroids (also called pulse corticosteroids) are often prescribed. Methylprednisolone 15 mg/kg or 1 g IV once/day for 3 days may be used. Oral prednisone is given concurrently. A dose of 1 mg/kg once/day is given for about 4 wk until patients improve. The dose is then tapered slowly, as tolerated, usually by 10 mg every week to 40 mg/day, by 5 mg every 2 wk to 20 mg/day, by 2.5 mg every 2 wk to 10 mg/day, and by 1 mg every month from there on until the drug is stopped. Changes in this tapering schedule may be necessary if the patient fails to improve or relapses.

- **Cyclophosphamide:** A dose of 2 mg/kg po once/day is usually recommended for at least 3 mo or until remission occurs. The WBC count must be closely monitored, and the dose must be adjusted to avoid leukopenia. (WBC count should be maintained at > 3500/µL.) If patients cannot tolerate oral cyclophosphamide, are unlikely to take oral drugs as directed, or have a high risk of bladder cancer, IV cyclophosphamide may be used. The recommended cumulative dose of cyclophosphamide is 0.75 to 1 g/m^2 monthly. The dose should be reduced in patients with significant renal insufficiency. Patients taking cyclophosphamide should also be given prophylactic treatment against *Pneumocystis jirovecii*.

Acrolein, a product of cyclophosphamide degradation, is toxic to the bladder epithelium and can lead to hemorrhagic cystitis. For patients who have taken cyclophosphamide long term, risk of cystitis is increased, and some develop transitional cell carcinoma of the bladder. During cyclophosphamide therapy, careful hydration is needed to reduce the risk of bladder hemorrhage, cystitis, and bladder cancer. Mesna binds acrolein and is mixed together with the IV cyclophosphamide infusion. One milligram of mesna is added for each milligram of cyclophosphamide. Recurrence of hematuria, especially without casts and dysmorphic red cells, should prompt a referral for urologic evaluation. Cystoscopy and renal imaging should be done to exclude cancer.

Remission maintenance: Corticosteroids are tapered to zero or to the lowest dose that can maintain remission. Usually, methotrexate (with folate) or azathioprine is prescribed to replace cyclophosphamide

because these drugs have a better adverse effects profile. The duration of this treatment varies, from one year to several years. Patients with frequent relapses may need to take immunosuppressants indefinitely.

Long-term use of corticosteroids can have significant adverse effects. Patients who are taking such therapy should be given Ca and vitamin D supplements and bisphosphonates to help prevent or minimize osteoporosis; bone density should be monitored yearly.

Behcet's Syndrome

Behcet's syndrome is a multisystem, relapsing, chronic vasculitic disorder with prominent mucosal inflammation. Common manifestations include recurrent oral ulcers, ocular inflammation, genital ulcers, and skin lesions. The most serious manifestations are blindness, neurologic or GI manifestations, venous thromboses, and arterial aneurysms. Diagnosis is clinical, using international criteria. Treatment is mainly symptomatic but may involve corticosteroids for acute severe ocular or neurologic manifestations or immunosuppressants for severe chronic lesions.

Behcet's syndrome involves small and large arteries and veins. Arterial thrombosis and superficial and deep venous thrombosis often occur.

The syndrome occurs nearly equally in men and women, typically beginning during their 20s. Occasionally, the syndrome develops in children. Incidence varies by location. Behcet's syndrome is most common along the silk route from the Mediterranean to China; it is uncommon in the US.

The cause is unknown. Immunologic (including autoimmune) and viral or bacterial triggers have been suggested, and HLA-B51 is associated with cases from Turkey, Iran, China, Korea, and Japan.

Neutrophil infiltration is detected in biopsy specimens from oral aphthous ulcers and erythema nodosum and pathergy lesions, but no histologic changes are pathognomonic.

Symptoms and Signs

Mucocutaneous: Almost all patients have recurrent painful oral ulcers resembling those of aphthous stomatitis; in most, these ulcers are the first manifestations. The ulcers are round or oval, 2 to 10 mm in diameter, and shallow or deep with a central yellowish necrotic center; they can occur anywhere in the oral cavity, often in clusters. Ulcers last 1 to 2 wk. Similar ulcers occur on the penis and scrotum, on the vulva where they are painful, or in the vagina where they may cause little or no pain.

Cutaneous lesions are common and may include acneiform lesions, nodules, erythema nodosum, superficial thrombophlebitis, pyoderma gangrenosum-type lesions, and palpable purpura.

Pathergy (an erythematous papular or pustular response to local skin injury) is defined as a papule > 2 mm that appears 24 to 48 h after oblique insertion of a 20- to 25-gauge needle into the skin. Pathergy has occurred in many parts of the world but is less common among North American and northern European patients than among Middle Eastern and Asian patients.

Ocular: The eyes are affected in 25 to 75% of patients. The following may occur:

- Relapsing uveitis or iridocyclitis (most common) often manifests as pain, photophobia, and red eye.
- Hypopyon (a layer of pus visible in the anterior chamber) may occur.
- Uveitis is typically bilateral and episodic, often involves the entire uveal tract (panuveitis), and may not resolve completely between episodes.
- Choroiditis, retinal vasculitis, vascular occlusion, and optic neuritis may irreversibly impair vision and even progress to blindness.

Musculoskeletal: Relatively mild, self-limiting, and nondestructive arthralgias or frank arthritis, especially in the knees and other large joints, occur in 50% of patients. Sacroiliac inflammation can occur.

Vascular: Superficial and deep venous thromboses are common. Large vessels are affected in about one third of patients. Perivascular and endovascular inflammation may lead to hemorrhage, stenosis, aneurysms, and thrombosis in arteries and veins. Superior and inferior vena cava occlusion, Budd-Chiari syndrome, and other venous obstructive lesions can also occur.

Disease of the aorta and large blood vessels may be life threatening. Hemoptysis may occur if fistulas between the pulmonary artery and bronchus develop.

Neurologic and psychiatric: CNS involvement is less common but is serious. Onset may be sudden or gradual. The first manifestations may be parenchymal involvement with pyramidal signs, small-vessel disease with a multiple sclerosis-like pattern, aseptic meningitis or meningoencephalitis, or dural sinus thrombosis.

Psychiatric disorders including personality changes and dementia may develop years later. Peripheral neuropathy, common in other vasculitic disorders, is uncommon in Behcet's syndrome.

GI: Abdominal discomfort, abdominal pain, and diarrhea with intestinal ulcers, occurring primarily in the ileum and colon and closely resembling Crohn's disease, may occur.

Diagnosis

• Clinical criteria

Behcet's syndrome should be suspected in young adults with recurrent oral aphthous ulcers, unexplained ocular findings, or genital ulcers. Diagnosis is clinical and may require months because many of the manifestations are nonspecific and can be insidious.

International criteria for diagnosis include recurrent oral ulcers (3 times in 1 yr) and 2 of the following:

• Recurrent genital ulcers

• Eye lesions

• Skin lesions

• Positive pathergy test with no other clinical explanation

Laboratory tests (eg, CBC, ESR or C-reactive protein, serum albumin and total protein levels) are done. Results are nonspecific but characteristic of inflammatory disease (elevated ESR, C-reactive protein, and α_2- and γ-globulins; mild leukocytosis).

Differential diagnosis includes reactive arthritis, SLE, Crohn's disease, ulcerative colitis, ankylosing spondylitis, and herpes simplex infection. Behcet's syndrome has no single pathognomonic finding but may be distinguished by its combinations of relapsing symptoms with spontaneous remissions and multiple organ involvement, particularly in patients with recurrent, deep mucosal ulcers.

Prognosis

Behcet's syndrome typically has a waxing and waning course characterized by exacerbations and remissions. Mucocutaneous and ocular lesions and arthralgias are often worse early in the disease. CNS and large-vessel manifestations, if they develop, typically occur later. Occasionally, the syndrome results in death, usually due to neurologic, vascular (eg, aneurysms), or GI manifestations. Many patients eventually go into remission.

Treatment

• Colchicine, thalidomide, etanercept, and interferon for mucosal disease

• Azathioprine or cyclosporine for eye disease

• Cyclophosphamide and chlorambucil for refractory or life-threatening disease

Treatment depends on the clinical manifestations.

Mucosal disease can be managed symptomatically. Colchicine 0.6 mg po bid may decrease the frequency and severity of oral or genital ulcers and may be effective for erythema nodosum and arthralgias. Thalidomide 100 to 300 mg po once/day may be used to treat oral, genital, and skin lesions, but lesions may recur when treatment is stopped. Etanercept 50 mg sc once/wk or 25 mg sc twice/wk may suppress mucocutaneous lesions. Etanercept can be given if colchicine is ineffective. Interferon alfa-2a 6 million units sc 3 times/wk can also be given if colchicine is ineffective.

Azathioprine 2.5 mg/kg po once/day helps preserve visual acuity and prevent new eye lesions. Azathioprine is also useful for mucocutaneous lesions and arthralgia. Cyclosporine 5 to 10 mg/kg po once/day may be reserved for patients with severe ocular manifestations and may be used with azathioprine to treat refractory uveitis. Interferon alfa-2a 6 million units sc 3 times/wk and infliximab (a tumor necrosis factor inhibitor) 3 to 10 mg/kg IV at 0, 2, 4, and then every 8 wk show promise for patients with ocular manifestations.

Cyclophosphamide and chlorambucil are used in patients with refractory disease, life-threatening conditions (eg, pulmonary aneurysms), or CNS manifestations.

The efficacy of corticosteroids is unsubstantiated, despite their wide use. Topical corticosteroids may temporarily relieve ocular manifestations and most oral lesions. However, topical or systemic corticosteroids do not alter the frequency of relapses. A few patients with severe uveitis or CNS manifestations respond to high-dose systemic corticosteroids (eg, prednisone 60 to 80 mg po once/day).

Whether immunosuppressants should be added to anticoagulation therapy when patients have thromboses has not been established.

Churg-Strauss Syndrome

(Allergic Angiitis and Granulomatosis)

Churg-Strauss syndrome is a pulmonary and systemic small-vessel necrotizing vasculitis, characterized by extravascular granulomas, eosinophilia, and tissue infiltration by eosinophils. It tends to occur in people with adult-onset asthma, allergic rhinitis, nasal polyposis, or a combination. Diagnosis is best confirmed by biopsy. Treatment is primarily with corticosteroids and, for severe disease, addition of other immunosuppressants.

Churg-Strauss syndrome occurs in about 3 people/million. Mean age at onset is 48.

Churg-Strauss syndrome is characterized by extravascular necrotizing granulomas (usually containing eosinophilic infiltrates), eosinophilia, and tissue infiltration by eosinophils. However, these abnormalities rarely coexist. The vasculitis typically affects pulmonary and systemic arteries and veins. Any organ can be affected, but the lungs, skin, cardiovascular system (eg, as coronary artery vasculitis), kidneys, peripheral nervous system, sinuses, joints, and GI tract are most commonly affected. Occasionally, pulmonary capillaritis may cause alveolar hemorrhage.

Etiology

The cause is unknown. However, an allergic mechanism, with tissue directly injured by eosinophils and neutrophil degranulation products, may be involved. Activation of T lymphocytes seems to help maintain eosinophilic inflammation. The syndrome occurs in patients who have adult-onset asthma, allergic rhinitis,

nasal polyposis, or a combination. Antineutrophil cytoplasmic autoantibodies (ANCA) are sometimes present.

Symptoms and Signs

The syndrome has 3 phases, which may overlap:

- Prodromal: This phase may persist for years. Patients have allergic rhinitis, nasal polyposis, asthma, or a combination.

- 2nd phase: Peripheral blood and tissue eosinophilia is typical. Clinical presentation, which may resemble Loffler's syndrome, includes chronic eosinophilic pneumonia and eosinophilic gastroenteritis.

- 3rd phase: Potentially life-threatening vasculitis develops. Systemic symptoms (eg, fever, malaise, weight loss, fatigue) are common.

However, the phases do not necessarily follow one another consecutively, and the time interval between them varies greatly.

Various organs and systems may be affected:

- **Respiratory:** Asthma, often with onset during adulthood, occurs in most patients. Sinusitis is common, typically without severe necrotizing inflammation. Sinusitis causes facial pain and increases nasal discharge. Patients may be short of breath. Cough and hemoptysis, due to alveolar hemorrhage, may be present. Transient patchy pulmonary infiltrates are common.

- **Neurologic:** Neurologic manifestations are common. Mononeuritis multiplex occurs in up to three fourths of patients. CNS involvement is rare but can include confusion, seizures, and coma, with or without cranial nerve palsies or evidence of cerebral infarction.

- **Cutaneous:** The skin is affected in about one half of patients. Nodules and papules appear on extensor surfaces of extremities. They are caused by extravascular palisading granulomatous lesions with central necrosis. Purpura or erythematous papules, due to leukocytoclastic vasculitis with or without prominent eosinophilic infiltration, may develop.

- **Musculoskeletal:** Occasionally, arthralgias, myalgias, or even arthritis can occur, usually during the vasculitic phase.

- **Cardiac:** Heart failure, MI, coronary artery vasculitis (possibly with MI), valvular disorders, or pericarditis may develop. The predominant histopathologic finding is eosinophilic myocarditis.

- **GI:** Up to one third of patients present with GI symptoms (eg, abdominal pain, diarrhea, bleeding) due to eosinophilic gastroenteritis or mesenteric ischemia due to vasculitis.

- **Renal:** The kidneys are affected less often than in other vasculitic disorders associated with ANCA. Typically, pauci-immune (few if any immune complexes), focal segmental necrotizing glomerulonephritis with crescent formation is present; eosinophilic or granulomatous inflammation of the kidneys is rare.

Renal, cardiac, or neurologic involvement indicates a worse prognosis.

Diagnosis

- Clinical criteria

- Routine laboratory tests

- Biopsy

Criteria for classification from the American College of Rheumatology consist of the following:

• Asthma

• Eosinophilia of > 10% in peripheral blood

• Paranasal sinusitis

• Pulmonary infiltrates, sometimes transient

• Histologic evidence of vasculitis with extravascular eosinophils

• Mononeuritis multiplex or polyneuropathy

If ≥ 4 criteria are present, sensitivity is 85%, and specificity is 99.7%.

Testing aims to establish the diagnosis and the extent of organ involvement and to distinguish Churg-Strauss syndrome from other eosinophilic disorders (eg, parasitic infections, drug reactions, acute and chronic eosinophilic pneumonia, allergic bronchopulmonary aspergillosis, idiopathic hypereosinophilic syndrome). Diagnosis is suggested by clinical findings and results of routine laboratory tests but should usually be confirmed by biopsy of lung or other affected tissue.

Blood tests and chest x-rays are done, but results are not diagnostic. CBC with differential is done to check for eosinophilia. Peripheral blood eosinophilia is also a marker of disease activity. IgE and C-reactive protein levels and ESR are determined periodically to evaluate inflammatory activity. Electrolyte levels are measured and urinalysis is done to check for evidence of renal involvement and to follow its severity.

Serologic testing is done. It detects ANCA in up to 50%; if ANCA is detected, enzyme-linked immunosorbent assay (ELISA) is done to check for specific antibodies. Perinuclear ANCA (p-ANCA) with antibodies against myeloperoxidase is the most common result, but ANCA is not specific for Churg-Strauss syndrome.

Chest x-ray often shows transient patchy pulmonary infiltrates.

Biopsy of the most accessible affected tissue should be done if possible.

Treatment

• Corticosteroids

Systemic corticosteroids are the mainstay of treatment. When to add other immunosuppressants is not clear, but Churg-Strauss syndrome is generally treated the same way as Wegener's granulomatosis (see p. 329) or microscopic polyangiitis (see p. 322). Recombinant interferon alfa-2a 3 million units sc daily has been used when the syndrome is refractory to other drugs or when eosinophilic inflammation is difficult to control.

Cutaneous Vasculitis

Cutaneous vasculitis affects small or medium-sized vessels in the skin and subcutaneous tissue. This disorder may be limited to the skin or be part of systemic vasculitis. Purpura, ulcers, livedo reticularis, or nodules may develop. Diagnosis requires biopsy. Treatment depends on etiology and extent of disease.

Common causes include serum sickness, infections (eg, hepatitis C), cancers, rheumatologic or other autoimmune disorders, and hypersensitivity to drugs.

Vessel inflammation often results from immune complex deposition, but other pathogenetic mechanisms

may be involved. Predominantly cutaneous vasculitis is a leukocytoclastic vasculitis, so-called because inflammation disrupts leukocytes, resulting in deposition of nuclear debris (leukocytoclasis) in the vessel wall.

Symptoms and Signs

Patients may present with skin symptoms such as lesions, including palpable purpura, urticaria, ulcers, livedo reticularis, and nodules. If cutaneous vasculitis occurs as part of a systemic vasculitis, symptoms may also include fever, arthralgias, other organ involvement, or a combination.

Diagnosis

- Exclusion of systemic vasculitis clinically and by routine tests (eg, CBC, ESR, urinalysis, chest x-ray, serum creatinine)

- Biopsy

- Tests for the cause of vasculitis (eg, cryoglobulins, antineutrophil cytoplasmic antibodies [ANCA], hepatitis B and C antibodies, complement levels)

A diagnosis of vasculitis limited to the skin requires a complete history and physical examination, focusing on excluding manifestations of inflammation or vasculitis in other organs, as in the following:

- Lungs: Shortness of breath, cough, hemoptysis, and signs of consolidation

- Kidneys: New-onset hypertension or edema

- Nerves: New-onset asymmetric weakness or paresthesias

- Intestine: New-onset abdominal pain, diarrhea, and bloody stools

Urinalysis should exclude blood, protein, and RBC casts. A chest x-ray is needed to check for infiltrates (suggesting alveolar hemorrhage). CBC and other blood tests are needed to check for anemia, to determine platelet count and serum creatinine level, and to check for elevated levels of acute-phase reactants (eg, ESR, C-reactive protein).

A skin biopsy is done, optimally within 24 to 48 h after vasculitic lesions appear. Diagnostic yield depends on the depth of the biopsy. Generally, punch biopsy or excision biopsy into the subcutis is preferred; these biopsies can sample small and medium-sized vessels. Shave biopsy is usually inadequate.

If histologic examination detects the following, cutaneous vasculitis is confirmed:

- Infiltration of the vessel wall by inflammatory cells, resulting in disruption and destruction of the vessel wall

- Intramural and intraluminal fibrin deposition (fibrinoid necrosis)

- Extravasation of RBCs

- Nuclear debris (leukocytoclasis)

Direct immunofluorescence staining is needed to check for IgA, IgM, and IgG and complement deposition in and around the vessel wall, which suggests an immune complex-mediated process and supports the diagnosis. Further testing to establish the cause of vasculitis includes checking for cryoglobulins, ANCA, and hepatitis B and C antibodies, measuring complement levels, and tests for any clinically suspected disorders that can cause vasculitis.

Treatment

• Antihistamines and sometimes low-dose corticosteroids to treat skin lesions

• Trial of colchicine, hydroxychloroquine, or dapsone to prevent recurrences

Treatment is first directed at any identified cause. If no cause is identified and vasculitis is limited to the skin, treatment is minimal and conservative. Support hose and antihistamines may be sufficient. If this treatment is ineffective, low-dose corticosteroids can be tried.

If lesions recur, colchicine, hydroxychloroquine, or dapsone may prevent further recurrences. Rarely, stronger immunosuppressants (eg, azathioprine, methotrexate) are used, particularly if lesions ulcerate.

Giant Cell Arteritis

(Temporal Arteritis; Cranial Arteritis; Horton's Disease)

Giant cell arteritis involves predominantly the thoracic aorta, large arteries emerging from the aorta in the neck, and extracranial branches of the carotid arteries. Simultaneous polymyalgia rheumatica is common. Focal symptoms and signs may include headaches, visual disturbances, temporal artery tenderness, and pain in the jaw muscles during chewing. Fever, weight loss, malaise, and fatigue are also common. ESR and C-reactive protein are typically elevated. Diagnosis is clinical and confirmed by temporal artery biopsy. Treatment with high-dose corticosteroids and aspirin is usually effective and prevents vision loss.

Giant cell arteritis is a relatively common form of vasculitis in the US and Europe. Incidence varies depending on ethnic background. Autopsy studies suggest that the disorder may be more common than is clinically apparent. Women are affected more often. Mean age at onset is about 70, with a range of 50 to > 90. About 40 to 60% of patients with giant cell arteritis have polymyalgia rheumatica. The intracranial vessels are usually not affected.

Pathophysiology

Vasculitis may be localized, multifocal, or widespread. The disorder tends to affect arteries containing elastic tissue, most often the temporal, cranial, or other carotid system arteries. The aortic arch branches, coronary arteries, and peripheral arteries can also be affected. Mononuclear cell infiltrates in the adventitia form granulomas containing activated T cells and macrophages. Multinucleated giant cells, when present, cluster near the disrupted elastic lamina. The intimal layer is markedly thickened, with concentric narrowing and occlusion of the lumen.

Symptoms and Signs

Symptoms may begin gradually over several weeks or abruptly.

Patients may present with systemic symptoms such as fever (usually low-grade), fatigue, malaise, unexplained weight loss, and sweats. Some patients are initially diagnosed as having FUO. Eventually, most patients develop symptoms related to the affected arteries.

Severe, sometimes throbbing headache (temporal, occipital, frontal, or diffuse) is the most common symptom. It may be accompanied by scalp pain elicited by touching the scalp or combing the hair.

Visual disturbances include diplopia, scotomas, ptosis, blurred vision, and loss of vision (which is an ominous sign). Brief periods of partial or complete vision loss (amaurosis fugax) in one eye may be rapidly followed by permanent irreversible loss of vision. If untreated, the other eye may also be affected. However, complete bilateral blindness is uncommon. Vision loss is caused by arteritis of branches of the ophthalmic artery or posterior ciliary arteries, which leads to ischemia of the optic nerve. Funduscopic findings may include ischemic optic neuritis with pallor and edema of the optic disk, scattered cotton-wool patches, and small hemorrhages. Later, the optic nerve atrophies. Rarely, central blindness results from infarction in the occipital cortex caused by arterial lesions in the distal cervical region or base of the brain.

Intermittent claudication (ischemic muscle pain) may occur in jaw muscles and muscles of the tongue or extremities. Jaw claudication is noted especially when firm foods are chewed.

Neurologic manifestations, such as strokes and transient ischemic attacks, can result when the carotid or vertebrobasilar arteries or branches are narrowed or occluded.

Thoracic aortic aneurysms and dissection of the aorta are serious, often late, complications.

Diagnosis

• ESR, C-reactive protein, and CBC

• Biopsy, usually of the temporal artery

Giant cell arteritis is suspected in patients > 55 if any of the following develops, especially if they also have symptoms of systemic inflammation:

• A new type of headache

• Any new symptom or sign compatible with ischemia of an artery above the neck

• Jaw pain during chewing

• Temporal artery tenderness

• Unexplained subacute fever or anemia

The diagnosis is more likely if patients also have symptoms of polymyalgia rheumatica.

Physical examination may detect swelling and tenderness, with or without nodularity or erythema, over the temporal arteries. Temporal arteries can become prominent. A temporal artery that rolls under the examiner's fingers, rather than collapses, is abnormal. The large arteries of the neck and limbs and the aorta should be evaluated for bruits.

If the diagnosis is suspected, ESR, C-reactive protein, and CBC are determined. In most patients, ESR and C-reactive protein are elevated; anemia of chronic disease is common. Occasionally, platelets are elevated, and serum albumin and total protein, measured for other reasons, are low. Mild leukocytosis is commonly detected but is nonspecific.

If the diagnosis is suspected, biopsy of an artery is recommended. Because inflamed segments often alternate with normal segments, a segment that appears abnormal should be sampled if possible. Usually, the temporal artery is biopsied, but the occipital artery can also be biopsied if it appears abnormal. The optimal length of the temporal artery to remove is unclear, but 5 cm is recommended if possible. Treatment should not be delayed to do the biopsy. Biopsy can be done up to 2 wk or perhaps more after treatment is started because the inflammatory infiltrate is slow to resolve.

If patients have pulse deficits, the aorta and its branches are imaged (see Table 34-3 on p. 328).

Treatment

• Corticosteroids

• Low-dose aspirin

Treatment should be started as soon as giant cell arteritis is suspected, even if biopsy is going to be delayed for several days.

Corticosteroids are the cornerstone of treatment. Corticosteroids rapidly reduce symptoms and prevent vision loss in most patients. The optimal initial dose, tapering schedule, and total length of treatment are debated. For most patients, an initial dose of prednisone 40 to 60 mg po once/day (or equivalent) for 4 wk, followed by gradual tapering, is effective. If patients have visual disturbances, an initial dose of IV methylprednisolone 500 to 1000 mg once/day for 3 to 5 days can be tried in an attempt to help prevent further decline in vision, particularly in the contralateral eye.

If symptoms lessen, prednisone can be tapered gradually from doses of up to 60 mg/day based on the patient's response, usually as follows: by 5 to 10 mg/day every week to 40 mg/day, by 2 to 5 mg/day every week to 10 to 20 mg/day, then by 1 mg/day every month thereafter until the drug is stopped. ESR alone should not be used alone to evaluate patient response (and disease activity). Clinical symptoms must also be used.

Most patients require at least 2 yr of treatment with corticosteroids. Long-term use of corticosteroids can have significant adverse effects and thus should be limited if possible. More than one half of patients taking these drugs have drug-related complications. Consequently, alternative therapies are being studied. If patients cannot tolerate corticosteroids or if symptoms return when the dose is tapered, methotrexate 0.3 mg/kg/wk may be useful.

Tumor necrosis factor inhibitors have not been shown to be effective.

Low-dose aspirin (100 mg po once/day) may help prevent ischemic events and should be prescribed for all patients unless contraindicated.

Henoch-Schonlein Purpura

Henoch-Schonlein purpura is vasculitis that affects primarily small vessels. It occurs most often in children. Common manifestations include palpable purpura, arthralgias, GI symptoms and signs, and glomerulonephritis. Diagnosis is clinical in children but usually warrants biopsy in adults. Disease is usually self-limited. Corticosteroids can relieve arthralgias and GI symptoms but do not alter the course of the disease. Progressive glomerulonephritis may require high-dose corticosteroids and cyclophosphamide.

In Henoch-Schonlein purpura, IgA-containing immune complexes are deposited in small vessels of the skin and other sites, with consequent activation of complement. Possible inciting antigens include viruses that cause URIs, streptococcal infection, drugs, foods, insect bites, and immunizations. Focal, segmental proliferative glomerulonephritis is typical but mild.

Symptoms and Signs

The disease begins with a sudden palpable purpuric rash typically occurring on the feet, legs, and arms and as a strip across the buttocks. The purpura may start as small areas of urticaria that become indurated and palpable. Crops of new lesions may appear over days to several weeks. Many patients also have fever and polyarthralgia with periarticular tenderness and swelling of the ankles, knees, hips, wrists, and elbows.

GI symptoms are common and include colicky abdominal pain, abdominal tenderness, and melena. Intussusception occasionally develops in children. Stool may test positive for occult blood.

Symptoms usually remit after about 4 wk but often recur at least once after a disease-free interval of several weeks. In most patients, the disorder subsides without serious sequelae; however, some patients develop chronic renal failure.

Diagnosis

• Biopsy of skin lesions

The diagnosis is suspected in patients, particularly children, with typical skin findings. It is confirmed by biopsy of skin lesions when leukocytoclastic vasculitis with IgA in the vessel walls is identified. Biopsy is unnecessary if clinical diagnosis is clear in children. Urinalysis is done; hematuria, proteinuria, and RBC casts indicate renal involvement. CBC and renal function tests are done.

If renal function is deteriorating, renal biopsy may help define the prognosis. Diffuse glomerular involvement or crescent formation in most glomeruli predicts progressive renal failure.

Treatment

• Primarily corticosteroids and symptomatic measures

If the cause is a drug, it has to be stopped. Otherwise, treatment is primarily symptomatic. Corticosteroids (eg, prednisone 2 mg/kg up to a total of 50 mg po once/day) may help control abdominal pain and are occasionally needed to treat severe joint pain or renal disease. Pulse IV methylprednisolone followed by oral prednisone and cyclophosphamide can be given to attempt to control inflammation when the kidneys are severely affected. However, the effects of corticosteroids on renal manifestations are not clear.

Microscopic Polyangiitis

Microscopic polyangiitis is a systemic pauci-immune necrotizing vasculitis that affects mainly small vessels. It may begin as a pulmonary-renal syndrome with rapidly progressing glomerulonephritis and alveolar hemorrhage, but the pattern of disease depends on the organs affected. Diagnosis is by biopsy. Treatment, which depends on disease severity, includes corticosteroids and immunosuppressants.

Microscopic polyangiitis is rare (about 13 to 19 cases/million). Pathogenesis is unknown. Like immune complex-associated vasculitis (eg, SLE, cryoglobulinemia, serum sickness, Henoch-Schonlein purpura), microscopic polyangiitis affects small vessels. Polyarteritis nodosa can cause some manifestations similar to the small vessel vasculitides, such as mononeuritis multiplex and bowel ischemia. Microscopic polyangiitis can be distinguished from immune complex-associated vasculitis and polyarteritis nodosa by the following:

• Microscopic polyangiitis affects predominantly small vessels, unlike polyarteritis nodosa, which affects medium-sized muscular arteries.

• Microscopic polyangiitis, unlike polyarteritis nodosa, may cause glomerulonephritis and may affect the lungs and cause alveolar hemorrhage.

• Immune complex deposits are scarce or absent (ie, pauci-immune) in contrast to immune complex-associated vasculitis.

Clinical manifestations resemble those of Wegener's granulomatosis except that granulomatous destructive lesions are absent and the upper respiratory tract is usually not severely affected. In both disorders, antineutrophil cytoplasmic antibodies (ANCA) may be present. Microscopic polyangiitis can occur in patients with viral hepatitis B or C.

Symptoms and Signs

Usually, a prodromal illness with systemic symptoms of fever, weight loss, myalgia, and arthralgia occurs. Other symptoms depend on which organs and systems are affected:

• **Renal:** The kidneys are affected in up to 90% of patients. Hematuria, proteinuria (sometimes > 3 g/24 h), and RBC casts are present. Without prompt diagnosis and treatment, renal failure may follow rapidly.

• **Cutaneous:** About one third of patients have a purpuric rash at the time of the diagnosis. Nail bed infarcts and splinter hemorrhages may occur; digital ischemia occurs rarely.

- **Respiratory:** If the lungs are affected, alveolar hemorrhage may occur, followed by pulmonary fibrosis. Rapid-onset dyspnea and anemia, with or without hemoptysis and bilateral patchy infiltrates (seen on chest x-ray) may be due to alveolar hemorrhage, a medical emergency that requires immediate treatment. Mild symptoms of rhinitis, epistaxis, and sinusitis may occur; however, if the upper respiratory tract is severely affected, the cause is more likely to be Wegener's granulomatosis.

- **GI:** GI symptoms include abdominal pain, nausea, vomiting, diarrhea, and bloody stools.

- **Neurologic:** If the nervous system is affected, mononeuritis multiplex that affects peripheral or cranial nerves usually occurs. Cerebral hemorrhage, infarction, seizures, or headache rarely results from cerebral vasculitis.

- **Cardiac:** Rarely, the heart is affected.

- **Ocular:** If the eyes are affected, episcleritis usually results.

Diagnosis

- Clinical findings

- Tests for ANCA and C-reactive protein and routine laboratory tests

- Biopsy

Microscopic polyangiitis may mimic many other disorders because its manifestations vary. The disorder should be suspected in patients who have unexplained combinations of GI symptoms or signs, alveolar hemorrhage, episcleritis, and peripheral neuropathy. Laboratory tests and sometimes x-rays are done, but the diagnosis is usually confirmed by biopsy.

Tests include CBC, ESR, C-reactive protein, urinalysis, serum creatinine, and tests for ANCA. ESR, C-reactive protein levels, and WBC and platelet counts are elevated, reflecting systemic inflammation. Anemia of chronic disease is common. An acute drop in Hct suggests alveolar hemorrhage or hemorrhage in the GI tract. Urinalysis (to check for hematuria, proteinuria, and cellular casts) should be done, and serum creatinine should be measured periodically to check for renal involvement.

Immunofluorescence staining can detect ANCA; this test is followed by enzyme-linked immunosorbent assay (ELISA) to check for specific antibodies. At least 60% of patients have ANCA, usually perinuclear ANCA (p-ANCA) with antibodies against myeloperoxidase.

Biopsy of the most accessible involved tissue should be done to confirm vasculitis. Renal biopsy may detect focal segmental pauci-immune necrotizing glomerulonephritis with fibrinoid necrosis of the glomerular capillary wall, leading to formation of cellular crescents.

In patients with respiratory symptoms, chest x-ray is done to check for infiltrates. Bilateral patchy infiltrates suggest alveolar hemorrhage even in patients without hemoptysis.

If patients have dyspnea and bilateral infiltrates, bronchoscopy should be done immediately to check for alveolar hemorrhages. Blood coming from both lungs and all bronchi, with more blood coming as the bronchoscope goes deeper in the airways, indicates active alveolar hemorrhage. Hemosiderin-laden macrophages appear within 24 to 72 h after onset of hemorrhage and may persist for up to 2 mo.

Treatment

- When vital organs are affected, corticosteroids plus cyclophosphamide

- For less severe cases, corticosteroids plus azathioprine or methotrexate

Treatment is similar to that of Wegener's granulomatosis. Cyclophosphamide given daily plus corticosteroids improves survival when vital organs are affected. However, induction and maintenance regimens vary, and adjunctive therapies such as plasma exchange and pulse IV methylprednisolone may or may not be used.

Less severe cases may be managed with corticosteroids plus azathioprine or methotrexate.

Polyarteritis Nodosa

(Polyarteritis; Periarteritis Nodosa)

Polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis that typically affects medium-sized muscular arteries and occasionally affects small muscular arteries, resulting in secondary tissue ischemia. The kidneys, skin, joints, muscles, peripheral nerves, and GI tract are most commonly affected, but any organ can be. However, the lungs are usually spared. Patients typically present with systemic symptoms (eg, fever, fatigue). Diagnosis requires a biopsy or arteriography. Treatment with corticosteroids and immunosuppressants is often effective.

PAN is rare (about 2 to 33 cases/million). It affects mainly middle-aged adults, and incidence increases with aging, peaking in people in their 50s.

Etiology

Most cases are idiopathic. About 20% of patients have hepatitis B or C.

The cause is unknown, but immune mechanisms appear to be involved. The variety of clinical and pathologic features suggests multiple pathogenic mechanisms. Drugs may be a cause. Usually, no predisposing antigen is identified. Patients with certain lymphomas and leukemias, RA, or Sjogren's syndrome may develop a systemic vasculitis similar to PAN.

Pathophysiology

PAN is characterized by segmental, transmural necrotizing inflammation of muscular arteries, most commonly at points of bifurcation. Unlike other vasculitic disorders, PAN does not involve postcapillary venules or veins. Lesions in all stages of development and healing are usually present. Early lesions contain PMNs and occasionally eosinophils; later lesions contain lymphocytes and plasma cells. Granulomatous inflammation does not occur. Intimal proliferation with secondary thrombosis and occlusion leads to organ and tissue infarction. Weakening of the muscular arterial wall may cause small aneurysms and arterial dissection. Healing can result in nodular fibrosis of the adventitia.

Mostly commonly affected are the kidneys, skin, peripheral nerves, joints, muscles, and GI tract. Often affected are the liver and heart. Renal ischemia and infarction occur, but glomerulonephritis is not a feature of PAN. Purpura is not a characteristic of PAN.

Symptoms and Signs

PAN mimics many disorders. The course may be acute and prolonged, subacute and fatal after several months, or insidious, chronic, and debilitating. Symptoms depend mainly on location and severity of the arteritis and extent of secondary ischemia. Only one organ or organ system may be affected.

Patients typically present with fever, fatigue, night sweats, loss of appetite, weight loss, and generalized weakness. Myalgias with areas of focal ischemic myositis and arthralgias are common. Affected muscles are tender and weak. Arthritis may occur.

Symptoms and signs vary, depending on organ or organ system predominantly affected:

- **Peripheral nervous system:** Patients usually present with asymmetric peripheral neuropathy, such as mononeuritis multiplex with signs of motor and sensory involvement of the peroneal, median, or ulnar

nerves. As additional nerve branches are affected, patients may appear to have a distal symmetric polyneuropathy.

- **CNS:** Headache and seizures can result. In a few patients, ischemic stroke and cerebral hemorrhage occur, sometimes resulting from hypertension.

- **Renal:** If small and medium-sized arteries in the kidneys are affected, patients may have hypertension, oliguria, uremia, and a nonspecific urinary sediment with hematuria, proteinuria, and no cellular casts. Hypertension may worsen rapidly. Rupture of renal arterial aneurysms can cause perirenal hematomas. In severe cases, multiple renal infarcts with lumbar pain and gross hematuria may occur. Renal ischemia and infarction can lead to renal failure.

- **GI:** Vasculitis of the liver or gallbladder causes right upper quadrant pain. Perforation of the gallbladder with acute abdomen may occur. Vasculitis of medium-sized mesenteric arteries causes abdominal pain, nausea, vomiting (with or without bloody diarrhea), malabsorption, intestinal perforation, and acute abdomen. Aneurysms may develop in hepatic or celiac arteries.

- **Cardiac:** Some patients have coronary artery disease, which is usually asymptomatic, but may cause angina. Heart failure may result from ischemic or hypertensive cardiomyopathy

- **Cutaneous:** Livedo reticularis, skin ulcers, tender erythematous nodules, bullous or vesicular eruptions, infarction and gangrene of fingers or toes, or a combination may occur. The nodules in PAN resemble erythema nodosum (inflammation of subcutaneous fat), but in PAN, necrotizing vasculitis occurs within the walls of medium-sized arteries, usually located in the deep dermis and subcutaneous fat.

- **Genital:** Orchitis with testicular pain and tenderness can occur.

Diagnosis

- Clinical findings

- Biopsy

- Arteriography if no clinically involved tissue is available for biopsy

PAN may be suspected in patients with unexplained fever, abdominal pain, renal failure, hypertension, arthralgia, muscle tenderness or weakness, subcutaneous nodules, skin ulcers, pain in the abdomen or extremities, or rapidly developing hypertension. If patients have insidious, nonspecific symptoms, diagnosis is much more difficult. The diagnosis is further clarified when clinical findings are combined with certain laboratory results and other causes are excluded. PAN is also suspected in patients with systemic symptoms or signs and peripheral (usually multiple) neuritis involving major nerve trunks (eg, radial, peroneal, sciatic) in a bilaterally symmetric or asymmetric fashion (mononeuritis multiplex).

Diagnosis is confirmed by biopsy showing necrotizing arteritis or by arteriography showing the typical aneurysms in medium-sized arteries. Magnetic resonance angiography may show microaneurysms, but some abnormalities may be too small for it to detect. Thus, magnetic resonance angiography is not the test used primarily for diagnosis. Biopsy of clinically uninvolved tissue is usually useless because the disease is focal; biopsy should target sites suggested by clinical evaluation. Samples of subcutaneous tissue, sural nerve, and muscle, if thought to be involved, are preferred to samples from the kidneys or liver. If clinical findings are absent or minimal, electromyography and nerve conduction studies may help select the site of muscle or nerve biopsy. If skin lesions are present, surgical skin biopsies that include deeper dermis and subcutaneous fat should be done. (Punch biopsies of the skin that sample the epidermis and superficial dermis miss the lesions of PAN.) Even though microscopic lesions in the testes are common, testicular biopsy should not be done if testicular symptoms are absent and if other possible sites are accessible because the yield is low. Also, men may be reluctant to have testicular biopsy.

Laboratory tests are nonspecific. Leukocytosis up to 20,000 to 40,000/µL, proteinuria, and microscopic hematuria are the most common abnormalities. Patients may have thrombocytosis, markedly elevated

ESR, anemia caused by blood loss or renal failure, hypoalbuminemia, and elevated serum immunoglobulins. AST and ALT are often mildly elevated. Testing for hepatitis B and C should be done. Other testing (eg, antineutrophil cytoplasmic antibodies [ANCA], rheumatoid factor, anticyclic citrullinated peptides [CCP], antinuclear antibodies [ANA], C3 and C4 complement levels, cryoglobulin levels, nuclear antigens and antibodies to extractable nuclear antigens such as anti-Smith, anti-Ro/SSA, anti-La/SSB, and anti-RNP) is done if the clinical presentation suggests other diagnoses, such as RA, SLE, or Sjogren's syndrome.

Prognosis

Without treatment, 5-yr survival is < 15%. With treatment, 5-yr survival is > 80% but may be lower for patients with hepatitis B. Prognosis is better if disease remission is achieved within 18 mo after diagnosis.

The following findings are associated with a poor prognosis:

• Renal insufficiency

• GI involvement

• Neurologic involvement

Treatment

• Corticosteroids alone or with cyclophosphamide, methotrexate, or azathioprine, depending on disease severity

• Addition of lamivudine and plasma exchange for patients with hepatitis B

Treatment depends on the severity of the disease. For systemic symptoms but no serious neurologic, renal, GI, or cardiac manifestations, corticosteroids may be sufficient, at least initially. For severe disease with neurologic, renal, GI, or cardiac manifestations, cyclophosphamide plus corticosteroids may improve outcome. For moderate disease, corticosteroids plus methotrexate or azathioprine can be used. Hypertension should be treated aggressively; ACE inhibitors are effective.

Hepatitis B-related PAN: Treatment aims at rapidly suppressing inflammation, then eliminating the virus and inducing seroconversion via plasma exchange. A short course of corticosteroids is used for a few weeks. Lamivudine 100 mg po once/day is given for a maximum of 6 mo. A lower dose is used in patients with renal insufficiency. Plasma exchanges are scheduled as follows: 3 times/wk for 3 wk, 2 times/wk for 2 wk and once/wk until hepatitis B e antigen (HBeAg) converts to hepatitis B e antibody (anti-HBe) or until clinical recovery is sustained for 2 to 3 mo. Although this approach has not been proved to improve survival when compared with immunosuppressive therapy only, it may reduce the risk of long-term complications of hepatitis B and suppress the side effects of long-term treatment with corticosteroids and immunosuppressants.

Traditional treatment with corticosteroids, sometimes with cytotoxic immunosuppressants (mainly cyclophosphamide), was often effective in the short term but did not prevent relapses and complications (eg, chronic hepatitis, cirrhosis) due to persistence of the hepatitis B virus.

Polymyalgia Rheumatica

Polymyalgia rheumatica is a syndrome closely associated with giant cell (temporal) arteritis. It affects adults > 55. It typically causes severe pain and stiffness in proximal muscles, without weakness or atrophy, and nonspecific systemic symptoms. ESR is markedly elevated. Diagnosis is clinical. Treatment with low-dose corticosteroids is effective.

Polymyalgia rheumatica affects adults > 55; the female:male ratio is 2:1.

Because polymyalgia rheumatica is closely associated with giant cell arteritis (see p. 319), some

authorities consider the two disorders to be different phases of the same process. Polymyalgia rheumatica appears to be more common. A few patients with polymyalgia rheumatica develop giant cell arteritis, but 40 to 60% of patients with giant cell arteritis have polymyalgia rheumatica. Polymyalgia rheumatica may precede or occur simultaneously with giant cell arteritis.

Etiology and pathogenesis are unknown. Whether symptoms result from vasculitis is unclear; they probably result from low-grade axial synovitis and bursitis.

Symptoms and Signs

Polymyalgia rheumatica is characterized by bilateral proximal aching of the shoulder and hip girdle muscles and the back (upper and lower) and neck muscles. Stiffness in the morning is typical. Shoulder symptoms may reflect proximal bursitis (eg, subdeltoid, subacromial) and less often bicipital tenosynovitis or joint synovitis. Discomfort is worse in the morning and is occasionally severe enough to prevent patients from getting out of bed and from doing simple activities. The pain may make patients feel weak, but objective muscle weakness is not a feature of the disorder.

Diagnosis

• Clinical findings

• Exclusion of other causes

Polymyalgia rheumatica is suspected in elderly patients with typical symptoms, but other possible causes must be excluded. Tests include ESR, CBC, thyroid-stimulating hormone levels, and CK. In > 80 % of patients, ESR is markedly elevated, often > 100 mm/h, usually > 50 mm/h (Westergren method). Electromyography, biopsy, and other tests (eg, rheumatoid factor), which are normal in polymyalgia rheumatica, are sometimes done to rule out other clinically suspected diagnoses.

The following findings in polymyalgia rheumatica distinguish it:

• From RA: Chronic small joint synovitis (although some joint swelling may be present), erosive or destructive lesions, rheumatoid nodules, and rheumatoid factor are absent.

• From polymyositis: Pain rather than weakness predominates; muscle enzyme levels and electromyography and muscle biopsy results are normal.

• From hypothyroidism: Thyroid function test results and muscle enzyme levels are normal.

• From multiple myeloma: Monoclonal gammopathy is absent.

• From fibromyalgia: Symptoms are more localized, and ESR is typically elevated.

Treatment

• Prednisone

Prednisone started at 15 to 20 mg po once/day results in dramatic improvement. If giant cell arteritis is thought to be present, the dose should be higher, and temporal artery biopsy should be done. As symptoms subside, corticosteroids are tapered to the lowest clinically effective dose, regardless of ESR. Some patients are able to stop corticosteroids in ≤ 1 yr; others require small doses for years. NSAIDs are rarely sufficient.

In elderly patients, physicians should watch for and treat complications of corticosteroid use (eg, diabetes, hypertension). Patients taking prednisone long term should be given a bisphosphonate to prevent osteoporosis.

Because patients may develop giant cell arteritis, they should be instructed to immediately report

headache, muscle pain during chewing, and, particularly, visual disturbances to their physician.

Takayasu's Arteritis

(Pulseless Disease; Occlusive Thromboaortopathy; Aortic Arch Syndrome)

Takayasu's arteritis is an inflammatory disease affecting the aorta, its branches, and pulmonary arteries. It occurs predominantly in young women. Etiology is unknown. Vascular inflammation may cause arterial stenosis, occlusion, dilation, or aneurysms. It causes asymmetric pulses and symptoms and signs of arterial obstruction. Diagnosis is by aortic arteriography or magnetic resonance angiography. Treatment is with corticosteroids and, for organ-threatening ischemia, vascular interventions such as bypass surgery.

Takayasu's arteritis is rare. It is more common among Asians but occurs worldwide. Female:male ratio is 8:1, and age at onset is typically 15 to 30. In North America, annual incidence is estimated to be 2.6 cases/million.

Etiology

The cause is unknown. Cell-mediated immune mechanisms may be involved and may be similar to those in giant cell arteritis.

Pathophysiology

Takayasu's arteritis affects primarily large elastic arteries. The most commonly affected are the innominate and subclavian arteries, aorta (mainly the ascending aorta and the arch), common carotid arteries, and renal arteries. Most patients have stenoses or occlusions. Aneurysms occur in about one third of patients. Usually, the wall of the aorta or its branches thickens irregularly, with intimal wrinkling. When the aortic arch is affected, orifices of the major arteries emerging from the aorta may be markedly narrowed or even obliterated by intimal thickening. In one half of patients, pulmonary arteries are also affected.

Histologically, early changes consist of adventitial mononuclear infiltrate with perivascular cuffing of the vasa vasorum. Later, intense mononuclear inflammation of the media may occur, sometimes accompanied by granulomatous changes, giant cells, and patchy necrosis of the media. Morphologic changes may be indistinguishable from those of giant cell arteritis. Panarteritic inflammatory infiltrates cause marked thickening of the affected artery and subsequent luminal narrowing and occlusion.

Symptoms and Signs

Most patients present with only focal symptoms that reflect hypoperfusion of the affected organ or limb. Takayasu's arteritis may have 3 stages:

- Systemic disease, usually with systemic, nonspecific symptoms (eg, fever, malaise, night sweats, weight loss, arthralgias, fatigue)

- Vascular inflammatory phase, with ischemic manifestations that may wax and wane

- Inactive (burned-out) disease, sometimes with acute or progressive occlusion (including thrombosis)

Only one third of patients have systemic symptoms at presentation or recall having had such symptoms.

Repetitive arm movements and sustained arm elevation may cause pain and fatigue. Arterial pulses in arms and legs may be diminished and asymmetric. Bruits are often audible over the subclavian arteries, brachial arteries, carotid arteries, abdominal aorta, or femoral arteries. Reduced BP in one or both arms is common.

When the carotid and vertebral arteries are affected, cerebral blood flow decreases, leading to dizziness,

syncope, orthostatic hypotension, headaches, transient visual disturbances, transient ischemic attacks, or strokes. Stenotic lesions in a subclavian artery near the origin of a patent vertebral artery can cause posterior circulation neurologic symptoms or syncope when the arm is used (called subclavian steal syndrome). Retrograde flow through the vertebral artery supplies the subclavian artery distal to the stenosis, and vasodilation of the arterial bed in the upper limb during exercise compromises posterior cerebral blood flow.

Angina pectoris or MI may result from narrowing of the coronary artery orifice due to aortitis or coronary arteritis. Aortic regurgitation may occur if the ascending aorta is markedly dilated. Heart failure can develop.

Obstruction of the descending thoracic aorta sometimes causes signs of aortic coarctation (eg, hypertension, headache, leg claudication). Renovascular hypertension may develop if the abdominal aorta or renal arteries are narrowed.

Pulmonary arteries are often affected, sometimes causing pulmonary hypertension. Because Takayasu's arteritis is chronic, collateral circulation can develop. Thus, ischemic ulcerations or gangrene due to obstruction of the arteries to the extremities is rare.

Diagnosis

• Aortic arteriography or magnetic resonance angiography

• Monitoring of disease activity

The diagnosis is suspected when symptoms suggest ischemia of organs supplied by the aorta or its branches or when peripheral pulses are decreased or absent in patients at low risk of atherosclerosis and other aortic disorders, especially in young women. In these patients, arterial bruits and right-left or upper extremity-lower extremity discrepancies in pulses or in BP also suggest the diagnosis. Confirmation of the diagnosis requires aortic arteriography or magnetic resonance angiography to evaluate all branches of the aorta. Characteristic findings include stenosis, occlusion, irregularities in arterial lumens, poststenotic dilation, collateral arteries around obstructed vessels, and aneurysms.

BP is measured in both arms. However, measurement can be difficult. If both subclavian arteries are severely affected, systemic BP can be accurately measured only in the legs. If the disorder affects both subclavian arteries in patients with coarctation of the descending aorta or involvement of both iliac or femoral arteries, BP cannot be accurately measured. Then, central arterial pressure must be measured via angiography to detect occult hypertension, which can cause complications.

Laboratory tests are nonspecific and not helpful in diagnosis. Common findings include anemia of chronic disease, elevated platelet levels, occasionally elevated WBC counts, and elevated ESR and C-reactive protein.

Once Takayasu's arteritis is diagnosed, disease activity must be monitored to look for the following:

• New systemic symptoms, which may reflect active arthritis or infection (secondary to immunosuppression therapy)

• Evidence of inflammation detected by blood tests (although markers of inflammation may miss active arteritis)

• Development of stenosis, aneurysms, or ischemic symptoms in previously unaffected arteries, as assessed with periodic imaging (usually magnetic resonance angiography)

Periodic imaging of the aorta and large arteries is important (see Table 34-3) because the disorder may progress silently, without clinical symptoms or evidence of inflammation in blood. Once the disorder is diagnosed, BP should be measured periodically in an unaffected limb because hypertension must be controlled.

Disorders that mimic Takayasu's arteritis must be excluded. They include inherited connective tissue disorders (eg, Ehlers-Danlos or Marfan syndrome), vascular infections (tuberculous, fungal, or syphilitic), fibromuscular

[Table 34-3. Imaging Tests Used in Takayasu's Arteritis]

dysplasias, disorders causing arterial thrombosis (eg, hypercoagulable states), and idiopathic inflammatory conditions (eg, ankylosing spondylitis with aortitis, Cogan's or Behcet's syndrome, Kawasaki disease, sarcoidosis); all can affect large vessels.

Prognosis

For 20% of patients, the course is monophasic. For the rest, the course is relapsing and remitting or chronic and progressive. Even when symptoms and laboratory abnormalities suggest quiescence, new lesions occur and are evident on imaging studies. A progressive course and the presence of complications (eg, hypertension, aortic regurgitation, heart failure, aneurysms) predict a less favorable prognosis.

Treatment

• Corticosteroids

• Sometimes immunosuppressants

• Antihypertensives

• Vascular interventions

Drugs: Corticosteroids are the cornerstone of treatment. The optimal dose, tapering schedule, and length of treatment have not been determined. Treatment with corticosteroids alone induces remission in most patients. Prednisone is usually used. The starting dose is 1 mg/kg po once/day for 1 to 3 mo; the dose is then tapered slowly over several months. Lower starting doses may also induce remission. About one half of patients relapse when the drug is tapered or stopped, despite initial response.

Methotrexate, cyclophosphamide, azathioprine, mycophenolate mofetil, and tumor necrosis factor inhibitors (eg, etanercept, infliximab) have been used in some patients. They can be tried if corticosteroids are insufficiently effective or cannot be tapered. Methotrexate is given with a corticosteroid. Often, the starting dose is 0.3 mg/kg once/wk, which is increased up to 25 mg/wk. Mycophenolate mofetil can also be tried. Cyclophosphamide should be considered in patients with coronary vasculitis or other serious complications thought to be due to active arteritis.

An antiplatelet drug (eg, aspirin 325 mg po once/day) is frequently used because platelet-mediated occlusion cannot be excluded. Hypertension should be treated aggressively; ACE inhibitors may be effective.

Procedures: Vascular intervention, usually a bypass procedure, may be needed to reestablish blood flow to ischemic tissues if drug therapy is ineffective. Indications include the following:

• Severe hypertension that is refractory to medical management because renal artery stenosis is present (although reocclusion and thrombosis of grafts is common)

• Ischemia in the extremities that interferes with daily activities

• Ischemia of cerebral arteries

• New York Heart Association (NYHA) class II heart failure secondary to a discrete coronary artery stenosis or occlusion

• Cardiac ischemia caused by stenosis of the coronary arteries

• Coarctation of the aorta

• Dissection or enlargement of an aortic aneurysm

Bypass grafting preferably with an autologous graft has the best patency rates. The anastomosis should be made at disease-free sites of the affected arteries to help prevent aneurysm formation and occlusion.

Percutaneous transluminal coronary angioplasty (PTCA) has few risks and may be effective for short lesions. But long-term restenosis rates seem much higher than those with bypass grafting. Vascular stenting is usually not recommended because the restenosis rate is high.

For aortic regurgitation, valvular surgery with aortic root replacement may be necessary.

Wegener's Granulomatosis

Wegener's granulomatosis is characterized by necrotizing granulomatous inflammation, small and medium-sized vessel vasculitis, and focal necrotizing glomerulonephritis, often with crescent formation. Typically, the upper and lower respiratory tract and the kidneys are affected, but any organ may be. Symptoms vary depending on the organs and systems affected. Patients may present with upper and lower respiratory tract symptoms (eg, recurrent nasal discharge or epistaxis, cough), followed by hypertension and edema, or with symptoms reflecting multiorgan involvement. Diagnosis usually requires biopsy. Treatment is with corticosteroids plus an immunosuppressant. Remission is usually possible, although relapses are common.

Wegener's granulomatosis occurs in about 1/25,000 people; it is most common among whites but can occur in all ethnic groups and at any age. Mean age at onset is 40.

The cause is unknown, although immunologic mechanisms play a role. Most patients with active generalized disease have antineutrophil cytoplasmic antibodies (ANCA).

Pathophysiology

Characteristically, granulomas form with histiocytic epithelioid cells and often with giant cells. Plasma cells, lymphocytes, neutrophils, and eosinophils are present. Inflammation affects tissues as well as vessels; vasculitis may be a small or large component of the disease. Micronecrosis, usually with neutrophils (microabscesses), occurs early. Micronecrosis progresses to macronecrosis. A central area of necrosis (called geographic necrosis) is rimmed by lymphocytes, plasma cells, macrophages, and giant cells. A zone of fibroblastic proliferation with palisading histiocytes may surround the area.

Nonspecific chronic inflammation and tissue necrosis occurs in the nose. The lungs are most likely to display the full spectrum of histopathologic abnormalities. In the kidneys, the most common finding is a proliferative crescentic focal glomerulonephritis with necrosis and thrombosis of individual loops or larger segments of the glomerulus. Vasculitic lesions and disseminated granulomas occur only occasionally.

Symptoms and Signs

Onset may be insidious or acute; the full spectrum of the disease may take years to evolve. Some patients present initially with upper and lower respiratory tract symptoms; at some point later, the kidneys are affected. In other patients, onset of systemic manifestations is relatively acute; several organs and systems, such as the upper respiratory tract, peripheral nervous system (causing mononeuritis multiplex), kidneys (causing glomerulonephritis), and lower respiratory tract (causing hemorrhage, lung nodules, cavities, or a combination), are simultaneously affected.

• **Upper respiratory tract:** Sinus pain, serosanguineous or purulent discharge, and epistaxis may occur. The mucosa appears granular (like cobblestones) and is friable; ulcers, thick dark crusts, and septal

perforation are common. Nasal chondritis can occur with swelling, pain, and collapse of the nasal bridge (saddle nose). Patients may report recurrent sinusitis that has responded inadequately to multiple antibiotic regimens and has required one or more sinus operations before diagnosis. Secondary infections (eg, due to *Staphylococcus aureus*) may develop. Subglottic stenosis may develop, causing symptoms such as pain in the larynx, hoarseness, dyspnea, wheezing, and stridor.

- **Ears:** Otitis, sensorineural hearing loss, vertigo, and chondritis may occur. The middle ear, inner ear, and mastoids are often affected.

- **Eyes:** Eyes may appear red and swollen. Nasolacrimal duct inflammation and obstruction may affect the eye; conjunctivitis, scleritis, uveitis, or retinal vasculitis may also occur. Inflammatory infiltrates in the retro-orbital space (orbital pseudotumor) can cause proptosis, compression of the optic nerve, and blindness. Extension into the extraocular muscles leads to diplopia. If serious eye symptoms develop, evaluation and treatment are required immediately to prevent permanent vision loss.

- **Lower respiratory tract:** Respiratory manifestations are common. Inflammation of the major bronchi and branches can cause localized wheezing, postobstructive pneumonia, and atelectasis. Single or multiple pulmonary nodules, with or without cavitation, and parenchymal infiltrates, sometimes cause symptoms, such as chest pain, shortness of breath, and productive cough. Dyspnea with bilateral infiltrates, with or without hemoptysis, may indicate alveolar hemorrhage, and must be evaluated immediately.

- **Heart:** Coronary artery disease may occur, but rarely.

- **Musculoskeletal system:** Patients may present with myalgias, arthralgias, or nonerosive inflammatory arthritis.

- **Skin:** Leukocytoclastic vasculitis, tender subcutaneous nodules, papules, livedo reticularis, or pyoderma gangrenosum may develop.

- **Nervous system:** Vasculitis may cause ischemic peripheral neuropathy, brain lesions, or extension of lesions from contiguous sites. Lesions that originate in the sinuses or middle ear may extend directly to the retropharyngeal area and base of the skull, leading to cranial neuropathy, proptosis, diabetes insipidus, or meningitis.

- **Kidneys:** Symptoms and signs of glomerulonephritis develop. Urinary sediment may be abnormal, and serum creatinine may increase rapidly. Edema and hypertension may result. Rapidly progressive glomerulonephritis, which is life threatening, can develop.

- **Other organs:** Occasionally, an inflammatory mass occurs in the breasts, kidneys, prostate, or other organs.

Diagnosis

- Routine laboratory tests, including urinalysis

- Tests for ANCA

- Biopsy for definitive diagnosis

Wegener's granulomatosis should be suspected in patients with chronic, unexplained respiratory symptoms and signs (including otitis media in adults), particularly if manifestations in other organ systems, especially the kidneys, also suggest the disorder. Routine laboratory tests are done, but ANCA testing and biopsy yield the most specific findings.

Routine laboratory tests include ESR or C-reactive protein, CBC with differential, serum albumin and total protein, serum creatinine, urinalysis, 24-h urine protein, and chest x-ray. In most patients with active disease, ESR and C-reactive protein are elevated, and serum albumin and total protein are decreased;

anemia, thrombocytosis, and mild to moderate eosinophilia are detected. Dysmorphic RBCs and RBC casts, detected during urinalysis, indicate glomerular involvement. Proteinuria may be detected. Serum creatinine may be increased.

Serologic testing to detect ANCA is followed by enzyme-linked immunosorbent assay (ELISA) to check for specific antibodies. Most patients with active disease have cytoplasmic ANCA (cANCA), with antibodies against proteinase-3 (PR3); these findings plus characteristic clinical findings suggest Wegener's granulomatosis.

Some patients with other disorders (eg, bacterial endocarditis, TB) test positive for ANCA. If characteristic clinical findings are absent, a positive ANCA result does not confirm Wegener's granulomatosis. ANCA testing should not be used to guide treatment. During apparent remission, ANCA may increase or ANCA test results may change from negative to positive. In some of these patients, symptoms do not recur; in others, symptoms recur or worsen soon after the test is done or during the next few weeks, months, or sometimes years.

Biopsy should be done if possible to confirm the diagnosis. Clinically abnormal sites may be biopsied first, but lung biopsy is most likely to detect characteristic findings. Open thoracotomy provides the best access to affected tissue. Biopsies of lung or sinus tissue are cultured to exclude infection. Renal biopsy may be necessary to confirm the diagnosis and to exclude other causes, especially if serum creatinine is elevated. Biopsy results may also provide histologic information that can help guide treatment (eg, renal fibrosis, which is irreversible with immunosuppressive treatment).

Differential diagnosis includes other vasculitic disorders that affect small and medium-sized vessels. Polyarteritis nodosa is unlikely if lung involvement is prominent and glomerulonephritis is present. Infections, especially due to slow-growing fungi or acid-fast organisms should be ruled out by staining and by culture of the sampled tissues. RA should not be diagnosed based only on the presence of rheumatoid factor, which is present in one half of patients with Wegener's granulomatosis.

Prognosis

Prognosis depends on the extent of the disorder—whether it is limited to nasal and pulmonary lesions, with little or no systemic involvement, or it affects many organs, causing severe systemic vasculitis.

Use of immunosuppressants for severe disease has dramatically improved prognosis. With treatment, complete remission is possible for about 70% of patients, but about one half of them eventually relapse; relapse may occur when treatment is stopped or many years after it is stopped. Resuming or increasing treatment can usually control the disorder. However, the disease or treatment causes significant morbidity in 90% of patients.

Treatment

• Emergency treatment with corticosteroids and cyclophosphamide for severe disease

• Corticosteroids and methotrexate for less severe disease

• Kidney transplantation if necessary

Treatment depends on the severity of disease. A multidisciplinary approach is required for multiorgan disease; a rheumatologist, an otorhinolaryngologist, a pulmonologist, and sometimes a nephrologist may be included.

Patients who have severe life- or organ-threatening manifestations (eg, alveolar hemorrhage, rapidly progressive glomerulonephritis, mononeuritis multiplex with motor involvement) require immediate treatment and hospital admission. These patients require high-dose corticosteroids and cyclophosphamide (see p. 314). The role of rituximab in severe or refractory disease is under study.

For less severe disease, corticosteroids and methotrexate are used. Methotrexate or azathioprine is used

to maintain remission.

Irrigation of sinuses with saline, with or without mupirocin 2% nasal ointment, helps minimize crusting and secondary staphylococcal infections.

Treatment of subglottic stenosis is difficult. Systemic immunosuppressants may not be effective. Intralesional injection of long-acting corticosteroids, with gentle progressive dilation, markedly improves outcomes and helps prevent unnecessary tracheostomies.

Patients should be taught about the disorder so that relapses can be detected early. Patients should learn how to test their urine for blood and protein and be instructed to notify their physician at the first sign of hematuria.

Kidney transplantation has been successful; the risk of relapse after transplantation is reduced compared with maintenance dialysis treatment (possibly in part due to use of immunosuppressants to prevent rejection).

Chapter 35. Joint Disorders

Introduction

Joint disorders may be inflammatory (RA, spondyloarthropathies, crystal-induced arthritis) or relatively less inflammatory (osteoarthritis, neurogenic arthropathy). Crystal-induced arthritis and infectious arthritis are discussed elsewhere in THE MANUAL.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that primarily involves the joints. RA causes damage mediated by cytokines, chemokines, and metalloproteases. Characteristically, peripheral joints (eg, wrists, metacarpophalangeal joints) are symmetrically inflamed, leading to progressive destruction of articular structures, usually accompanied by systemic symptoms. Diagnosis is based on specific clinical, laboratory, and imaging features. Treatment involves drugs, physical measures, and sometimes surgery. Disease-modifying antirheumatic drugs help control symptoms and slow disease progression.

RA affects about 1% of the population. Women are affected 2 to 3 times more often than men. Onset may be at any age, most often between 35 yr and 50 yr, but can be during childhood (see Juvenile Idiopathic Arthritis on p. 339) or old age.

Etiology

Although RA involves autoimmune reactions, the precise cause is unknown; many factors may contribute. A genetic predisposition has been identified and, in white populations, localized to a shared epitope in the HLA-DR β_1 locus of class II histocompatibility antigens. Unknown environmental factors (eg, viral infections) are thought to play a role.

Pathophysiology

Prominent immunologic abnormalities include immune complexes produced by synovial lining cells and in inflamed blood vessels. Plasma cells produce antibodies (eg, rheumatoid factor [RF]) that contribute to these complexes, but destructive arthritis can occur in the absence of RF. Macrophages also migrate to diseased synovium in early disease; increased macrophage-derived lining cells are prominent along with vessel inflammation. Lymphocytes that infiltrate the synovial tissue are primarily CD4+ T cells. Macrophages and lymphocytes produce pro-inflammatory cytokines and chemokines (eg, tumor necrosis factors [TNF], granulocyte-macrophage colony-stimulating factor [GM-CSF], various ILs, interferon-γ) in the synovium. Release of inflammatory mediators probably contributes to the systemic and joint manifestations of RA.

In chronically affected joints, the normally thin synovium thickens and develops many villous folds. The synovial lining cells produce various materials, including collagenase and stromelysin, which contribute to cartilage destruction, and IL-1 and TNF-α, which stimulate cartilage destruction, osteoclast-mediated bone absorption, synovial inflammation, and prostaglandins (which potentiate inflammation). Fibrin deposition, fibrosis, and necrosis are also present. Hyperplastic synovial tissue (pannus) releases these inflammatory mediators, which erode cartilage, subchondral bone, articular capsule, and ligaments. PMNs on average make up about 60% of WBCs in the synovial fluid.

Rheumatoid nodules develop in about 30% of patients with RA. They are granulomas consisting of a central necrotic area surrounded by palisaded histiocytic macrophages, all enveloped by lymphocytes, plasma cells, and fibroblasts. Nodules and vasculitis can also develop in visceral organs.

Symptoms and Signs

Onset is usually insidious, often beginning with systemic and joint symptoms. Systemic symptoms include early morning stiffness of affected joints, generalized afternoon fatigue and malaise, anorexia, generalized

weakness, and occasionally low-grade fever. Joint symptoms include pain, swelling, and stiffness.

The disease progresses most rapidly during the first 6 yr, particularly the first year; 80% of patients develop some permanent joint abnormalities within 10 yr. The course is unpredictable in individual patients.

Joint symptoms are characteristically symmetric. Typically, stiffness lasts > 60 min after rising in the morning but may occur after any prolonged inactivity. Involved joints become tender, with erythema, warmth, swelling, and limitation of motion. The joints involved include the following:

• Wrists and the index and middle metacarpophalangeal joints (most commonly involved)

• Proximal interphalangeal joints

• Metatarsophalangeal joints

• Shoulders

• Elbows

• Hips

• Knees

• Ankles

However, virtually any joint except uncommonly the distal interphalangeal (DIP) joints may be involved. The axial skeleton is rarely involved except for the upper cervical spine. Synovial thickening is detectable. Joints are often held in flexion to minimize pain, which results from joint capsular distention.

Fixed deformities, particularly flexion contractures, may develop rapidly; ulnar deviation of the fingers with an ulnar slippage of the extensor tendons off the metacarpophalangeal joints is typical, as are swan-neck and boutonniere deformities (see
Fig. 43-2 on p. 387). Joint instability can also occur. Carpal tunnel syndrome can result from wrist synovitis compressing the median nerve. Popliteal (Baker's) cysts can develop, causing calf swelling and tenderness suggestive of deep venous thrombosis.

Extra-articular manifestations: Subcutaneous rheumatoid nodules are not usually an early sign but eventually develop in up to 30% of patients, usually at sites of pressure and chronic irritation (eg, the extensor surface of the forearm, metacarpophalangeal joints, occiput). Visceral nodules, usually asymptomatic, are common in severe RA. Other extra-articular signs include vasculitis causing leg ulcers or mononeuritis multiplex, pleural or pericardial effusions, pulmonary nodules, pulmonary infiltrates or fibrosis, pericarditis, myocarditis, lymphadenopathy, Felty's syndrome, Sjogren's syndrome, scleromalacia, and episcleritis. Involvement of the cervical spine can cause atlantoaxial subluxation (see p. 385) and spinal cord compression (see p. 1810); it may worsen with extension of the neck (eg, during endotracheal intubation).

Diagnosis

• Clinical criteria

• Serum rheumatoid factor (RF) or anticyclic citrullinated peptide antibody (anti-CCP)

• X-rays

RA should be suspected in patients with polyarticular, symmetric arthritis, particularly if the wrists and 2nd and 3rd metacarpophalangeal joints are involved. Criteria for the diagnosis of RA are listed in
Table 35-1. The presence of ≥ 4 criteria suggests the diagnosis. Other causes of symmetric polyarthritis,

particularly hepatitis C, must be excluded. Patients should have a serum RF test, hand and wrist x-rays, and baseline x-rays of affected joints to document future erosive changes.

[Table 35-1. Diagnosing Rheumatoid Arthritis*]

RFs, antibodies to human γ-globulin, are present in about 70% of patients with RA. However, RF, often in low titers, occurs in patients with other diseases, including other connective tissue diseases (eg, SLE), granulomatous diseases, chronic infections (eg, viral hepatitis, subacute bacterial endocarditis, TB), and cancers. Low RF titers can also occur in 3% of the general population and 20% of the elderly. An RF titer measured by latex agglutination of > 1:80 or a positive anti-CCP test supports the diagnosis of RA.

Anti-CCP antibodies have high specificity (90%) and sensitivity (96%) for RA and, like RF, predict a worse prognosis.

X-rays show only soft-tissue swelling during the first months of disease. Subsequently, periarticular osteoporosis, joint space (articular cartilage) narrowing, and marginal erosions may become visible. Erosions often develop within the first year but may occur any time. MRI seems to be more sensitive and detects earlier articular inflammation and erosions. In addition, abnormal subchondral bone signals (eg, bone marrow lesions, bone marrow edema) around the knee suggest progressive disease.

If RA is diagnosed, additional tests help detect complications and unexpected abnormalities. CBC with differential should be obtained. A normochromic (or slightly hypochromic)-normocytic anemia occurs in 80%; Hb is usually > 10 g/dL. If Hb is ≤ 10 g/dL, superimposed iron deficiency or other causes of anemia should be considered. Neutropenia occurs in 1 to 2% of cases, often with splenomegaly (Felty's syndrome). Acute-phase reactants (eg, thrombocytosis, elevated ESR, elevated C-reactive protein) reflect disease activity. A mild polyclonal hypergammaglobulinemia often occurs. ESR is elevated in 90% of patients with active disease.

Synovial fluid examination is necessary with any new-onset effusion to rule out other disorders and differentiate RA from other inflammatory arthritides (eg, septic and crystal-induced arthritis). In RA, during active joint inflammation, synovial fluid is turbid, yellow, and sterile, with reduced viscosity and usually 10,000 to 50,000 WBCs/μL; PMNs typically predominate, but > 50% may be lymphocytes and other mononuclear cells. Crystals are absent.

Differential diagnosis: Many disorders can simulate RA:

• Crystal-induced arthritis

• Osteoarthritis

• SLE

• Sarcoidosis

• Reactive arthritis

• Psoriatic arthritis

• Ankylosing spondylitis

RF can be nonspecific and is often present in several autoimmune diseases; the presence of anti-CCP antibodies is more specific for RA.

Some patients with crystal-induced arthritis may meet criteria for RA; however, synovial fluid examination should clarify the diagnosis. The presence of crystals makes RA unlikely. Joint involvement and subcutaneous nodules can result from gout, cholesterol, and amyloidosis as well as RA; aspiration or biopsy of the nodules may occasionally be needed.

SLE usually can be distinguished if there are skin lesions on light-exposed areas, hair loss, oral and nasal mucosal lesions, absence of joint erosions in even long-standing arthritis, joint fluid that often has < 2000 WBCs/μL (predominantly mononuclear cells), antibodies to double-stranded DNA, renal disease, and low serum complement levels. In contrast to RA, deformities in SLE are usually reducible because of the lack of erosions and bone or cartilage damage. Arthritis similar to RA can also occur in other rheumatic disorders (eg, polyarteritis, systemic sclerosis, dermatomyositis, or polymyositis) or there can be features of more than one disease, which suggests an overlap syndrome or mixed connective tissue disease.

Sarcoidosis, Whipple's disease, multicentric reticulohistiocytosis, and other systemic diseases may involve joints; other clinical features and tissue biopsy sometimes help differentiate these conditions. Acute rheumatic fever has a migratory pattern of joint involvement and evidence of antecedent streptococcal infection (culture or changing antistreptolysin-O titer); in contrast, RA has an additive arthritis.

Reactive arthritis (see p. 343) can be differentiated by antecedent GI or GU symptoms; asymmetric involvement and pain at the Achilles insertion of the heel, sacroiliac joints, and large joints of the leg; conjunctivitis; iritis; painless buccal ulcers; balanitis circinata; or keratoderma blennorrhagicum on the soles and elsewhere.

Psoriatic arthritis (see p. 344) tends to be asymmetric and is not usually associated with RF, but differentiation may be difficult in the absence of nail or skin lesions. DIP joint involvement and severely mutilating arthritis (arthritis mutilans) is strongly suggestive, as is the presence of a diffusely swollen (sausage) digit. Ankylosing spondylitis (see p. 341) may be differentiated by spinal and axial joint involvement, absence of subcutaneous nodules, and negative RF test.

Osteoarthritis (see p. 345) can be differentiated by the joints involved; the absence of rheumatoid nodules, systemic manifestations, or significant amounts of RF; and synovial fluid WBC counts < 2000/μL. Osteoarthritis of the hands most typically involves the DIP and proximal interphalangeal joints. RA does not affect the DIP joints.

Prognosis

RA decreases life expectancy by 3 to 7 yr, with heart disease, infection, and GI bleeding accounting for most excess mortality; drug treatment, cancer, as well as the underlying disease may be responsible.

At least 10% of patients eventually are severely disabled despite full treatment. Whites and women have a poorer prognosis, as do patients with subcutaneous nodules, advanced age at disease onset, inflammation in ≥ 20 joints, early erosions, cigarette smoking, high ESR, and high levels of RF or anti-CCP.

Treatment

• Supportive measures (eg, nutrition, rest, physical measures, analgesics)

• NSAIDs

• Drugs that modify disease progression

Treatment involves a balance of rest and exercise, adequate nutrition, physical measures, drugs, and sometimes surgery.

Rest and nutrition: Complete bed rest is rarely indicated, even for a short time; however, a program including judicious rest should be prescribed. An ordinary nutritious diet is generally sufficient. Rarely, patients have food-associated exacerbations; no specific foods have been noted to exacerbate RA. Food and diet quackery is common and should be discouraged. Substituting ω-3 fatty acids (in fish oils) for dietary ω-6 fatty acids (in meats) may partially relieve symptoms by transiently decreasing production of inflammatory prostaglandins.

Physical measures: Joint splinting reduces local inflammation and may relieve severe symptoms. Cold may be applied to reduce pain from temporary worsening in one joint. Orthopedic or athletic shoes with good heel and arch support are frequently helpful; metatarsal supports placed posteriorly to painful metatarsophalangeal joints decrease the pain of weight bearing. Molded shoes may be needed for severe deformities. Self-help devices enable many patients with debilitating RA to perform activities of daily living.

Exercise should proceed as tolerated. During acute inflammation, passive range-of-motion exercise helps prevent flexion contractures. Heat therapy can be helpful. Range-of-motion exercises done in warm water are helpful because heat improves muscle function by reducing stiffness and muscle spasm. However, contractures can be prevented and muscle strength can be restored more successfully after inflammation begins to subside; active exercise (including walking and specific exercises for involved joints) to restore muscle mass and preserve range of joint motion should not be fatiguing. Flexion contractures may require intensive exercise, casting, or immobilization (eg, splinting) in progressively more stretched-open positions. Paraffin baths can warm digits and facilitate finger exercise. Massage by trained therapists, traction, and deep heat treatment with diathermy or ultrasonography may be useful.

Surgery: Surgery must always be considered in terms of the total disease and patient expectations. For example, deformed hands and arms limit crutch use during rehabilitation; seriously affected knees and feet limit benefit from hip surgery. Reasonable objectives for each patient must be determined, and function must be considered. Surgery may be done while the disease is active.

Arthroplasty with prosthetic joint replacement is indicated if damage severely limits function; total hip and knee replacements are most consistently successful. Prosthetic hips and knees cannot tolerate vigorous activity (eg, competitive athletics). Excision of subluxed painful metatarsophalangeal joints may greatly aid walking. Thumb fusions may provide stability for pinch. Neck fusion may be needed for C1-2 subluxation with severe pain or potential for spinal cord compression. Arthroscopic or open synovectomy can relieve joint inflammation but only temporarily unless disease activity can be controlled.

Drugs for RA

The goal is to reduce inflammation as a means of preventing erosions and progressive deformity. Disease-modifying antirheumatic drugs (DMARDs) are used early, often in combination. Other drug classes, including biologic agents, TNF-α antagonists, and IL-1 receptor antagonists, seem to slow the progression of RA. NSAIDs are of some help for the pain of RA but do not prevent erosions or disease progression. Sometimes low-dose systemic corticosteroids (prednisone < 10 mg daily) are added to control severe polyarticular symptoms, usually with the objective of replacement with a DMARD. Intra-articular depot corticosteroids can control severe monarticular or even oligoarticular symptoms. The optimal combinations of drugs are not yet clear. However, some data suggest that certain combinations of drugs from different classes (eg, methotrexate plus other DMARDs, a rapidly tapered corticosteroid plus a DMARD, methotrexate plus a TNF-α antagonist or an IL-1 receptor antagonist, a TNF-α antagonist or an IL-1 receptor antagonist plus a DMARD) are more effective than using DMARDs alone sequentially or in combination.

NSAIDs: Aspirin is no longer used for RA, as effective doses are often toxic. Only one NSAID should be given at a time (see
Table 35-2), although patients may also take aspirin at ≤ 325 mg/day for its antiplatelet cardioprotective effect. Because the maximal response for NSAIDs can take up to 2 wk, doses should be increased no more frequently than this. Doses of drugs with flexible dosing can be increased until response is maximal or maximum dosage is reached. All NSAIDs treat the symptoms of RA and decrease inflammation but do not alter the course of the disease.

NSAIDs inhibit cyclooxygenase (COX) enzymes and thus decrease production of prostaglandins. Some prostaglandins under COX-1 control have important effects in

[**Table 35-2.** NSAID Treatment of Rheumatoid Arthritis]

many parts of the body (ie, they protect gastric mucosa and inhibit platelet adhesiveness). Other prostaglandins are induced by inflammation and are produced by COX-2. Selective COX-2 inhibitors, also called coxibs (eg, celecoxib), seem to have efficacy comparable to nonselective NSAIDs and are less likely to cause GI toxicity; however, they do not seem less likely to cause renal toxicity.

NSAIDs other than coxibs should be avoided in patients with previous peptic ulcer disease or dyspepsia. Other possible adverse effects of all NSAIDs include headache, confusion and other CNS symptoms, increased BP, worsening of hypertension, edema, and decreased platelet function. The effect of NSAIDs on cardiovascular risk is still unclear. Creatinine levels can rise reversibly because of inhibited renal prostaglandins; less frequently, interstitial nephritis can occur. Patients with urticaria, rhinitis, or asthma from aspirin can have the same problems with these other NSAIDs.

Traditional DMARDs: (See Table 35-3 for specific dosage information and adverse effects of other drugs used to treat RA.)

These drugs seem to slow the progression of RA and are indicated in nearly all patients with RA. They differ from each other chemically and pharmacologically. Many take weeks or months to have an effect. About two thirds of patients improve overall, but complete remissions are uncommon. Many result in evidence of decreased damage on imaging studies, presumably reflecting decreased disease activity. They have minimal immediate analgesic effects, so NSAIDs or low-dose corticosteroids must often be continued. Patients should be fully apprised of the risks of DMARDs and monitored carefully for evidence of toxicity.

Combinations of DMARDs may be more effective than single drugs. For example, hydroxychloroquine, sulfasalazine, and methotrexate together are more effective than methotrexate alone or the other two together. Also, combining a DMARD with another drug, such as methotrexate plus a TNF-α antagonist or an IL-1 receptor antagonist or a rapidly tapered corticosteroid, may be more effective than using DMARDs alone.

Methotrexate is a folate antagonist with immunosuppressive effects at high dose. It is anti-inflammatory at doses used in RA. It is very effective and has a relatively rapid onset (clinical benefit often within 3 to 4 wk). Methotrexate should be used with caution, if at all, in patients with hepatic dysfunction or renal failure. Alcohol should be avoided. Supplemental folate, 1 mg po once/day, reduces the likelihood of adverse effects. CBC, AST, ALT, and albumin and creatinine levels should be determined about every 8 wk. Rarely, a liver biopsy is needed if liver function test findings are persistently twice the upper limit of normal or more and the patient needs to continue to use methotrexate. Severe relapses of arthritis can occur after withdrawal of methotrexate. Paradoxically, rheumatoid nodules may enlarge with methotrexate therapy.

Hydroxychloroquine can also control symptoms of mild RA. Funduscopic examination should be done and visual fields should be assessed before and every 12 mo during treatment. The drug should be stopped if no improvement occurs after 9 mo.

Sulfasalazine can alleviate symptoms and slow development of joint damage. It is usually given as enteric-coated tablets. Benefit should occur within 3 mo. Enteric coating or dose reduction may increase tolerability. CBCs should be obtained after 1 to 2 wk and then about every 12 wk during therapy. AST and ALT should be obtained at about 6-mo intervals and whenever the dose is increased.

Leflunomide interferes with an enzyme involved with pyrimidine metabolism. It is about as effective as methotrexate but is less likely to suppress bone marrow, cause abnormal liver function, or cause pneumonitis.

Parenteral **gold compounds** are not commonly used anymore.

Corticosteroids: Systemic corticosteroids decrease inflammation and other symptoms more rapidly and to a greater degree than other drugs. They also seem to slow bone erosion. However, they do not prevent joint destruction, and their clinical benefit often diminishes with time. Furthermore, rebound often follows the withdrawal of corticosteroids in active disease. Because of their long-term adverse effects,

many doctors recommend that corticosteroids are given to maintain function only until another DMARD has taken effect.

Corticosteroids may be used for severe joint or systemic manifestations of RA (eg, vasculitis, pleurisy, pericarditis). Relative contraindications include peptic ulcer disease, hypertension, untreated infections, diabetes mellitus, and glaucoma. The risk of latent TB should be considered before corticosteroid therapy is begun.

Intra-articular injections of depot corticosteroids may temporarily help control pain and swelling in particularly painful joints. Triamcinolone hexacetonide may suppress inflammation for the longest time. Triamcinolone acetonide and methylprednisolone acetate are also effective. No single joint should be injected with a corticosteroid more than 3 to 4 times a year, as too-frequent injections may accelerate joint destruction (although there are no specific data from humans to support this effect). Because injectable corticosteroid esters are crystalline, local inflammation transiently increases within a few hours in < 2% of injections. Although infection occurs in only < 1:40,000, it must be considered if pain occurs > 24 h after injection.

Immunomodulatory, cytotoxic, and immunosuppressive drugs: Treatment with azathioprine, cyclosporine (an immunomodulatory drug), or cyclophosphamide provides efficacy similar to DMARDs. However, these drugs are more toxic, particularly cyclophosphamide. Thus, they are used only for patients in whom treatment with DMARDs has failed or to decrease the need for corticosteroids. They are used infrequently unless there are extra-articular complications. For maintenance therapy with azathioprine, the lowest effective dose should be used. Low-dose cyclosporine may be effective alone or when combined with methotrexate. It may be less toxic than azathioprine and cyclophosphamide.

Biologic agents: Biologic response modifiers other than TNF-α antagonists can be used to target B cells or T cells.

Rituximab is an anti-CD 20 antibody that depletes B cells. It can be used in refractory patients. Response is often delayed but may last 6 mo. The course can be repeated in 6 mo. Mild adverse effects are common, and analgesia, corticosteroids, diphenhydramine, or a combination may need to be given concomitantly. Rituximab is given only to patients who have not improved after using a TNF inhibitor and methotrexate.

Abatacept, a soluble fusion cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) Ig, is indicated for patients with RA with an inadequate response to other DMARDs.

[Table 35-3. Other Drugs Used to Treat RA]

Other agents: Anakinra is a recombinant IL-1 receptor antagonist. IL-1 is heavily involved in the pathogenesis of RA. Infection and leukopenia can be a problem, particularly when given in combination with a TNF antagonist.

TNF-α antagonists (eg, adalimumab, etanercept, and infliximab) reduce the progression of erosions and reduce the number of new erosions. Although not all patients respond, many have a prompt, dramatic feeling of well being, sometimes with the first injection. Inflammation is often dramatically reduced.

Although there are some differences among agents, the most serious problem is infection, particularly with reactivated TB. Patients should be screened for TB with PPD. Etanercept, infliximab, and adalimumab can and probably should be used with methotrexate. High-dose infliximab should not be used in patients with severe heart failure.

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is a group of rheumatic diseases that begins at or before age 16. Arthritis, fever, rash, adenopathy, splenomegaly, and iridocyclitis are typical of some forms. Diagnosis is clinical. Treatment involves NSAIDs and disease-modifying antirheumatic drugs.

JIA is uncommon. The cause is unknown, but there seems to be a genetic predisposition and an autoimmune pathophysiology. JIA may be similar to adult RA (see p. 332), but most forms are slightly different.

Symptoms and Signs

Patients with JIA can have joint stiffness, swelling, effusion, pain, and tenderness. JIA may interfere with growth and development. Micrognathia (receded chin) due to early closure of mandibular epiphyses may occur. Iridocyclitis may develop, which may cause conjunctival injection, pain, and photophobia but can be asymptomatic; scarring and glaucoma with band keratopathy can result. The initial symptoms and signs of JIA tend to fall into 3 possible patterns.

Systemic onset (Still's disease) occurs in about 20% of patients. High fever, rash, splenomegaly, generalized adenopathy, and serositis with pericarditis or pleuritis are common. These symptoms may precede the development of arthritis. Fever (quotidian) is often highest in the afternoon or evening and may persist for up to 2 wk. A typical transient rash often appears with the fever or may be diffuse and migratory, with urticarial or macular lesions.

Pauciarticular onset is characterized by involvement of ≤ 4 joints. It occurs in about 40% of patients, usually young girls. Iridocyclitis is most common in pauciarticular JIA, developing in nearly 20%. Many affected older boys have the HLA-B27 allele. Most of these boys subsequently develop classic features of one of the spondyloarthropathies (eg, ankylosing spondylitis, psoriatic arthritis, reactive arthritis).

Polyarticular onset involves ≥ 5 joints, often ≥ 20. It occurs in the remaining 40% of patients and is often similar to adult RA. Arthritis tends to be symmetric and develop slowly.

Diagnosis

• Clinical criteria

• Rheumatoid factor (RF) and antinuclear antibodies (ANA)

JIA should be suspected in children with symptoms of arthritis, signs of iridocyclitis, generalized adenopathy, splenomegaly, or unexplained rash or fever lasting more than a few days. Diagnosis is primarily clinical. Patients suspected of having JIA should be tested for RF, ANA, and ESR because these tests may be helpful in diagnosing JIA and distinguishing its subtypes. In Still's disease, RF and ANA are absent. In pauciarticular-onset JIA, ANA are present in up to 75% and RF is absent. In polyarticular-onset JIA, RF usually is negative, but in some patients, mostly adolescent girls, it can be positive.

To diagnose iridocyclitis, slit-lamp examination should be done, even in the absence of ocular symptoms. A recently diagnosed patient with pauciarticular onset should have an eye examination every 3 to 4 mo, and a patient with polyarticular onset should have an eye examination about every 6 mo.

Prognosis

Complete remissions occur in 50 to 75% of treated patients. Patients with polyarticular onset and a positive RF have a less favorable prognosis.

Treatment

• Drugs that slow disease progression

• Usually NSAIDs

Similar to the therapy of patients with adult RA, disease-modifying antirheumatic drugs (DMARDs), particularly the biologic agents, have dramatically changed the therapeutic approach.

Symptoms may be reduced with NSAIDs. Naproxen 5 to 10 mg/kg po bid, ibuprofen 5 to 10 mg/kg po qid,

and indomethacin 0.5 to 1.0 mg/kg po tid are among the most useful. Salicylates are rarely used because of their possible role in causing Reye's syndrome (see p. 2937).

Except for severe systemic disease, systemic corticosteroids can usually be avoided. When necessary, the lowest possible dose is used (eg, oral prednisone, 0.0125 to 0.5 mg/kg qid, or the same daily dose given once or twice daily). Growth retardation, osteoporosis, and osteonecrosis are the major hazards of prolonged corticosteroid use in children. Intra-articular depot corticosteroids can be given. The dosage for children is adjusted based on weight. Children may need to be sedated for intra-articular injection.

Methotrexate is useful for pauciarticular and polyarticular disease. Adverse effects are monitored as in adults. Bone marrow depression and hepatic toxicity are monitored with CBC, AST, ALT, and albumin. Occasionally, sulfasalazine is used, especially in cases of suspected spondyloarthropathy. IM gold and penicillamine are rarely used.

Etanercept, used as in adults, blocks tumor necrosis factor-α (TNF-α) and is often effective; 0.4 mg/kg sc (up to a maximum of 25 mg) is given twice/wk. Anakinra is particularly effective in some patients with systemic-onset disease.

Physical therapy, exercises, splints, and other supportive measures help prevent flexion contractures. Adaptive devices can improve function and minimize unnecessary stresses on inflamed joints. Iridocyclitis is treated with ophthalmic corticosteroid drops and mydriatics (see p. 609).

Seronegative Spondyloarthropathies

(Seronegative Spondyloarthritides)

Seronegative spondyloarthropathies share certain clinical characteristics (eg, back pain, uveitis, GI symptoms, rashes). Some are strongly associated with the HLA-B27 allele. Clinical and genetic similarities suggest that they also share similar causes or pathophysiologies. Rheumatoid factor (RF) is negative in the spondyloarthropathies (hence, why they are called seronegative spondyloarthropathies). They include ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and other disorders.

Ankylosing Spondylitis

Ankylosing spondylitis (AS) is a systemic disorder characterized by inflammation of the axial skeleton, large peripheral joints, and digits; nocturnal back pain; back stiffness; accentuated kyphosis; constitutional symptoms; aortitis; cardiac conduction abnormalities; and anterior uveitis. Diagnosis requires showing sacroiliitis on x-ray. Treatment is with NSAIDs or tumor necrosis factor antagonists and physical measures that maintain joint flexibility.

AS is 3 times more frequent in men than in women and begins most often between ages 20 and 40. It is 10 to 20 times more common among 1st-degree relatives of AS patients than in the general population. The risk of AS in 1st-degree relatives with the HLA-B27 allele is about 20%. Increased prevalence of HLA-B27 in whites or HLA-B7 in blacks supports a genetic predisposition. However, the concordance rate in identical twins is only about 50%, suggesting that environmental factors contribute. The pathophysiology probably involves immune-mediated inflammation.

Symptoms and Signs

The most frequent manifestation is back pain, but disease can begin in peripheral joints, especially in children and women, and rarely with acute iridocyclitis (iritis or anterior uveitis). Other early symptoms and signs are diminished chest expansion from diffuse costovertebral involvement, low-grade fever, fatigue, anorexia, weight loss, and anemia.

Back pain—often nocturnal and of varying intensity—eventually becomes recurrent. Morning stiffness, typically relieved by activity, and paraspinal muscle spasm develop. A flexed or bent-over posture eases back pain and paraspinal muscle spasm; thus, kyphosis is common in untreated patients. Severe hip arthritis can eventually develop. In late stages, the patient has accentuated kyphosis, loss of lumbar

lordosis, and fixed bent-forward posturing, with compromised pulmonary function and inability to lie flat. There may be peripheral potentially deforming joint involvement, sometimes involving the digits (dactylitis). Achilles tendinitis can occur.

Systemic manifestations occur in one third of patients. Recurrent, acute anterior uveitis is common but usually self-limited; uncommonly it becomes protracted and severe enough to impair vision. Neurologic signs occasionally result from compression radiculitis or sciatica, vertebral fracture or subluxation, or cauda equina syndrome (see p. 1806). Cardiovascular manifestations can include aortic insufficiency, aortitis, angina, pericarditis, and cardiac conduction abnormalities (which may be asymptomatic). Dyspnea, cough, or hemoptysis can result from nontuberculous fibrosis or cavitation of an upper lobe of the lung; secondary infection with *Aspergillus* can develop. Rarely, AS results in secondary amyloidosis. Subcutaneous nodules do not develop.

Diagnosis

• Lumbosacral spine imaging

• Blood tests (ESR, C-reactive protein, and CBC) or explicit clinical criteria (modified New York criteria)

AS should be suspected in patients, particularly young men, with nocturnal back pain and kyphosis, diminished chest expansion, Achilles tendinitis, or unexplained anterior uveitis. A 1st-degree relative with AS should heighten suspicion. Patients should generally be tested with ESR, C-reactive protein, and CBC. IgM, RF, and antinuclear antibodies are needed only if peripheral arthritis suggests other diagnoses. No laboratory test is diagnostic, but results can increase suspicion for the disorder or rule out other disorders than can simulate AS. If, after these tests, AS is still suspected, patients should undergo imaging of the lumbosacral spine; demonstration of sacroiliitis on x-ray strongly supports the diagnosis.

Alternatively, AS can be diagnosed by the modified New York criteria. Using these criteria, the patient must have imaging study evidence of sacroiliitis and one of the following:

• Restriction of lumbar spinal motion in both the sagittal (looking from the side) and frontal (looking from the back) planes

• Restriction of chest expansion, adjusted for age

• A history of inflammatory back pain

Historical features that distinguish inflammatory back pain from noninflammatory back pain include onset at ≤ 40 yr, gradual onset, morning stiffness, improvement with activity, and duration ≥ 3 mo before seeking medical attention.

ESR and other acute-phase reactants (eg, C-reactive protein) are inconsistently elevated in patients with active AS. Tests for RF and antinuclear antibodies are negative. The HLA-B27 genetic marker is not of diagnostic value.

The earliest x-ray abnormalities are pseudowidening from subchondral erosions, followed by sclerosis or later narrowing and eventually fusion in the sacroiliac joints. Changes are symmetric. Early changes in the spine are upper lumbar vertebral squaring with sclerosis at the corners; spotty ligamentous calcification; and one or two evolving syndesmophytes. Late changes result in a "bamboo spine" appearance, resulting from prominent syndesmophytes, diffuse paraspinal ligamentous calcification, and osteoporosis; these changes develop in some patients on average over 10 yr.

Changes typical of AS may not become visible on plain x-rays for years. CT and MRI show changes earlier, but there is no consensus regarding their role in routine diagnosis.

A herniated intervertebral disk can cause back pain and radiculopathy similar to AS, but the pain is limited to the spine, usually causes more sudden symptoms, and causes no systemic manifestations or

laboratory test abnormalities. If necessary, CT or MRI can differentiate it from AS. Involvement of a single sacroiliac joint suggests a different spondyloarthropathy, possibly infection. Tuberculous spondylitis can simulate AS (see p. 1313).

Diffuse idiopathic skeletal hyperostosis (DISH) occurs primarily in men > 50 yr and may resemble AS clinically and on x-ray. Patients uncommonly have spinal pain, stiffness, and insidious loss of motion. X-ray findings in DISH include large ossifications anterior to spinal ligaments (the calcification appears as if someone poured candle wax in front and on the sides of the vertebrae), bridging several vertebrae and usually starting at the lower thoracic spine, eventually affecting the cervical and lumbar spine. There is often subperiosteal bone growth along the pelvic brim and at insertion of tendons (such as the Achilles tendon insertion). However, the anterior spinal ligament is intact and frequently bulging, and sacroiliac and spinal apophyseal joints are not eroded. Additional differentiating features are stiffness that is not accentuated in the morning and a normal ESR.

Prognosis

AS is characterized by mild or moderate flares of active inflammation alternating with periods of little or no inflammation. Proper treatment in most patients results in minimal or no disability and in a full, productive life despite back stiffness. Occasionally, the course is severe and progressive, resulting in pronounced incapacitating deformities.

Treatment

• NSAIDs

• Sulfasalazine, methotrexate, or tumor necrosis factor (TNF) antagonists

• Exercises and supportive measures

The goals of treatment are relieving pain, maintaining joint range of motion, and preventing end-organ damage. Because the condition may cause lung fibrosis, cigarette smoking is discouraged.

NSAIDs reduce pain and suppress joint inflammation and muscle spasm, thereby increasing range of motion, which facilitates exercise and prevents contractures. Most NSAIDs work in AS, and tolerance and toxicity dictate drug choice. The daily dose of NSAIDs should be as low as possible, but maximum doses may be needed with active disease. Drug withdrawal should be attempted only slowly, after systemic and joint signs of active disease have been suppressed for several months.

Sulfasalazine may help reduce peripheral joint symptoms and laboratory markers of inflammation. Dosage should be started at 500 mg/day and increased by 500 mg/day at 1-wk intervals to 1 to 1.5 g bid maintenance. Peripheral joint symptoms may also abate with methotrexate (see p. 337). Systemic corticosteroids, immunosuppressants, and most disease-modifying antirheumatic drugs have no proven benefit and should generally not be used. TNF-α antagonists (eg, etanercept, infliximab, adalimumab) are effective treatments for inflammatory back pain.

For proper posture and joint motion, daily exercise and other supportive measures (eg, postural training, therapeutic exercise) are vital to strengthen muscle groups that oppose the direction of potential deformities (ie, the extensor rather than flexor muscles). Reading while lying prone and pushing up on the elbows or pillows and thus extending the back may help keep the back flexible. Because chest wall motion can be restricted, which impairs lung function, cigarette smoking, which also impairs lung function, is strongly discouraged.

Intra-articular depot corticosteroids may be beneficial, particularly when one or two peripheral joints are more severely inflamed than others, thereby compromising exercise and rehabilitation. They may also help if systemic drugs are ineffective. Corticosteroids injected into the sacroiliac joints may occasionally help severe sacroiliitis.

For acute uveitis, topical corticosteroids and mydriatics are usually adequate. If severe hip arthritis

develops, total hip arthroplasty may lessen pain and improve flexibility dramatically.

Reactive Arthritis

Reactive arthritis is an acute spondyloarthropathy that often seems precipitated by an infection, usually GU or GI. Common manifestations include asymmetric arthritis of variable severity that tends to affect the lower extremities, sausage-shaped deformities of fingers or toes or both, constitutional symptoms, enthesitis, tendinitis, and mucocutaneous ulcers, including hyperkeratotic or crusted vesicular lesions (keratoderma blennorrhagicum). Diagnosis is clinical. Treatment involves NSAIDs and sometimes sulfasalazine or immunosuppressants.

Spondyloarthropathy associated with urethritis or cervicitis, conjunctivitis, and mucocutaneous lesions (previously called Reiter's syndrome) is one type of reactive arthritis.

Etiology

Two forms of reactive arthritis are common: sexually transmitted and dysenteric. The sexually transmitted form occurs primarily in men aged 20 to 40. Genital infections with *Chlamydia trachomatis* are most often implicated. Men or women can acquire the dysenteric form after enteric infections, primarily *Shigella*, *Salmonella*, *Yersinia*, or *Campylobacter*. Reactive arthritis probably results from joint infection or postinfectious inflammation. Although there is evidence of microbial antigens in the synovium, organisms cannot be cultured from joint fluid.

Epidemiology: The prevalence of the HLA-B27 allele in patients is 63 to 96% vs 6 to 15% in healthy white controls, thus supporting a genetic predisposition.

Symptoms and Signs

Reactive arthritis can range from transient monarticular arthritis to a severe, multisystem disorder. Constitutional symptoms may include fever, fatigue, and weight loss. Arthritis may be mild or severe. Joint involvement is generally asymmetric and oligoarticular or polyarticular, occurring predominantly in the large joints of the lower extremities and in the toes. Back pain may occur, usually with severe disease. Enthesopathy (inflammation at tendinous insertion into bone—eg, plantar fasciitis, digital periostitis, Achilles tendinitis) is common and characteristic. Mucocutaneous lesions—small, transient, relatively painless, superficial ulcers—commonly occur on the oral mucosa, tongue, and glans penis (balanitis circinata). Particularly characteristic are vesicles (sometimes identical to pustular psoriasis) of the palms and soles and around the nails that become hyperkeratotic and form crusts (keratoderma blennorrhagicum). Rarely, cardiovascular complications (eg, aortitis, aortic insufficiency, cardiac conduction defects), pleuritis, and CNS or peripheral nervous system symptoms develop.

Urethritis may develop 7 to 14 days after sexual contact (or occasionally after dysentery); low-grade fever, conjunctivitis, and arthritis develop over the next few weeks. Not all features may occur, so incomplete forms need to be considered. In men, the urethritis is less painful and productive of purulent discharge than acute gonococcal urethritis and may be associated with hemorrhagic cystitis or prostatitis. In women, urethritis and cervicitis may be mild (with dysuria or slight vaginal discharge) or asymptomatic. Conjunctivitis is the most common eye lesion. It usually causes eye redness and grittiness, but keratitis and anterior uveitis can develop also, causing eye pain, photophobia, and tearing.

Diagnosis

• Typical arthritis

• Symptoms of GI or GU infection

• One other extra-articular feature

Reactive arthritis should be suspected in patients with acute, asymmetric arthritis affecting the large joints of the lower extremities or toes, particularly if there is tendinitis or a history of an antecedent diarrhea or

dysuria. Diagnosis is ultimately clinical and requires the typical peripheral arthritis with symptoms of GU or GI infection or one of the other extra-articular features. Because these features may manifest at different times, definitive diagnosis may require several months. Serum and synovial fluid complement levels are high, but these findings are not usually diagnostic and need not be measured.

Disseminated gonococcal infection can closely simulate reactive arthritis (see p. 1472). Arthrocentesis may fail to differentiate them, owing to inflammatory characteristics of synovial fluid in both disorders and the difficulty of culturing gonococci from this fluid. Clinical characteristics may help; disseminated gonococcal infection tends to involve upper and lower extremities equally, be more migratory, and not produce back pain, and vesicles tend not to be hyperkeratotic. A positive gonococcal culture from blood or skin lesions helps differentiate the two disorders, but a positive culture from the urethra or cervix does not. If differentiation is still difficult, ceftriaxone may be required for simultaneous diagnosis and treatment.

Psoriatic arthritis can simulate reactive arthritis, causing similar skin lesions, uveitis, and asymmetric arthritis. However, psoriatic arthritis often affects mostly the upper extremities and especially the distal interphalangeal joints, may be abrupt in onset but may also develop gradually, causes less enthesopathy, and tends not to cause mouth ulcers or symptoms of GU or GI infection.

Prognosis

Reactive arthritis often resolves in 3 to 4 mo, but up to 50% of patients experience recurrent or prolonged symptoms over several years. Joint, spinal, or sacroiliac inflammation or deformity may occur with chronic or recurrent disease. Some patients are disabled.

Treatment

• NSAIDs

• Sometimes sulfasalazine, doxycycline, azathioprine or methotrexate, or a combination

• Supportive measures

NSAIDs (eg, indomethacin 25 to 50 mg po tid) usually help relieve symptoms. If induced by infection with *C. trachomatis*, doxycycline 100 mg po bid for up to 3 mo may accelerate recovery, but this is controversial. Sulfasalazine as used to treat RA may also be helpful (see p. 337). If symptoms are severe despite NSAIDs and sulfasalazine, azathioprine or methotrexate may be considered. Systemic corticosteroids have no proven value.

Local injection of depot corticosteroids for enthesopathy or resistant oligoarthritis may relieve symptoms. Physical therapy aimed at maintaining joint mobility is helpful during the recovery phase. Anterior uveitis is treated as usual, with corticosteroid and mydriatic eye drops to prevent scarring. Conjunctivitis and mucocutaneous lesions require only symptomatic treatment.

Psoriatic Arthritis

Psoriatic arthritis is a chronic inflammatory arthritis that occurs in people with psoriasis of the skin or nails. The arthritis is often asymmetric, and some forms involve the distal interphalangeal joints. Diagnosis is clinical. Treatment is usually similar to that of RA but can also involve phototherapy.

Psoriatic arthritis develops in 5 to 40% of patients with psoriasis. Prevalence is increased in patients with AIDS. Risk of some involvement is increased in patients with HLA-B27 or some other specific alleles and in family members. Etiology and pathophysiology are unknown.

Symptoms and Signs

Psoriasis of the skin or nails may precede or follow joint involvement. Skin lesions may be hidden in the scalp, gluteal folds, or umbilicus and go unrecognized by the patient.

The distal interphalangeal (DIP) joints of fingers and toes are especially affected. Asymmetric involvement of large and small joints, including the sacroiliacs and spine, is common. Joint and skin symptoms may lessen or worsen simultaneously. Inflammation of the fingers, toes, or both may lead to sausage-shaped deformities. Rheumatoid nodules are absent. Arthritic remissions tend to be more frequent, rapid, and complete than in RA, but progression to chronic arthritis and crippling may occur. There may be arthritis mutilans (destruction of multiple hand joints with telescoping of the digits).

Back pain may be present. It is often accompanied by asymmetric syndesmophytes of the spine.

Diagnosis

• Clinical evaluation

• RF

Psoriatic arthritis should be suspected in patients with both psoriasis and arthritis. Because psoriasis may be overlooked or hidden or develop only after arthritis occurs, psoriatic arthritis should be considered in any patient with seronegative inflammatory arthritis; these patients should be examined for psoriasis and nail pitting and should be questioned about a family history of psoriasis. Patients suspected of having psoriatic arthritis should be tested for rheumatoid factor, which can coexist. Psoriatic arthritis is diagnosed clinically and by excluding other disorders that can cause such similar manifestations. X-ray findings common in psoriatic arthritis include DIP involvement; resorption of terminal phalanges; arthritis mutilans; and extensive destruction, proliferative bone reaction, and dislocation of large and small joints.

Treatment

• Arthritis treated generally similarly to RA

• Phototherapy

Treatment is directed at control of skin lesions (see p. 677) and at joint inflammation. Drug therapy is similar to that for RA, particularly methotrexate. Hydroxychloroquine is inconsistently of benefit and may cause exfoliative dermatitis or aggravate underlying psoriasis. Benefit may be gained from NSAIDs, cyclosporine, and TNF antagonists (see p. 335 under Drugs for RA); TNF antagonists have been particularly effective.

Phototherapy using long-wave psoralen plus ultraviolet A (PUVA) combined with oral methoxsalen 600 µg/kg po 2 h before PUVA twice/wk seems to be highly effective for psoriatic lesions and somewhat effective for peripheral arthritis, but not for spine involvement.

Other Spondyloarthropathies

Spondyloarthropathy can develop in association with GI conditions (sometimes called enteropathic arthritis) such as inflammatory bowel disease, intestinal bypass surgery, or Whipple's disease.

Juvenile-onset spondyloarthropathy is an asymmetric, mostly lower extremity spondyloarthropathy that begins most commonly in boys aged 7 to 16.

Spondyloarthropathy can also develop in people without characteristics of other specific spondyloarthropathy (undifferentiated spondyloarthropathy). Treatment of the arthritis of these other spondyloarthropathies is similar to that of treatment of reactive arthritis (see p. 344).

Osteoarthritis

(Degenerative Joint Disease; Osteoarthrosis; Hypertrophic Osteoarthritis)

Osteoarthritis (OA) is a chronic arthropathy characterized by disruption and potential loss of

joint cartilage along with other joint changes, including bone hypertrophy (osteophyte formation). Symptoms include gradually developing pain aggravated or triggered by activity, stiffness lasting < 30 min on awakening and after inactivity, and occasional joint swelling. Diagnosis is confirmed by x-rays. Treatment includes physical measures (including rehabilitation), patient education, and drugs.

OA, the most common joint disorder, often becomes symptomatic in the 40s and 50s and is nearly universal (although not always symptomatic) by age 80. Only half of patients with pathologic changes of OA have symptoms. Below age 40, most OA is in men and results from trauma. Women predominate from age 40 to 70, after which men and women are equally affected.

Classification

OA is classified as primary (idiopathic) or secondary to some known cause.

Primary OA may be localized to certain joints (eg, chondromalacia patellae is a mild OA that occurs in young people). Primary OA is usually subdivided by the site of involvement (eg, hands and feet, knee, hip). If primary OA involves multiple joints, it is classified as primary generalized OA.

Secondary OA results from conditions that change the microenvironment of the cartilage. These conditions include significant trauma, congenital joint abnormalities, metabolic defects (eg, hemochromatosis, Wilson's disease), infections (causing postinfectious arthritis), endocrine and neuropathic diseases, and disorders that alter the normal structure and function of hyaline cartilage (eg, RA, gout, chondrocalcinosis).

Pathophysiology

Normal joints have little friction with movement and do not wear out with typical use, overuse, or trauma. Hyaline cartilage is avascular, aneural, and alymphatic. It is 95% water and extracellular cartilage matrix and only 5% chondrocytes. Chondrocytes have the longest cell cycle in the body (similar to CNS and muscle cells). Cartilage health and function depend on compression and release of weight bearing and use (ie, compression pumps fluid from the cartilage into the joint space and into capillaries and venules, whereas release allows the cartilage to reexpand, hyperhydrate, and absorb necessary electrolytes and nutrients).

OA begins with tissue damage from mechanical injury (eg, torn meniscus), transmission of inflammatory mediators from the synovium into cartilage, or defects in cartilage metabolism. The tissue damage stimulates chondrocytes to attempt repair, which increases production of proteoglycans and collagen. However, efforts at repair also stimulate the enzymes that degrade cartilage, as well as inflammatory cytokines, which are normally present in small amounts. Inflammatory mediators trigger an inflammatory cycle that further stimulates the chondrocytes and synovial lining cells, eventually breaking down the cartilage. Chondrocytes undergo programmed cell death (apoptosis). Once cartilage is destroyed, exposed bone becomes eburnated and sclerotic.

All articular and some periarticular tissues become involved in OA. Subchondral bone stiffens, then undergoes infarction, and develops subchondral cysts. Attempts at bony repair cause subchondral sclerosis and osteophytes at the joint margins. The osteophytes seem to develop in an attempt to stabilize the joint. The synovium becomes inflamed and thickened and produces synovial fluid with less viscosity and greater volume. Periarticular tendons and ligaments become stressed, resulting in tendinitis and contractures. As the joint becomes less mobile, surrounding muscles thin and become less supportive. Menisci fissure and may fragment.

OA of the spine can, at the disk level, cause marked thickening and proliferation of the posterior longitudinal ligaments, which are posterior to the vertebral body but anterior to the spinal cord. The result can be transverse bars that encroach on the anterior spinal cord. Hypertrophy and hyperplasia of the ligamenta flava, which are posterior to the spinal cord, often compress the posterior canal, causing lumbar spinal stenosis. In contrast, the anterior and posterior nerve roots, ganglia, and common spinal nerve are relatively well protected in the intervertebral foramina, where they occupy only 25% of the

available and well-cushioned space.

Symptoms and Signs

Onset is most often gradual, usually beginning with one or a few joints. Pain is the earliest symptom, sometimes described as a deep ache. Pain is usually worsened by weight bearing and relieved by rest but can eventually become constant. Stiffness follows awakening or inactivity but lasts < 30 min and lessens with movement. As OA progresses, joint motion becomes restricted, and tenderness and crepitus or grating sensations develop. Proliferation of cartilage, bone, ligament, tendon, capsules, and synovium, along with varying amounts of joint effusion, ultimately cause the joint enlargement characteristic of OA. Flexion contractures may eventually develop. Acute and severe synovitis is uncommon.

Tenderness on palpation and pain on passive motion are relatively late signs. Muscle spasm and contracture add to the pain. Mechanical block by intra-articular loose bodies or abnormally placed menisci can occur and cause locking or catching. Deformity and subluxations can also develop.

The joints most often affected in generalized OA include the following:

- Distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints (causing Heberden's and Bouchard's nodes)
- Thumb carpometacarpal joint
- Intervertebral disks and zygapophyseal joints in the cervical and lumbar vertebrae
- First metatarsophalangeal joint
- Hip
- Knee

Cervical and lumbar spinal OA may lead to myelopathy or radiculopathy. However, the clinical signs of myelopathy are usually mild. Lumbar spinal stenosis may cause lower back or leg pain that is worsened by walking or back extension. Radiculopathy can be prominent but is less common because the nerve roots and ganglia are well protected. Insufficiency of the vertebral arteries, infarction of the spinal cord, and dysphagia due to esophageal impingement by osteophytes occasionally occur. Symptoms and signs from OA in general may also derive from subchondral bone, ligamentous structures, synovium, periarticular bursae, capsules, muscles, tendons, disks, and periosteum, all of which are pain sensitive. Venous pressure may increase within the subchondral bone marrow and cause pain (sometimes called bone angina).

Hip OA causes gradual loss of range of motion. Pain may be felt in the inguinal area or greater trochanter or referred to the knee.

Knee OA causes cartilage to be lost (medial loss occurs in 70% of cases). The ligaments become lax and the joint becomes less stable, with local pain arising from the ligaments and tendons.

Erosive OA causes synovitis and cysts in the hand. It primarily affects the DIP or PIP joints. The thumb carpometacarpal joints are involved in 20% of hand OA, but the metacarpophalangeal joints and wrists are usually spared. At this time, it is uncertain whether erosive interphalangeal OA is a variant of hand OA or whether it represents a separate entity.

OA is usually sporadically progressive but occasionally, with no predictability, stops or reverses.

Diagnosis

- X-rays

OA should be suspected in patients with gradual onset of symptoms and signs, particularly in older adults. If OA is suspected, plain x-rays should be taken of the most symptomatic joints. X-rays generally reveal marginal osteophytes, narrowing of the joint space, increased density of the subchondral bone, subchondral cyst formation, bony remodeling, and joint effusions. Standing x-rays of knees are more sensitive in detecting joint space narrowing.

Laboratory studies are normal in OA but may be required to rule out other disorders (eg, RA) or to diagnose an underlying disorder causing secondary OA. If OA causes joint effusions, synovial fluid analysis can help differentiate it from inflammatory arthritides; in OA, synovial fluid is usually clear, viscous, and has ≤ 2000 WBC/μL.

OA involvement outside the usual joints suggests secondary OA; further evaluation may be required to determine the underlying primary disorder (eg, endocrine, metabolic, neoplastic, biomechanical disorders).

Treatment

• Rehabilitative and supportive measures

• Adjunctive drug therapy

Treatment goals are relieving pain, maintaining joint flexibility, and optimizing joint and overall function. Primary treatments include physical measures that involve rehabilitation; support devices; exercise for strength, flexibility, and endurance; patient education; and modifications in activities of daily living. Adjunctive therapies include drug treatment and surgery.

Physical measures: Rehabilitation techniques are best begun before disability develops. Exercises (range of motion, isometric, isotonic, isokinetic, postural, strengthening—see p. 3453) maintain range of motion and increase the capacity for tendons and muscles to absorb stress during joint motion. Exercise can sometimes arrest or even reverse hip and knee OA. Stretching exercises should be done daily. Immobilization for any prolonged period of time can promote contractures and worsen the clinical course. However, a few minutes of rest (every 4 to 6 h in the daytime) can help if balanced with exercise and use.

Modifying activities of daily living can help. For example, a patient with lumbar spine, hip, or knee OA should avoid soft deep chairs and recliners in which posture is poor and from which rising is difficult. The regular use of pillows under the knees while reclining encourages contractures and should also be avoided. Patients should sit in straight-back chairs without slumping, sleep on a firm bed, perhaps with a bed board, use a car seat shifted forward and designed for comfort, do postural exercises, wear well-supported shoes or athletic shoes, and continue employment and physical activity.

In OA of the spine, knee, or thumb carpometacarpal joint, various supports can relieve pain and increase function, but to preserve flexibility, they should be accompanied by specific exercise programs. In erosive OA, range-of-motion exercises done in warm water can help prevent contractures.

Drugs: Drug therapy is an adjunct to the physical program. Acetaminophen in doses of up to 1 g po qid may relieve pain and is safe. More potent analgesia may be required.

NSAIDs, including cyclooxygenase-2 (COX-2) inhibitors or coxibs, may be considered if patients have refractory pain or signs of inflammation (eg, redness, warmth). NSAIDs may be used simultaneously with other analgesics (eg, tramadol, opioids) to provide better relief of symptoms.

Muscle relaxants (usually in low doses) occasionally relieve pain that arises from muscles strained by attempting to support OA joints. In the elderly, however, they may cause more adverse effects than relief.

Oral corticosteroids have no role. However, intra-articular depot corticosteroids help relieve pain and increase joint flexibility.

Synthetic hyaluronans (similar to hyaluronic acid, a normal component of the joint) can be injected into

the knee, with pain relief for prolonged periods of time (up to a year). However, the effect seems to be small. The treatment is a series of 3 to 5 weekly injections.

Glucosamine sulfate 1500 mg po once/day has been suggested to relieve pain and slow joint deterioration; chondroitin sulfate 1200 mg once/day has also been suggested for pain relief. Studies to date have shown mixed results in terms of pain relief.

Other adjunctive and experimental therapies: Other adjunctive measures can relieve pain, including massage, heating pads, weight loss, acupuncture, transcutaneous electrical nerve stimulation, and local rubs (eg, with capsaicin). Laminectomy, osteotomy, and total joint replacement should be considered if all nonsurgical approaches fail. (See also the Agency for Healthcare Research and Quality's Evidence-Based Practice Program's evidence report.)

Experimental therapies that may preserve cartilage or allow chondrocyte grafting are being studied. It is not clear whether using a lidocaine 5% patch relieves pain. Flavocoxid, a new drug, can be tried.

Neurogenic Arthropathy

(Neuropathic Arthropathy; Charcot's Joints)

Neurogenic arthropathy is a rapidly destructive arthropathy due to impaired pain perception and position sense, which can result from various underlying disorders, most commonly diabetes and stroke. Common manifestations include joint swelling, effusion, deformity, and instability. Pain may be disproportionately mild due to the underlying neuropathy. Diagnosis requires x-ray confirmation. Treatment consists of joint immobilization, which slows disease progression, and sometimes surgery if the disease is advanced.

Pathophysiology

Many conditions predispose to neurogenic arthropathy (see Table 35-4). Impaired deep pain sensation or proprioception affects the joint's normal protective reflexes, often allowing trauma (especially repeated minor episodes) and small periarticular fractures to go unrecognized. Increased blood flow to bone from reflex vasodilation, resulting in active bone resorption, contributes to bone and joint damage. Each new injury sustained by the joint causes more distortion as it heals. Hemorrhagic joint effusions and multiple small fractures can occur, accelerating disease progression. Ligamentous laxity, muscular hypotonia, and rapid destruction of joint cartilage are common, predisposing to joint dislocations, which also accelerate disease progression. Advanced neurogenic arthropathy can cause hypertrophic changes, destructive changes, or both.

[**Table 35-4.** Conditions Underlying Neurogenic Arthropathy]

Symptoms and Signs

Arthropathy does not usually develop until years after onset of the neurologic condition but can then progress rapidly and lead to complete joint disorganization in a few months. Pain is a common early symptom. However, because the ability to sense pain is commonly impaired, the degree of pain is often unexpectedly mild for the degree of joint damage. A prominent, often hemorrhagic, effusion and subluxation and instability of the joint are usually present during early stages. Acute joint dislocation sometimes occurs also.

During later stages, pain may be more severe if the disease has caused rapid joint destruction (eg, periarticular fractures or tense hematomas). During advanced stages, the joint is swollen from bony overgrowth and massive synovial effusion. Deformity results from dislocations and displaced fractures. Fractures and bony healing may produce many loose pieces of cartilage or bone that can slough into the joint, causing a coarse, grating, often audible crepitus usually more unpleasant for the observer than for the patient. The joint may feel like a "bag of bones."

Although many joints can be involved, the knee and the ankle are most often affected. Distribution

depends largely on the underlying disease. Thus, tabes dorsalis affects the knee and hip, and diabetes mellitus affects the foot and ankle. Syringomyelia commonly affects the spine and upper limb joints, especially the elbow and shoulder. Frequently, only one joint is affected and usually no more than two or three (except for the small joints of the feet), in an asymmetric distribution.

Infectious arthritis may develop with or without systemic symptoms (eg, fever, malaise), particularly with diabetes. Structures such as blood vessels, nerves, and the spinal cord can become compressed due to the tissue overgrowth.

Diagnosis

• X-rays

The diagnosis should be considered in a patient with a predisposing neurologic disorder who develops a destructive but unexpectedly painless arthropathy, usually several years after the onset of the underlying neurologic condition. If neurogenic arthropathy is suspected, x-rays should be taken. Diagnosis is established by characteristic x-ray abnormalities in a patient with a predisposing condition and typical symptoms and signs.

X-ray abnormalities in early neurogenic arthropathy are often similar to those in osteoarthritis (OA). The cardinal signs are bone fragmentation, bone destruction, new bone growth, and loss of joint space. There may also be synovial effusion and joint subluxation. Later, the bones are deformed, and new bone forms adjacent to the cortex, starting within the joint capsule and often extending up the shaft, particularly in long bones. Rarely, calcification and ossification occur in the soft tissues. Large, bizarrely shaped osteophytes may be present at the joint margins or within joints. Large curved (parrot's beak) osteophytes frequently develop in the spine in the absence of clinical spinal disease.

In its early stages, neurogenic arthropathy can simulate OA. However, neurogenic arthropathy progresses more rapidly than OA and frequently causes proportionately less pain.

Treatment

• Treatment of cause

• Sometimes surgery

Early diagnosis of asymptomatic or minimally symptomatic fractures facilitates early treatment; immobilization (with splints, special boots, or calipers) protects the joint from further injury, possibly stopping disease evolution. Prevention of neurogenic arthropathy may even be possible in a patient at risk.

Treatment of the underlying neurologic condition may slow progression of the arthropathy and, if joint destruction is still in the early stages, partially reverse the process. For a grossly disorganized joint, arthrodesis using internal fixation, compression, and an adequate bone graft may be successful. For grossly disorganized hip and knee joints, if neurogenic arthropathy is not expected to be progressive, good results can be obtained with total hip and knee replacements. However, loosening and dislocation of the prosthesis are major hazards.

Chapter 36. Crystal-Induced Arthritides

Introduction

Arthritis can result from intra-articular deposition of crystals: monosodium urate, Ca pyrophosphate dihydrate, basic Ca phosphate (apatite), and, rarely, others such as Ca oxalate crystals. Diagnosis requires synovial fluid analysis (see p. 287). Polarized light microscopy is used to specifically identify most crystals; basic Ca phosphate crystals are of ultramicroscopic size and require other methods. Crystals may be engulfed in WBCs or may be extracellular. The presence of crystals does not exclude the possibility of simultaneous infectious or other inflammatory forms of arthritis.

Gout

Gout is precipitation of monosodium urate crystals into tissue, usually in and around joints, most often causing recurrent acute or chronic arthritis. Acute arthritis is initially monarticular and often involves the 1st metatarsophalangeal joint. Symptoms include acute pain, tenderness, warmth, redness, and swelling. Diagnosis requires identification of crystals in synovial fluid. Treatment of acute attacks is with anti-inflammatory drugs. The frequency of attacks can be reduced by regular use of NSAIDs, colchicine, or both and by treating hyperuricemia with allopurinol or uricosuric drugs.

Gout is more common among men than women. Usually, gout develops during middle age in men and after menopause in women. Gout is rare in younger people but is often more severe in people who develop the disorder before age 30. Gout often runs in families.

Pathophysiology

The greater the degree and duration of hyperuricemia, the greater is the likelihood of gout and the more severe are the symptoms. Urate levels can be elevated because of

• Decreased excretion

• Increased production

• Increased purine intake

Why only some people with elevated serum uric acid (urate) levels develop gout is not known.

Decreased renal excretion is by far the most common cause of hyperuricemia. It may be hereditary and also occurs in patients receiving diuretics and in those with diseases that decrease GFR. Ethanol increases purine catabolism in the liver and increases the formation of lactic acid, which blocks urate secretion by the renal tubules. Lead poisoning and cyclosporine, usually given to transplant patients, irreversibly damage renal tubules, leading to urate retention.

Increased production of urate may be caused by increased nucleoprotein turnover in hematologic conditions (eg, lymphoma, leukemia, hemolytic anemia) and in conditions with increased rates of cellular proliferation and cell death (eg, psoriasis, cytotoxic cancer therapy, radiation therapy). Increased urate production may also occur as a primary hereditary abnormality and in obesity, because urate production correlates with body surface area. In most cases, the cause is unknown, but a few cases are attributable to enzyme abnormalities; deficiency of hypoxanthine-guanine phosphoribosyltransferase (complete deficiency is Lesch-Nyhan syndrome) is a possible cause, as is overactivity of phosphoribosylpyrophosphate synthetase.

Increased intake of purine-rich foods (eg, liver, kidney, anchovies, asparagus, consomme, herring, meat gravies and broths, mushrooms, mussels, sardines, sweetbreads) can contribute to hyperuricemia. However, a strict low-purine diet lowers serum urate by only about 1 mg/dL.

Urate precipitates as needle-shaped monosodium urate (MSU) crystals, which are deposited

extracellularly in avascular tissues (eg, cartilage) or in relatively avascular tissues (eg, tendons, tendon sheaths, ligaments, walls of bursae) and skin around cooler distal joints and tissues (eg, ears). In severe, longstanding hyperuricemia, MSU crystals may be deposited in larger central joints and in the parenchyma of organs such as the kidney. At the acid pH of urine, urate precipitates readily as small platelike or irregular crystals that may aggregate to form gravel or stones, which may cause obstruction. Tophi are MSU crystal aggregates that most often develop in joint and cutaneous tissue.

Acute gouty arthritis may be triggered by trauma, medical stress (eg, pneumonia or other infection), and especially vascular occlusions (eg, stroke or MI), or by surgery, use of thiazide diuretics or drugs with uricosuric activity (eg, allopurinol), or indulgence in purine-rich food or alcohol. Attacks are often precipitated by a sudden increase or, more commonly, a sudden decrease in serum urate levels. Why acute attacks follow some of these precipitating conditions is unknown. Tophi in and around joints can limit motion and cause deformities, called chronic tophaceous gouty arthritis.

Symptoms and Signs

Acute gouty arthritis usually begins with sudden onset of pain (often nocturnal). The metatarsophalangeal joint of a great toe is most often involved (podagra), but the instep, ankle, knee, wrist, and elbow are also common sites. Rarely, the hip, shoulder, sacroiliac, sternoclavicular, or cervical spine joints are involved. The pain becomes progressively more severe, usually over a few hours, and is often excruciating. Swelling, warmth, redness, and exquisite tenderness may suggest infection. The overlying skin may become tense, warm, shiny, and red or purplish. Fever, tachycardia, chills, and malaise sometimes occur. Coexisting hypertension, hyperlipidemia, and obesity are common.

Course: The first few attacks usually affect only a single joint and last only a few days. Later attacks may affect several joints simultaneously or sequentially and persist up to 3 wk if untreated. Subsequent attacks develop after progressively shorter symptom-free intervals. Eventually, several attacks may occur each year.

Tophi: Tophi develop most often in patients with chronic gout, but they can occur in patients who have never had acute gouty arthritis. They are usually firm yellow or white papules or nodules, single or multiple. They can develop in various locations, commonly the fingers, hands, feet, and around the olecranon or Achilles tendon. Tophi can also develop in the kidneys and other organs and under the skin on the ears. Patients with osteoarthritic Heberden's nodes may develop tophi in the nodes. This development occurs most often in elderly women taking diuretics. Normally painless, tophi, especially in the olecranon bursae, can become acutely inflamed and painful. Tophi may even erupt through the skin, discharging chalky masses of urate crystals. Tophi may eventually cause deformities.

Chronic gout: Chronic gouty arthritis can cause pain, deformity, and limited joint motion. Inflammation can be flaring in some joints while subsiding in others. About 20% of patients with gout develop urolithiasis with uric acid stones or Ca oxalate stones. Complications include obstruction and infection, with secondary tubulointerstitial disease. Untreated progressive renal dysfunction, most often related to coexisting hypertension or, less often, some other cause of nephropathy, further impairs excretion of urate, accelerating crystal deposition in tissues.

Cardiovascular disease and the metabolic syndrome are common among patients with gout.

Diagnosis

• Clinical criteria

• Synovial fluid analysis

Gout should be suspected in patients with acute monarticular or oligoarthritis, particularly older adults or those with other risk factors. Podagra and recurrent instep inflammation are particularly suggestive. Similar symptoms can result from

• Ca pyrophosphate dihydrate (CPPD) crystal deposition disease (see p. 354) (however, CPPD generally

attacks larger joints and its clinical course is usually milder)

- Acute rheumatic fever with joint involvement and juvenile RA (however, these disorders occur mostly in young people, who rarely get gout)

- RA (however, in RA, all affected joints flare and subside together, whereas in gout, inflammation is usually flaring in some joints while subsiding in others)

- Acute fracture in patients unable to provide a history of injury

- Infectious arthritis (see pp. 365 and 369; differentiation may require synovial fluid analysis)

- Palindromic rheumatism

Palindromic rheumatism is characterized by acute, recurrent attacks of inflammation in or near one or occasionally several joints with spontaneous resolution; pain and erythema can be as severe as in gout. Attacks subside spontaneously and completely in 1 to 3 days. Such attacks may herald the onset of RA, and rheumatoid factor tests can help in differentiation; they are positive in about 50% of patients (these tests are positive in 10% of gouty patients also).

Synovial fluid analysis: If acute gouty arthritis is suspected, arthrocentesis and synovial fluid analysis should be done at the initial presentation. A typical recurrence in a patient with known gout does not mandate arthrocentesis, but it should be done if there is any question of the diagnosis or if the patient's risk factors or any clinical characteristics suggest infectious arthritis. Synovial fluid analysis can confirm the diagnosis by identifying needle-shaped, strongly negatively birefringent urate crystals that are free in the fluid or engulfed by phagocytes. Synovial fluid during attacks has inflammatory characteristics (see Table 36-1), usually 2,000 to 100,000 WBCs/μL, with > 80% polymorphonuclear WBCs. These findings overlap considerably with infectious arthritis, which must be excluded by Gram stain and culture.

Serum urate level: An elevated serum urate level supports the diagnosis of gout but is neither specific nor sensitive; at least 30% of patients have a normal serum urate level during an acute attack. However, the serum urate level reflects the size of the extracellular miscible urate pool. The level should be measured on 2 or 3 occasions in patients with newly proven gout to establish a baseline; if elevated (> 7 mg/dL [> 0.41 mmol/L]), 24-h urinary urate excretion can also be measured. Normal 24-h excretion in people eating a regular diet is about 600 to 900 mg. Quantification of urinary uric acid can indicate whether hyperuricemia results from impaired excretion or increased production and help guide any serum urate-lowering therapy. Patients with elevated urine excretion of urate are at increased risk of urolithiasis.

X-rays: X-rays of the affected joint may be taken to look for bony tophi but are probably unnecessary if the diagnosis has been established by synovial fluid analysis. In CPPD, radiopaque deposits are present in fibrocartilage, hyaline articular cartilage (particularly the knee), or both.

Diagnosis of chronic gouty arthritis: Chronic gouty arthritis should be suspected in patients with persistent joint disease or subcutaneous

[**Table 36-1.** Microscopic Examination of Crystals in Joints]

or bony tophi. Plain x-rays of the 1st metatarsophalangeal joint or other affected joint may be useful. These x-rays may show punched-out lesions of subchondral bone with overhanging bony margins, most commonly in the 1st metatarsophalangeal joint; lesions must be ≥ 5 mm in diameter to be visible on x-ray.

Bone lesions are not specific or diagnostic but nearly always precede the appearance of subcutaneous tophi.

Prognosis

With early diagnosis, therapy enables most patients to live a normal life. For many patients with advanced disease, aggressive lowering of the serum urate level can resolve tophi and improve joint function. Gout

is generally more severe in patients whose initial symptoms appear before age 30. The metabolic syndrome and cardiovascular disease probably increase mortality in patients with gout.

Some patients do not improve sufficiently with treatment. The usual reasons include nonadherence, alcoholism, and undertreatment by physicians.

Treatment

• Termination of an acute attack with NSAIDs or corticosteroids

• Prevention of recurrent acute attacks with daily colchicine or an NSAID

• Prevention of further deposition of MSU crystals and resolution of existing tophi by lowering the serum urate level

• Treatment of coexisting hypertension, hyperlipidemia, and obesity

Treatment of acute attacks: NSAIDs are effective in treating acute attacks and are generally well tolerated. However, they can still cause adverse effects, including GI upset, hyperkalemia, increases in creatinine, and fluid retention. Elderly and dehydrated patients are at particular risk, especially if there is a history of renal disease. Virtually any NSAID used in anti-inflammatory (high) doses is effective and is likely to exert an analgesic effect in a few hours (see Table 35-2 on p. 336). Treatment should be continued for several days after the pain and signs of inflammation have resolved to prevent relapse.

Oral colchicine, a traditional therapy, often produces a dramatic response if begun soon after the onset of symptoms. Joint pain generally begins to subside after 12 to 24 h of treatment and ceases within 3 to 7 days. One regimen is colchicine 0.6 mg po q 1 h until symptoms abate to a maximum total dose of 4 to 5 mg or until diarrhea or vomiting occurs. However, diarrhea, sometimes severe, develops in up to 80% of patients given this regimen of oral colchicine for an acute attack. If treatment is started very early, regimens such as 0.6 to 1.2 mg bid to tid for 1 to 2 days are better tolerated and may be effective. If colchicine is tolerated, 0.6 to 1.2 mg once/day can be continued as the attack subsides.

IV colchicine is much less likely to cause GI symptoms and provides an alternative, particularly for postoperative patients. Colchicine 1 mg is diluted with 0.9% saline to 20 mL and injected slowly (over 2 to 5 min); a second 1-mg dose can be given in 12 h if needed; no more than 2 mg is given in 24 h (and no more than 4 mg over 7 days). *IV colchicine should not be given to patients with renal or liver disease or those receiving prophylactic oral colchicine, because severe bone marrow suppression, shock, and death may occur.* IV colchicine is also locally irritating, particularly if extravasated. Although effective and perhaps the option of choice in certain specific situations, IV colchicine should only be used with careful adherence to prescribing indications and contraindications.

Corticosteroids are sometimes used to treat acute attacks; however, this use is controversial because inflammation may continue while symptoms are masked. Aspiration of affected joints, followed by instillation of corticosteroid ester crystal suspension, is very effective, particularly for monarticular symptoms; prednisolone tebutate 4 to 40 mg or prednisolone acetate 5 to 25 mg can be used, with dose depending on the size of the affected joint. Oral prednisone (about 40 mg once/day), IM or IV corticosteroids, or single-dose ACTH 80 U IM is also very effective, particularly if multiple joints are involved. As with NSAID therapy, corticosteroids should be continued until after the attack fully resolves to prevent relapse.

In addition to NSAIDs or corticosteroids, supplementary analgesics, rest, ice application, and splinting of the inflamed joint may be helpful. Because lowering the serum urate level during an attack prolongs the attack or predisposes to recurrence, drugs that lower the serum urate level should not be initiated until acute symptoms have been completely controlled.

Prevention of recurrent attacks: The frequency of acute attacks is reduced by taking one to two 0.6-mg tablets of colchicine daily (depending on tolerance and severity). An extra two or three 0.6-mg tablets

of colchicine taken at the first suggestion of an attack may abort flares. A (reversible) neuropathy or myopathy can develop during chronic colchicine ingestion. This condition may occur in patients with renal insufficiency, in patients also receiving a statin or macrolide, or in patients with none of these risk factors. Attack frequency can also be decreased with daily low-dose NSAIDs.

Lowering the serum urate level: Colchicine, NSAIDs, and corticosteroids do not retard the progressive joint damage caused by tophi. Such damage can be prevented and, if present, reversed with urate-lowering drugs. Tophaceous deposits are resorbed by lowering serum urate. Lowering serum urate may also decrease the frequency of acute arthritic attacks. This decrease is accomplished by

- Blocking urate production with allopurinol
- Increasing urate excretion with a uricosuric drug
- Using both types of drugs together in severe tophaceous gout

Uricase can also be given but is not yet routinely used. Uricase is an enzyme that converts urate to allantoin, which is more soluble. IV uricase transiently lowers serum urate by a large amount.

Hypouricemic therapy is indicated for patients with

- Tophaceous deposits
- Frequent or disabling attacks of gouty arthritis (eg, more than 2 attacks/yr or very severe attacks) despite prophylactic colchicine, an NSAID, or both
- Gout with persistent serum urate ≥ 9 mg/dL
- Urolithiasis
- Multiple comorbidities (eg, peptic ulcer disease, chronic kidney disease) that are relative contraindications to the drugs used to treat acute attacks (NSAIDs or corticosteroids)

Hyperuricemia is not usually treated in the absence of gout.

If the goal of hypouricemic therapy is to dissolve tophi, the serum urate level should be lowered to 4.5 mg/dL (0.26 mmol/L), the saturation level at the normal temperature (31° C) of the bunion joint, or even lower. If tophi do not need to be dissolved, a level of 5 to 6 mg/dL (0.30 to 0.36 mmol/L), which is below the level of saturation (> 7.0 mg/dL [> 0.41 mmol/L] at normal core body temperature and pH), is acceptable. These target levels should be maintained indefinitely. Low levels are often difficult to maintain.

Drugs are effective in lowering serum urate; dietary restriction of purines is less effective, but high intake of high-purine food and alcohol (beer in particular) should be avoided. Carbohydrate restriction and weight loss can lower serum urate in patients with insulin resistance because high insulin levels suppress urate excretion. Because acute attacks tend to develop during the first months of hypouricemic therapy, such therapy should be started in conjunction with once or twice daily colchicine or NSAIDs and during a symptom-free period. Resolution of tophi may take many months even with maintenance of serum urate at low levels. Serum urate should be measured periodically, usually monthly while determining required drug dosage and then yearly to confirm the effectiveness of therapy.

Allopurinol, which inhibits urate synthesis, is the most commonly prescribed hypouricemic therapy. It is especially helpful in treating patients who repeatedly pass uric acid or Ca oxalate stones or who have severe renal dysfunction. Uric acid stones or gravel may dissolve during allopurinol treatment. Treatment begins with 100 mg po once/day and can be increased up to 800 mg po once/day, or even higher, to achieve target urate levels; however, the dose must be decreased in patients with renal insufficiency. The most common daily dose is 300 mg. Adverse effects include mild GI distress and skin rash, which can be a harbinger of Stevens-Johnson syndrome, life-threatening hepatitis, vasculitis, or leukopenia. Adverse

effects are more common among patients with renal dysfunction.

Uricosuric therapy is preferred to allopurinol as initial therapy for patients ≤ 60 yr with normal renal function, no history of urolithiasis, and decreased renal urate excretion. Probenecid or sulfinpyrazone can be used. Probenecid treatment begins with 250 mg po bid, with doses increased as needed, to a maximum of 1 g po tid. Sulfinpyrazone treatment begins with 50 to 100 mg po bid, with doses increased as needed, to a maximum of 100 mg po qid. Sulfinpyrazone is more potent than probenecid but is more toxic. Salicylates at low doses antagonize both drugs and can increase urate levels. Low doses may worsen hyperuricemia, but a therapeutic trial of a cardioprotective dose while monitoring urate levels may be indicated for patients at high risk of cardiovascular disease. Acetaminophen provides comparable analgesia without interfering with drug efficacy.

Other treatments: Fluid intake ≥ 3 L/day is desirable for all patients, especially those who chronically pass urate gravel or stones. Alkalinization of urine (with K citrate 20 to 40 mEq po bid or acetazolamide 500 mg po at bedtime) is also occasionally effective for patients with persistent uric acid urolithiasis despite hypouricemic therapy and adequate hydration. However, excessive urine alkalinization may cause deposition of Ca oxalate crystals. Extracorporeal shock wave lithotripsy may be needed to disintegrate renal stones. Large tophi in areas with healthy skin may be removed surgically; all others should slowly resolve under adequate hypouricemic therapy. Losartan, which has uricosuric effects, can be considered as an alternative to thiazide diuretics.

Asymptomatic Hyperuricemia

Asymptomatic hyperuricemia is elevation of serum urate > 7 mg/dL (> 0.42 mmol/L) in the absence of clinical gout. Generally, treatment is not required. However, patients with overexcretion of urate who are at risk of urolithiasis may receive allopurinol.

Calcium Pyrophosphate Dihydrate Crystal Deposition Disease

(Pseudogout)

Calcium pyrophosphate dihydrate (CPPD) crystal deposition disease involves intra-articular and/or extra-articular deposition of CPPD crystals. Manifestations are protean and may be minimal or include intermittent attacks of acute arthritis and a degenerative arthropathy that is often severe. Diagnosis requires identification of CPPD crystals in synovial fluid. Treatment is with intra-articular corticosteroids or oral NSAIDs or colchicine.

CPPD crystal deposition (chondrocalcinosis), whether symptomatic and asymptomatic, becomes more common with age.

The incidence of radiologic (usually asymptomatic) chondrocalcinosis in patients aged 70 is about 3%, reaching nearly 50% in patients aged 90. Asymptomatic chondrocalcinosis is common in the knee, hip, anulus fibrosus, and symphysis pubis. Men and women are affected equally.

Etiology

The cause is unknown. Frequent association with other conditions, such as trauma (including surgery), amyloidosis, myxedema, hypomagnesemia, hyperparathyroidism, gout, hemochromatosis, and old age, suggests that CPPD crystal deposits are secondary to degenerative or metabolic changes in the affected tissues. Some cases are familial, usually transmitted in an autosomal dominant pattern, with complete penetration by age 40.

Symptoms and Signs

Acute, subacute, or chronic arthritis can occur, usually in the knee or other large peripheral joints, which can mimic many other forms of arthritis. Attacks are sometimes similar to gout but are usually less severe. There may be no symptoms between attacks or continuous low-grade symptoms in multiple joints, similar to RA or osteoarthritis. These patterns tend to persist for life.

Diagnosis

• Synovial fluid analysis

• Identification of crystals microscopically

CPPD crystal deposition disease should be suspected in older patients with arthritis, particularly inflammatory arthritis. Diagnosis is established by identifying rhomboid or rod-shaped, weakly positively birefringent crystals on polarized light microscopy of synovial fluid (see Table 36-1). Coincident infectious arthritis must be ruled out by Gram stain and culture. X-rays are indicated if synovial fluid cannot be obtained for analysis; findings of multiple linear or punctate calcification in articular cartilage, especially fibrocartilages, support the diagnosis but do not exclude gout or infection.

Prognosis

The prognosis for individual attacks is usually excellent. However, chronic arthritis can occur, and severe destructive arthropathy resembling neuropathic (Charcot's) joints occasionally occurs.

Treatment

• Intra-articular corticosteroids

• NSAIDs

• Colchicine maintenance

Symptoms of acute synovial effusion abate with synovial fluid drainage and instillation of a microcrystalline corticosteroid ester suspension into the joint space (eg, 40 mg prednisolone acetate or prednisolone tertiary butylacetate into a knee). Indomethacin, naproxen, or another NSAID given at anti-inflammatory doses (see Table 35-2 on p. 336) often stops acute attacks promptly. Colchicine 0.6 mg po once/day or bid may decrease the number of acute attacks.

Basic Calcium Phosphate and Calcium Oxalate Crystal Deposition Diseases

Basic Ca phosphate (apatite) and Ca oxalate crystal disorders tend to cause clinical manifestations similar to other crystal-induced arthritides.

Basic Ca phosphate crystal deposition disease: Most pathologic calcifications throughout the body contain mixtures of carbonate-substituted hydroxyapatite and octacalcium phosphate. Because these ultramicroscopic crystals are nonacidic Ca phosphates, the term basic Ca phosphate (BCP) is much more precise than apatite. These ultramicroscopic crystals occur in snowball-like clumps in rheumatic conditions (eg, calcific tendinitis, calcific periarthritis, some cases of progressive systemic sclerosis and dermatomyositis). They also occur in joint fluids of patients with all degenerative arthropathies sufficiently advanced to cause joint space narrowing on x-ray.

BCP crystals can destroy joints and can cause severe intra-articular or periarticular inflammation. Milwaukee shoulder syndrome is one example, a profoundly destructive arthropathy affecting predominantly elderly women that usually develops in the shoulders and (often) knees.

Acute podagra due to periarticular BCP deposition can mimic gout; it occurs as a discrete syndrome in young women (less often in young men) and is treated the same as acute gout.

Besides synovial fluid analysis, x-rays should be taken of symptomatic joints. On x-ray, BCP crystals may be visible as periarticular cloudlike opacities. Definitive assay for BCP crystals in synovial fluid is not readily available. Clumped crystals can be identified only with transmission electron microscopy. The clumps are not birefringent under polarized light.

Treatment with oral or IV colchicine, an NSAID, or, if a large joint is involved, intra-articular corticosteroid ester crystal suspension is helpful. Treatment is the same as that for acute gout (see p. 352).

Ca oxalate crystal deposition disease: Ca oxalate crystal deposition is rare. It occurs most often in azotemic patients receiving hemodialysis or peritoneal dialysis, particularly those treated with ascorbic acid (vitamin C), which is metabolized to oxalate. Crystals may deposit in blood vessel walls and skin, as well as joints. The crystals appear as birefringent bipyramidal structures (see Table 36-1). Synovial fluid may have > 2000 WBC/µL. On x-ray, Ca oxalate crystals are indistinguishable from BCP periarticular calcifications or Ca pyrophosphate dihydrate (CPPD) crystal deposits in cartilage. Treatment is the same as that for CPPD crystals (see above).

Chapter 37. Osteoporosis

Introduction

Osteoporosis is a progressive metabolic bone disease that decreases bone density (bone mass per unit volume), with deterioration of bone structure. Skeletal weakness leads to fractures with minor or inapparent trauma, particularly in the thoracic and lumbar spine, wrist, and hip. Acute or chronic back pain is common. Diagnosis is by dual-energy x-ray absorptiometry. Prevention and treatment involve Ca and vitamin D supplements, exercises to maximize bone and muscle strength and minimize the risk of falls, and drug therapy to preserve bone mass or stimulate new bone formation.

Pathophysiology

Normally, bone formation and resorption are closely coupled. Osteoblasts (cells that make the organic matrix of bone and then mineralize bone) and osteoclasts (cells that resorb bone) are regulated by parathyroid hormone (PTH), calcitonin, estrogen, vitamin D, various cytokines, and other local factors such as prostaglandins.

Peak bone mass in men and women occurs by the mid 20s. Blacks reach higher bone mass than whites and Asians, whereas Hispanics have intermediate values. Men have higher bone mass than women. Bone mass plateaus for about 10 yr, during which time bone formation approximately equals bone resorption. After this, bone loss occurs at a rate of about 0.3 to 0.5%/yr. Beginning with menopause, bone loss accelerates in women to about 3 to 5%/yr for about 5 to 7 yr.

Osteoporotic bone loss affects cortical and trabecular (cancellous) bone. Cortical thickness and the number and size of trabeculae decrease, resulting in increased porosity. Trabeculae may be disrupted or entirely absent.

Classification

Osteoporosis can develop as a primary disorder or secondarily due to some other factor.

Primary osteoporosis: More than 95% of osteoporosis in women and probably about 80% in men is primary. Most cases occur in postmenopausal women and older men. The terms postmenopausal, involutional, senile, and age-related osteoporosis have been used to describe primary osteoporosis in elderly patients. Estrogen deficiency is an important factor in men as well as women. Other contributing factors may include decreased Ca intake, low vitamin D levels, and secondary hyperparathyroidism.

The major mechanism is increased bone resorption, which results in decreased bone mass and microarchitectural deterioration, but other mechanisms also contribute not only in primary osteoporosis but also in the various secondary forms of osteoporosis. The mechanisms of bone loss may involve the following:

- Local changes in the production of bone-resorbing cytokines, such as increases in cytokines that stimulate bone resorption

- Impaired formation response during bone remodeling (probably caused by age-related decline in the number and activity of osteoblasts)

- Other factors such as a decline in local and systemic growth factors

Trabecular bone loss occurs more rapidly than cortical bone loss because trabecular bone is more porous and bone turnover is high. However, loss of both types contributes to skeletal fragility.

The most common sites for fragility fractures are the distal radius (dorsally displaced fractures), spine (vertebral compression fractures), femoral neck, and greater trochanter. Other sites include the proximal humerus and pelvis. Fragility fractures rarely occur in children or young adults with normal gonadal

function and no detectable secondary cause. This condition is called idiopathic osteoporosis.

Secondary osteoporosis: Secondary osteoporosis accounts for < 5% of osteoporosis cases in women but probably more in men. The causes (see Table 37-1) may also aggravate bone loss and increase fracture risk in patients with primary osteoporosis.

Risk Factors

Because stress, including weight bearing, is necessary for bone growth, immobilization or extended sedentary periods result in bone loss. Being thin predisposes to decreased bone mass. Insufficient dietary intake of Ca, P, and vitamin D predisposes to bone loss, as does endogenous acidosis (eg, high-protein diets). Cigarette smoking and excessive caffeine or alcohol use also adversely affect bone mass. Whites and Asians are at higher risk. A family history of osteoporosis also increases risk. Other risk factors (eg, decreasing

[**Table 37-1.** Causes of Secondary Osteoporosis]

amounts of sex hormones) predispose to specific types of osteoporosis. Patients who have had one fragility fracture are at increased risk of having other clinical (symptomatic) fractures as well as clinically asymptomatic vertebral compression fractures.

Symptoms and Signs

Most of the chronic pain typical of osteoporosis results from fractures, which may develop after minimal, inapparent, or no trauma. Patients may be asymptomatic for years, until fractures begin to occur. Eventually, patients often develop pain in the bones or muscles, particularly of the back. Vertebral compression fractures are common, usually in weight-bearing vertebrae (T6 and below). The pain begins acutely, usually does not radiate, is aggravated by weight bearing, may cause local tenderness, and generally begins to subside in 1 wk. However, residual pain may last for months or be constant.

Multiple thoracic compression fractures eventually cause dorsal kyphosis, with exaggerated cervical lordosis (dowager's hump). Abnormal stress on the spinal muscles and ligaments may cause chronic, dull, aching pain, particularly in the lower back. Fractures can develop at other sites, commonly the hip or wrist, usually from falls.

Diagnosis

• Dual-energy x-ray absorptiometry (DEXA)

Osteoporosis should be suspected in patients who sustain fractures after only mild or trivial trauma; older adults, particularly those with risk factors and unexplained back pain; patients with decreased bone density that is incidentally noted on imaging studies; and patients at risk of secondary osteoporosis. If imaging studies have been done or are necessary to evaluate symptoms (eg, back pain), osteoporosis may be obvious. However, imaging studies are often equivocal, and the diagnosis should be established by bone density measurement.

Plain x-rays: Bones show decreased radiodensity and loss of trabecular structure, but not until about 30% of bone has been lost. A loss of horizontally oriented trabeculae increases the prominence of the cortical end plates and of vertically oriented, weight-bearing trabeculae. Loss of height and increased biconcavity characterize vertebral compression fractures. Thoracic vertebral fractures may cause anterior wedging. In long bones, although the cortices may be thin, the periosteal surface remains smooth. Vertebral fractures at T4 or above suggest cancer rather than osteoporosis.

Corticosteroid-induced osteoporosis is likely to cause rib fractures and exuberant callus formation at sites of healing fractures. Osteomalacia may cause abnormalities on imaging tests similar to those of osteoporosis (see Sidebar 37-1). Hyperparathyroidism can be differentiated when it causes subperiosteal resorption or cystic bone lesions, but these are uncommon.

Bone density measurement: DEXA is used to measure bone density. DEXA is diagnostic for osteoporosis, predicts the risk of fracture, and can be used to follow treatment response. Bone density of the lumbar spine, hip, distal radius or ulna, or the entire body can be measured. (Quantitative CT scanning can produce similar measurements in the spine or hip.) Usually, the lumbar spine, total proximal femur, or femoral neck is measured. DEXA results are reported as T scores. A T score corresponds to the number of standard deviations by which bone density differs from a healthy, young person of the same sex and race. A DEXA result of > 1 is defined as osteopenia and suggests an increased risk of osteoporosis; > 2.5 is diagnostic for osteoporosis.

If DEXA scanning of the central skeleton is unavailable, portable, less expensive systems such as peripheral DEXA or quantitative ultrasonography of the heel can be used. However, monitoring the response to treatment with serial measurements of bone density should be done only with central DEXA scanning.

Sidebar 37-1 Osteopenia: Differentiating Osteoporosis and Osteomalacia

Osteopenia is decreased bone mass. Two metabolic bone diseases decrease bone mass: osteoporosis and osteomalacia. In osteoporosis, bone mass decreases, but the ratio of bone mineral to bone matrix is normal. In osteomalacia, the ratio of bone mineral to bone matrix is low.

Osteoporosis results from a combination of low peak bone mass, increased bone resorption, and impaired bone formation. Osteomalacia is due to impaired mineralization, usually because of severe vitamin D deficiency or abnormal vitamin D metabolism (see p. 41). Osteoporosis is much more common than osteomalacia in the US. The 2 disorders may coexist, and their clinical expression is similar; moreover, mild to moderate vitamin D deficiency can occur in osteoporosis.

Current central DEXA systems can also assess vertebral deformities in the lower thoracic and lumbar spine, a procedure termed vertebral fracture analysis (VFA). Vertebral deformities, even those clinically silent, may indicate increased risk of future fractures. VFA is more likely to be useful in patients with loss of ≥ 3 cm in height.

Other testing: Once osteoporosis is diagnosed, patients should be checked for causes of secondary osteoporosis. Serum Ca should be measured to rule out asymptomatic hyperparathyroidism. PTH levels may be increased in patients with decreased Ca absorption or hypercalciuria. Other tests such as thyroid-stimulating hormone or free thyroxine to check for hyperthyroidism, vitamin D levels, measurements of urinary free cortisol, and blood counts and other tests to rule out cancer, especially myeloma (eg, serum protein electrophoresis), should be considered depending on the clinical findings. Serum alkaline phosphatase is usually normal but may be elevated by recent fracture.

Patients with weight loss should be screened for GI disorders as well as cancer. Bone biopsy is reserved for unusual cases (eg, young patients with pathologic fractures and no apparent cause). Levels of serum or urine N-telopeptide crosslinks (NTX) or free deoxypyridinoline (DPYR) may reflect increased breakdown of collagen. These tests are not sufficiently accurate for routine clinical use but may be used to assess the effectiveness of therapy.

Screening

DEXA screening is recommended for all women > 65. Bone density should also be measured in women between 50 and 65 who have risk factors, including a family history of osteoporosis, a history of fragility fractures, and low body weight. Screening is also recommended for both men and women who have had fragility fractures, even at younger ages.

Treatment

• Risk factor modification

• Ca and vitamin D supplements

• Bisphosphonates or sometimes other antiresorptive drugs

The goals of treatment are to preserve bone mass, prevent fractures, decrease pain, and maintain function.

Preserving bone mass: The rate of bone loss can be slowed with drugs and, when possible, modification of risk factors. Ca and vitamin D intake and physical activity must be adequate for drug treatment to be effective.

Risk factor modification can include maintaining adequate body weight, increasing weight-bearing exercise, minimizing caffeine and alcohol intake, and stopping smoking. The optimal amount of weight-bearing exercise is not established, but an average of 30 min/day is recommended. A physical therapist can develop a safe exercise program.

All men and women should consume at least 1000 mg of elemental Ca daily. An intake of 1200 to 1500 mg/day is recommended for postmenopausal women and older men and for periods of increased requirements, such as pubertal growth, pregnancy, and lactation. Diet alone is rarely adequate; Ca supplements are needed, most commonly as Ca carbonate or Ca citrate. Supplements differ in their elemental Ca concentration. Ca citrate is better absorbed in patients with achlorhydria, but both are well absorbed when taken with meals. Ca should be taken in divided doses of 500 to 600 mg bid or tid.

Vitamin D in doses of 800 U once/day is generally recommended, but up to 2000 U/day is safe and may be helpful in osteoporotic patients. Patients with vitamin D deficiency may need even higher doses. Supplemental vitamin D is usually given as cholecalciferol, the natural form of vitamin D, although ergocalciferol, the synthetic plant derived form, is probably also acceptable.

Bisphosphonates are first-line drug therapy. By inhibiting bone resorption, bisphosphonates preserve bone mass and can decrease vertebral and hip fractures by 50%. To treat osteoporosis, bisphosphonates can be given orally. Alendronate can be given at doses of 10 mg po once/day or 70 mg po once/wk, ibandronate 2.5 mg po once/day or 150 mg once/mo, or risedronate at 5 mg po once/day or 35 mg once/wk. All increase bone mineral density and decrease risk of at least vertebral fractures. Oral bisphosphonates must be taken on an empty stomach with a full glass of water, and the patient must remain upright for ≥ 30 min. They can cause esophageal irritation. Esophageal disorders that delay transit time and symptoms of upper GI disorders are relative contraindications to oral bisphosphonates. Weekly or monthly therapy is generally preferred for its greater convenience and probably fewer adverse effects.

Parenteral zolendronate is an alternative to oral bisphosphonates. Doses of 5 mg IV once/year increase bone mass and decrease risk of vertebral and nonvertebral fractures. Pamidronate can also be given IV but has not yet been shown to prevent fractures.

Osteonecrosis of the jaw has been associated with use of bisphosphonates; however, this condition is rare in patients taking oral bisphosphonates. Risk factors include IV bisphosphonate use and cancer. Bisphosphonates may also be associated with atrial fibrillation, but the mechanism is not clear and there has been no association with increased cardiovascular mortality.

Salmon calcitonin is less effective than bisphosphonates for treating osteoporosis. The subcutaneous dose is 100 IU/day or every other day; the nasal spray dose is 200 U/day in alternating nostrils (1 spray). Salmon calcitonin may provide short-term analgesia after an acute fracture.

Estrogen can preserve bone density and prevent fractures. Most effective if started within 4 to 6 yr of menopause, estrogen may slow bone loss and possibly reduce fractures even when started much later. It is usually given as conjugated estrogen 0.625 to 1.25 mg po once/day. However, 0.3 mg po once/day may be as effective. Use of estrogen increases the risk of thromboembolism and endometrial cancer and may increase the risk of breast cancer. The risk of endometrial cancer can be reduced in women with an intact uterus by taking a progestin with estrogen (see p. 2519). However, taking a combination of a progestin

and estrogen increases the risk of breast cancer, coronary artery disease, stroke, and biliary disease.

Raloxifene is a selective estrogen receptor modulator (SERM) that may be appropriate for treatment of osteoporosis in women who cannot take bisphosphonates. It reduces vertebral fractures by about 50% but has not been shown to reduce nonvertebral fractures. Raloxifene does not stimulate the uterus and antagonizes estrogen effects in the breast, probably reducing the risk of breast cancer.

PTH, which stimulates new bone formation, is generally reserved for patients who have the following characteristics:

- Cannot tolerate antiresorptive drugs or have contraindications to their use
- Fail to respond to antiresorptive drugs, as well as Ca, vitamin D, and exercise, developing new fractures and loss of bone mineral density
- Possibly have severe osteoporosis (eg, T score < 3.5)

When given daily by injection for an average of 20 mo, synthetic PTH (PTH 1-34; teriparatide) increases bone mass and reduces risk of fractures.

Preventing fractures: Many elderly patients are at risk of falls because of poor coordination, poor vision, muscle weakness, confusion, and use of drugs that cause postural hypotension or alter the sensorium. Educating patients about the risks of falls and fractures and developing individualized programs to increase physical stability and attenuate risk can help. Strengthening exercises may increase stability. Hip pads can reduce the incidence of hip fracture despite continued falls.

Treating pain and maintaining function: Acute back pain from a vertebral compression fracture should be treated with orthopedic support, analgesics, and (when muscle spasm is prominent) heat and massage (see p. 3459). Chronic backache may be relieved by an orthopedic garment and exercises to strengthen paravertebral muscles. Avoiding heavy lifting can help. Bed rest should be minimized, and consistent, carefully designed weight-bearing exercise should be encouraged.

In some cases, vertebroplasty, sometimes preceded by kyphoplasty, can relieve severe pain. In vertebroplasty, methyl methacrylate is injected into the vertebral body. In kyphoplasty, the vertebral body is expanded with a balloon. These procedures may reduce deformity in the injected vertebrae but do not reduce and may even increase the risk of fractures in adjacent vertebrae. Other risks may include rib fractures, cement leakage, and pulmonary edema or MI.

Prevention

The goals of prevention are to preserve bone mass and prevent fractures. Preventive measures are indicated in postmenopausal women and older men, patients taking long-term systemic corticosteroids, and patients at high risk (eg, osteopenia with multiple risk factors or secondary causes).

Preventive measures are similar to treatment measures, including those aimed at preserving bone mass. Bisphosphonates and other drugs can be given as for treatment of osteoporosis, but alendronate is given at a reduced dose (5 mg po once/day or 35 mg once/wk). Measures to prevent fractures are also indicated.

Chapter 38. Paget's Disease of Bone

Introduction

(Osteitis Deformans)

Paget's disease of bone is a chronic disorder of the adult skeleton in which bone turnover is accelerated in localized areas. Normal matrix is replaced with softened and enlarged bone. The disease may be asymptomatic or cause gradual onset of bone pain or deformity. Diagnosis is by x-ray. Treatment includes symptomatic measures and often drugs, usually bisphosphonates.

About 1% of adults in the US > 40 have Paget's disease, with a 3:2 male predominance. Prevalence increases with aging. However, overall prevalence seems to be decreasing. The disease is most common in Europe (except Scandinavia), Australia, and New Zealand. It is particularly common in England.

Etiology

Several genetic abnormalities, many affecting osteoclast generation and activity, have been identified. Mutations of the *Sequestrum 1* gene from chromosome 6 are commonly related to Paget's disease. Appearance of involved bone on electron microscopy suggests a viral infection, but a viral cause has not been established.

Pathophysiology

Any bone can be involved. The bones most commonly affected are, in decreasing order, the pelvis, femur, skull, tibia, vertebrae, clavicle, and humerus.

Bone turnover is accelerated at involved sites. Pagetic lesions are metabolically active and highly vascular. Excessively active osteoclasts are often large and contain many nuclei. Osteoblastic repair is also hyperactive, causing coarsely woven, thickened lamellae and trabeculae. This abnormal structure weakens the bone, despite bone enlargement and heavy calcification.

Complications: Overgrown bone may compress nerves and other structures passing through small foramina. Spinal stenosis or spinal cord compression may develop. Osteoarthritis may develop in joints adjacent to involved bone.

In about 10 to 15% of patients, increased bone formation and Ca requirement leads to secondary hyperparathyroidism; if this need is not matched by an increase in Ca intake, hypocalcemia may occur. Hypercalcemia (see p. 843) occasionally develops in patients who are immobile. It also occurs in patients with Paget's disease who develop secondary hyperparathyroidism.

Large or numerous lesions may lead to high-output heart failure.

Symptoms and Signs

There are usually no symptoms for a prolonged period. If symptoms occur, they develop insidiously, with pain, stiffness, fatigue, and bone deformity. Bone pain is aching, deep, and occasionally severe, sometimes worse at night. Pain also may arise from compression neuropathy or osteoarthritis. If the skull is involved, there may be headaches and hearing impairment.

Signs may include skull enlargement bitemporally and frontally (frontal bossing); dilated scalp veins; nerve deafness in one or both ears; angioid streaks in the fundus of the eye; a short kyphotic trunk with simian appearance; hobbling gait; and anterolateral angulation (bowing) of the thigh or leg, often with warmth and tenderness. Deformities may develop from bowing of the long bones or osteoarthritis. Pathologic fractures may be the presenting manifestation. Sarcomatous degeneration develops in < 1% and is often suggested by increasingly severe pain.

Diagnosis

• Plain x-rays

• Serum alkaline phosphatase, Ca, and PO_4

• Bone scan after the diagnosis is established

Paget's disease should be suspected in patients with the following:

• Unexplained bone pain or deformity

• Suggestive findings on x-ray

• Unexplained elevation of serum alkaline phosphatase on laboratory tests done for other reasons, particularly if γ-glutamyl-transpeptidase (GGT) is normal

• Hypercalcemia that develops during bed rest, particularly among elderly patients

• Bone sarcoma in elderly patients

If Paget's disease is suspected, plain x-rays and serum alkaline phosphatase, Ca, and PO_4 levels should be obtained. Confirmation on x-ray is required to establish the diagnosis. Characteristic x-ray findings include the following:

• Increased bone sclerosis

• Abnormal architecture with coarse cortical trabeculation or cortical thickening

• Bowing

• Bone enlargement

There may be stress microfractures of the tibia or femur.

Characteristic laboratory findings include elevated serum alkaline phosphatase (increased anabolic activity of bone) but usually normal GGT and serum PO_4 levels. Serum Ca is usually normal but can increase because of immobilization or hyperparathyroidism or decrease (often transiently) because of increased bone synthesis. If alkaline phosphatase is not elevated or it is unclear whether the increased serum alkaline phosphatase is of bony origin (ie, if GGT is increased in proportion to alkaline phosphatase), a bone-specific fraction can be measured.

Occasionally, increased catabolic activity of bone, as demonstrated by elevated urine markers of bone collagen turnover (eg, pyridinoline crosslinks), supplements the findings.

Radionuclide bone scan using technetium-labeled phosphonates should be done at baseline to determine the extent of bone involvement.

Treatment

• Supportive care for symptoms and complications

• Bisphosphonates

Localized, asymptomatic disease requires no treatment. Symptomatic treatment includes

[
Table 38-1. Drug Therapy for Paget's Disease]

analgesics or NSAIDs for pain. Orthotics help correct abnormal gait caused by bowed lower extremities. Some patients require orthopedic surgery (eg, hip or knee replacement, decompression of the spinal cord). Weight bearing should be encouraged, and bed rest should be avoided.

Drug therapy: Drug therapy suppresses osteoclast activity. It is indicated for the following:

- To prevent or reduce bleeding during orthopedic surgery
- To prevent or retard progression of complications (eg, hearing loss, deformity, osteoarthritis, paraparesis or paraplegia related to vertebral Paget's disease, or other neurologic deficits, particularly in a poor surgical candidate)
- To treat pain clearly related to the pagetic process and not to another source (eg, osteoarthritis)
- When serum alkaline phosphatase (of bony origin) is > 2 times the normal level, even in the absence of symptoms

Although disease progression can be retarded, existing deficits (eg, deformity, osteoarthritis, hearing loss, neural impingement) are not reversed.

Several bisphosphonates are available and are the drugs of choice (see Table 38-1 on p. 361). Synthetic salmon calcitonin is an alternative to bisphosphonates for patients intolerant of or resistant to them. The newer bisphosphonates (amino-containing bisphosphonates, eg, zolendronate) seem to provide more prolonged response.

Chapter 39. Osteonecrosis

Introduction

(Avascular Necrosis; Aseptic Necrosis; Ischemic Necrosis of Bone)

Osteonecrosis (ON) is a focal infarct of bone that may be caused by specific etiologic factors or may be idiopathic. It can cause pain, limitation of motion, joint collapse, and osteoarthritis. Diagnosis is by x-rays and MRI. In early stages, surgical procedures may slow or prevent progression. In later stages, joint replacement may be required for relief of pain and maintenance of function.

In the US, ON affects about 20,000 new patients annually. The hip (femoral head) is most commonly affected, followed by the knee and shoulder (humeral head). The wrist and ankle are less often involved. It is unusual for ON to involve the shoulder or other less commonly affected sites without the hip also being involved.

Etiology

The most common cause of ON is trauma. Nontraumatic ON affects men more often than women, is bilateral in > 60% of cases, and occurs primarily in patients between ages 30 and 50.

Traumatic ON: The most common cause of traumatic ON is a displaced subcapital fracture of the hip (see p. 3211); ON is uncommon after intertrochanteric fractures. The incidence of ON after hip dislocation is high without prompt reduction; the sooner reduction occurs, the lower the incidence. Fracture or dislocation may cause ON by grossly disrupting or compressing nearby blood vessels.

Spontaneous ON of the knee (SPONK) is localized ON of the femoral condyle or tibial plateau in elderly women (occasionally men). SPONK is thought to be caused by an insufficiency fracture (a type of fragility fracture caused by normal wear and tear on osteoporotic bone that occurs without direct trauma).

Nontraumatic ON: Factors causing or contributing to nontraumatic ON are listed in Table 39-1. The most common factors are the following:

• Chronic corticosteroid use

• Excessive alcohol consumption

The risk of ON is increased when the dose of prednisone or an equivalent corticosteroid is > 25 mg/day for several weeks or months, resulting in a cumulative dose usually > 3000 mg. The risk of ON also is increased when > 3 drinks/day (> 500 mL ethanol/wk) are consumed for several years. Some genetic factors increase susceptibility to ON. Subtle clotting abnormalities due to deficiencies in protein C, protein S, or antithrombin III or to anticardiolipin antibodies (see Ch. 110) can be detected in a high percentage of patients with ON. Some disorders that are themselves associated with ON are treated with corticosteroids (eg, SLE), so it is not clear whether risk is increased because of corticosteroid use or the disorder. About 20% of cases are idiopathic.

[**Table 39-1.** Nontraumatic Risk Factors for Osteonecrosis]

ON of the jaw has recently been reported in several patients who have received high-dose IV bisphosphonate therapy (see Sidebar 39-1). Nontraumatic ON of the hip is bilateral in 60% of patients.

Pathophysiology

ON involves the death of osteocytes and bone marrow. Mechanisms of nontraumatic ON may include embolization by blood clots or lipid droplets, intravascular thrombosis, and extravascular compression. After the vascular insult, the repair processes attempt to remove necrotic bone and marrow and replace them with viable tissue. If the infarct is small, particularly if it is not subject to major weight bearing, this

process may succeed. However, in about 80% of patients, the process is not successful and the infarct gradually collapses. The overlying articular surface becomes flattened and irregular, causing increased pain and eventually leading to osteoarthritis.

Symptoms and Signs

General symptoms: Affected areas may remain asymptomatic for weeks to months after the vascular insult. Usually pain then develops gradually, although it may be acute. With progressive collapse of the joint, pain increases and is exacerbated by motion and weight bearing and is relieved by rest.

Joint-specific symptoms: ON of the hip causes groin pain that may radiate down the thigh or into the buttock. Motion becomes limited, and a limp usually develops. SPONK usually causes sudden knee pain without preceding trauma. This pain is most often on the medial side of the femoral condyle or tibial plateau and manifests with tenderness, joint effusion, painful motion, and a limp. ON of the humeral head often causes less pain and disability than hip and knee involvement. With advanced disease, patients have pain and decreased motion, although passive range of motion is less affected than active range of motion.

Sidebar 39-1 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has no unanimously accepted definition but is generally held to be an oral lesion involving bare mandibular or maxillary bone, which usually manifests with pain and purulent discharge, although it may be asymptomatic. ONJ may occur spontaneously or after dental extraction or trauma, radiation therapy to the head and neck (osteoradionecrosis), or high-dose IV bisphosphonate therapy (eg, for cancer treatment). It is not clear whether routine use of oral bisphosphonates for treatment or prevention of osteoporosis increases risk of ONJ. Currently, otherwise appropriate bisphosphonate use should not be discouraged. However, it seems reasonable to do any necessary oral surgery before beginning bisphosphonate therapy and to encourage good oral hygiene while patients are taking bisphosphonates.

Once established, ONJ is challenging to treat and should be managed by an oral surgeon with experience treating ONJ. Treatment typically involves limited debridement, antibiotics, and oral rinses. Surgical resection of the affected area may worsen the condition and should not be the initial treatment.

Diagnosis

• X-rays

• MRI

ON should be suspected in patients with the following:

• Fractures associated with an increased incidence of ON, particularly if pain persists or worsens

• Persistent spontaneous hip, knee, or shoulder pain, particularly if risk factors for ON are present

Plain x-rays should be done initially. They may show no abnormalities for months. The earliest findings are localized areas of sclerosis and lucency. Later, a subchondral crescent sign may appear. Then, gross collapse and flattening of the articular surface is seen, followed by advanced degenerative changes.

When x-rays are normal or nondiagnostic, an MRI, which is much more sensitive and more specific, should be done. Both hips should be imaged. Bone scans are less sensitive and less specific than MRI. CT is rarely needed, although it may occasionally be of value to detect joint collapse, which does not appear on plain x-rays.

Laboratory studies are usually normal and of little value in detecting ON. However, they might help detect

an underlying disorder (eg, coagulation defects, hemoglobinopathies, lipid abnormalities).

Treatment

• Symptomatic measures (eg, rest, physical therapy, NSAIDs)

• Surgical decompression or other procedures to stimulate healing

• Hip replacement

Nonsurgical treatments: Small, asymptomatic lesions may heal spontaneously and may not need treatment.

Larger lesions, both symptomatic and asymptomatic, have a poor prognosis if untreated, especially when in the femoral head. Therefore, early treatment to slow or prevent progression and save the joint is desirable. No completely effective treatment is yet available. Nonsurgical treatments include drugs (eg, bisphosphonates) and physical modalities (eg, electromagnetic fields and acoustic waves). Drug therapy and physical modalities have shown promise in limited studies but are not currently in general use.

Surgical treatments: Surgical treatments are most effective when done before joint collapse. They have been used most often in treating ON of the hip when the prognosis without treatment is worse than that for other regions. Core decompression is the procedure most frequently done; one or more cores of bone are removed from the necrotic region or multiple small tracks or perforations are made in an attempt to decrease intraosseous pressure and stimulate repair. Core decompression is technically simple, and the complication rate is very low if the procedure is done correctly. Protected weight bearing is needed for about 6 wk. Most reports indicate satisfactory or good results in 65% of patients, including those whose hips have some degree of collapse, and in 80% of patients whose hips have small, early lesions. Other established procedures include various proximal femoral osteotomies and bone grafting, both vascularized and nonvascularized. These procedures are technically demanding, require protected weight bearing for up to 6 mo, and have not been done often in the US. Reports vary as to their indications and effectiveness. They should be done primarily at selected centers that have the surgical experience and facilities to achieve optimal results. An approach currently being evaluated is injection of autologous marrow into the necrotic lesion.

If extensive collapse of the femoral head and degenerative changes in the acetabulum cause sufficient pain and disability, an arthroplasty usually is the only way to effectively relieve pain and increase range of motion. The conventional approach is total hip replacement. Good to excellent results are achieved in 95% of total hip and total knee replacements, complication rates are low, and patients resume most activities of daily living within 3 mo. Most prosthetic hips and knees last > 15 to 20 yr.

Two alternatives under investigation include surface replacement arthroplasty (SRA) and hemi-SRA. SRA, which can be done instead of total hip replacement, involves the insertion of 2 metal caps, one into the acetabulum and one onto the femoral head, producing a metal-on-metal articulation. Hemi-SRA involves placement of a metal cap onto only the femoral head. It is done only if disease is limited to the femoral head and is considered a temporizing procedure.

ON of the knee and shoulder can be managed nonsurgically more often than ON of the hip. Limited experience with core decompression has been promising. In advanced stages, partial or total joint replacement may be indicated.

Prevention

Risk of ON caused by corticosteroids can be minimized by using them only when essential and by giving them in as low a dose as needed and for as short a duration as possible. To prevent ON caused by decompression sickness, people should follow accepted rules for decompression when diving and when working in pressurized environments. Excessive alcohol use and smoking should be discouraged. Various drugs (eg, anticoagulants, vasodilators, lipid-lowering drugs) are being evaluated for prevention of ON in patients at high risk.

Chapter 40. Infections of Joints and Bones

Acute Infectious Arthritis

Acute infectious arthritis is a joint infection that evolves over hours or days. The infection resides in synovial or periarticular tissues and is usually bacterial—in younger adults, frequently *Neisseria gonorrhoeae*. However, nongonococcal bacterial infections can also occur and can rapidly destroy joint structures. Symptoms include rapid onset of pain, effusion, and restriction of both active and passive range of motion, usually within a single joint. Diagnosis requires synovial fluid analysis and culture. Treatment is IV antibiotics and drainage of pus from joints.

Acute infectious arthritis may occur in children. About 50% of children with joint infection are < 3 yr. However, routine childhood vaccination for *Haemophilus influenzae* and *Streptococcus pneumoniae* is decreasing the incidence in this age group.

Risk factors are listed in Table 40-1. Risk is substantially increased in patients with RA and other disorders causing chronic joint damage, a past history of joint infection, IV drug abuse, or a prosthetic joint (see p. 370). RA patients are at particular risk of bacterial arthritis (prevalence 0.3 to 3.0%; annual incidence 0.5%). Most children who develop infectious arthritis do not have identified risk factors.

Etiology

Infectious organisms reach joints by direct penetration (eg, trauma, surgery, arthrocentesis, bites), extension from an adjacent infection (eg, osteomyelitis, a soft-tissue abscess, an infected wound), or hematogenous spread from a remote site of infection.

[**Table 40-1.** Risk Factors for Infectious Arthritis]

Common organisms are listed in Table 40-2. In adults, most cases result from bacteria and are classified as gonococcal or nongonococcal. In adults overall, *Staphylococcus aureus* tends to be the most frequent cause of infectious arthritis. Methicillin resistance has become more common among community isolates of *S. aureus*. In young adults and adolescents, *Neisseria gonorrhoeae* is the most common cause and results when *N. gonorrhoeae*

[**Table 40-2.** Organisms that Commonly Cause Acute Infectious Arthritis]

spreads from infected mucosal surfaces (cervix, urethra, rectum, pharynx) via the bloodstream. Affected patients often have simultaneous genital infections with *Chlamydia trachomatis* (see p. 1468). *Streptococcus* species are also frequent causes, particularly in patients with polyarticular infections.

Pathophysiology

Infecting organisms multiply in the synovial fluid and synovial lining. Some bacteria (eg, *S. aureus*) produce virulence factors (adhesins), which allow bacteria to penetrate, remain within, and infect joint tissues. Other bacterial products (eg, endotoxin from gram-negative organisms, cell wall fragments, exotoxins from gram-positive organisms, immune complexes formed by bacterial antigens and host antibodies) augment the inflammatory reaction.

PMNs migrate into the joint and phagocytose the infecting organisms. Phagocytosis of bacteria also results in PMN autolysis with release of lysosomal enzymes into the joint, which damage synovia, ligaments, and cartilage. Therefore, PMNs are both the major host defense system and the cause of joint damage. Articular cartilage can be destroyed within hours or days. Inflammatory synovitis may occasionally persist even after the infection has been eradicated by antibiotics. Particularly in gonococcal cases, persistent antigen debris from bacteria or infection may alter cartilage, causing it to become antigenic, and—together with the adjuvant effects of bacterial components—immune-mediated, "sterile"

chronic inflammatory synovitis results.

Symptoms and Signs

Over a few hours to a few days, patients develop moderate to severe joint pain, warmth, tenderness, effusion, restricted active and passive motion, and sometimes redness. Systemic symptoms may be minimal or absent. Infants and children may present with limited spontaneous movement of a limb (pseudoparalysis), irritability, feeding disturbances, and a high, low-grade, or no fever.

Gonococcal arthritis: Gonococcal arthritis can cause a distinctive dermatitis-polyarthritistenosynovitis syndrome. Classic manifestations are fever (for 5 to 7 days); shaking chills; multiple skin lesions (petechiae, papules, pustules, hemorrhagic vesicles or bullae, necrotic lesions) on mucosal surfaces and on the skin of the trunk, hands, or lower extremities; and migratory arthralgias, arthritis, and tenosynovitis, which evolves into persistent inflammatory arthritis in one or more joints, most often the small joints of the hands, wrists, elbows, knees, and ankles, and rarely the axial skeletal joints. Symptoms of the original mucosal infection (eg, urethritis, cervicitis) may not be present.

Nongonococcal bacterial arthritis: Nongonococcal bacterial arthritis causes progressive moderate to severe joint pain that is markedly worsened by movement or palpation. Most infected joints are swollen, red, and warm. Fever is absent or low grade in up to 50% of patients; 20% of patients report a shaking chill. Virulent organisms (eg, *S. aureus, Pseudomonas aeruginosa*) generally cause a more fulminant arthritis, whereas less virulent organisms (eg, coagulase-negative staphylococci, *Propionibacterium acnes*) cause a less fulminant arthritis. In 80% of adults, nongonococcal bacterial arthritis is monarticular and usually occurs in a peripheral joint: knee, hip, shoulder, wrist, ankle, or elbow. In children, ≥ 90% is monarticular: knee (39%), hip (26%), and ankle (13%). Polyarticular involvement is somewhat more common among patients who are immunosuppressed or have an underlying chronic arthritis (eg, RA, osteoarthritis). In IV drug users and patients with indwelling vascular catheters, axial joints (eg, sternoclavicular, costochondral, hip, shoulder, vertebral, symphysis pubis, sacroiliac) are often involved.

Infectious arthritis secondary to bite wounds: Infection due to human, dog, or cat bites usually develops within 48 h. Rat bites cause systemic symptoms such as fever, rash, and joint pain or true arthritis with regional adenopathy within about 2 to 10 days.

Viral infectious arthritis: Viral infectious arthritis sometimes causes symptoms similar to acute nongonococcal bacterial arthritis and is more likely to be polyarticular than bacterial arthritis.

***Borrelia burgdorferi* arthritis:** Patients with *B. burgdorferi* arthritis may have other symptoms of Lyme disease (see p. 1269) or present only with acute monarthritis or oligoarthritis.

Diagnosis

• Arthrocentesis with synovial fluid examination and culture

• Blood culture

• Sometimes imaging studies

• Often CBC and ESR (or C-reactive protein)

Infectious arthritis is suspected in patients with acute monarticular arthritis and in patients with other combinations of symptoms characteristic of particular infectious arthritis syndromes (eg, migratory polyarthritis, tenosynovitis and skin lesions typical of disseminated gonococcal infection; erythema migrans or other symptoms and signs of Lyme disease—see p. 1269). Even mild monarticular joint symptoms should arouse suspicion in patients with risk factors (eg, RA), a prosthetic joint, or an extra-articular infection capable of spreading to a joint (eg, genital gonococcal infection, bacteremia, any anaerobic infection).

General arthritis: Synovial fluid examination is the cornerstone of diagnosis. Fluid is examined

grossly and sent for cell count and differential, Gram stain, aerobic and anaerobic culture, and crystals. Foul-smelling synovial fluid suggests anaerobic infection. Fluid from an acutely infected joint usually reveals a WBC count > 20,000/µL (often > 100,000/µL) consisting of > 95% PMNs. WBC counts tend to be higher in nongonococcal bacterial than in gonococcal infectious arthritis. WBC counts may also be lower in early or partially treated infections. Gram stain reveals organisms in only 50 to 75% of joints with acute bacterial arthritis, most often with staphylococci. If positive, Gram stain is usually relatively specific, but cultures are definitive. The presence of crystals does not exclude infectious arthritis. Sometimes synovial fluid analysis cannot differentiate between infectious and other inflammatory synovial fluid. If differentiation is impossible by clinical means or synovial fluid examination, infectious arthritis is assumed, pending culture results.

Blood tests, such as blood cultures, CBC, and ESR (or C-reactive protein), are usually obtained. However, normal results do not exclude infection. Likewise, WBC count, ESR, or C-reactive protein may be increased in noninfectious as well as infectious joint inflammation.

Plain x-rays of the involved joint are not diagnostic of acute infection but can exclude other conditions under consideration (eg, fractures). Abnormalities in early acute bacterial arthritis are limited to soft-tissue swelling and signs of synovial effusions. After 10 to 14 days of untreated bacterial infection, destructive changes of joint space narrowing (reflecting cartilage destruction) and erosions or foci of subchondral osteomyelitis may appear. Gas visible within the joints suggests infection with *Escherichia coli* or anaerobes.

MRI is considered if the joint is not easily accessible for examination and aspiration (eg, an axial joint). MRI or ultrasonography can identify sites of effusion or abscess that can be aspirated or drained for both diagnosis and therapy. MRI can provide early suggestion of associated osteomyelitis. Bone scans using technetium-99m can be falsely negative in infectious arthritis. Also, because they show increased uptake with increased blood flow in inflamed synovial membranes and in metabolically active bone, they can be falsely positive in noninfectious inflammatory arthritis. Nuclear imaging and MRI do not distinguish infection from crystal-induced arthritis.

Gonococcal arthritis: If gonococcal arthritis is suspected, blood and synovial fluid samples should be *immediately* plated on nonselective chocolate agar, and specimens from the urethra, endocervix, rectum, and pharynx should be plated on selective Thayer-Martin medium. Genital chlamydial cultures are also done. Blood cultures are positive in 60 to 75% of cases during the first week and may be the only method by which to identify the organism; cultures from joints with early tenosynovitis or arthritis are often negative. Synovial fluid cultures from joints with frank purulent arthritis are usually positive, and fluid from skin lesions may be positive. If disseminated gonococcal infection is suspected based on clinical criteria, it is assumed to be present even if all gonococcal cultures are negative. Clinical response to antibiotics (anticipated within 5 to 7 days) can help confirm the diagnosis.

Prognosis

Acute nongonococcal bacterial arthritis can destroy articular cartilage, permanently damaging the joint within hours or days. Gonococcal arthritis does not usually damage joints permanently. Factors that increase susceptibility to infectious arthritis may also increase disease severity. In patients with RA, functional outcome is particularly poor, and the mortality rate is increased.

Treatment

- IV antibiotics

- Drainage of pus from infected joints (for acute nongonococcal bacterial arthritis or any septic arthritis with persistent effusion

Antibiotic therapy: Initial antibiotic selection is directed at the most likely pathogens. The regimen is adjusted based on the results of culture and susceptibility testing.

Gonococcal arthritis is treated with ceftriaxone 1 g IV once/day until at least 24 h after symptoms and

signs resolve, followed by cefixime 400 mg po bid for 7 days. Joint drainage and debridement may be unnecessary. Coexisting genital infection with *C. trachomatis* is also treated, often with doxycycline 100 mg po bid for 7 days, and sexual contacts of the patient are treated as necessary (see p. 1470).

If nongonococcal gram-positive infection is suspected by Gram stain in an adult, the empiric choice is one of the following: a semisynthetic penicillin (eg, nafcillin 2 g IV q 4 h), a cephalosporin (eg, cefazolin 2 g IV q 8 h), or vancomycin 1 g IV q 12 h (if methicillin resistance is common among local community isolates of *S. aureus*). If gram-negative infection is suspected, empiric treatment includes a parenteral 3rd-generation cephalosporin with antipseudomonal activity (eg, ceftazidime 2 g IV q 8 h) and, if infection is severe, an aminoglycoside.

Parenteral antibiotics are continued until clinical improvement is clear (usually 2 to 4 wk), and oral antibiotics should be given at high doses for another 2 to 6 wk according to the clinical response. Infections caused by streptococci and *Haemophilus* are usually eradicated after 2 wk of oral antibiotics after IV treatment. Staphylococcal infections require at least 3 wk and often 6 wk or longer, especially in patients with prior arthritis.

Other therapies: In addition to antibiotics, acute nongonococcal bacterial arthritis requires large-bore needle aspiration of intra-articular pus at least once/day, or tidal irrigation lavage, arthroscopic lavage, or arthrotomy for debridement. Infected RA joints should generally undergo even earlier and more aggressive surgical debridement and drainage. For gonococcal arthritis with persistent effusion, pus is aspirated and drainage may need to be repeated as necessary. Acute bacterial arthritis requires joint splinting for the first few days to reduce pain, followed by passive and active range-of-motion exercises to limit contractures, with muscle strengthening as soon as tolerated. NSAIDs can help decrease pain and inflammation.

Viral arthritis and arthritis secondary to bite wounds: Viral arthritis is treated supportively. Bite wounds are treated with antibiotics and surgical drainage as necessary (see p. 3307).

Chronic Infectious Arthritis

Chronic infectious arthritis develops over weeks and is usually caused by mycobacteria, fungi, or bacteria with low pathogenicity.

Chronic infectious arthritis accounts for 5% of infectious arthritis. It can develop in healthy people, but patients at increased risk include those with

- RA
- HIV infection
- Immunosuppression (eg, hematologic or other cancers, immunosuppressive drug use)
- Prosthetic joints (see p. 370)

Examples of possible causes are *Mycobacterium tuberculosis, M. marinum, M. kansasii, Candida* sp, *Coccidioides immitis, Histoplasma capsulatum, Cryptococcus neoformans, Blastomyces dermatitidis, Sporothrix schenckii, Aspergillus fumigatus, Actinomyces israelii*, and *Brucella* sp. The arthritis of Lyme disease is usually acute but may be chronic and recurrent. Unusual opportunistic organisms are possible in patients with hematologic cancers or HIV infection or who are taking immunosuppressive drugs. In chronic infectious arthritis, the synovial membrane can proliferate and can erode articular cartilage and subchondral bone.

Onset is often indolent, with gradual swelling, mild warmth, minimal or no redness of the joint area, and aching pain that may be mild. Usually a single joint is involved. A prolonged duration and lack of response to conventional antibiotics suggest a mycobacterial or fungal cause.

Patients should have fungal and mycobacterial cultures taken of synovial fluid or synovial tissue, as well

as routine studies. Plain x-ray findings may differ from those of acute infectious arthritis in that joint space is preserved longer, and marginal erosions and bony sclerosis may occur. Mycobacterial and fungal joint infections require prolonged treatment. Mycobacterial infections are often treated with multiple antibiotics, guided by sensitivity testing results.

Prosthetic Joint Infectious Arthritis

Prosthetic joints are at risk of acute and chronic infection, which can cause sepsis, morbidity, or mortality.

Etiology

Infections are more common in prosthetic joints. They are frequently caused by perioperative inoculations of bacteria into the joint or by postoperative bacteremia resulting from skin infection, pneumonia, dental procedures, invasive instrumentation, UTI, or possibly falls. They develop within 1 yr of surgery in two thirds of cases. During the first few months after surgery, the causes are *Staphylococcus aureus* in 50% of cases, mixed flora in 35%, gram-negative organisms in 10%, and anaerobes in 5%.

Symptoms and Signs

There is a history of a fall within 2 wk of symptom onset in about 25% of patients and of prior surgical revisions in about 20%. Some patients have had a postoperative wound infection that appeared to resolve, satisfactory postoperative recovery for many months, and then development of persistent joint pain at rest and during weight bearing. Symptoms and signs may include pain, swelling, and limited motion; temperature may be normal.

Diagnosis

• Clinical, microbiologic, pathologic, and radiographic criteria

The diagnosis often uses a combination of clinical, microbiologic, pathologic, and radiographic criteria. Communication between a sinus tract and the prosthesis may also be considered diagnostic of infection. Synovial fluid should be sampled for cell count and culture. X-rays may show loosening of the prosthesis or periosteal reaction but are not diagnostic. Technetium-99m bone scanning and indium-labeled WBC scanning are more sensitive than plain x-rays but may lack specificity in the immediate postoperative period. Ultimately, periprosthetic tissue collected at the time of surgery may be sent for culture and histologic analysis.

Treatment

• Arthrotomy with debridement

• Long-term systemic antibiotic therapy

Treatment must be prolonged and usually involves arthrotomy for prosthesis removal with meticulous debridement of all cement, abscesses, and devitalized tissues. Debridement is followed by immediate prosthesis revision or placement of an antibiotic-impregnated spacer and then delayed (2 to 4 mo) implantation of a new prosthesis using antibiotic-impregnated cement. Long-term systemic antibiotic therapy is used in either case; empiric therapy is initiated after intraoperative culture is done and usually combines coverage for methicillin-resistant gram-positive organisms (eg, vancomycin 1 g IV q 12 h) and aerobic gram-negative organisms (eg, piperacillin/tazobactam 3.375 g IV q 6 h or ceftazidime 2 g IV q 8 h) and is revised based on results of culture and sensitivity testing. Infection develops in 38% of new implants, whether replaced immediately or after delay.

If patients cannot tolerate surgery, long-term antibiotic therapy alone can be tried. Excision arthroplasty with or without fusion usually is reserved for patients with uncontrolled infection and insufficient bone stock.

Prevention

In the absence of other indications (eg, valvular heart disease), patients with prosthetic joints do not need prophylactic antibiotics before procedures such as dental work and urologic instrumentation. Detailed recommendations are available at www.aaos.org.

Osteomyelitis

Osteomyelitis is inflammation and destruction of bone caused by bacteria, mycobacteria, or fungi. Common symptoms are localized bone pain and tenderness with constitutional symptoms (in acute osteomyelitis) or without constitutional symptoms (in chronic osteomyelitis). Diagnosis is by imaging studies and cultures. Treatment is with antibiotics and sometimes surgery.

Etiology

Osteomyelitis is caused by

• Contiguous spread (from infected tissue or an infected prosthetic joint)

• Bloodborne organisms (hematogenous osteomyelitis)

• Open wounds (from contaminated open fractures or bone surgery)

Trauma, ischemia, and foreign bodies predispose to osteomyelitis. Osteomyelitis may form under deep decubitus ulcers.

About 80% of osteomyelitis results from contiguous spread or from open wounds; it is often polymicrobial. *Staphylococcus aureus* (including both methicillin-sensitive and methicillin-resistant strains) is present in ≥ 50%; other common bacteria include streptococci, gram-negative enteric organisms, and anaerobic bacteria. Osteomyelitis that results from contiguous spread is common in the feet (in patients with diabetes or peripheral vascular disease), at sites where bone was penetrated during trauma or surgery, at sites damaged by radiation therapy, and in bones contiguous to decubitus ulcers, such as the hips and sacrum. A sinus, gum, or tooth infection may spread to the skull.

Hematogenously spread osteomyelitis usually results from a single organism. In children, gram-positive bacteria are most common, usually affecting the metaphyses of the tibia, femur, or humerus. Hematogenously spread osteomyelitis in adults usually affects the vertebrae. Risk factors in adults are older age, debilitation, hemodialysis, sickle cell disease, and IV drug use. Common infecting organisms include *S. aureus* (methicillin-resistant *S. aureus* [MRSA] is common) and enteric gram-negative bacteria (in adults who are older, debilitated, or receiving hemodialysis); *S. aureus*, *Pseudomonas aeruginosa*, and *Serratia* sp (in IV drug users); and *Salmonella* sp (in patients with sickle cell disease). Fungi and mycobacteria can cause hematogenous osteomyelitis, usually in immunocompromised patients or in areas of endemic infection with histoplasmosis, blastomycosis, or coccidioidomycosis. The vertebrae are often involved.

Pathophysiology

Osteomyelitis tends to occlude local blood vessels, which causes bone necrosis and local spread of infection. Infection may expand through the bone cortex and spread under the periosteum, with formation of subcutaneous abscesses that may drain spontaneously through the skin. In vertebral osteomyelitis, paravertebral or epidural abscess can develop.

If treatment of acute osteomyelitis is only partially successful, low-grade chronic osteomyelitis develops.

Symptoms and Signs

Patients with acute osteomyelitis of peripheral bones usually experience weight loss, fatigue, fever, and

localized warmth, swelling, erythema, and tenderness.

Vertebral osteomyelitis causes localized back pain and tenderness with paravertebral muscle spasm that is unresponsive to conservative treatment. Patients are usually afebrile.

Chronic osteomyelitis causes intermittent (months to many years) bone pain, tenderness, and draining sinuses.

Diagnosis

• ESR or C-reactive protein

• X-rays, MRI, or radioisotopic bone scanning

• Culture of bone, abscess, or both

Acute osteomyelitis is suspected in patients with localized peripheral bone pain, fever, and malaise or with localized refractory vertebral pain, particularly in patients with recent risk factors for bacteremia. Chronic osteomyelitis is suspected in patients with persistent localized bone pain, particularly if they have risk factors.

If osteomyelitis is suspected, CBC and ESR or C-reactive protein, as well as plain x-rays of the affected bone, are obtained. The WBC count may not be elevated, but the ESR and C-reactive protein usually are. X-rays become abnormal after 2 to 4 wk, showing periosteal elevation, bone destruction, soft-tissue swelling, and, in the vertebrae, loss of vertebral body height or narrowing of the adjacent infected intervertebral disk space and destruction of the end plates above and below the disk.

If x-rays are equivocal or symptoms are acute, CT and MRI are the current imaging techniques of choice to define abnormalities and reveal abscesses (eg, paravertebral or epidural abscesses). Alternatively, a radioisotope bone scan with technetium-99m can be done. The bone scan shows abnormalities earlier than plain x-rays but does not distinguish among infection, fractures, and tumors. A white blood cell scan using indium-111-labeled cells may help to better identify areas of infection seen on bone scan. Bacteriologic diagnosis is necessary for optimal therapy of osteomyelitis; bone biopsy with a needle or surgical excision and aspiration or debridement of abscesses provides tissue for culture and antibiotic sensitivity testing. Culture of sinus drainage does not necessarily reveal the bone pathogen. Biopsy and culture should precede antibiotic therapy unless the patient is in shock or has neurologic dysfunction.

Treatment

• Antibiotics

• Surgery for abscess, constitutional symptoms, potential spinal instability, or much necrotic bone

Antibiotics effective against both gram-positive and gram-negative organisms are given until culture results and sensitivities are available. Initial antibiotic treatment for acute hematogenous osteomyelitis should include a penicillinase-resistant semisynthetic penicillin (eg, nafcillin or oxacillin 2 g IV q 4 h) or vancomycin 1 g IV q 12 h (when MRSA is prevalent in a community) and a 3rd- or 4th-generation cephalosporin (such as ceftazidime 2 g IV q 8 h or cefepime 2 g IV q 12 h). Empiric treatment of chronic osteomyelitis arising from a contiguous soft-tissue focus, particularly in patients with diabetes, must be effective against anaerobic organisms in addition to gram-positive and gram-negative aerobes. Ampicillin/sulbactam 3 g IV q 6 h or piperacillin/tazobactam 3.375 g IV q 6 h is commonly used; vancomycin 1 g IV q 12 h is added when infection is severe or MRSA is prevalent. Antibiotics must be given parenterally for 4 to 8 wk and tailored to results of appropriate cultures. If any constitutional findings (eg, fever, malaise, weight loss) persist or if large areas of bone are destroyed, necrotic tissue is debrided surgically. Surgery may also be needed to drain coexisting paravertebral or epidural abscesses or to stabilize the spine to prevent injury. Skin or pedicle grafts may be needed to close large surgical defects. Broad-spectrum antibiotics should be continued for > 3 wk after surgery. In chronic osteomyelitis, long-term antibiotic therapy may be needed.

Chapter 41. Bursa, Muscle, and Tendon Disorders

Introduction

Often, muscles, bursae, and tendons are injured during sports activities. Injury, overuse, infection, and occasionally disease can temporarily or permanently damage these structures. Damage can cause pain, limit control of movement, and reduce range of motion.

Bursitis

Bursitis is acute or chronic inflammation of a bursa. The cause is usually unknown, but trauma, repetitive or acute, may contribute, as may infection and crystal-induced disease. Symptoms include pain (particularly with motion or pressure), swelling, and tenderness. Diagnosis is usually clinical; however, ultrasonography may be needed to evaluate deep bursae. Diagnosis of infection and crystal-induced disease requires analysis of bursal fluid. Treatment includes splinting, NSAIDs, sometimes corticosteroid injections, and treatment of the cause.

Bursae are fluid-filled sac-like cavities or potential cavities that are located where friction occurs (eg, where tendons or muscles pass over bony prominences). Bursae minimize friction between moving parts and facilitate movement. Some communicate with joints.

Bursitis may occur in the shoulder (subacromial or subdeltoid bursitis), particularly in patients with rotator cuff tendinitis, which is usually the primary lesion in the shoulder. Other commonly affected bursae include olecranon (miners' or barfly's elbow), prepatellar (housemaid's knee), suprapatellar, retrocalcaneal, iliopectineal (iliopsoas), ischial (tailor's or weaver's bottom), greater trochanteric, pes anserine, and first metatarsal head (bunion) bursae. Occasionally, bursitis causes inflammation in a communicating joint.

Etiology

Bursitis may be caused by the following:

• Injury

• Chronic overuse

• Inflammatory arthritis (eg, gout, RA)

• Acute or chronic infection (eg, pyogenic organisms, particularly *Staphylococcus aureus*)

Idiopathic and traumatic causes are by far the most common. Acute bursitis may follow unusual exercise or strain and usually causes bursal effusion. Infection most often affects olecranon and prepatellar bursae.

Chronic bursitis may develop after previous attacks of bursitis or repeated trauma. The bursal wall is thickened, with proliferation of its synovial lining; bursal adhesions, villus formation, tags, and chalky deposits may develop.

Symptoms and Signs

Acute bursitis causes pain, particularly when the bursa is compressed or stretched during motion. Swelling, sometimes with other signs of inflammation, is common if the bursa is superficial (eg, prepatellar, olecranon). Swelling may be more prominent than pain in olecranon bursitis. Crystal- or bacterial-induced bursitis is usually accompanied by erythema, pitting edema, pain, and warmth in the area over the bursa.

Chronic bursitis may last for several months and may recur frequently. Bouts may last a few days to several weeks. If inflammation persists near a joint, the joint's range of motion may be limited. Limited

motion may lead to muscle atrophy.

Diagnosis

• Clinical evaluation

• Ultrasonography or MRI for deep bursitis

• Aspiration for suspected infection or crystal-induced bursitis

Superficial bursitis should be suspected in patients with swelling or signs of inflammation over bursae. Deep bursitis is suspected in patients with unexplained pain worsened by motion in a location compatible with bursitis. Usually, bursitis can be diagnosed clinically. Ultrasonography or MRI can help confirm the diagnosis when deep bursae are not readily accessible for inspection, palpation, or aspiration. These tests are done to confirm or exclude a suspected diagnosis. These imaging techniques increase the accuracy of identifying the involved structures.

If bursal swelling is particularly painful, red, or warm or if the olecranon or prepatellar bursa is affected, infection and crystal-induced disease should be excluded by bursal aspiration. After a local anesthetic is injected, fluid is withdrawn from the bursa using sterile techniques; analysis includes cell count, Gram stain and culture, and microscopic search for crystals. Gram stain, although helpful, may not be specific, and WBC counts in infected bursae are usually lower than those in septic joints. Urate crystals are easily seen with polarized light, but the apatite crystals typical of calcific tendinitis appear only as shiny chunks that are not birefringent. X-rays should be taken if bursitis is persistent or if calcification is suspected.

Acute bursitis should be distinguished from hemorrhage into a bursa, which can cause similar manifestations because blood is inflammatory. Fluid in traumatic bursitis is serosanguineous. Cellulitis can cause signs of inflammation but does not normally cause bursal effusion; cellulitis overlying the bursa is a relative contraindication to bursal puncture through the cellulitis, but if septic bursitis is strongly suspected, aspiration must occasionally be done.

Treatment

• Rest

• High-dose NSAIDs

• Treatment of crystal-induced disease or infection

Crystal-induced disease (see p. 349) or infection should be treated if present. For infection, choice of antibiotic is determined by results of Gram stain and culture. Empiric antibiotics effective against *S. aureus* should be given. Infectious bursitis requires drainage or excision in addition to antibiotics.

Acute nonseptic bursitis is treated with temporary rest or immobilization and high-dose NSAIDs and sometimes with other analgesics. Voluntary movement should be increased as pain subsides. Pendulum exercises are helpful for the shoulder joint.

If oral drugs and rest are inadequate, aspiration and intrabursal injection of depot corticosteroids 0.5 to 1 mL (eg, triamcinolone acetonide 40 mg/mL) are the treatment of choice. About 1 mL of local anesthetic (eg, 2% lidocaine) can be injected before the corticosteroid injection. The same needle is used; it is kept in place and the syringes are changed. Dose and volume of the corticosteroid may vary according to the size of the bursa. Infrequently, a flare-up occurs within several hours of injection of a depot corticosteroid; the flare-up is probably a form of crystal-induced synovitis. It usually lasts ≤ 24 h and responds to cold compresses plus analgesics. Oral corticosteroids (eg, prednisone) can be used if a local injection is not feasible.

Chronic bursitis is treated the same as acute bursitis, except that splinting and rest are less likely to help and range-of-motion exercises are especially important. Rarely, the bursa needs to be excised.

Tendinitis and Tenosynovitis

Tendinitis is inflammation of a tendon, often developing after degeneration (tendinopathy); tenosynovitis is tendinitis with inflammation of the tendon sheath lining. Symptoms usually include pain with motion and tenderness with palpation. Chronic deterioration or inflammation can cause scars that restrict motion. Diagnosis is clinical, sometimes supplemented with imaging. Treatment includes rest, NSAIDs, and sometimes corticosteroid injections.

Tendinopathy usually results from repeated small tears or degenerative changes (sometimes with Ca deposit) that occur over years in the tendon.

Tendinitis and tenosynovitis most commonly affect tendons associated with the shoulder (rotator cuff), the tendon of the long head of the biceps muscle (bicipital tendon), flexor carpi radialis or ulnaris, flexor digitorum (for infectious flexor tenosynovitis, see p. 390), popliteus tendon, Achilles tendon (see p. 3304), and the abductor pollicis longus and extensor pollicis brevis, which share a common fibrous sheath (the resulting disorder is de Quervain's syndrome—see p. 393).

Etiology

The cause of tendinitis is often unknown. It usually occurs in people who are middle-aged or older as the vascularity of tendons decreases; repetitive microtrauma may contribute. Repeated or extreme trauma (short of rupture), strain, and excessive or unaccustomed exercise probably also contribute. Some quinolone antibiotics may increase the risk of tendinopathy and tendon rupture.

Risk of tendinitis may be increased by certain systemic disorders—most commonly RA, systemic sclerosis, gout, reactive arthritis, and diabetes or, very rarely, amyloidosis or markedly elevated blood cholesterol levels. In younger adults, particularly women, disseminated gonococcal infection may cause acute migratory tenosynovitis.

Symptoms and Signs

Affected tendons are usually painful when moved. Occasionally, tendon sheaths become swollen and fluid accumulates, usually when patients have infection, RA, or gout. Swelling may be visible or only palpable. Along the tendon, palpation elicits localized tenderness of varying severity.

In systemic sclerosis, the tendon sheath may remain dry, but movement of the tendon in its sheath causes friction, which can be felt, or heard with a stethoscope.

Diagnosis

• Clinical evaluation

• Sometimes imaging

Usually, the diagnosis can be based on symptoms and physical examination, including palpation or specific maneuvers to assess pain. MRI or ultrasonography may be done to confirm the diagnosis or rule out other disorders. MRI can detect tendon tears and inflammation (as can ultrasonography).

• **Rotator cuff tendinitis:** This disorder is the most common cause of shoulder pain. Active abduction in an arc of 40 to 120° and internal rotation cause pain (see p. 3298). Passive abduction causes less pain. Ca deposits in the tendon just below the acromion are sometimes visible on x-ray. Ultrasonography or MRI may help with further evaluation and with treatment decisions.

• **Bicipital tendinitis:** Pain in the biceps tendon is aggravated by shoulder flexion or resisted supination of the forearm. Examiners can elicit tenderness proximally over the bicipital groove of the humerus by rolling (flipping) the bicipital tendon under their thumb.

- **Volar flexor tenosynovitis** (digital tendinitis): This common musculoskeletal disorder is often overlooked (see p. 393). Pain occurs in the palm on the volar aspect of the thumb or other digits and may radiate distally. Palpation of the tendon and sheath elicits tenderness; swelling and sometimes a nodule are present. In later stages, the digit may lock when it is flexed, then extend suddenly with a snap (trigger finger).

- **Gluteus medius tendinitis:** Patients with trochanteric bursitis almost always have gluteus medius tendinitis. In patients with trochanteric bursitis, palpation over the lateral prominence of the greater trochanter elicits tenderness. Patients often have a history of chronic pressure on the joint, trauma, a change in gait (eg, due to osteoarthritis, stroke, or leg-length discrepancy), or inflammation at this site (eg, in RA).

Treatment

- Rest or immobilization, heat or cold, followed by exercise

- High-dose NSAIDs

- Sometimes corticosteroid injection

Symptoms are relieved by rest or immobilization (splint or sling) of the tendon, application of heat (usually for chronic inflammation) or cold (usually for acute inflammation), and high-dose NSAIDs (see Table 35-2 on p. 336) for 7 to 10 days. Indomethacin or colchicine may be helpful if gout is the cause (see p. 349). After inflammation is controlled, exercises that gradually increase range of motion should be done several times a day, especially for the shoulder, which can develop contractures rapidly.

Injecting a sustained-release corticosteroid (eg, betamethasone 6 mg/mL, triamcinolone 40 mg/mL, methylprednisolone 20 to 40 mg/mL) in the tendon sheath may help; injection is usually indicated if pain is severe or if the problem has been chronic. Injection volume may range from 0.3 mL to 1 mL, depending on the site. An injection through the same needle of an equal or double volume of local anesthetic (eg, 1 to 2% lidocaine) confirms the diagnosis if pain is relieved immediately. Clinicians should be careful not to inject the tendon (which can be recognized by marked resistance to injection); doing so may weaken it, increasing risk of rupture. Patients are advised to rest the injected joint to reduce the slight risk of rupture. Infrequently, symptoms can worsen for up to 24 h after the injection.

Repeat injections and symptomatic treatment may be required. Rarely, for persistent cases, particularly rotator cuff tendinitis, surgical exploration with removal of Ca deposits or tendon repair, followed by graded physical therapy, is needed. Occasionally, patients require surgery to release scars that limit function or tenosynovectomy to relieve chronic inflammation.

Fibromyalgia

(Myofascial Pain Syndrome; Fibrositis; Fibromyositis)

Fibromyalgia is a common nonarticular disorder of unknown cause characterized by generalized aching (sometimes severe); widespread tenderness of muscles, areas around tendon insertions, and adjacent soft tissues; muscle stiffness; fatigue; and poor sleep. Diagnosis is clinical. Treatment includes exercise, local heat, stress management, drugs to improve sleep, and analgesics.

In fibromyalgia, any fibromuscular tissues may be involved, especially those of the occiput, neck, shoulders, thorax, low back, and thighs. There is no specific histologic abnormality. Symptoms and signs are generalized, in contrast to localized soft-tissue pain and tenderness (myofascial pain syndrome—see also p. 533), which is often related to overuse or microtrauma.

Fibromyalgia is common; it is about 7 times more common among women, usually young or middle-aged women, but can occur in men, children, and adolescents. Because of the sex difference, it is sometimes overlooked in men. It sometimes occurs in patients with systemic rheumatic disorders.

The cause is unknown, but disruption of stage 4 sleep may contribute, as can emotional stress. Patients may tend to be perfectionists. Fibromyalgia may be precipitated by a viral or other systemic infection (eg, Lyme disease) or a traumatic event.

Symptoms and Signs

Stiffness and pain frequently begin gradually and diffusely and have an achy quality. Symptoms can be exacerbated by environmental or emotional stress, poor sleep, trauma, or exposure to dampness or cold or by a physician who implies that the disorder is "all in the head."

Patients tend to be stressed, tense, anxious, fatigued, ambitious, and sometimes depressed. Many patients also have irritable bowel syndrome symptoms or migraine or tension headaches. Pain may worsen with fatigue, muscle strain, or overuse. Specific, discrete areas of muscle (tender points) may be tender when palpated.

Diagnosis

• Clinical criteria

Fibromyalgia is suspected in patients with the following:

• Generalized pain and tenderness, especially if disproportionate to physical findings

• Negative laboratory results despite widespread symptoms

• Fatigue as the predominant symptom

Tests should include ESR or C-reactive protein, CK, and probably tests for hypothyroidism and hepatitis C (which can cause fatigue and generalized myalgias). The diagnosis is based on clinical criteria, including tenderness at some of the 18 specified tender points (see Fig. 41-1). Most experts no longer require a specific number of tender points to make the diagnosis, as originally proposed (≥ 11 of 18). Patients with only some of the specified features may still have fibromyalgia.

[**Fig. 41-1.** Diagnosing fibromyalgia.]

To avoid potential pitfalls, clinicians should consider the following:

• Fibromyalgia is often overlooked in men, children, and adolescents.

• Chronic fatigue syndrome (see p. 3442) can cause similar generalized myalgias and fatigue and typically produces normal laboratory test results.

• Polymyalgia rheumatica (see p. 325) can cause generalized myalgias, particularly in older adults; it can be distinguished because it tends to affect proximal muscles selectively and ESR is high.

• In patients with systemic rheumatic disorders, diagnosing fibromyalgia may be difficult. For example, fibromyalgia may be misinterpreted as an exacerbation of RA or SLE.

Prognosis

Fibromyalgia tends to be chronic but may remit spontaneously if stress decreases. It can also recur at frequent intervals. Functional prognosis is usually favorable for patients being treated with a comprehensive, supportive program, although symptoms tend to persist to some degree.

Treatment

• Stretching and aerobic exercise, local heat, and massage

• Stress management

• Tricyclic antidepressants or cyclobenzaprine to improve sleep

• Analgesics

Stretching exercises, aerobic exercises, sufficient sound sleep, local applications of heat, and gentle massage may provide relief. Overall stress management (eg, deep breathing exercises, meditation, psychologic support, counseling if necessary) is important.

Exercises to gently stretch the affected muscles should be done daily; stretches should be held for about 30 sec and repeated about 5 times. Aerobic exercise (eg, fast walking, swimming, exercise bicycle) can lessen symptoms.

Improving sleep is critical. Low-dose oral tricyclic antidepressants at bedtime (eg, amitriptyline 10 to 50 mg, trazodone 50 to 150 mg, doxepin 10 to 25 mg) or the pharmacologically similar cyclobenzaprine 10 to 40 mg may promote deeper sleep and decrease muscle pain. The lowest effective dose should be used. Drowsiness, dry mouth, and other adverse effects may make some or all of these drugs intolerable, particularly for the elderly.

Nonopioid analgesics (eg, tramadol, propoxyphene, acetaminophen, NSAIDs) may help some patients but on average are not effective. Opioids should be avoided. Pregabalin, used as an adjunct to exercise, measures to improve sleep, and stress management, may help reduce pain.

Rarely, injections of 0.5% bupivacaine or 1% lidocaine 1 to 5 mL are used to treat incapacitating areas of focal tenderness, but such injections should not be relied on as primary treatment.

Drugs taken by the patient should be reviewed to identify those that may aggravate sleep problems. Such drugs should be stopped, and future use should be avoided. Anxiety or depression, if present, may require treatment.

Muscle Cramps

A muscle cramp is a sudden, brief, painful contraction of a muscle or group of muscles.

Cramps (charley horses) can occur in healthy people (usually middle-aged and elderly people), sometimes during rest, but particularly during or after exercise. Leg cramps can occur during sleep, causing pain and plantar flexion of the foot and toes.

Tight calf muscles (eg, from lack of stretching, inactivity, or sometimes chronic lower leg edema) are a common cause of leg cramps. Cramps may also be caused by electrolyte abnormalities (eg, hypokalemia). Exertional muscle pain from ischemia due to peripheral arterial disease (claudication) may cause similar calf pain, but this pain is due to inadequate blood flow to muscles and not to a muscle contraction as with a cramp.

Treatment

• Stretching

If a cramp occurs, stretching the affected muscle often relieves the cramp. For example, for a calf cramp, the person could use a hand to pull the foot and toes upward (dorsiflexion) or do the runner's stretch.

Prevention

Measures to prevent cramps include the following:

- Not exercising immediately after eating
- Gently stretching the muscles before exercising or going to bed
- Drinking plenty of fluids (particularly beverages that contain potassium) after exercise
- Not consuming stimulants (eg, caffeine, nicotine, ephedrine, pseudoephedrine)

The runner's stretch is most useful. A person stands with one leg forward and bent at the knee and the other leg behind and the knee straight—a lunge position. The hands can be placed on the wall for balance. Both heels remain on the floor. The knee of the front leg is bent further until a stretch is felt along the back of the other leg. The greater the distance between the two feet and the more the front knee is bent, the greater the stretch. The stretch is held for 30 sec and repeated 5 times. The set of stretches is repeated on the other side.

Most of the drugs prescribed to prevent cramps (eg, quinine, magnesium, benzodiazepines) have no demonstrated efficacy and are not recommended. Mexiletine sometimes helps, but whether using it is worth the risk of adverse effects is unclear. These adverse effects include nausea, vomiting, heartburn, dizziness, and tremor. Ca supplements are safe and have few adverse effects but have not proved effective.

Chapter 42. Neck and Back Pain

Introduction

Neck pain and back pain are among the most common reasons for physician visits. This discussion covers neck pain involving the posterior neck (not pain limited to the anterior neck) and does not cover most major traumatic injuries (eg, fractures, dislocations, subluxations).

Pathophysiology

Depending on the cause, neck or back pain may be accompanied by neurologic symptoms.

If a nerve root is affected, pain may radiate distally along the distribution of that root (called radicular pain or, in the low back, sciatica). Strength, sensation, and reflexes of the area innervated by that root may be impaired.

If the spinal cord is affected, strength, sensation, and reflexes may be impaired at the affected spinal cord level and all levels below (called segmental neurologic deficits).

If the cauda equina is affected, segmental deficits develop in the lumbosacral region, typically with loss of bowel and bladder function, loss of perianal sensation, erectile dysfunction, urinary retention, and loss of rectal tone and sphincter (eg, bulbocavernosus, anal wink) reflexes.

Any painful disorder of the spine may also cause reflex tightening (spasm) of paraspinal muscles, which can be excruciating.

Etiology

Most neck and back pain is caused by disorders of the spine. Fibromyalgia is also a common cause. Occasionally, pain is referred from extraspinal disorders (particularly vascular, GI, or GU disorders). Some uncommon causes—spinal and extraspinal—are serious.

Most spinal disorders are mechanical. Only a few involve infection, inflammation, or cancer (considered nonmechanical).

Common causes: Most mechanical spine disorders that cause neck or back pain involve a nonspecific mechanical derangement:

• Muscle strain, ligament sprain, spasm, or a combination

Only about 15% involve specific structural lesions that clearly cause the symptoms, primarily the following:

• Disk herniation

• Compression fracture

• Lumbar spinal stenosis

• Osteoarthritis

• Spondylolisthesis

In the other mechanical disorders, there are no specific lesions, or the findings (eg, disk bulging or degeneration, osteophytes, spondylolysis, congenital facet abnormalities) are common among people without neck or back pain, and thus are questionable as the etiology of pain. However, etiology of back pain, particularly if mechanical, is often multifactorial, with an underlying disorder exacerbated by fatigue, physical deconditioning, and sometimes psychosocial stress or psychiatric abnormality. Thus, identifying

a single cause is often difficult or impossible.

Serious uncommon causes: Serious causes may require timely treatment to prevent disability or death.

Serious **extraspinal** disorders include the following:

• Abdominal aortic aneurysm

• Aortic dissection

• Carotid or vertebral artery dissection

• Acute meningitis

• Angina or MI

• Certain GI disorders (eg, cholecystitis, diverticulitis, diverticular abscess, pancreatitis, penetrating peptic ulcer, retrocecal appendicitis)

• Certain pelvic disorders (eg, ectopic pregnancy, ovarian cancer, salpingitis)

• Certain pulmonary disorders (eg, pleuritis, pneumonia)

• Certain urinary tract disorders (eg, prostatitis, pyelonephritis)

Serious **spinal** disorders include the following:

• Infections (eg, diskitis, epidural abscess, osteomyelitis)

• Primary tumors (of spinal cord or vertebrae)

• Metastatic vertebral tumors (most often from breasts, lungs, or prostate)

Mechanical spine disorders can be serious if they compress the spinal nerve roots or, particularly, the spinal cord. Spinal cord compression may result from disorders such as tumors and spinal epidural abscess or hematoma.

Other uncommon causes: Neck or back pain can result from many other disorders, such as Paget's disease of bone, torticollis, thoracic outlet syndrome, temporomandibular joint syndrome, herpes zoster, and spondyloarthropathies (ankylosing spondylitis most often, but also enteropathic arthritis, psoriatic arthritis, reactive arthritis, and undifferentiated spondyloarthropathy).

Evaluation

General: Because the cause is often multifactorial, a definitive diagnosis cannot be established in many patients. However, clinicians should determine the following if possible:

• Whether pain has a spinal or extraspinal cause

• Whether the cause is a serious disorder

History: History of present illness should include quality, onset, duration, severity, location, radiation, and time course of pain, as well as modifying factors such as rest, activity, changes in position, weight bearing, and time of day (eg, at night, when awakening). Accompanying symptoms to note include stiffness, numbness, paresthesias, weakness, urinary retention, and incontinence.

Review of systems should note symptoms suggesting a cause, including fever and chills (infection); weight loss and poor appetite (infection or cancer); fatigue, depressive symptoms, and headaches

(multifactorial mechanical back pain); worsening of neck pain during swallowing (esophageal disorders); anorexia, nausea, vomiting, and change in bowel function or stool (GI disorders); urinary symptoms and flank pain (urinary tract disorders); cough, dyspnea, and worsening during inspiration (pulmonary disorders); vaginal bleeding or discharge and pain related to menstrual cycle phase (pelvic disorders).

Past medical history includes known neck or back disorders (including osteoporosis, osteoarthritis, disk disorders, recent or remote injury) and surgery, risk factors for back disorders (eg, cancer, osteoporosis), risk factors for aneurysm (eg, smoking, hypertension), and risk factors for infection (eg, immunosuppression; IV drug use; recent surgery, penetrating trauma, or bacterial infection).

Physical examination: Temperature and general appearance are noted. When possible, patients should be unobtrusively observed as they move into the examination room, undress, and climb onto the table. If symptoms are exacerbated by psychologic issues, true functional level can be assessed more accurately when patients are not aware they are being evaluated.

The examination focuses on the spine and the neurologic examination. If no mechanical spinal source of pain is obvious, patients are checked for sources of referred pain.

In the spinal examination, the back and neck are inspected for any visible deformity, area of erythema, or vesicular rash. The spine and paravertebral muscles are palpated for tenderness and muscle spasm. Gross range of motion is tested.

In the neurologic examination, strength and deep tendon reflexes are tested. In patients with neurologic symptoms, sensation and sacral nerve function (eg, rectal tone, anal wink reflex, bulbocavernosus reflex) are tested. These tests are among the most reliable physical tests for confirming normal spinal cord function. Corticospinal tract dysfunction is indicated by the extensor plantar response and Hoffman's sign. To test for Hoffman's sign, clinicians tap the nail or flick the volar surface of the 3rd finger; if the distal phalanx of the thumb flexes, the test is positive, usually indicating corticospinal tract dysfunction caused by stenosis of the cervical cord. Sensory findings are subjective and may be unreliable.

The straight leg raise test helps confirm sciatica. The patient is supine with both knees extended and the ankles dorsiflexed. The clinician raises the affected leg, keeping the knee extended. If sciatica is present, 10 to 60° of elevation typically causes symptoms. For the crossed straight leg raise test, the unaffected leg is raised; the test is positive if sciatica occurs in the affected leg. A positive straight leg test is sensitive but not specific for herniated disk; the crossed straight leg raise test is less sensitive but 90% specific. The seated straight leg raise test is done while patients are seated with the hip joint flexed at 90°; the lower leg is slowly raised until the knee is fully extended. If sciatica is present, the pain occurs as the leg is extended.

In the general examination, the lungs are auscultated. The abdomen is checked for tenderness, masses, and, particularly in patients > 55, a pulsatile mass (which suggests abdominal aortic aneurysm). With a fist, clinicians percuss the costovertebral angle for tenderness, suggesting pyelonephritis.

Rectal examination, including stool testing for occult blood and, in men, prostate examination, is done. In women with symptoms suggesting a pelvic disorder or with unexplained fever, pelvic examination is done.

Lower-extremity pulses are checked.

Red flags: The following findings are of particular concern:

• Abdominal aorta that is > 5 cm (particularly if tender) or lower-extremity pulse deficits

• Acute, tearing mid-back pain

• Cancer, diagnosed or suspected

• Duration of pain > 6 wk

- Neurologic deficit
- Fever
- GI findings such as localized abdominal tenderness, peritonitis, melena, or hematochezia
- Infection risk factors (eg, immunosuppression; IV drug use; recent surgery, penetrating trauma, or bacterial infection)
- Meningismus
- Severe nocturnal or disabling pain
- Unexplained pain after age 55
- Unexplained weight loss

Interpretation of findings: Although serious extraspinal disorders (eg, cancers, aortic aneurysms, epidural abscesses, osteomyelitis) are uncommon causes of back pain, they are not rare, particularly in high-risk groups.

A spinal cause is more likely (but not definitive) than referred pain from an extraspinal cause when

- Pain is worsened by movement or weight bearing and is relieved by rest or recumbency
- Vertebral or paravertebral tenderness is present

Red flag findings should heighten suspicion of a serious cause (see Table 42-1).

Other findings are also helpful. Erythema and tenderness over the spine suggests infection, particularly in patients with risk factors. Worsening of pain with flexion is consistent with intervertebral disk disease; worsening with extension suggests spinal stenosis, arthritis affecting the facet joints, or retroperitoneal inflammation or infiltration (eg, pancreatic or kidney inflammation or tumor). Tenderness over certain specific trigger points suggests fibromyalgia. Deformities of the proximal interphalangeal (PIP) and distal interphalangeal (DIP) finger joints and stiffness that lessens within 30 min after awakening suggest osteoarthritis. Neck pain that is unrelated to swallowing and is exertional may indicate angina.

Testing: Usually, if duration of pain is short (< 4 to 6 wk), no testing is required unless red flag findings are present, patients have had a serious injury (eg, vehicular crash, fall from a height, penetrating trauma), or evaluation suggests a specific nonmechanical cause (eg, pyelonephritis).

Plain x-rays can identify most osteoporotic fractures and osteoarthritis. However, they do not identify abnormalities in soft tissue (the most common cause of back and neck pain) or nerve tissue (as occurs in many serious disorders). Thus, x-rays are usually unnecessary and do not change management. Sometimes

[**Table 42-1.** Interpretation of Red Flag Findings in Patients with Back Pain]

x-rays are done to identify obvious bone abnormalities (eg, those due to infection or tumors) and to avoid MRI and CT, which are harder to obtain but which are much more accurate and usually necessary.

Testing is guided by findings and suspected cause:

- Neurologic deficits, particularly those consistent with spinal cord compression: MRI or CT myelography, done as soon as possible
- Possible infection: WBC count, ESR, imaging (usually MRI or CT), and culture of infected tissue

- Possible cancer: CT or MRI and possibly biopsy
- Possible aneurysm: CT, angiography, or sometimes ultrasonography
- Possible aortic dissection: Angiography, CT, or MRI
- Symptoms that are disabling or that persist > 6 wk: Imaging (usually MRI or CT) and, if infection is suspected, WBC count and ESR
- Other extraspinal disorders: Testing as appropriate (eg, chest x-ray for pulmonary disorders, urinalysis for urinary tract disorders)

Treatment

Underlying disorders are treated.

Acute musculoskeletal pain (with or without radiculopathy) is treated with

- Analgesics
- Heat and cold
- Early mobilization followed by stabilization exercises

Acetaminophen or NSAIDs are the initial choice of analgesics, but opioids may be necessary for severe pain. Adequate analgesia is important immediately after acute injury to help limit the cycle of pain and spasm.

Acute muscle spasms may also be relieved by cold or heat. Cold is usually preferred to heat during the first 2 days after an injury. Ice and cold packs should not be applied directly to the skin. They should be enclosed (eg, in plastic) and placed over a towel or cloth. The ice is removed after 20 min, then later reapplied for 20 min over a period of 60 to 90 min. This process can be repeated several times during the first 24 h. Heat, using a heating pad, can be applied for the same periods of time. Because the skin on the back may be insensitive to heat, heating pads must be used cautiously to prevent burns. Patients are advised not to use a heating pad at bedtime to avoid prolonged exposure due to falling asleep with the pad still on their back. Diathermy may help reduce muscle spasm and pain after the acute stage.

Oral muscle relaxants (eg, cyclobenzaprine, methocarbamol, metaxalone) are controversial. Benefits of these drugs should be weighed against their CNS and other adverse effects, particularly in elderly patients, who may have more severe adverse effects.

Although a brief initial period (eg, 1 to 2 days) of decreased activity is sometimes needed for comfort, prolonged bed rest, spinal traction, and corsets are not beneficial. Patients with severe torticollis may benefit from a cervical collar and contour pillow until pain is relieved and they can participate in a stabilization program.

Spinal manipulation may help relieve pain caused by muscle spasm or an acute neck or back injury; however, some forms of manipulation may have risks for patients with disk disorders or osteoporosis.

When acute pain decreases enough that motion is possible, a lumbar stabilization program is begun. This program includes exercises that strengthen abdominal and low back muscles plus instruction in work posture; the aim is to strengthen the supporting structures of the back and reduce the likelihood of the condition becoming chronic or recurrent.

Clinicians should reassure patients with acute nonspecific musculoskeletal back pain that the prognosis is good and that activity and exercise are safe even when they cause some discomfort. Clinicians should be thorough, kind, firm, and nonjudgmental. If depression or secondary gain persists for several months,

psychologic evaluation should be considered.

Geriatrics Essentials

Low back pain affects 50% of adults > 60.

Abdominal aortic aneurysm (and CT or ultrasonography to detect it) should be considered in elderly patients with atraumatic low back pain, even if no physical findings suggest this diagnosis.

Imaging of the spine may be appropriate for elderly patients (eg, to rule out cancer) even when the cause appears to be uncomplicated musculoskeletal back pain.

Oral muscle relaxants (eg, cyclobenzaprine, methocarbamol, metaxalone) are controversial; anticholinergic, CNS, and other adverse effects may outweigh potential benefits in elderly patients.

Key Points

- Most neck and back pain is caused by mechanical spinal disorders, usually nonspecific, self-limited musculoskeletal derangements.
- Most mechanical disorders are treated with analgesics, early mobilization, and exercises; prolonged bed rest and immobilization are avoided.
- Back pain is often multifactorial, making diagnosis difficult.
- Serious spinal or extraspinal disorders are unusual causes.
- Red flag findings often indicate a serious disorder and the need for testing.
- Patients with segmental neurologic deficits suggesting spinal cord compression require MRI or CT myelography as soon as possible.
- Normal spinal cord function during physical examination is best confirmed by tests of sacral nerve function (eg, rectal tone, anal wink reflex, bulbocavernosus reflex).
- Pain not worsened by movement is often extraspinal, particularly if no vertebral or paravertebral tenderness is detected.
- Abdominal aortic aneurysm should be considered in any elderly patient with low back pain, even if no physical findings suggest this diagnosis.

Spasmodic Torticollis

Spasmodic torticollis is characterized by involuntary tonic contractions or intermittent spasms of neck muscles. The cause is unknown. Diagnosis is clinical. Treatment can include physical therapy, drugs, and selective denervation of neck muscles with surgery or locally injected botulinum toxin.

In torticollis, contraction of the neck muscles causes the neck to turn from its usual position. It is the most common dystonia (see p. 1760).

Spasmodic (or adult-onset) torticollis is usually idiopathic. About 5% of patients with spasmodic torticollis have a family history. One third of these patients have other dystonias (eg, eyelids, face, jaw, hand). Torticollis can also be congenital or secondary to other conditions such as lesions of the brain stem and basal ganglia.

Symptoms and Signs

Symptoms may begin at any age but usually begin between age 20 and 60, with a peak between age 30 and 50.

Symptoms usually begin gradually but may begin suddenly. Painful tonic contractions or intermittent spasms of the sternocleidomastoid, trapezius, and other neck muscles occur, usually unilaterally, and result in abnormal head position. Sternocleidomastoid muscle contraction causes the head to rotate to the opposite side and the neck to flex laterally to the same side. Rotation may involve any plane but almost always has a horizontal component. Besides rotational tilting (torticollis), the head can tilt laterally (laterocollis), forward (anterocollis), or backward (retrocollis). During sleep, muscle spasms disappear.

Spasmodic torticollis ranges from mild to severe. Usually, it progresses slowly for 1 to 5 yr, then plateaus. About 10 to 20% of patients recover spontaneously within 5 yr of onset (usually in milder cases with younger age onset). However, it may persist for life and can result in restricted movement and postural deformity.

Diagnosis

• Clinical evaluation

The diagnosis is based on characteristic symptoms and signs and exclusion of alternative diagnoses, such as the following:

• Tardive dyskinesia can cause torticollis but can usually be distinguished by a history of chronic antipsychotic use and involuntary movements in muscles outside of the neck.

• Basal ganglia disease and occasionally CNS infections can cause movement disorders but usually also involve other muscles. Also, CNS infections are usually acute and cause other symptoms.

• Neck infections or tumors are usually differentiated by features of the primary process.

• Antipsychotics and other drugs can cause acute torticollis, but the symptoms usually develop in hours and resolve within days.

Treatment

• Physical measures

• Sometimes botulinum toxin or oral drugs

Spasms can sometimes be temporarily inhibited by physical therapy and massage, including sensory biofeedback techniques (slight tactile pressure to the jaw on the same side as head rotation) and any light touch.

Injections of botulinum toxin type A into the dystonic muscles can reduce painful spasms for 1 to 3 mo in about 70% of patients, restoring a more neutral position of the head. However, this treatment can lose effectiveness with repeated injections because antibodies develop against the toxin. Drugs can usually relieve pain, but they suppress dystonic movements in only about 25 to 33% of patients. Anticholinergics such as trihexyphenidyl 10 to 25 mg po once/day or bid may help, but adverse effects may limit their use; benzodiazepines (particularly clonazepam 0.5 mg po bid) and baclofen and carbamazepine may help. All drugs should be started in low doses. Doses should be increased until symptoms are controlled or intolerable adverse effects (particularly likely in the elderly) develop.

Surgery is controversial. The most successful surgical approach selectively severs nerves to affected neck muscles, permanently weakening or paralyzing them. Results are favorable when the procedure is done at centers with extensive experience.

Rarely, an emotional problem contributes to spasmodic torticollis; psychiatric treatment is indicated.

Psychiatric prognosis is best if symptom onset coincided with exogenous stress.

Sciatica

Sciatica is pain along the sciatic nerve. It usually results from compression of nerve roots in the lower back. Common causes include intervertebral disk herniation, osteophytes, and narrowing of the spinal canal (spinal stenosis). Symptoms include pain radiating from the buttocks down the leg. Diagnosis sometimes involves MRI or CT. Electromyography and nerve conduction studies can identify the affected level. Treatment includes symptomatic measures and sometimes surgery, particularly if there is a neurologic deficit.

Etiology

Sciatica is typically caused by nerve root compression, usually due to intervertebral disk herniation (see p. 1810), bony irregularities (eg, osteoarthritic osteophytes, spondylolisthesis), or, much less often, intraspinal tumor or abscess. Compression may occur within the spinal canal or intervertebral foramen. The nerves can also be compressed outside the vertebral column, in the pelvis or buttocks. L5-S1, L4-L5, and L3-L4 nerve roots are most often affected (see Table 186-1 on p. 1805).

Symptoms and Signs

Pain radiates along the course of the sciatic nerve, most often down the buttocks and posterior aspect of the leg to below the knee. The pain is typically burning, lancinating, or stabbing. It may occur with or without low back pain. The Valsalva maneuver or coughing may worsen pain due to disk herniation. Patients may complain of numbness and sometimes weakness in the affected leg.

Nerve root compression can cause sensory, motor, or, the most objective finding, reflex deficits see p. 1810). L5-S1 disk herniation may affect the ankle jerk reflex; L3-L4 herniation may affect the knee jerk. Straight leg raising may cause pain that radiates down the leg when the leg is raised above 60° and sometimes less. This finding is sensitive for sciatica; pain radiating down the affected leg when the contralateral leg is lifted (crossed straight leg raising) is more specific for sciatica.

Diagnosis

• Clinical evaluation

• Sometimes MRI, electrodiagnostic studies, or both

Sciatica is suspected based on the characteristic pain. If it is suspected, strength, reflexes, and sensation should be tested. If there are neurologic deficits or if symptoms persist for > 6 wk, imaging and electrodiagnostic studies should be done. Structural abnormalities causing sciatica (including spinal stenosis) are most accurately diagnosed by MRI or CT. Electrodiagnostic studies can confirm the presence and degree of nerve root compression and can exclude conditions that may mimic sciatica, such as polyneuropathy. These studies may help determine whether the lesion involves single or multiple nerve levels and whether the clinical findings correlate with MRI abnormalities (especially valuable before surgery). However, abnormalities may not be evident on electrodiagnostic studies for up to a few weeks after symptoms begin.

Treatment

• Bed rest (brief), analgesics, and sometimes drugs that relieve neuropathic pain

• Surgery for severe cases

Acute pain relief can come from 24 to 48 h of bed rest in a recumbent position with the head of the bed elevated about 30° (semi-Fowler's position). Measures used to treat low back pain, including nonopioid analgesics (eg, NSAIDs, acetaminophen), can be tried for up to 6 wk. Drugs that decrease neuropathic

pain (see p. 1633), such as gabapentin or other anticonvulsants or low-dose tricyclic antidepressants (no tricyclic is superior to another), may relieve symptoms. Gabapentin 100 to 300 mg po at bedtime is used initially, but doses typically have to be much higher, up to 3600 mg/day. As with all sedating drugs, care should be taken in the elderly, patients at risk of falls, and those with arrhythmias.

Muscle spasm may be relieved with therapeutic heat or cold (see p. 3459), and physical therapy may be useful. Whether corticosteroids should be used to treat acute radicular pain is controversial. Given epidurally, corticosteroids may accelerate pain relief, but they probably should not be used unless pain is severe or persistent.

Surgery is indicated only for unequivocal disk herniation plus one of the following:

- Muscular weakness
- Progressive neurologic deficit
- Intolerable, intractable pain that interferes with job or personal functions in an emotionally stable patient and that has not lessened after 6 wk of conservative treatment

Some of these patients benefit from epidural corticosteroids instead of surgery.

Classic diskectomy with limited laminotomy for intervertebral disk herniation is the standard procedure. If herniation is localized, microdiskectomy may be done; with it, the skin incision and laminotomy can be smaller. Chemonucleolysis, using intradiskal injection of chymopapain, is no longer used.

Predictors of poor surgical outcome include

- Prominent psychiatric factors
- Persistence of symptoms for > 6 mo
- Heavy manual labor
- Prominence of back pain (nonradicular)
- Secondary gain (ie, litigation and compensability)

Lumbar Spinal Stenosis

Lumbar spinal stenosis (LSS) is narrowing of the lumbar spinal canal, which puts pressure on the sciatic nerve roots (or sometimes the cord) before their exit from the foramina. It causes positional back pain, symptoms of nerve root compression, and lower-extremity pain during walking or weight bearing.

Spinal stenosis can be congenital or acquired. It may involve the cervical or lumbar spine. Acquired LSS is a common cause of sciatica in middle-aged or elderly patients. The most common causes of LSS are osteoarthritis, degenerative disk disorders, and spondylolisthesis with compression of the cauda equina. Other causes include Paget's disease of bone, RA, and ankylosing spondylitis.

Symptoms and Signs

Pain occurs in the buttocks, thighs, or calves during walking, running, climbing stairs, or even standing. The pain is not relieved by standing still but by flexing the back or by sitting (although paresthesias may continue). Walking up hills is less painful than walking down because the back is slightly flexed. Patients may have pain, paresthesias, weakness, and diminished reflexes in the affected nerve root distribution. Rarely, spinal cord compression may cause cauda equina syndrome (see p. 1806).

Diagnosis

• Clinical evaluation

• Sometimes MRI, electrodiagnostic studies, or both

Spinal stenosis is suspected based on characteristic symptoms. Diagnostic tests are the same as for sciatica (see p. 383). Calf symptoms may simulate those of intermittent claudication. Claudication can be differentiated by relief with rest (not position change), skin atrophy, and abnormalities in pulses, capillary refill, and vascular tests.

Treatment

• Bed rest (brief), analgesics, and sometimes drugs that relieve neuropathic pain

• Surgery for severe cases

Conservative treatments and indications for surgery are similar to those for sciatica. For advanced spinal stenosis, surgery involves decompression of nerve root entrapment by vertebral canal and foraminal encroachments, which sometimes requires laminectomy at 2 or 3 levels plus foraminotomies.

Spinal stability must be preserved. Spinal fusion is indicated if there is instability or severe, well-localized arthritic changes in 1 or 2 vertebral interspaces.

Nontraumatic Subluxation

Spinal dislocation and subluxation (partial dislocation) are usually due to trauma. For example, atlantoaxial subluxation and spondylolisthesis can result from obvious major trauma, such as a high-speed deceleration injury. However, these disorders can occur with minimal, unrecognized, or no trauma. Rarely, cervical disk disorders can cause nontraumatic spinal subluxation.

Atlantoaxial Subluxation

(C1-C2 Subluxation)

Atlantoaxial subluxation is misalignment of the 1st and 2nd cervical vertebrae, which may occur only with neck flexion.

Atlantoaxial subluxation can result from major trauma or can occur without trauma in patients with RA, juvenile RA, or ankylosing spondylitis.

Atlantoaxial subluxation is usually asymptomatic but may cause vague neck pain, occipital headache, or occasionally intermittent (and potentially fatal) cervical spinal cord compression.

Diagnosis

• Plain x-rays

• MRI if cord compression suspected

It is usually diagnosed with plain cervical x-rays; however, flexion views may be required to show intermittent subluxation. Views during flexion, done by the patient, show dynamic instability of the entire cervical spine. If x-rays are normal and subluxation is still suspected, MRI, which is more sensitive, should be done. MRI also provides the most sensitive evaluation of spinal cord compression and is done immediately if cord compression is suspected.

Treatment

Indications for treatment include pain, neurologic deficits, and potential spinal instability. Treatment includes symptomatic measures and cervical immobilization, usually beginning with a rigid cervical collar. Surgery may be needed to stabilize the spine.

Spondylolisthesis

Spondylolisthesis is subluxation of lumbar vertebrae, usually occurring during adolescence. It usually results from a congenital defect in the pars interarticularis (spondylolysis).

Spondylolisthesis is usually fixed. It usually involves the L3-L4, L4-L5, or L5-S1 vertebrae. Spondylolisthesis often occurs in adolescents or young adults who are athletes and who have had only minimal trauma; the cause is a lumbar vertebra weakened by a congenital defect in the pars interarticularis. This defect is easily fractured; separation of the fracture fragments causes the subluxation. Spondylolisthesis can also occur with minimal trauma in patients who are > 60 and have osteoarthritis. If mild to moderate (subluxation of ≤ 50%), spondylolisthesis, particularly in the young, may cause little or no pain. Spondylolisthesis can predispose to later development of spinal stenosis. If due to major trauma, spondylolisthesis can cause spinal cord compression or other neurologic deficits (see p. 1810); these deficits rarely occur.

Spondylolisthesis is staged according to the degree of subluxation of adjacent vertebral bodies:

- Stage I: 0 to 25%
- Stage II: 25 to 50%
- Stage III: 50 to 75%
- Stage IV: 75 to 100%

Spondylolisthesis is evident on plain lumbar x-rays. The lateral view is usually used for staging.

Treatment is usually symptomatic.

Chapter 43. Hand Disorders

Introduction

Common hand disorders include a variety of deformities, ganglia, infections, Kienbock's disease, nerve compression syndromes, noninfectious tenosynovitis, and osteoarthritis. Complex regional pain syndrome (reflex sympathetic dystrophy) is discussed on p. 1633, and hand injuries are discussed in Ch. 323.

Evaluation

History and physical examination findings are often diagnostic in hand disorders.

History: The history should include information about the trauma or other events that may be associated with symptoms. The presence and duration of deformity and difficulty with motion are noted. The presence, duration, severity, and factors that exacerbate or relieve pain are elicited. Associated symptoms, such as fever, swelling, rashes, Raynaud's syndrome (see p. 2221), paresthesias, and weakness, are also recorded.

Physical examination: Examination should include inspection for redness, swelling, or deformity and palpation for tenderness. Active range of motion should be tested for any possible tendon injury. Passive range of motion can assess whether specific motions aggravate pain. Sensation is tested most accurately by 2-point discrimination, using 2 ends of a paper clip. Motor function testing involves muscles innervated by the radial, median, and ulnar nerves. Vascular examination should include evaluation of capillary refill, radial and ulnar pulses, and Allen's test (see p. 1856). Stress testing is helpful when specific ligament injuries are suspected (eg, ulnar collateral ligament in gamekeeper's thumb—see p. 3216). Provocative testing can aid in the diagnosis of tenosynovitis and nerve compression syndromes.

Laboratory testing: Laboratory testing has a limited role. Plain x-rays and MRI are helpful for injuries, arthritis, and Kienbock's disease or to rule out hidden foreign bodies that could be sources of infections. Nerve conduction testing can help diagnose nerve compression syndromes. Bone scans may assist in diagnosing occult fractures and reflex sympathetic dystrophy.

Deformities

Deformities can result from generalized disorders (eg, arthritis) or dislocations, fractures, and other localized disorders. Most nontraumatic localized disorders can be diagnosed by physical examination. Once a hand deformity becomes firmly established, it cannot be significantly altered by splinting, exercise, or other nonsurgical treatment.

Mallet Finger

Mallet finger is a flexion deformity of the distal interphalangeal joint preventing extension (see Fig. 43-1).

This deformity results from an extensor tendon rupture or an avulsion fracture of the distal phalanx. The deformity may not be obvious immediately after injury, but on examination, patients cannot fully extend the distal interphalangeal (DIP) joint. Closed injuries may be treated with splinting that holds the DIP joint in extension and leaves the proximal interphalangeal (PIP) joint free. Avulsion fractures are usually united after 6 wk, but pure tendon injuries require an additional 2 to 4 wk of nighttime splinting. Surgery may be required if there is a fracture that involves a large proportion of the articular surface or if the joint is subluxated.

Swan-Neck Deformity

A swan-neck deformity consists of hyperextension of the PIP joint, flexion of the DIP joint, and sometimes flexion of the metacarpophalangeal joint (see Fig. 43-2).

Although characteristic in RA, swan-neck deformity has several causes, including untreated mallet finger, laxity of the ligaments of the volar aspect of the PIP joint, spasticity of intrinsic hand muscles, rupture of the flexor tendon of the PIP joint, and malunion of a fracture of the middle or proximal phalanx. The inability to correct or compensate for hyperextension of the PIP joint makes finger closure impossible and can cause severe disability. Treatment is aimed at correcting the underlying disorder when possible (eg, correcting the mallet finger or any bony malalignment, releasing spastic intrinsic muscles). Mild deformities in patients with RA may be treated with a functional ring splint.

True swan-neck deformity does not affect the thumb, which has only one interphalangeal

[Fig. 43-1. Mallet finger.]

[Fig. 43-2. Boutonniere and swan-neck deformities.]

joint. However, severe hyperextension of the interphalangeal joint of the thumb with flexion of the metacarpophalangeal (MCP) joint can occur; this is called a duck bill, Z (zigzag) type, or 90°-angle deformity. With simultaneous thumb instability, pinch is greatly impaired. This deformity can usually be corrected by interphalangeal arthrodesis along with tendon reconstruction at the MCP joint.

Boutonniere Deformity

(Buttonhole Deformity)

A boutonniere deformity consists of flexion of the PIP joint accompanied by hyperextension of the DIP joint (see Fig. 43-2).

This deformity can result from tendon laceration, dislocation, fracture, osteoarthritis, or RA. Classically, the deformity is caused by disruption of the central slip attachment of the extensor tendon to the base of the middle phalanx, allowing the proximal phalanx to protrude ("buttonhole") between the lateral bands of the extensor tendon. Initial treatment consists of splinting, but it must occur before scarring and fixed deformities develop. Surgical reconstruction often cannot restore normal motion but may decrease the deformity and improve hand function.

Dupuytren's Contracture

(Palmar Fibromatosis)

Dupuytren's contracture is progressive contracture of the palmar fascial bands, causing flexion deformities of the fingers.

Dupuytren's contracture is one of the more common hand deformities; the incidence is higher among men and increases after age 45. This autosomal dominant condition with variable penetrance may occur more commonly among patients with diabetes, alcoholism, or epilepsy. However, the specific factor that causes the palmar fascia to thicken and contract is unknown.

Symptoms and Signs

The earliest manifestation is usually a tender nodule in the palm, most often near the middle or ring finger; it gradually becomes painless. Next, a superficial cord forms and contracts the MCP joints and interphalangeal joints of the fingers. The hand eventually becomes arched. The disease is occasionally associated with fibrous thickening of the dorsum of the PIP joints (Garrod's pads), Peyronie's disease (penile fibromatosis) in about 7 to 10% of patients, and rarely nodules on the plantar surface of the feet (plantar fibromatosis). Other types of flexion deformities of the fingers can also occur in diabetes, systemic sclerosis, and chronic reflex sympathetic dystrophy, which need to be differentiated.

Treatment

• Corticosteroid injection (before contractures develop)

• Surgery for disabling contractures

Injection of a corticosteroid suspension into the nodule can relieve local tenderness if begun before contractures develop. If the hand cannot be placed flat on a table or, especially, when significant contracture develops at the PIP joints, surgery is usually indicated. Excision of the diseased fascia must be meticulous because it surrounds neurovascular bundles and tendons. Incomplete excision or new disease results in recurrent contracture, especially in patients who are young at disease onset or who have a family history, Garrod's pads, Peyronie's disease, or plantar foot involvement. Injectable collagenase may reverse some contractures, although this treatment is not yet in widespread clinical use.

Ganglia

(Ganglion Cysts)

Ganglia are cystic swellings occurring usually on the hands, especially on the dorsal aspect of the wrists. Aspiration or excision is indicated for symptomatic ganglia.

Ganglia constitute about 60% of chronic soft-tissue swellings affecting the hand and wrist. They usually develop spontaneously in adults aged 20 to 50, with a female:male preponderance of 3:1.

Etiology

The cause of most ganglia is unknown. The cystic structures are near or attached (often by a pedicle) to tendon sheaths and joint capsules. The wall of the ganglion is smooth, fibrous, and of variable thickness. The cyst is filled with clear gelatinous, sticky, or mucoid fluid of high viscosity. The fluid in the cyst is sometimes almost pure hyaluronic acid.

Most ganglia are isolated abnormalities. The dorsal wrist ganglion arises from the scapholunate joint and constitutes about 65% of ganglia of the wrist and hand. The volar wrist ganglion arises over the distal aspect of the radius and constitutes about 20 to 25% of ganglia. Flexor tendon sheath ganglia and mucous cysts (arising from dorsal distal interphalangeal joint) make up the remaining 10 to 15%. Ganglia may spontaneously regress.

Diagnosis

• Examination

Ganglia are evident on examination. Another type of ganglion on the dorsal wrist occurs in patients with RA; it is easily differentiated by its soft irregular appearance and association with proliferative rheumatoid extensor tenosynovitis.

Treatment

• Aspiration or excision if troublesome

Most ganglia do not require treatment. However, if the patient is disturbed by its appearance or if the ganglion is painful or tender, a single aspiration with a large-bore needle is effective in about 50% of patients. Attempting to rupture the ganglion by hitting it with a hard object risks local injury without likely benefit. Nonsurgical treatment fails in about 40 to 70% of patients, necessitating surgical excision. Recurrence rates after surgical removal are about 5 to 15%.

Infections

Common bacterial hand infections include paronychia (see p. 735), infected bite wounds, felon, palm abscess, and infectious flexor tenosynovitis. Herpetic whitlow is a viral hand infection. Infections often begin with constant, intense, throbbing pain and are usually diagnosed by physical examination. X-rays are taken in some infections (eg, bite wounds, infectious flexor tenosynovitis) to detect occult foreign

bodies but may not detect small or radiolucent objects.

Treatment

• Surgical measures and antibiotics

The increased incidence of community-acquired and nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) should be taken into consideration. Uncomplicated MRSA infections are best treated with incision and drainage. If there is a high incidence of MRSA and the infection is severe, hospitalization and vancomycin or daptomycin (for IV therapy) are recommended, as is consultation with an infectious disease specialist. For outpatients, trimethoprim/sulfamethoxazole, clindamycin, doxycycline, or linezolid (for oral therapy) can be given. Once culture and sensitivity results rule out MRSA, nafcillin, cloxacillin, dicloxacillin, or a 1st- or 2nd-generation cephalosporin can be given.

Infected Bite Wounds

A small puncture wound, particularly from a human or cat bite, may involve significant injury to the tendon, joint capsule, or articular cartilage. The most common cause of human bites is a tooth-induced injury to the metacar-pophalangeal

[
Fig. 43-3. Splint in the functional position (20° wrist extension, 60° metacarpophalangeal joint flexion, slight interphalangeal joint flexion).]

joint as a result of a punch to the mouth (clenched fist injury). The oral flora of humans includes *Eikenella corrodens*, staphylococci, streptococci, and anaerobes. Patients with clenched fist injuries tend to wait hours or days after the wound occurs before seeking medical attention, which increases the severity of the infection. Animal bites usually contain multiple potential pathogens, including *Pasteurella multocida* (particularly in cat bites), staphylococci, streptococci, and anaerobes. Serious complications include infectious arthritis and osteomyelitis.

Diagnosis

• Clinical evaluation

• X-rays

Erythema and pain localized to the bite suggest infection. Tenderness along the course of a tendon suggests spread to the tendon sheath. Pain worsening significantly with motion suggests infection of a joint or tendon sheath.

The diagnosis is clinical, but if the skin is broken, x-rays should be taken to detect fracture or teeth or other foreign bodies that could be a nidus of continuing infection.

Treatment

• Debridement

• Antibiotics

Treatment includes surgical debridement, with the wound left open, and antibiotics. For outpatient treatment, empiric antibiotics usually include monotherapy with amoxicillin/clavulanate 500 mg po tid or combined therapy with a penicillin 500 mg po qid (for *E. corrodens*, *P. multocida*, streptococci, and anaerobes) plus a cephalosporin (eg, cephalexin 500 mg po qid) or semisynthetic penicillin (eg, dicloxacillin 500 mg po qid) for staphylococci. In areas where MRSA is prevalent, trimethoprim/sulfamethoxazole, clindamycin, doxycycline, or linezolid should be used instead of a cephalosporin. If the patient is allergic to penicillin, clindamycin 300 mg po q 6 h can be used. The hand should be splinted in the functional position and elevated (see Fig. 43-3).

Noninfected bites may require surgical debridement and prophylaxis with 50% of the dose of antibiotic used to treat infected wounds.

Felon

A felon is an infection of the pulp space of the fingertip, usually with staphylococci and streptococci.

The most common site is the distal pulp, which may be involved centrally, laterally, or apically. The septa between pulp spaces ordinarily limit the spread of infection, resulting in an abscess, which creates pressure and necrosis of adjacent tissues. The underlying bone, joint, or flexor tendons may become infected. There is intense throbbing pain and a swollen, warm, extremely tender pulp. Treatment involves prompt incision and drainage (using a mid-lateral incision that adequately divides the fibrous septa) and oral antibiotic therapy. Empiric treatment with a cephalosporin is adequate. In areas where MRSA is prevalent, trimethoprim/sulfamethoxazole, clindamycin, doxycycline, or linezolid should be used instead of a cephalosporin.

Palm Abscess

A palm abscess is a purulent infection of deep spaces in the palm, typically with staphylococci or streptococci.

Palm abscesses can include collar-button abscesses, thenar space abscesses, and midpalmar space abscesses. An abscess can occur in any of the deep palmar compartments and spread between the metacarpals, from the midpalmar space to the dorsum, manifesting as an infection on the dorsum of the hand. Intense throbbing pain occurs with swelling and severe tenderness on palpation. X-rays should be taken to detect occult foreign bodies. Incision and drainage in the operating room (with cultures), with care to avoid the many important anatomic structures, and antibiotics (eg, a cephalosporin) are required. In areas where MRSA is prevalent, trimethoprim/sulfamethoxazole, clindamycin, doxycycline, or linezolid should be used instead of a cephalosporin.

Infectious Flexor Tenosynovitis

Infectious flexor tenosynovitis is an acute infection within the flexor tendon sheath.

The usual cause is a penetration and bacterial inoculation of the sheath.

Diagnosis

• Kanavel's signs

• X-rays

Infectious flexor tenosynovitis causes Kanavel's signs:

• Flexed resting position of the digit

• Fusiform swelling

• Tenderness along the flexor tendon sheath

• Pain with passive extension of the digit

X-rays should be taken to detect occult foreign bodies. Acute calcific tendinitis and RA can restrict motion and cause pain in the tendon sheath but can usually be differentiated from infectious flexor tenosynovitis by a more gradual onset and the absence of some of Kanavel's signs. Disseminated gonococcal infection can cause tenosynovitis but often involves multiple joints (particularly those of the wrists, fingers, ankles,

and toes), and patients often have recent fever, rash, polyarthralgias, and often risk factors for an STD. Infection of the tendon sheath may involve atypical mycobacteria, but these infections are usually indolent and chronic.

Treatment

• Surgical drainage and antibiotics

Treatment is surgical drainage (eg, irrigation of the tendon sheath by inserting a cannula into one end and allowing the irrigating fluid to pass along the tendon sheath to the other end). Antibiotic therapy (beginning empirically with a cephalosporin) and cultures are also required. In areas where MRSA is prevalent, trimethoprim/sulfamethoxazole, clindamycin, doxycycline, or linezolid should be used instead of a cephalosporin.

Herpetic Whitlow

Herpetic whitlow is a cutaneous infection of the distal aspect of the finger caused by herpes simplex virus.

Herpetic whitlow may cause intense pain. The digital pulp is not very tense. Vesicles develop on the volar or dorsal distal phalanx but often not until 2 to 3 days after pain begins. The intense pain can simulate a felon, but herpetic whitlow can usually be differentiated by the absence of tenseness in the pulp or the presence of vesicles. The condition is self-limited but may recur. Incision and drainage are contraindicated. Topical acyclovir 5% can shorten the duration of a first episode. Oral acyclovir (800 mg po bid) may prevent recurrences if given immediately after onset of recurrent symptoms. Open or draining vesicles should be covered to prevent transmission.

Kienbock's Disease

Kienbock's disease is avascular necrosis of the lunate bone.

Kienbock's disease occurs most commonly in the dominant hand of men aged 20 to 45, usually in workers doing heavy manual labor. Overall, Kienbock's disease is relatively rare. Its cause is unknown. The lunate can eventually collapse and cause fixed rotation of the scaphoid and subsequent degeneration of the carpal joints.

Symptoms and Signs

Symptoms generally start with insidious onset of wrist pain, localized to the region of the lunate carpal bone; patients have no recollection of trauma. Kienbock's disease is bilateral in 10% of cases. There is localized tenderness in the lunate bone.

Diagnosis

• Imaging

MRI and CT are the most sensitive; plain x-rays show abnormalities later, usually beginning with a sclerotic lunate, then later cystic changes, fragmentation, and collapse.

Treatment

• Surgical procedures

Treatment is aimed at relieving pressure on the lunate by surgically shortening the radius or lengthening the ulna. Alternative treatments attempt to revascularize the lunate (eg, implanting a blood vessel or bone graft on a vascular pedicle). Salvage procedures (eg, proximal row carpectomy or intercarpal fusions) may help preserve some wrist function if the carpal joints have degenerated. Total wrist arthrodesis can be done as a last resort to relieve pain. Nonsurgical treatments are not effective.

Nerve Compression Syndromes

Common nerve compression syndromes include carpal tunnel syndrome, cubital tunnel syndrome, and radial tunnel syndrome. Compression of nerves often causes paresthesias; these paresthesias can often be reproduced by tapping the compressed nerve, usually with the examiner's fingertip (Tinel's sign). Suspected nerve compression can be confirmed by testing nerve conduction velocity and distal latencies, which accurately measure motor and sensory nerve conduction. Initial treatment is usually conservative, but surgical decompression may be necessary if conservative measures fail or if there are significant motor or sensory deficits.

Carpal Tunnel Syndrome

Carpal tunnel syndrome is compression of the median nerve as it passes through the carpal tunnel in the wrist. Symptoms include pain and paresthesias in the median nerve distribution. Diagnosis is suggested by symptoms and signs and is confirmed by nerve conduction velocity testing. Treatments include ergonomic improvements, analgesia, splinting, and sometimes corticosteroid injection or surgery.

Carpal tunnel syndrome is very common and most often occurs in women aged 30 to 50. Risk factors include RA or other wrist arthritis (sometimes the presenting manifestation), diabetes mellitus, hypothyroidism, acromegaly, amyloidosis, hemodialysis, and pregnancy-induced edema in the carpal tunnel. Activities or jobs that require repetitive flexion and extension of the wrist may contribute, but rarely. Most cases are idiopathic.

Symptoms and Signs

Symptoms include pain of the hand and wrist associated with tingling and numbness, classically distributed along the median nerve (the palmar side of the thumb, the index and middle fingers, and the radial half of the ring finger) but possibly involving the entire hand. Typically, the patient wakes at night with burning or aching pain and with numbness and tingling and shakes the hand to obtain relief and restore sensation. Thenar atrophy and weakness of thumb opposition and abduction may develop late.

Diagnosis

• Clinical evaluation

• Nerve conduction testing

The diagnosis is strongly suggested by Tinel's sign, in which median nerve paresthesias are reproduced by tapping at the volar surface of the wrist over the site of the median nerve in the carpal tunnel. Reproduction of tingling with wrist flexion (Phalen's sign) is also suggestive. However, clinical differentiation from other types of peripheral neuropathy may sometimes be difficult. If symptoms are severe or the diagnosis is uncertain, nerve conduction testing should be done on the affected arm for diagnosis and to exclude a more proximal neuropathy.

Treatment

• Splinting

• Sometimes corticosteroid/anesthetic injection

• Sometimes surgical decompression

Changing the position of computer keyboards and making other ergonomic corrections may occasionally provide relief. Otherwise, treatment includes wearing a lightweight neutral wrist splint (see Fig. 43-4), especially at night, and taking mild analgesics (eg, acetaminophen, NSAIDs). If these measures do not control symptoms, a mixture of a corticosteroid and an anesthetic (eg, 1.5 mL of a 4-

mg/mL dexamethasone solution mixed with 1.5 mL of 1% lidocaine) should be injected into the carpal tunnel at a site just ulnar to the palmaris longus tendon and proximal to the distal crease at the wrist. If bothersome symptoms persist or recur or if hand weakness and thenar wasting develop, the carpal tunnel can be surgically decompressed by using an open or endoscopic technique.

[Fig. 43-4. Neutral wrist splint.]

Cubital Tunnel Syndrome

(Ulnar Neuropathy)

Cubital tunnel syndrome is compression or traction of the ulnar nerve at the elbow.

The ulnar nerve is commonly irritated at the elbow or, rarely, the wrist. Cubital tunnel syndrome is most often caused by leaning on the elbow or by prolonged and excessive elbow flexion. It is less common than carpal tunnel syndrome. Baseball pitching (particularly sliders), which can injure the medial elbow ligaments, confers risk.

Symptoms and Signs

Symptoms include numbness and paresthesia along the ulnar nerve distribution (in the ring and little fingers and the ulnar aspect of the hand) and elbow pain. In advanced stages, weakness of the intrinsic muscles of the hand and the flexors of the ring and little fingers may develop. Weakness interferes with pinch between the thumb and index finger and with hand grip.

Diagnosis

• Clinical evaluation

• Sometimes nerve conduction studies

Diagnosis is often possible clinically. However, if clinical diagnosis is equivocal and when surgery is being considered, nerve conduction studies are done. Cubital tunnel syndrome is differentiated from ulnar nerve entrapment at the wrist (in Guyon's canal) by the presence of sensory deficits (on sensory testing or with Tinel's sign) over the ulnar dorsal hand and by the presence of ulnar nerve deficits proximal to the wrist on muscle testing or nerve conduction velocity testing.

Treatment

Treatment involves splinting at night, with the elbow extended at 45°, and use of an elbow pad during the day. Surgical decompression can help if conservative treatment fails.

Radial Tunnel Syndrome

(Posterior Interosseous Nerve Syndrome)

Radial tunnel syndrome is compression of the radial nerve in the proximal forearm.

Compression at the elbow can result from trauma, ganglia, lipomas, bone tumors, or radiocapitellar (elbow) synovitis.

Symptoms and Signs

Symptoms include lancinating pain in the dorsum of the forearm and lateral elbow. Pain is precipitated by attempted extension of the wrist and fingers and forearm supination. Sensory loss is rare because the radial nerve is principally a motor nerve at this level. This disorder is sometimes confused with backhand tennis elbow (lateral epicondylitis). When weakness of the extensor muscles is the primary finding, the condition is referred to as posterior interosseus nerve palsy.

Diagnosis

• Clinical evaluation

Lateral epicondylitis can cause similar tenderness around the lateral epicondyle but does not cause Tinel's sign or tenderness along the course of the radial nerve.

Treatment

• Splinting

Splinting allows avoidance of the forceful or repeated motion of supination or wrist dorsiflexion, reducing pressure on the nerve. If wristdrop or weakened digital extension develops, or conservative treatment fails to provide relief after 3 mo, surgical decompression may be needed.

Noninfectious Tenosynovitis

(See also p. 374.)

Although the digital flexor tendons and extensor pollicis brevis are commonly affected, tenosynovitis may involve any of the tendons in or around the hand.

Digital Flexor Tendinitis and Tenosynovitis

(Trigger Finger)

Digital flexor tendinitis and tenosynovitis are inflammation, sometimes with subsequent fibrosis, of tendons and tendon sheaths of the digits.

These conditions are idiopathic but are common among patients with RA or diabetes mellitus. Repetitive use of the hands (as may occur when using heavy gardening shears) may contribute. In diabetes, they often coexist with carpal tunnel syndrome and occasionally with fibrosis of the palmar fascia. Pathologic changes begin with a thickening or nodule within the tendon; when located at the site of the tight first annular pulley, the thickening or nodule blocks smooth extension or flexion of the finger. The finger may lock in flexion, or "trigger," suddenly extending with a snap.

Treatment

• Conservative measures

• Sometimes corticosteroid injection

Treatment of acute inflammation and pain includes splinting, moist heat, and anti-inflammatory doses of NSAIDs (see p. 335). If these measures fail, injection of a corticosteroid suspension into the flexor tendon sheath, along with splinting, may provide safe, rapid relief of pain and triggering. Operative release can be done if corticosteroid therapy fails.

De Quervain's Syndrome

(Washerwoman's Sprain)

De Quervain's syndrome is stenosing tenosynovitis of the short extensor (extensor pollicis brevis) and long abductor tendon (abductor pollicis longus) of the thumb within the first extensor compartment.

De Quervain's syndrome usually occurs after repetitive use (especially wringing) of the wrist, although it occasionally occurs in association with RA. The major symptom is aching pain at the wrist and thumb,

aggravated by motion. Tenderness can be elicited just proximal to the radial styloid process over the site of the involved tendon sheaths. Diagnosis is highly suggested by the Finkelstein test. The patient adducts the involved thumb into the palm and wraps the fingers over the thumb. The test is positive if gentle passive ulnar deviation of the wrist provokes severe pain at the affected tendon sheaths.

Treatment

• Corticosteroid injection

• Thumb spica splint

Rest, warm soaks, and NSAIDs may help in very mild cases. Local corticosteroid injections and a thumb spica splint help 70 to 80% of cases. Tendon rupture is a rare complication of injection and can be prevented by confining infiltration to the tendon sheath and avoiding injection of the corticosteroid into the tendon. Intratendinous location of the needle is likely if injection is met with moderate or severe resistance. Surgical release of the first extensor compartment is very effective when conservative therapy fails.

Osteoarthritis of the Hand

Hand involvement is extremely common in osteoarthritis.

Osteoarthritis affecting the hand may be asymptomatic enlargement of nodules at the proximal interphalangeal joint (Bouchard's nodules) or distal interphalangeal joint (Heberden's nodes) or angulation at these joints. Pain and stiffness of these joints and the base of the thumb are also common. The wrist usually is spared, and there is usually minimal or no metacarpophalangeal joint involvement unless the patient also has a metabolic disorder (eg, hemochromatosis). Differentiation of hand changes in osteoarthritis from those in RA is discussed in
Table 32-7 on p. 296.

Treatment

• Conservative measures

• Occasionally corticosteroid injection or surgery

Treatment is symptomatic with analgesics, appropriate rest, splinting, and occasionally corticosteroid injection as needed. Surgical procedures can help relieve pain and correct deformity for severe changes at the base of the thumb and, less commonly, for advanced degeneration of the interphalangeal joints.

Chapter 44. Foot and Ankle Disorders

Introduction

Most foot problems result from anatomic disorders or abnormal function of articular or extra-articular structures (see Fig. 44-1). Less commonly, foot problems reflect a systemic disorder (see Table 44-1).

In people with diabetes and people with peripheral vascular disease, careful examination of the feet, with evaluation of vascular sufficiency and neurologic integrity, should be done at least twice/yr. People with these diseases should examine their own feet at least once/day.

The feet are also common sites for corns and calluses (see p. 660) and infections by fungus (see Tinea Pedis on p. 708), bacteria (see p. 694), and viruses (see Warts on p. 715).

Table 44-2 lists foot and ankle disorders according to anatomic site.
Table 44-3 lists common causes of heel pain according to location.

Tibialis Posterior Tendinosis

Tibialis posterior tendinosis, degeneration of the tibialis posterior tendon, is the most common cause of pain behind the medial malleolus.

The posterior tibial tendon lies immediately behind the medial malleolus. Degeneration results from long-standing biomechanical problems, such as excessive pronation often in obese people. The tendon can also be involved by primary inflammatory disorders, such as RA or gout.

Symptoms and Signs

Early on, patients experience occasional pain behind the medial malleolus. Over time, the pain becomes severe, with painful swelling behind the medial malleolus. Normal standing, walking, and standing on the toes become difficult.

[**Fig. 44-1.** Bones of the foot.]

[**Table 44-1.** Foot Manifestations of Systemic Disorders]

Diagnosis

• MRI

Clinical findings suggest the diagnosis. Palpation of the tendon in an inverted-plantar flexed position usually elicits pain. Standing on the toes is usually painful and may not be possible if the tendon is ruptured. Pain and swelling behind the medial malleolus, especially with tibialis posterior tendon pain on

[**Table 44-2.** Common Foot and Ankle Disorders by Anatomic Site]

palpation, are highly suggestive. MRI or ultrasonography can confirm injury to the tendon and its extent.

Treatment

• Orthotics and braces or surgery

Complete rupture requires surgery if normal function is the goal. Surgery is especially important in young active patients with acute tears. Conservative therapy consists of mechanically off-loading the tendon by using orthotics and ankle braces. Corticosteroid injections exacerbate the degenerative process (see Sidebar 44-1). If the tendon is inflamed, rest and aggressive anti-inflammatory therapy are warranted.

Tarsal Tunnel Syndrome

(Posterior Tibial Nerve Neuralgia)

Tarsal tunnel syndrome is pain along the course of the posterior tibial nerve, usually resulting from nerve compression within the tarsal tunnel.

At the level of the ankle, the posterior tibial nerve passes through a fibro-osseous canal and divides into the medial and lateral plantar nerves. Tarsal tunnel syndrome refers to compression of the nerve within this canal, but the term has been loosely applied to neuralgia of the posterior tibial nerve resulting from any cause. Synovitis of the flexor tendons of the ankle caused by abnormal foot function, inflammatory arthritis (eg, RA), fracture, and ankle venous stasis edema are contributing factors. Patients with hypothyroidism may develop tarsal tunnel-like symptoms as a result of perineural mucin deposition.

Symptoms and Signs

Pain (occasionally burning and tingling) is usually retromalleolar and sometimes in the plantar medial heel and may extend along the plantar surface as far as the toes. Although the pain is worse during standing and walking, pain at rest may occur as the disorder progresses.

Diagnosis

• Examination and electrodiagnostic testing

Tapping or palpating the posterior tibial nerve below the medial malleolus at a site of compression or injury often causes distal tingling (Tinel's sign). While false-negative results on electrodiagnostic tests are somewhat common, a positive history combined with supportive physical findings and positive electrodiagnostic results makes the diagnosis of tarsal tunnel syndrome highly likely. The cause of any swelling near the nerve should be determined.

Treatment

• Foot inversion, injection, surgery, or a combination

Strapping the foot in a neutral or slightly inverted position or wearing an orthotic that keeps the foot inverted reduces nerve tension. Local infiltration of a mixture of an insoluble corticosteroid and an anesthetic may be effective if the cause is inflammation or fibrosis. Surgical decompression may be necessary to relieve suspected fibro-osseus compression with recalcitrant symptoms.

[Table 44-3. Disorders Associated with Heel Pain According to Location]

Metatarsalgia

Metatarsalgia is a general term for pain in the area of the metatarsophalangeal joints (ball of the foot). Most common causes include Freiberg's disease, interdigital nerve pain (Morton's neuroma), metatarsophalangeal joint pain, and sesamoiditis.

Freiberg's Disease

Freiberg's disease is avascular necrosis of the metatarsal head.

Freiberg's disease is caused by microtrauma at the metaphysis and growth plate. Avascular necrosis flattens the metatarsal head. The 2nd metatarsal head is most often affected. Freiberg's disease occurs more frequently among pubertal females and among people who have a short 1st metatarsal bone, which increases stress on the 2nd metatarsal head and joint.

Symptoms and Signs

The pain is most pronounced in the forefoot at the metatarsal head with weight bearing, particularly when pushing off or when wearing high-heeled footwear. The metatarsophalangeal joint may also be swollen and have limited and painful passive range of motion.

Diagnosis

• X-rays

The diagnosis is confirmed with x-rays. Typically, the head of the 2nd metatarsal is widened and flattened, and the metatarsal joint is sclerotic and irregular.

Sidebar 44-1 Considerations for Using Corticosteroid Injections

Corticosteroid injections should be used judiciously to avoid adverse effects. Injectable corticosteroids should be reserved for inflammation, which is not present in most foot disorders. Because the tarsus, ankle, retrocalcaneal space, and dorsum of the toes have little connective tissue between the skin and underlying bone, injection of insoluble corticosteroids into these structures may cause depigmentation, atrophy, or ulceration, especially in elderly patients with peripheral arterial disease.

Insoluble corticosteroids can be given deeply rather than superficially with greater safety (eg, in the heel pad, tarsal canal, or metatarsal interspaces). The foot should be immobilized for a few days after tendon sheaths are injected. Unusual resistance to injection suggests injection into a tendon. Repeated injection into a tendon should be avoided because the tendon may weaken (partially tear), predisposing to subsequent rupture.

Treatment

• Immobilization and weight unloading if acute, then modification of footwear

Corticosteroid injections and immobilization may help to alleviate acutely painful flare-ups. Long-term management may require orthoses with metatarsal bars and low-heeled footwear to reduce stress on the 2nd metatarsal head and joint. Corticosteroid injections can be tried, and, rarely, surgical excision of the metatarsal head may be necessary to relieve recalcitrant pain.

Interdigital Nerve Pain

(Morton's Neuroma/Neuralgia)

Interdigital nerve irritation (neuralgia) or persistent benign enlargement of the perineurium (neuroma) can cause pain, which may be nonspecific, burning, or lancinating, or a foreign body sensation. Diagnosis is usually clinical. Treatment may involve correction of footwear, local injection, or sometimes surgical excision.

The interdigital nerves of the foot travel beneath and between the metatarsals, extending distally to innervate the toes. Neuralgia of the interdigital nerve along its distal innervation near the ball of the foot develops primarily as a result of improper or constrictive footwear or, less commonly, nerve traction resulting from abnormal foot structure. As a result of chronic repetitive trauma, a benign thickening of the nerve develops (Morton's neuroma).

Symptoms and Signs

Interdigital neuralgia is characterized by pain around the metatarsal heads or the toes. Early interdigital neuralgia often causes an occasional mild ache or discomfort in the ball of the foot, usually when wearing a specific shoe, such as those that are too narrow at the front. Neuralgia is usually unilateral. As the condition progresses, the nerve thickens. The pain becomes worse, often with a burning or lancinating

quality or paresthesias. In time, patients are unable to wear most shoes. While walking, patients often falsely sense a pebble in their shoes, which they take off for relief. Neuroma most frequently affects the 3rd interspace. Only slightly less common is involvement of the 2nd interspace. Sometimes both interspaces or feet are involved simultaneously.

Diagnosis

• Clinical evaluation

The symptoms are often specific, and the diagnosis is confirmed by tenderness on plantar palpation of the interdigital space and reproduction of the radiating burning pain by squeezing the space. Although MRI does not usually confirm neuroma, it may be useful to rule out other interspace lesions or arthritis causing similar symptoms.

Treatment

• Modification of footwear and injection

Neuralgia of recent onset usually resolves quickly with properly fitting shoes and insoles or with local anesthetic injection. In contrast, neuromas may require one or more perineural infiltrations of long-acting corticosteroids with a local anesthetic. Injection is at a 45° angle to the foot, into the interspace at the level of the dorsal aspect of the metatarsophalangeal joints. An appropriate orthotic often relieves symptoms. If conservative therapy is ineffective, excision often brings complete relief. However, another neuroma occasionally develops at the site of nerve excision (amputation or stump neuroma).

Metatarsophalangeal Joint Pain

Metatarsophalangeal joint pain usually results from tissue changes due to aberrant foot biomechanics. Symptoms and signs include pain with walking and tenderness. Diagnosis is clinical; however, infection or systemic rheumatic diseases (eg, RA) may need to be excluded by testing. Treatment includes orthotics, sometimes local injection, and occasionally surgery.

Metatarsophalangeal joint pain most commonly results from misalignment of the joint surfaces with altered foot biomechanics, causing joint subluxations, capsular impingement, and joint cartilage destruction (osteoarthrosis). Misaligned joints may cause synovial impingement, with minimal if any heat and swelling (osteoarthritic synovitis).

Metatarsophalangeal joint subluxations also occur as a result of inflammatory arthropathy, particularly RA. Inflammatory synovitis and interosseous muscle atrophy in RA lead to subluxations of the lesser metatarsophalangeal joints as well, resulting in hammer toe deformities. Consequently, the metatarsal fat pad, which usually cushions the stress between the metatarsals and interdigital nerves during walking, moves distally under the toes; interdigital neuralgia or Morton's neuroma may result. To compensate for the loss of cushioning, adventitial calluses and bursae may develop.

Metatarsophalangeal joint pain may also result from functional hallux limitus, which limits passive and active joint motion and usually occurs at the 1st metatarsophalangeal joint. Patients usually have foot pronation disorders that result in elevation of the 1st ray with lowering of the medial longitudinal arch during weight bearing. As a result of the 1st ray elevation, the proximal phalanx of the great toe cannot freely extend on the 1st metatarsal head; the result is jamming at the dorsal joint leading to osteoarthritic changes and loss of joint motion. Over time, pain may develop, and the joint may become less mobile with an arthrosis (hallux rigidus), which can be debilitating.

Symptoms and Signs

Symptoms include pain on walking. Dorsal and plantar joint tenderness is usually present on palpation and during passive range of motion. Mild swelling with minimal heat occurs in osteoarthritic synovitis. Significant warmth, swelling, or redness suggests inflammatory arthropathies or infection.

Diagnosis

• Mainly clinical evaluation

• Exclusion of infection or arthropathy if signs of inflammation

Metatarsophalangeal joint pain can usually be differentiated from neuralgia or neuroma of the interdigital nerves by the absence of burning, numbness, and tingling and interspace pain, although these symptoms may develop from joint inflammation; if so, palpation can help with differentiation.

Monarticular heat, redness, and swelling indicate infection until proven otherwise, although gout is more likely. When warmth, redness, and swelling involve multiple joints, evaluation for a systemic cause of joint inflammation (eg, gout, RA, viral-associated arthritis, enteropathic arthritis) with a rheumatic disease assessment (eg, antinuclear antibodies, rheumatoid factor, ESR) is indicated.

Treatment

• Orthoses

Foot orthoses may help to redistribute and relieve pressure from the noninflamed joints. With excess subtalar eversion or when the feet are highly arched, an orthotic that corrects these abnormal motions should be prescribed. For functional hallux limitus, orthosis modifications may further help to plantarflex the 1st ray to improve metatarsophalangeal joint motion and reduce pain. For more severe limitation of 1st metatarsophalangeal motion or pain, the use of rigid orthoses, carbon fiber plates, or external shoe bars or rocker soles may be necessary to reduce motion at the joint. Surgery may be needed if conservative therapies are ineffective. If inflammation (synovitis) is present, injection of a local corticosteroid/anesthetic mixture may be useful.

Sesamoiditis

Sesamoiditis is pain at the sesamoid bones beneath the head of the 1st metatarsal, with or without inflammation or fracture. Diagnosis is usually clinical. Treatment is usually modification of footwear.

The 2 semilunar-shaped sesamoid bones aid the foot in locomotion. The medial bone is the tibial sesamoid, and the lateral bone is the fibular sesamoid. Direct trauma or positional change of the sesamoids due to alterations in foot structure (eg, lateral displacement of a sesamoid due to lateral deviation of the great toe) can make the sesamoids painful. Sesamoiditis is particularly common among dancers, joggers, and those who have high-arched feet or wear high heels. Many people with sesamoiditis have bunions.

Symptoms and Signs

The pain of sesamoiditis is beneath the head of the 1st metatarsal; the pain is usually made worse by walking and may be worse when wearing certain shoes. Occasionally, inflammation occurs, causing mild warmth and swelling or occasionally redness that may extend medially and appear to involve the 1st metatarsophalangeal joint. Sesamoid fracture can also cause pain, moderate swelling, and possibly inflammation.

Diagnosis

• Clinical evaluation

• Imaging if fracture, infection, or gout is suspected

With the foot and 1st (big) toe dorsiflexed, the examiner inspects the metatarsal head and palpates each sesamoid. Tenderness is localized to a sesamoid, usually the tibial sesamoid. Hyperkeratotic tissue may indicate that a wart or corn is causing pain. If inflammation causes swelling around the 1st

metatarsophalangeal joint, arthrocentesis is usually indicated to exclude gout and infectious arthritis. If fracture, osteoarthritis, or displacement is suspected, x-rays are taken. Sesamoids separated by cartilage or fibrous tissue (bipartite sesamoids) may appear fractured on x-rays. If plain x-rays are equivocal, MRI may be ordered.

Treatment

• New shoes, orthotics, or both

Simply not wearing the shoes that cause pain may be sufficient. If symptoms persist, shoes with a thick sole and orthotics are prescribed and help by reducing sesamoid pressure. If fracture without displacement is present, conservative therapy may be sufficient and may also involve immobilization of the joint with the use of a flat, rigid, surgical shoe. NSAIDs and injections of a corticosteroid/local anesthetic solution can be helpful. Although surgery may help in recalcitrant cases, it is controversial because of the potential for disturbing biomechanics and locomotion of the foot. If inflammation is present, treatment includes conservative measures plus local infiltration of a corticosteroid/anesthetic solution to help reduce symptoms.

Plantar Fasciosis

(Plantar Fasciitis)

Plantar fasciosis is pain at the site of the attachment of the plantar fascia and the calcaneus, with or without accompanying pain along the medial band of the plantar fascia. Diagnosis is mainly clinical. Treatment involves calf muscle and plantar soft-tissue foot-stretching exercises, night splints, and orthotics.

Syndromes of pain in the plantar fascia have been called plantar fasciitis; however, because there is usually no inflammation, plantar fasciosis is more correct. Other terms used include calcaneal enthesopathy pain or calcaneal spur syndrome; however, there may be no bone spurs on the calcaneus. Plantar fasciosis may involve acute or chronic stretching, tearing, and degeneration of the fascia at its attachment site.

Etiology

Recognized causes include shortening or contracture of the calf muscles and plantar fascia. Risk factors for such shortening include a sedentary lifestyle, occupations requiring sitting, very high or low arches in the feet, and wearing high-heel shoes. The disorder is also common among runners and dancers and may occur in people whose occupations involve standing or walking on hard surfaces for prolonged periods. Disorders that may be associated with plantar fasciosis are obesity, RA, reactive arthritis, and psoriatic arthritis. Multiple injections of corticosteroids may contribute by causing degenerative changes of the fascia and possible loss of the cushioning subcalcaneal fat pad.

Symptoms and Signs

Plantar fasciosis is characterized by pain at the bottom of the heel on weight bearing, particularly when first arising in the morning; pain usually improves within 5 to 10 min, only to return later in the day. It is often worse when pushing off of the heel (the propulsive phase of gait). Acute severe heel pain, especially with mild local puffiness, may indicate an acute tear. Some patients describe burning or sticking pain along the plantar medial border of the foot when walking.

Diagnosis

• Pain reproduced by calcaneal pressure during dorsiflexion

Other disorders causing heel pain can mimic plantar fasciosis:

• Throbbing heel pain, particularly when the shoes are removed or when mild heat and puffiness are

present, is more suggestive of calcaneal bursitis (see p. 401).

- Acute severe retrocalcaneal pain, with redness and heat, may indicate gout.
- Pain that radiates from the low back to the heel may be an S1 radiculopathy due to an L5 disk herniation.

Plantar fasciosis is confirmed if firm thumb pressure applied to the calcaneus when the foot is dorsiflexed elicits pain. Fascial pain along the plantar medial border of the fascia may also be present. If findings are equivocal, demonstration of a heel spur on x-ray may support the diagnosis; however, absence does not rule out the diagnosis, and visible spurs are not generally the cause of symptoms. Also, infrequently, calcaneal spurs appear ill defined on x-ray, exhibiting fluffy new bone formation, suggesting spondyloarthropathy (eg, ankylosing spondylitis, reactive arthritis). If an acute fascial tear is suspected, MRI is done.

Treatment

- Splinting, stretching, and cushioning or orthotics

To alleviate the stress and pain on the fascia, the person can take shorter steps and avoid walking barefoot. Activities that involve foot impact, such as jogging, should be avoided. The most effective treatments include the use of in-shoe heel and arch cushioning with calf-stretching exercises and night splinting devices that stretch the calf and plantar fascia while the patient sleeps. Prefabricated or custom-made foot orthotics may also alleviate fascial tension and symptoms. Other treatments may include activity modifications, NSAIDs, weight loss in obese patients, cold and ice massage therapy, and occasional corticosteroid injections. However, because corticosteroid injections can predispose to plantar fasciosis, many clinicians limit these injections. For recalcitrant cases, physical medicine, oral corticosteroids, and cast immobilization should be used before surgical intervention is considered.

Inferior Calcaneal Bursitis

Bursitis can develop at the inferior calcaneus, near the insertion of the plantar fascia. Symptoms and signs include throbbing heel pain, particularly when the shoes are removed; mild warmth; and swelling. The pain is most pronounced when the heel first contacts the ground during walking or running activity. Treatment is injection of a local anesthetic/corticosteroid mixture and soft-soled shoes with added protective heel cushion padding.

Achilles Tendon Enthesopathy

Achilles tendon enthesopathy is pain at the insertion of the Achilles tendon at the posterosuperior aspect of the calcaneus.

The cause is chronic traction of the Achilles tendon on the calcaneus. Contracted or shortened calf muscles (resulting from a sedentary lifestyle and obesity) and athletic overuse are factors. Enthesopathy may be caused by a spondyloarthropathy.

Pain at the posterior heel below the top of the shoe counter during ambulation is characteristic. Pain on palpation of the tendon at its insertion is diagnostic. Manual dorsiflexion of the ankle during palpation usually exacerbates the pain. Recurrent and especially multifocal enthesitis should prompt evaluation (history and examination) for a spondyloarthropathy.

Treatment

- Stretching, splinting, and heel lifts

Physical therapy aimed at calf muscle stretching should be done 10 min three times/day. The patient can exert pressure posteriorly to stretch the calf muscle while facing a wall at arms' length, with knees extended and foot dorsiflexed. To minimize stress to the Achilles tendon with weight bearing, the patient

should move the foot and ankle actively through their range of motion for about 1 min when rising after extended periods of rest. Night splints may also be prescribed to provide passive stretch during sleep and help prevent contractures. Heel lifts should be used temporarily to decrease tendon stress during weight bearing and relieve pain. Heel lifts should be used bilaterally to prevent gait disturbance even if pain is only in one heel.

Anterior Achilles Tendon Bursitis

(Albert's Disease; Retromalleolar Bursitis)

Anterior Achilles tendon bursitis is inflammation of the retromalleolar (retrocalcaneal) bursa, located anterior (deep) to the attachment of the Achilles tendon to the calcaneus.

Bursitis is due to trauma (eg, from rigid or poorly fitting shoes) or inflammatory arthritis (eg, RA, gout). On occasion, small calcaneal erosions may develop from severe inflammation.

Symptoms and Signs

Symptoms and signs caused by trauma or gout develop rapidly; those caused by another systemic disorder develop gradually. Pain, swelling, and warmth around the heel are common, as are difficulty walking and wearing shoes. The bursa is tender. Initially, the swelling is localized anterior to the Achilles tendon but in time extends medially and laterally.

Using the thumb and index finger, side-to-side compression anterior to the Achilles tendon causes pain.

Diagnosis

• Clinical evaluation and x-rays

Fracture of the posterolateral talar tubercle also causes tenderness anterior to the insertion of the Achilles tendon. Bursitis is often differentiated from the fracture by the localization of warmth and swelling contiguous to the tendon and pain localized primarily in the soft tissue. Also, x-rays are taken to rule out fracture as well as erosive calcaneal changes characteristic of chronic RA or other rheumatic disorders.

Treatment

• Intrabursal injection of a soluble corticosteroid/anesthetic solution

A corticosteroid/anesthetic injection, NSAIDs, and warm or cold compresses may be effective. Care must be taken to inject only the bursal sac and not the tendon proper because tendon injection may lead to tendon weakening or tearing, predisposing to subsequent rupture.

Posterior Achilles Tendon Bursitis

Posterior Achilles tendon bursitis is inflammation of a bursa that forms in response to shoe pressure and is located at the top edge of the posterior shoe counter between the skin and Achilles tendon.

This disorder occurs mainly in young women. Wearing high-heeled shoes is a risk factor. Many patients have a bony prominence (Haglund's deformity) on the calcaneus.

Symptoms and Signs

Symptoms and signs develop at the top edge of the posterior shoe counter. Early symptoms may be limited to redness, pain, and warmth. Later, superficial skin erosion may occur. After months or longer, a fluctuant, tender, cystic nodule 1- to 3-cm in diameter develops. It is red or flesh-colored. In chronic cases, the bursa becomes fibrotic.

Diagnosis

• Symptoms and a small, tender, flesh-colored or red nodule

The presence of the small, tender, flesh-colored or red nodule in a patient with compatible symptoms is diagnostic. Rarely, an Achilles tendon xanthoma develops at the top edge of the posterior shoe counter but tends to be pink and asymptomatic. Achilles tendon enthesopathy causes pain mainly at the tendon's insertion but may also cause pain at the top edge of the posterior shoe counter. Enthesopathy is differentiated by the absence of a soft-tissue lesion.

Treatment

• Modification of footwear

Properly fitting shoes with low heels are essential. A foam rubber or felt heel pad may be needed to lift the heel high enough so that the bursa does not hit the shoe counter. Padding around the bursa or the wearing of a backless shoe until inflammation subsides is indicated. Foot orthotics may enhance rear foot stability and help reduce irritating motion on the posterior calcaneus while walking. Warm or cool compresses, NSAIDs, and intrabursal injection of a local anesthetic/corticosteroid solution offer temporary relief; the Achilles tendon itself must not be injected. Surgical removal of a portion of the underlying bone may rarely be necessary to reduce soft-tissue impingement.

Epiphysitis of the Calcaneus

(Sever's Disease)

Epiphysitis of the calcaneus is painful disruption between the calcaneal apophysis and the body of the heel that occurs before calcaneal ossification is complete.

The calcaneus develops from two centers of ossification: one begins at birth, the other usually after age 8. Ossification is usually complete by age 15. The cartilaginous disruption in calcaneal epiphysitis may result from an excessive pull on the apophysis by contracted or shortened calf muscles. Bone growth spurts without adaptive calf muscle lengthening may play a role.

Pain develops in a patient (usually aged 9 to 14) with a history of athletic activity; it affects the sides or margins of the heel and is aggravated by standing on tip toes or running. Warmth and swelling are occasionally present.

The diagnosis is clinical. X-rays are not helpful.

Treatment

• Heel pads and splinting or casting

Heel pads relieve symptoms by reducing the pull of the Achilles tendon on the heel. Night splints may be used to passively stretch the calf muscles, helping maintain flexibility. In more severe or recalcitrant cases, cast immobilization may be used to relieve pain and stretch the calf muscles. Reassurance is important because symptoms may last several months.

Medial Plantar Nerve Entrapment

Medial plantar nerve entrapment is symptomatic compression of the medial branch of the posterior tibial nerve at the medial heel.

Symptoms include almost constant pain, with and without weight bearing. Simple standing is often difficult. Burning, numbness, and paresthesias are usually absent.

Diagnosis

• Clinical evaluation

Medial plantar nerve entrapment may be confused with plantar fasciosis and heel spur pain as well as tarsal tunnel syndrome. In medial plantar nerve entrapment, the following are present:

• Tenderness is at the medial heel.

• Other signs of tarsal tunnel syndrome are absent.

• Symptoms can be reproduced by palpation over the proximal aspect of the abductor hal-lucis, the origin of the plantar fascia, or both at the medial tubercle of the calcaneus.

Treatment

• Orthoses, immobilization, and physical therapy

Immobilization and foot orthoses to prevent irritating motion and pressure may be helpful, as may physical therapy and cryotherapy. If these treatments are ineffective, injection with a sclerosing agent that contains alcohol or careful surgical decompression of the nerve may help relieve pain.

Plantar Fibromatosis

Plantar fibromatosis is a benign proliferative neoplasia of the plantar fascia.

In plantar fibromatosis, nodules are displayed most easily when the foot is dorsiflexed against the leg. Most patients also have palmar nodules, usually located at the 4th metacarpophalangeal joint. Reported associations with diabetes, epilepsy, and alcoholism may be anecdotal. Treatment is usually not indicated unless the nodules become large enough to cause pressure-related pain with weight bearing. If so, orthoses can help redistribute pressure away from the fibrotic nodular lesions. Surgery usually results in recurrence and may also result in unintentional instability of the foot when fascial removal is excessive.

Hammer Toe Deformity

Hammer toe is a C-shaped deformity caused by dorsal subluxation at the metatarsophalangeal joint.

[
Fig. 44-2. Hammer toe.]

The usual cause is misalignment of the joint surfaces due to a genetic predisposition toward aberrant foot biomechanics and tendon contractures. RA and neurologic disorders such as Charcot-Marie-Tooth disease are other causes. The 2nd toe is the most common digit to develop a hammer toe deformity (see Fig. 44-2). Second toe hammer toes commonly result from an elongated 2nd metatarsal and from pressure due to an excessively abducted great toe (hallux valgus deformity) causing a bunion (see below). Painful corns (see p. 660) often develop in hammer toe deformity, particularly of the 5th toe. Reactive adventitial bursas often develop beneath corns, which may become inflamed.

Symptoms include pain while wearing shoes, especially shoes with low and narrow toe boxes, and sometimes metatarsalgia. Diagnosis is clinical. Joints are examined for coexistent arthritis (eg, RA).

Treatment

• Wide toe box, toe pads, orthotics, or a combination

Shoes should have a wide toe box. Toe pads sold in pharmacies also help by shielding the affected toes from the overlying shoe. If these measures are ineffective, surgical correction of the deformity often relieves symptoms. If there is accompanying metatarsalgia, OTC or prescription orthotic devices with

metatarsal pads and cushioning may help alleviate the pain.

Bunion

Bunion is a prominence of the medial portion of the head of the 1st metatarsal bone. The cause is often variations in position of the 1st metatarsal bone or great toe, such as lateral angulation of the great toe (hallux valgus). Secondary osteoarthritis and spur formation are common. Symptoms may include pain and redness, bursitis medial to the joint, and mild synovitis. Diagnosis is usually clinical. Treatment is usually a shoe with a wide toe box, protective pads, and orthotics. For bursitis or synovitis, corticosteroid injection may be helpful.

Contributing factors may include excessive turning in (pronation) of the ankles, wearing tight and pointed-toe shoes, and occasionally trauma. Joint misalignment causes osteoarthritis with cartilage erosion and exostosis formation, resulting in joint motion being limited (hallux limitus) or eliminated (hallux rigidus). In late stages, synovitis occurs, causing joint swelling. In reaction to pressure from tight shoes, an adventitious bursa can develop medial to the joint prominence, which can become painful, swollen, and inflamed (see
Fig. 44-3).

Symptoms and Signs

The initial symptom may be pain at the joint prominence when wearing certain shoes. The joint capsule may be tender at any stage. Later symptoms may include a painful, warm, red, cystic, movable, fluctuant swelling located medially (adventitial bursitis) and swellings and mild inflammation affecting the entire joint (osteoarthritic synovitis), which is more circumferential. With hallux limitus or rigidus, there is restriction of passive joint motion, tenderness of the lateral aspect of the joint, and increased dorsiflexion of the distal phalanx.

[**Fig. 44-3.** Bunion.]

Diagnosis

• Clinical evaluation

Clinical findings are usually specific. Acute circumferential intense pain, warmth, swelling, and redness suggest gouty arthritis or infectious arthritis, mandating examination of synovial fluid. If multiple joints are affected, gout or another systemic rheumatic disease should be considered. If clinical diagnosis of osteoarthritic synovitis is equivocal, x-rays are taken. Suggestive findings include joint space narrowing and bony spurs extending from the metatarsal head or sometimes from the base of the proximal phalanx. Periarticular erosions (Martel's sign) seen on imaging studies suggest gout.

Treatment

• Wide toe box, bunion pads, orthotics, or a combination

• Treatment of complications

Mild discomfort may lessen by wearing a shoe with a wide toe box. If not, bunion pads purchased in most pharmacies can shield the painful area. Orthotics can also be prescribed to redistribute and relieve pressure from the affected articulation. If conservative therapy fails or if the patient is unwilling to wear large, wide shoes and orthotics because they are unattractive, surgery aimed at correcting abnormal bony alignments and restoring joint mobility should be strongly considered. For bursitis, bursal aspiration and injection of a corticosteroid are indicated. For osteoarthritic synovitis, oral NSAIDs or an intra-articular injection of a corticosteroid/anesthetic solution reduces symptoms. For hallux limitus or hallux rigidus, treatment aims to preserve joint mobility by using passive stretching exercises, which occasionally require injection of a local anesthetic to relieve muscle spasm. Sometimes surgical release of contractures is necessary.

Chapter 45. Tumors of Bones and Joints

Introduction

Bone tumors may be primary or metastatic and benign or malignant.

In children, most bone tumors are primary and benign; some are malignant primary tumors (eg, osteosarcoma, Ewing's sarcoma). Very few are metastatic tumors (eg, neuroblastoma, Wilms' tumor). Bone also can be affected by childhood leukemia and lymphomas.

In adults, especially those over age 40, metastatic tumors are about 100 times more common than primary malignant tumors. Excluding marrow cell tumors (eg, multiple myeloma), there are only about 2500 cases of primary malignant bone tumors in the US each year among children and adults.

Synovial tumors are extremely rare in both children and adults. Pigmented villonodular synovitis is a benign but at times destructive tumor of synovial cells. Synovial sarcoma (often with both spindle cell and glandular-like components) is a malignant soft-tissue tumor not of synovial origin, which seldom occurs inside of a joint.

Symptoms and Signs

Bone tumors typically cause unexplained, progressive pain and swelling. Pain can occur without weight bearing or bone stress and can occur at rest and at night.

Diagnosis

• Plain x-rays

• MRI usually and sometimes CT

• Bone scan if multicentric or metastatic tumors are suspected

• Biopsy unless imaging studies clearly show benign characteristics

The most common reason that diagnosis of bone tumors is delayed is that physicians fail to suspect the tumor and order appropriate imaging studies. Persistent or progressive unexplained pain of the trunk or extremities, particularly if associated with a mass, is suggestive. Plain x-rays are the first test. Tumors should also be suspected if a radiographic study shows an unexplained abnormality consistent with a tumor. Lesions suggestive of tumors usually require further assessment, often with additional imaging studies and a biopsy.

Characteristic findings: Some tumors (eg, Paget's disease, nonossifying fibroma, fibrous dysplasia, enchondromas) may have characteristic radiographic findings and can be diagnosed without biopsy.

Radiographic findings that suggest cancer include the following:

• A lytic, destructive, or permeative appearance

• Irregular tumor borders

• Areas, especially multiple areas, of bone destruction (moth-eaten appearance)

• Cortical destruction

• Soft-tissue extension

• Pathologic fracture

A lytic appearance is characterized by clear areas of bone destruction that are sharply demarcated. A permeative appearance is characterized by a faint, gradual loss of bone or an infiltrating pattern without clear borders. Certain tumors have a characteristic appearance (eg, Ewing's sarcoma typically shows permeative-type bone destruction, including a large soft-tissue mass with periosteal onion-skin reactive bone often before there is an extensive, lytic, destructive appearance; giant cell tumor has a cystic appearance without a sclerotic interface between the tumor and normal bone). The tumor's location may narrow diagnostic possibilities (eg, Ewing's sarcoma commonly appears in the shaft of a long bone; osteosarcoma usually appears in the metaphyseal-diaphyseal region toward the end of a long bone; giant cell tumor usually occurs in the epiphysis).

Some benign conditions, however, can mimic a malignant tumor:

- Heterotopic ossification (myositis ossificans) and exuberant callus formation after fracture can cause mineralization around bony cortices and in adjacent soft tissues, mimicking malignant tumors.

- Langerhans' cell histiocytosis (histiocytosis X, Letterer-Siwe disease, Hand-Schuller-Christian disease, eosinophilic granuloma) can cause solitary or multiple bone lesions that are usually distinguishable on x-ray. In solitary lesions, there may be periosteal new bone formation, suggesting a malignant bone tumor.

- Osteopoikilosis (spotted bones) is an asymptomatic condition of no clinical consequence but can simulate osteoblastic bone metastases of breast cancer. It is characterized by multiple small, round, or oval foci of bony sclerosis, usually in the tarsal, carpal, or pelvic bones or the metaphyseal-epiphyseal regions of tubular bones.

Other testing: CT and MRI may help define the location and extent of a bone tumor and sometimes suggest a specific diagnosis. MRI is usually done if cancer is suspected. If tumors are suspected of being metastatic or involving multiple foci (multicentric), then radioisotopic technetium bone scanning should be done to search for all tumors.

Biopsy is usually essential for diagnosis of malignant tumors, unless the imaging studies have a classically benign appearance. The pathologist should be given pertinent details of the clinical history and should review imaging studies. Histopathologic diagnosis may be difficult and requires sufficient viable tissue from a representative portion of the tumor (usually the soft portion). The best results are obtained in centers with extensive experience in bone biopsies. Immediate, accurate, definitive diagnosis is possible in > 90% of cases. If a malignant diagnosis is suspected on frozen section histology, often the surgeon will wait upon permanent histology before treating definitively. Mistakes occur more frequently in hospitals that infrequently encounter patients with malignant primary tumors.

Benign Bone Tumors

Osteochondroma: Osteochondromas (osteocartilaginous exostoses), the most common benign bone tumors, may arise from any bone but tend to occur near the ends of long bones. These tumors manifest most often in people aged 10 to 20 and may be single or multiple. Multiple osteochondromas tend to run in families. Secondary malignant chondrosarcoma develops in about 10% of patients with multiple osteochondromas and in well < 1% of those with single osteochondromas. Osteochondromas rarely cause the bone to fracture.

On imaging studies, the lesion appears as a bony prominence with a cartilage cap (< 2 cm) off the surface of the bone with no underlying cortex under the prominence.

Excision is needed if the tumor is compressing a large nerve; causes pain (especially when impinging on muscle and creating an inflammatory bursa); disturbs growth; or on imaging study has a destructive appearance, soft-tissue mass, or thickened cartilaginous cap (> 2 cm) suggesting transformation into malignant chondrosarcoma.

Enchondroma: Enchondromas may occur at any age but tend to be recognized in patients aged 10 to 40. They are usually located within the medullary bone metaphyseal-diaphyseal region. These tumors are

usually asymptomatic but may enlarge and become painful. They are often found when x-rays are taken for another reason.

On x-ray, the tumor may appear as a lobulated calcified area within bone; some lesions are less calcified, with areas of stippled calcification either on plain films or CT. If adjacent to the cortex, enchondromas show minor endosteal scalloping. Almost all enchondromas have increased uptake on a bone scan and thus create concern of cancer. X-ray findings, including MRI and CT, may be diagnostic; if they are not, and especially if the tumor (not the associated joint) is painful, the diagnosis should be confirmed by biopsy. To help differentiate bone pain from joint pain, the joint can be injected, usually with a long-lasting anesthetic (eg, bupivacaine); if pain persists, it may be caused by the bone lesion.

An asymptomatic enchondroma does not need biopsy, excision, or other treatment (usually curettage); however, follow-up imaging studies are indicated to rule out disease progression. These are done at 6 mo and again at 1 yr or whenever symptoms develop.

Chondroblastoma: Chondroblastoma is rare and occurs most commonly among people aged 10 to 20. Arising in the epiphysis, this tumor may continue to grow and destroy bone and the joint. It appears on imaging studies as a sclerotic marginated cyst containing spots of punctate calcification. MRI can help diagnostically by showing characteristic changes well away from the lesion.

The tumor must be surgically removed by curettage, and the cavity must be bone grafted. Local recurrence rate is about 10 to 20%, and recurrent lesions often resolve with repeat bone curettage and bone grafting.

Chondromyxofibroma: Chondromyxofibroma is very rare and usually occurs before age 30. The appearance on imaging studies (usually eccentric, sharply circumscribed, lytic, and located near the end of long bones) suggests the diagnosis. Treatment after biopsy is surgical excision or curettage.

Osteoid osteoma: Osteoid osteoma, which tends to affect young people (commonly aged 10 to 35), can occur in any bone but is most common among long bones. It can cause pain (usually worse at night) that is typically relieved by mild analgesics, particularly aspirin or other NSAIDs. In growing children, the inflammatory response and associated hyperemia, if close to the open growth plate, may cause overgrowth and limb length discrepancy. Physical examination may reveal atrophy of regional muscles because the pain causes muscle disuse.

Characteristic appearance on imaging studies is a small radiolucent zone surrounded by a larger sclerotic zone. If a tumor is suspected, a technetium-99m bone scan should be done; an osteoid osteoma appears as an area of increased uptake. CT with fine image sequences is also done and is most helpful in distinguishing the lesion.

Removal of the small radiolucent zone with percutaneous radiofrequency ablation provides permanent relief. Most osteoid osteomas are treated by an interventional musculoskeletal radiologist using percutaneous techniques and anesthesia. Less often, osteoid osteomas are surgically curetted or excised.

Benign giant cell tumor: These tumors, which most commonly affect people in their 20s and 30s, occur in the epiphyses and may eventually erode the rest of the bone and extend into the soft tissues. They may cause pain. Giant cell tumors are notorious for their tendency to recur. Rarely, a giant cell tumor may metastasize to the lung, even though it remains histologically benign.

Benign giant cell tumors appear as expansile lytic lesions on imaging. On imaging studies, there is a margin without a sclerotic rim where the tumor ends and normal trabecular bone begins.

Most benign giant cell tumors are treated by curettage and packing with methyl methacrylate or by bone graft. To reduce recurrence rate, surgeons often prefer using an adjuvant such as thermal heat (provided by the hardening of methyl methacrylate) or chemically by phenol or freezing with liquid nitrogen. If a tumor is very large and destructive to the joint, complete excision with joint reconstruction may be necessary.

Primary Malignant Bone Tumors

(See also Ch. 117.)

Multiple myeloma: Multiple myeloma is the most common primary malignant bone tumor but is often considered a marrow cell tumor within the bone rather than a bone tumor. It is of hematopoietic derivation (see also p. 1029) and occurs mostly in older adults. The neoplastic process is usually multicentric and often involves the bone marrow so diffusely that bone marrow aspiration is diagnostic. Imaging studies usually show sharply circumscribed lytic lesions or diffuse demineralization. Rarely, the lesion can appear as sclerotic or as diffuse osteopenia, especially in a vertebral body. An isolated single myeloma lesion without systemic marrow involvement is called a plasmacytoma.

Osteosarcoma: Osteosarcoma (osteogenic sarcoma) is the 2nd most common primary bone tumor and is highly malignant. It is most common among people aged 10 to 25, although it can occur at any age. Osteosarcoma produces malignant osteoid (immature bone) from tumor bone cells. Osteosarcoma usually develops around the knee (distal femur more often than proximal tibia) or in other long bones, particularly the metaphyseal-diaphyseal area, and may metastasize, usually to lung or other bone. Pain and swelling are the usual symptoms.

Findings on imaging studies vary and may include sclerotic or lytic features. Diagnosis requires biopsy. Patients need a chest x-ray and CT to detect lung metastases and a bone scan to detect bone metastases.

Treatment is a combination of chemotherapy and surgery. Use of adjuvant chemotherapy increases survival from < 20% to > 65% at 5 yr. Chemotherapy usually begins before any surgery. Decreased tumor size on x-ray, decreased pain level, and decreased serum alkaline phosphatase indicate some response, but the desired response is for > 95% tumor necrosis on mapping of the resected specimen. After several courses of chemotherapy (over several months), limb-sparing surgery and limb reconstruction can proceed. In limb-sparing surgery, the tumor is resected en bloc, including all surrounding reactive tissue and a rim of surrounding normal tissue; to avoid microscopic spillage of tumor cells, the tumor is not violated. More than 80% of patients can be treated with limb-sparing surgery without decreasing long-term survival rate. Continuation of chemotherapy after surgery is usually necessary. If there is nearly complete tumor necrosis (about 99%) from preoperative chemotherapy, 5-yr survival rate is > 90%.

Fibrosarcoma: Fibrosarcomas have similar characteristics to osteosarcomas but produce fibrous tumor cells (rather than bone tumor cells), affect the same age group, and pose similar problems.

Malignant fibrous histiocytoma: This tumor is clinically similar to osteosarcoma and fibrosarcoma, although malignant fibrous histiocytomas have been classified as different from the osteosarcoma group because of a different histology (no tumor bone production). Malignant fibrous histiocytomas tend to occur in children and teenagers but can also occur in older adults as secondary lesions in bone infarcts and radiation fields. Treatment is similar to that of osteosarcoma.

Chondrosarcoma: Chondrosarcomas are malignant tumors of cartilage. They differ from osteosarcomas clinically, therapeutically, and prognostically. Of chondrosarcomas, 90% are primary tumors. Chondrosarcomas arise in other pre-existing conditions, particularly multiple osteochondromas and multiple enchondromatosis (eg, in Ollier's disease and Maffucci's syndrome). Chondrosarcomas tend to occur in older adults. They often develop in flat bones (eg, pelvis, scapula) but can develop in any portion of any bone and can implant in surrounding soft tissues.

X-rays often reveal punctate calcifications. Primary chondrosarcomas often also exhibit cortical bone destruction and loss of normal bone trabeculae. Secondary chondrosarcoma may be suggested by the appearance of punctate calcifications or an increase in size of an osteochondroma. Technetium-99m bone scintigraphy is a helpful screening study; all cartilaginous lesions show increased uptake on the scan, although chondrosarcomas exhibit particularly high uptake. Biopsy is required for diagnosis and can also determine the tumor's grade (probability of metastasizing).

Low-grade chondrosarcomas (grade 1/2 or grade 1) are often treated intralesionally (wide curettage) with addition of an adjuvant (often freezing liquid nitrogen; argon beam; heat of methyl methacrylate; radiofrequency; or phenol). Other tumors are treated with total surgical resection. When surgical resection with maintenance of function is impossible, amputation may be necessary. Because of the potential to implant the tumor, meticulous care must be taken to avoid spillage of tumor cells into the soft tissues during biopsy or surgery. Recurrence is inevitable if tumor cells spill. If no spillage occurs, the cure rate depends on the tumor grade. Low-grade tumors are nearly all cured with adequate treatment. Because these tumors have limited vascularity, chemotherapy and radiation therapy have little efficacy.

Ewing's sarcoma of bone: Ewing's sarcoma is a round-cell bone tumor with a peak incidence between 10 and 25 yr. Most develop in the extremities, but any bone may be involved. Ewing's sarcoma tends to be extensive, sometimes involving the entire bone shaft, most often the diaphyseal region. About 15 to 20% occur around the metaphyseal region. Pain and swelling are the most common symptoms.

Lytic destruction, particularly a permeative infiltrating pattern without clear borders, is the most common finding on imaging, but multiple layers of subperiosteal reactive new bone formation may give an onion-skin appearance. X-rays do not usually reveal the full extent of bone involvement, and a large soft-tissue mass usually surrounds the affected bone. MRI better defines disease extent, which can help guide treatment. Many other benign and malignant tumors can appear very similar, so diagnosis is made by biopsy. At times this tumor may be confused with an infection. Accurate histologic diagnosis can be accomplished with molecular markers, including evaluation for a typical clonal chromosomal abnormality.

Treatment includes various combinations of surgery, chemotherapy, and radiation therapy. Currently, > 60% of patients with primary localized Ewing's sarcoma may be cured by this multimodal approach. Cure is sometimes possible even with metastatic disease. Chemotherapy in conjunction with surgical en bloc resection, if applicable, often yields better long-term results.

Lymphoma of bone: Lymphoma of bone (previously known as reticulum cell sarcoma) affects adults, usually in their 40s and 50s. It may arise in any bone. The tumor consists of small round cells, often with a mixture of reticulum cells, lymphoblasts, and lymphocytes. It can develop as an isolated primary bone tumor, in association with similar tumors in other tissues, or as a metastasis from known soft-tissue lymphomatous disease. Pain and swelling are the usual symptoms. Pathologic fracture is common.

Imaging studies reveal bone destruction, which may be in a mottled or patchy or even infiltrating, permeative pattern, often with a clinical and radiographic large soft-tissue mass. In advanced disease, the entire outline of the affected bone may be lost.

In isolated primary bone lymphoma, the 5-yr survival rate is ≥ 50%. Combination radiation therapy and chemotherapy is as curative as amputation or other extensive ablative surgery. Stabilization of long bones is often necessary to prevent pathologic fracture. Amputation is indicated only rarely, when function is lost because of pathologic fracture or extensive soft-tissue involvement that cannot be managed otherwise.

Malignant giant cell tumor: Malignant giant cell tumor, which is rare, is usually located at the extreme end of a long bone. X-ray reveals classic features of malignant destruction (predominantly lytic destruction, cortical destruction, soft-tissue extension, and pathologic fracture). A malignant giant cell tumor that develops in a previously benign giant cell tumor is characteristically radioresistant. Treatment is similar to that of osteosarcoma, but the cure rate is low.

Chordoma: Chordoma, which is rare, develops from the remnants of the primitive notochord. It tends to occur at the ends of the spinal column, usually in the middle of the sacrum or near the base of the skull. A chordoma in the sacrococcygeal region causes nearly constant pain. A chordoma in the base of the skull can cause deficits in a cranial nerve, most commonly in nerves to the eye.

Symptoms may exist for months to several years before diagnosis. A chordoma appears on imaging studies as an expansile, destructive bone lesion that may be associated with a soft-tissue mass. Metastasis is unusual, but local recurrence is not. Chordomas in the sacrococcygeal region may be cured by radical en bloc excision. Chordomas in the base of the skull are usually inaccessible to surgery but may respond to radiation therapy.

Metastatic Bone Tumors

Any cancer may metastasize to bone, but metastases from carcinomas are the most common, particularly those arising in the following areas:

• Breast

• Lung

• Prostate

• Kidney

• Thyroid

• Colon

Prostate cancer in men and breast cancer in women are the most common types of cancers. Lung cancer is the most common cause of cancer death in both sexes. Breast cancer is the most common cancer to metastasize to bone. Any bone may be involved with metastases. Metastatic disease does not commonly spread to bone below the mid forearm or mid calf, but when it occurs in those sites, it results most often from lung or sometimes kidney cancer.

Symptoms and Signs

Metastases manifest as bone pain, although they may remain asymptomatic for some time. Bone metastases may cause symptoms before the primary tumor is suspected or may appear in patients with a known diagnosis of cancer.

Diagnosis

• X-ray

• Radionuclide scanning to identify all metastases

• Clinical evaluation and testing to diagnose the primary tumor (if unknown)

• Often biopsy if the primary tumor is unknown after assessment

Metastatic bone tumors are considered in all patients with unexplained bone pain, but particularly in patients who have

• Known cancer

• Pain at more than one site

• Findings on imaging studies that suggest metastases

Prostate cancer is most often blastic, lung cancer is most often lytic, and breast cancer may be blastic or lytic.

CT and MRI are highly sensitive for specific metastases. However, if metastases are suspected, a radionuclide whole-body scan, which is not quite as sensitive, is usually done. Bone scan is more sensitive for early and asymptomatic metastases than plain x-rays and can be used to scan the entire body. Lesions on the scan are usually presumed to be metastases if the patient has a known primary cancer. Metastases should be suspected in patients who have multiple lesions on bone scan. Although metastases are suspected in patients with known cancer and a single bone lesion, the lesion may not be

a metastasis; thus, a needle biopsy of the lesion is often done to confirm the diagnosis of a metastasis. PET for almost whole-body scanning is now often used for some tumors.

If bone metastases are suspected because multiple lytic lesions are found, assessment for the primary tumor can begin with clinical evaluation for primary cancers (particularly focused on the breast, prostate, and thyroid), chest x-ray, mammography, and measurement of prostate-specific antigen level. Initial CT of the chest, abdomen, and pelvis may also reveal the primary tumor. However, bone biopsy, especially fine-needle or core biopsy, is necessary if metastatic tumor is suspected and the primary tumor has not been otherwise diagnosed. Biopsy with use of immunohistologic stains may give clues to the primary tumor type.

Treatment

• Usually radiation therapy

• Surgery to stabilize bone at risk of pathologic fracture

• Kyphoplasty or vertebraplasty for certain painful vertebral fractures

Treatment depends on the type of tissue involved (which organ tissue type). Radiation therapy, combined with selected chemotherapeutic or hormonal drugs, is the most common treatment modality. Early use of radiation (30 Gy) and bisphosphonates (eg, zoledronate, pamidronate) slows bone destruction. Some tumors are more likely to heal after radiation therapy; for example, blastic lesions of prostate and breast cancer are more likely to heal than lytic destructive lesions of lung cancer and renal cell carcinoma.

If bone destruction is extensive, resulting in imminent or actual pathologic fracture, surgical fixation or resection and reconstruction may be required to provide stabilization and help minimize morbidity. When the primary cancer has been removed and only a single bone metastasis remains (especially if the metastatic lesion appears ≥ 1 yr after the primary tumor), en bloc excision sometimes combined with radiation therapy, chemotherapy, or both rarely may be curative. Insertion of methyl methacrylate into the spine (kyphoplasty or vertebraplasty) relieves pain and expands and stabilizes compression fractures that do not have epidural soft-tissue extension.

Other Bone Lesions

Many nonneoplastic conditions of bone may clinically or radiologically mimic solitary bone tumors.

Unicameral bone cyst: Simple unicameral bone cysts occur in the long bones starting distal to the epiphyseal plate in children. The cyst causes the cortex to thin and predisposes the area to a buckle-like pathologic fracture, which is usually how the cyst is recognized. Cysts < 5 cm may heal and may disappear as the fracture heals. Cysts > 5 cm, particularly in children, may require excision or curettage and bone grafting; however, many respond to injections of corticosteroids, demineralized bone matrix, or synthetic bone substitutes. The response may be variable and may require multiple injections. Regardless of treatment, cysts persist in about 10 to 15% of patients.

Fibrous dysplasia: Fibrous dysplasia involves abnormal bone development during childhood. It may affect one or several bones. Cutaneous pigmentation and endocrine abnormalities may be present (Albright's syndrome). The abnormal bone lesions of fibrous dysplasia commonly stop developing at puberty. They rarely undergo malignant degeneration. On x-ray, the lesions can appear cystic and may be extensive and deforming. Calcitonin may help relieve pain. Progressive deformities, fractures that do not heal with immobilization, or intractable pain may be effectively treated with orthopedic surgery.

Aneurysmal bone cyst: An aneurysmal bone cyst is an idiopathic expansile lesion that usually develops before age 25 yr. This cystic lesion usually occurs in the metaphyseal region of the long bones, but almost any bone may be affected. It tends to grow slowly. A periosteal new bone shell forms around the expansile lesion and is often wider than the original bone. Pain and swelling are common. The lesion may be present for a few weeks to a year before diagnosis. The appearance on x-ray is often characteristic: The rarefied area is usually well circumscribed and eccentric; the periosteum bulges, extending into the

soft tissues, and may be surrounded by new bone formation.

Surgical removal of the entire lesion is the most successful treatment; regression after incomplete removal sometimes occurs. Radiation should be avoided when possible because sarcomas occasionally develop. However, radiation may be the treatment of choice in completely surgically inaccessible vertebral lesions that are compressing the spinal cord.

Joint Tumors

Tumors rarely affect joints, unless by direct extension of an adjacent bone or soft-tissue tumor. However, 2 conditions—synovial chondromatosis and pigmented villonodular synovitis—occur in the lining (synovium) of joints. These conditions are benign but locally aggressive. Both usually affect one joint, most often the knee and second most often the hip, and can cause pain and effusion. Both are treated by synovectomy and removal of any intra-articular bodies.

Synovial chondromatosis: Synovial chondromatosis (previously called synovial osteochondromatosis) is considered metaplastic. It is characterized by numerous calcified cartilaginous bodies in the synovium, which often become loose. Each body may be no larger than a grain of rice, in a swollen, painful joint. Malignant change is very rare. Recurrence is common.

Pigmented villonodular synovitis: Pigmented villonodular synovitis is considered neoplastic. The synovium becomes thickened and contains hemosiderin, which gives the tissue its blood-stained appearance and characteristic appearance on MRI. This tissue tends to invade adjacent bone, causing cystic destruction and damage to the cartilage. Pigmented villonodular synovitis is usually monarticular but may be polyarticular. Late management, especially after recurrence, may require total joint replacement. On rare occasions after several synovectomies, radiation therapy can be used.

5 - Ear, Nose, Throat, and Dental Disorders

Chapter 46. Approach to the Patient With Ear Problems

Introduction

Earache, hearing loss, otorrhea, tinnitus, and vertigo are the principal symptoms of ear problems. Hearing loss is discussed in Ch. 47.

In addition to the ears, nose, nasopharynx, and paranasal sinuses, the teeth, tongue, tonsils, hypopharynx, larynx, salivary glands, and temporomandibular joint are examined; pain and discomfort may be referred from them to the ears. It is important to examine cranial nerve function (see pp. 1587 and 1745) and to perform tests of hearing (see p. 431) and of the vestibular apparatus. The patient is also examined for nystagmus (a rhythmic movement of the eyes—see Sidebar 46-1).

Testing

Patients with abnormal hearing on history or physical examination or with tinnitus or vertigo undergo an audiogram (see p. 433). Patients with nystagmus or altered vestibular function may benefit from computerized electronystagmography (ENG), which quantifies spontaneous, gaze, or positional nystagmus that might not be visually detectable. Computerized ENG caloric testing quantifies the strength of response of the vestibular system to cool and warm irrigations in each ear, enabling the physician to discriminate unilateral weakness. Different components of the vestibular system can be tested by varying head and body position or by presenting visual stimuli.

Sidebar 46-1 Nystagmus

Nystagmus is a rhythmic movement of the eyes that can have various causes. Vestibular disorders can result in nystagmus because the vestibular system and the oculomotor nuclei are interconnected. The presence of vestibular nystagmus helps identify vestibular disorders and sometimes distinguishes central from peripheral vertigo. Vestibular nystagmus has a slow component caused by the vestibular input and a quick, corrective component that causes movement in the opposite direction. The direction of the nystagmus is defined by the direction of the quick component because it is easier to see. Nystagmus may be rotary, vertical, or horizontal and may occur spontaneously, with gaze, or with head motion.

Initial inspection for nystagmus is done with the patient lying supine with unfocused gaze (+30 diopter or Frenzel lenses can be used to prevent gaze fixation). The patient is then slowly rotated to a left and then to a right lateral position. The direction and duration of nystagmus are noted. If nystagmus is not detected, the Dix-Hallpike (or Barany) maneuver is done. In this maneuver, the patient sits erect on a stretcher so that when lying back, the head extends beyond the end. With support, the patient is rapidly lowered to horizontal, and the head is extended back 45° below horizontal and rotated 45° to the left. Direction and duration of nystagmus and development of vertigo are noted. The patient is returned to an upright position, and the maneuver is repeated with rotation to the right. Any position or maneuver that causes nystagmus should be repeated to see whether it fatigues.

Nystagmus secondary to peripheral nervous system disorders has a latency period of 3 to 10 sec and fatigues rapidly, whereas nystagmus secondary to CNS has no latency period and does not fatigue. During induced nystagmus, the patient is instructed to focus on an object. Nystagmus caused by peripheral disorders is inhibited by visual fixation. Because Frenzel lenses prevent visual fixation, they must be removed to assess visual fixation.

Caloric stimulation of the ear canal induces nystagmus in a person with an intact vestibular system. Failure to induce nystagmus or > 20% difference in duration between sides suggests a lesion on the side of the decreased response. Quantification of caloric response is best done with formal (computerized) electronystagmography.

Ability of the vestibular system to respond to peripheral stimulation can be assessed at the bedside. Care

should be taken not to irrigate an ear with a known tympanic membrane perforation or chronic infection. With the patient supine and the head elevated 30°, each ear is irrigated sequentially with 3 mL of ice water. Alternatively, 240 mL of warm water (40 to 44°C) may be used, taking care not to burn the patient with overly hot water. Cold water causes nystagmus to the opposite side; warm water causes nystagmus to the same side. A mnemonic device is COWS (*C*old to the *O*pposite and *W*arm to the *S*ame).

Primary imaging tests include CT of the temporal bone with or without radiopaque dye and gadolinium-enhanced MRI of the brain, with attention paid to the internal auditory canals to rule out an acoustic neuroma. These tests may be indicated in cases of trauma to the ear, head, or both; chronic infection; hearing loss; vertigo; facial paralysis; and otalgia of obscure origin.

Earache

(Otalgia)

Earache may occur in isolation or along with discharge or, rarely, hearing loss.

Pathophysiology

Pain may come from a process within the ear itself or may be referred to the ear from a nearby nonotologic disorder.

Pain from the ear itself may result from a pressure gradient between the middle ear and outside air, from local inflammation, or both. A middle ear pressure gradient usually involves eustachian tube obstruction, which inhibits equilibration between middle ear pressure and atmospheric pressure and also allows fluid to accumulate in the middle ear. Otitis media causes painful inflammation of the tympanic membrane (TM) as well as pain from increased middle ear pressure (causing bulging of the TM).

Referred pain can result from disorders in areas innervated by cranial nerves responsible for sensation in the external and middle ear (5th, 9th, and 10th). Specific areas include the nose, paranasal sinuses, nasopharynx, teeth, gingiva, temporomandibular joint (TMJ), mandible, parotid glands, tongue, palatine tonsils, pharynx, larynx, trachea, and esophagus. Disorders in these areas sometimes also obstruct the eustachian tube, causing pain from a middle ear pressure gradient.

Etiology

Earache results from otologic causes (involving the middle ear or external ear) or from nonotologic causes referred to the ear from nearby disease processes (see Table 46-1).

With **acute pain**, the most common causes are

• Middle ear infection

• External ear infection

With **chronic pain** (> 2 to 3 wk), the most common causes are

• TMJ dysfunction

• Chronic eustachian tube dysfunction

• Chronic otitis externa

Also with chronic pain, a tumor must be considered, particularly in elderly patients and if the pain is associated with ear drainage. People with diabetes or in other immunocompromised states may develop a particularly severe form of external otitis termed malignant or necrotizing external otitis. In this situation, if

abnormal soft tissue is found on examination of the ear canal, the tissue must be biopsied to rule out cancer.

TMJ dysfunction is a common cause of earache in patients with a normal ear examination.

Evaluation

History: History of present illness should assess the location, duration, and severity of pain and whether it is constant or intermittent. If intermittent, it is important to determine whether it is random or occurs mainly with swallowing or jaw movement. Important associated symptoms include ear drainage, hearing loss, and sore throat. The patient should be asked about any attempts at cleaning the ear canal (eg, with cotton swab) or other recent instrumentation, foreign bodies, recent air travel or scuba diving, and swimming or other recurrent water exposure to ears.

Review of systems should ask about symptoms of chronic illness, such as weight loss and fevers.

Past medical history should ask about known diabetes or other immunocompromised state, previous ear disorders (particularly infections), and amount and duration of tobacco and alcohol use.

Physical examination: Vital signs should be checked for fever.

Examination focuses on the ears, nose, and throat.

The pinna and area over the mastoid process should be inspected for redness and swelling. The ear canal should be examined for redness, discharge, cerumen or foreign body, and any other lesions. The TM should be examined for redness, perforation, and signs of middle ear fluid collection (eg, bulging, distortion, change in normal light reflex). A brief bedside test of hearing (see p. 431) should be conducted.

The throat should be examined for erythema, tonsillar exudate, peritonsillar swelling, and any mucosal lesions suggesting cancer.

TMJ function should be assessed by palpation of the joints on opening and closing of the mouth, and notation should be made of trismus or evidence of bruxism.

The neck should be palpated for lymphadenopathy. In-office fiberoptic examination of the pharynx and larynx should be considered, particularly if no cause for the pain is identified on routine examination and if nonotologic symptoms such as hoarseness, difficulty swallowing, or nasal obstruction are reported.

Red flags: The following findings are of particular concern:

• Diabetes or immunocompromised state

• Redness and fluctuance over mastoid and protrusion of auricle

• Severe swelling at external auditory canal meatus

• Chronic pain, especially if associated with other head/neck symptoms

Interpretation of findings: An important differentiator is whether the ear examination

[**Table 46-1.** Some Causes of Earache]

is normal; middle and external ear disorders cause abnormal physical findings, which, when combined with history, usually suggest an etiology (see Table 46-1). For example, those with chronic eustachian tube dysfunction have abnormalities of the TM, typically a retraction pocket.

Those with a normal ear examination may have a visible oropharyngeal cause, such as tonsillitis or peritonsillar abscess. Ear pain due to neuralgia has a classic manifestation as brief (usually seconds,

always < 2 min) episodes of extremely severe, sharp pain. Chronic ear pain without abnormality on ear examination might be due to a TMJ disorder, but patients should have a thorough head and neck examination (including fiberoptic examination) to rule out cancer.

Testing: Most cases are clear after history and physical examination. Depending on clinical findings, nonotologic causes may require testing (see Table 46-1). Those with a normal ear examination, particularly with chronic or recurrent pain, may warrant evaluation with an MRI to rule out cancer.

Treatment

Underlying disorders are treated.

Pain is treated with oral analgesics; usually an NSAID or acetaminophen is adequate, but sometimes a brief course of an oral opioid is necessary, particularly for cases of severe otitis externa. In cases of severe otitis externa, effective treatment requires suction of debris from the ear canal and insertion of a wick to allow for delivery of antibiotic ear drops to the infected tissue. Topical analgesics (eg, antipyrine-benzocaine combinations) are generally not very effective but can be used on a limited basis.

Patients should be instructed to avoid digging in their ears with any objects (no matter how soft the objects are or how careful the patient claims to be). Also, patients should not irrigate their ears unless instructed by a physician to do so, and then only gently. An oral irrigator should never be used to irrigate the ear.

Key Points

• Most cases are due to infection of the middle or external ear.

• History and physical examination are usually adequate for diagnosis.

• Nonotologic causes should be considered when ear examination is normal.

Otorrhea

Ear discharge (otorrhea) is drainage exiting the ear. It may be serous, serosanguineous, or purulent. Associated symptoms may include ear pain, fever, pruritus, vertigo, tinnitus, and hearing loss.

Etiology

Causes may originate from the ear canal, the middle ear, or the cranial vault. Certain causes tend to manifest acutely because of the severity of their symptoms or associated conditions. Others usually have a more indolent, chronic course but sometimes manifest acutely (see Table 46-2).

Overall, the most common causes are

• Acute otitis media with perforation

• Chronic otitis media (with a perforation of the eardrum, cholesteatoma, or both)

• Otitis externa

The most serious causes are necrotizing external otitis and cancer of the ear.

Evaluation

History: History of present illness should cover duration of symptoms and whether symptoms have been recurrent. Important associated symptoms include pain, itching, decreased hearing, vertigo, and tinnitus. Patients are questioned about activities that can affect the canal or tympanic membrane (TM

—eg, swimming; insertion of objects, including cotton swabs; use of ear drops). Head trauma sufficient to cause a CSF leak is readily apparent.

Review of systems should seek symptoms of cranial nerve deficit and systemic symptoms suggesting Wegener's granulomatosis (eg, nasal discharge, cough, joint pains).

Past medical history should note any previous known ear disorders, ear surgery (particularly tympanostomy tube placement), and diabetes or immunodeficiency.

Physical examination: Examination begins with a review of vital signs for fever.

Ear and surrounding tissues (particularly the area over the mastoid) are inspected for erythema and edema. The pinna is pulled and the tragus is pushed gently to see whether pain is worsened. The ear canal is inspected with an otoscope; the character of discharge and presence of canal lesions, granulation tissue, or foreign body are noted. Edema and discharge may block visualization of all but the distal canal (irrigation should not be used in case there is a TM perforation), but when

[**Table 46-2.** Some Causes of Ear Discharge]

possible, the TM is inspected for inflammation, perforation, distortion, and signs of cholesteatoma (eg, canal debris, polypoid mass from TM).

When the ear canal is severely swollen at the meatus (eg, as with severe otitis externa) or there is copious drainage, careful suctioning can permit an adequate examination and also allow treatment (eg, application of drops, with or without a wick).

The cranial nerves are tested. The nasal mucosa is examined for raised, granular lesions, and the skin is inspected for vasculitic lesions, both of which may suggest Wegener's granulomatosis.

Red flags: The following findings are of particular concern:

• Recent major head trauma

• Any cranial nerve dysfunction (including sensorineural hearing loss)

• Fever

• Erythema of ear or periauricular tissue

• Diabetes or immunodeficiency

Interpretation of findings: Otoscopic examination can usually diagnose perforated TM, external otitis media, foreign body, or other uncomplicated sources of otorrhea. Some findings are highly suggestive (see Table 46-2). Other findings are less specific but indicate a more serious problem that involves more than a localized external ear or middle ear disorder:

• Vertigo and tinnitus (disorder of the inner ear)

• Cranial nerve deficits (disorder involving the skull base)

• Erythema and tenderness of ear, surrounding tissues, or both (significant infection)

Testing: Many cases are clear after clinical evaluation.

If CSF leakage is in question, discharge can be tested for glucose or β_2-transferrin; these substances are present in CSF but not in other types of discharge.

Patients without an obvious etiology on examination require audiogram and CT of the temporal bone or

gadolinium-enhanced MRI. Biopsy should be considered when auditory canal granulation tissue is present.

Treatment

Treatment is directed at the cause. Most physicians do not treat a suspected CSF leak with antibiotics without a definitive diagnosis because drugs might mask the onset of meningitis.

Key Points

- Acute discharge in a patient without chronic ear problems or immunodeficiency is likely the result of otitis externa or perforated otitis media.
- Severe otitis externa may require specialty referral for more extensive cleaning and possible wick placement.
- Those with recurrent ear symptoms (diagnosed or undiagnosed), cranial nerve findings, or systemic symptoms should have specialty referral.

Tinnitus

Tinnitus is a noise in the ears. It is experienced by 10 to 15% of the population.

Subjective tinnitus is perception of sound in the absence of an acoustic stimulus and is heard only by the patient. Most tinnitus is subjective.

Objective tinnitus is uncommon and results from noise generated by structures near the ear. Sometimes the tinnitus is loud enough to be heard by the examiner.

Characteristics: Tinnitus may be described as buzzing, ringing, roaring, whistling, or hissing and is sometimes variable and complex. Objective tinnitus typically is pulsatile (synchronous with the heartbeat) or intermittent. Tinnitus is most noticeable in quiet environments and in the absence of distracting stimuli and, thus, frequently seems worse at bedtime.

Tinnitus may be intermittent or continuous. Continuous tinnitus is at best annoying and is often quite distressing. Some patients adapt to its presence better than others; depression occasionally results. Stress generally exacerbates tinnitus.

Pathophysiology

Subjective tinnitus is thought to be caused by abnormal neuronal activity in the auditory cortex. This activity results when input from the auditory pathway (cochlea, auditory nerve, brain stem nuclei, auditory cortex) is disrupted or altered in some manner. This disruption may cause loss of suppression of intrinsic cortical activity and perhaps creation of new neural connections. Some believe the phenomenon is similar to the development of phantom limb pain after amputation. Conductive hearing loss (eg, caused by cerumen impaction, otitis media, or eustachian tube dysfunction) may also be associated with subjective tinnitus, by altering sound input to the central auditory system.

Objective tinnitus represents actual noise generated by physiologic phenomena occurring near the middle ear. Usually the noise comes from blood vessels, either normal vessels in conditions of increased or turbulent flow (eg, caused by atherosclerosis) or abnormal vessels (eg, in tumors or vascular malformations). Sometimes muscle spasms or myoclonus of palatal muscles or muscles in the middle ear (stapedius, tensor tympani) cause clicking sounds.

Etiology

Causes may be considered by whether they cause subjective or objective tinnitus (see Table 46-3).

Subjective tinnitus: Subjective tinnitus may occur with almost any disorder affecting the auditory pathways.

The most common disorders are those that involve sensorineural hearing loss, particularly

• Acoustic trauma (noise-induced sensorineural hearing loss)

• Aging (presbycusis)

• Ototoxic drugs

• Meniere's disease

Infections and CNS lesions (eg, caused by tumor, stroke, multiple sclerosis) that affect auditory pathways also may be responsible.

Disorders causing conductive hearing loss also may cause tinnitus. These include obstruction of the ear canal by cerumen, a foreign body, or external otitis. Otitis media, barotrauma, eustachian tube dysfunction, and otosclerosis may also be associated with tinnitus.

Temporomandibular joint dysfunction may be associated with tinnitus in some patients.

Objective tinnitus: Objective tinnitus usually involves noise from vascular flow, which causes an audible pulsating sound synchronous with the pulse. Causes include

• Turbulent flow through the carotid artery or jugular vein

• Highly vascular middle ear tumors

• Dural arteriovenous malformations (AVMs)

Muscle spasms or myoclonus of palatal muscles or those of the middle ear (stapedius, tensor tympani) may cause perceptible noise, typically a rhythmic clicking. Such spasms may be idiopathic or caused by tumors, head trauma, and infectious or demyelinating diseases (eg, multiple sclerosis). Palatal myoclonus causes visible movement of the palate, tympanic membrane, or both that coincides with tinnitus.

Evaluation

History: History of present illness should note duration of tinnitus, whether it is in one or both ears, and whether it is a constant tone or intermittent. If intermittent, the clinician should determine whether it is regular and whether it is about the rate of the pulse or sporadic. Any exacerbating or relieving factors (eg, swallowing, head position) should be noted. Important associated symptoms include hearing loss, vertigo, ear pain, and ear discharge.

Review of systems should seek symptoms of possible causes, including diplopia and difficulty swallowing or speaking (lesions of the brain stem) and focal weakness and sensory changes (peripheral nervous system disorders). The impact of the tinnitus on the patient also should be assessed. Whether the tinnitus is sufficiently distressing to cause significant anxiety, depression, or sleeplessness should be noted.

Past medical history should ask about risk factors for tinnitus, including exposure to loud noise, sudden pressure change (from diving or air travel), history of ear or CNS infections or trauma, radiation therapy to the head, and recent major weight loss (risk of eustachian dysfunction). Drug use should be ascertained, particularly any salicylates, aminoglycosides, or loop diuretics.

Physical examination: Physical examination focuses on the ear and the nervous system.

The ear canal should be inspected for discharge, foreign body, and cerumen. The tympanic membrane should be inspected for signs of acute infection (eg, redness, bulging), chronic infection (eg, perforation, cholesteatoma), and tumor (red or bluish mass). A bedside hearing test should be done.

Cranial nerves, particularly vestibular function (see p. 423), are tested along with peripheral strength, sensation, and reflexes. A stethoscope is used to listen for vascular noise over the course of the carotid arteries and jugular veins and over and adjacent to the ear.

Red flags: The following findings are of particular concern:

• Bruit, particularly over the ear or skull

• Accompanying neurologic symptoms or signs (other than hearing loss)

• Unilateral tinnitus

Interpretation of findings: In some cases, tinnitus may indicate retrocochlear pathology, such as an acoustic neuroma (benign but invasive tumor originating from the vestibular portion of the 8th cranial nerve in the internal auditory canal).

It is important to note whether the tinnitus is unilateral because acoustic neuromas may manifest only with unilateral tinnitus. This diagnosis is more likely if there is also unilateral sensorineural hearing loss or asymmetric hearing loss with worse hearing in the ear with tinnitus.

It also is important to distinguish the uncommon cases of objective tinnitus from the more common cases of subjective tinnitus. Tinnitus that is pulsatile or intermittent is almost always objective (although not always detectable by the examiner), as is that associated with a bruit. Pulsatile tinnitus is nearly always benign. Continuous tinnitus is usually subjective (except perhaps for that caused by a venous hum, which may be identified by presence of a bruit and often by a change in tinnitus with head rotation or jugular vein compression).

Specific causes can often be suspected by findings on examination (see Table 46-3). In particular, exposure to loud noise, barotrauma, or certain drugs before onset suggests those factors as the cause.

Testing: All patients with significant tinnitus should be referred for comprehensive audiologic evaluation to determine the presence, degree, and type of hearing loss.

In patients with unilateral tinnitus and hearing loss, acoustic neuroma should be ruled out by gadolinium-enhanced MRI. In those with unilateral tinnitus and normal hearing and physical examination, MRI is not necessary unless tinnitus persists > 6 mo.

Other testing depends on patient presentation (see Table 46-3).

Those with visible evidence of a vascular tumor in the middle ear require CT, gadolinium-enhanced MRI, and referral to a subspecialist if the diagnosis is confirmed.

Those with pulsatile, objective tinnitus and no ear abnormalities on examination or audiology require further investigation of the vascular system (carotid, vertebral, and intracranial vessels). The usual test sequence is to begin with magnetic resonance angiography (MRA). However, because MRA is not very sensitive for dural AVMs, many clinicians then consider doing an arteriogram. However, because dural AVMs are rare, the significant risks of arteriography must be weighed against the potential benefit of diagnosis and treatment (with embolization) of this vascular anomaly.

Treatment

Treatment of the underlying disorder may lessen tinnitus. Correcting hearing loss (eg, with a hearing aid) relieves tinnitus in about 50% of patients.

Because stress and other mental factors (eg, depression) can exacerbate symptoms, efforts to recognize and treat these factors may help. Many patients are reassured by learning that their tinnitus does not represent a serious medical problem. Tinnitus also can be worsened by caffeine and other stimulants, so patients should try eliminating use of these substances.

Although no specific medical or surgical therapy is available, many patients find that background sound masks the tinnitus and may help them fall asleep. Some patients benefit from a tinnitus masker, a device worn like a hearing aid that provides a low-level sound that can cover up the tinnitus. Tinnitus retraining therapy, offered by programs that specialize in tinnitus treatment, are helpful for many patients. Electrical stimulation of the inner ear, as with a cochlear implant, occasionally

[Table 46-3. Some Causes of Tinnitus]

reduces the tinnitus but is appropriate only for patients who are profoundly deaf.

Geriatrics Essentials

One out of 4 people > 65 yr have significant hearing impairment. Because tinnitus is common in people with sensorineural hearing loss, tinnitus is a common complaint among the elderly.

Key Points

• Subjective tinnitus is caused by an abnormality somewhere in the auditory pathway.

• Objective tinnitus is caused by an actual noise produced in a vascular structure near the ear.

• Loud noise, aging, Meniere's disease, and drugs are the most common causes of subjective tinnitus.

• Unilateral tinnitus with hearing loss or dizziness/dysequilibrium warrants gadolinium-enhanced MRI to rule out acoustic neuroma.

• Any tinnitus accompanied by a neurologic deficit is of concern.

Dizziness and Vertigo

Dizziness is an imprecise term patients often use to describe various related sensations, including

• Faintness (a feeling of impending syncope)

• Light-headedness

• Feeling of imbalance or unsteadiness

• A vague spaced-out or swimmy-headed feeling

Vertigo is a false sensation of movement of the self or the environment. Usually the perceived movement is rotary—a spinning or wheeling sensation—but some patients simply feel pulled to one side. Vertigo is not a diagnosis—it is a description of a sensation.

Both sensations may be accompanied by nausea and vomiting or difficulty with balance, gait, or both.

Perhaps because these sensations are hard to describe in words, patients often use "dizziness," "vertigo," and other terms interchangeably and inconsistently. Different patients with the same underlying disorder may describe their symptoms very differently. A patient may even give different descriptions of the same "dizzy" event during a given visit depending on how the question is asked. Because of this discrepancy, even though vertigo seems to be a clearly delineated subset of dizziness, many clinicians prefer to consider the two symptoms together.

However they are described, dizziness and vertigo may be disturbing and even incapacitating, particularly when accompanied by nausea and vomiting. Symptoms cause particular problems for people doing an exacting or dangerous task, such as driving, flying, or operating heavy machinery.

Dizziness accounts for about 5 to 6% of physician visits. It may occur at any age but becomes more common with increasing age; it affects about 40% of people over 40 yr at some time. Dizziness may be temporary or chronic. Chronic dizziness, defined as lasting > 1 mo, is more common among elderly people.

Pathophysiology

The **vestibular system** is the main neurologic system involved in balance. This system includes

• The vestibular apparatus of the inner ear

• The 8th (vestibulocochlear) cranial nerve, which conducts signals from the vestibular apparatus to the central components of the system

• The vestibular nuclei in the brain stem and cerebellum

Disorders of the inner ear and 8th cranial nerve are considered peripheral disorders. Those of the vestibular nuclei and their pathways in the brain stem and cerebellum are considered central disorders.

The sense of balance also incorporates visual input from the eyes and proprioceptive input from the peripheral nerves (via the spinal cord). The cerebral cortex receives output from the lower centers and integrates the information to produce the perception of motion.

Vestibular apparatus: Perception of stability, motion, and orientation to gravity originates in the vestibular apparatus, which consists of

• The 3 semicircular canals

• The 2 otolith organs—the saccule and utricle

Rotary motion causes flow of endolymph in the semicircular canal oriented in the plane of motion. Depending on the direction of flow, endolymph movement either stimulates or inhibits neuronal output from hair cells lining the canal. Similar hair cells in the saccule and utricle are embedded in a matrix of Ca carbonate crystals (otoliths). Deflection of the otoliths by gravity stimulates or inhibits neuronal output from the attached hair cells.

Etiology

There are numerous structural (trauma, tumors, degenerative), vascular, infectious, toxic (including drug-related), and idiopathic causes (see Table 46-4), but only about 5% of cases are caused by a serious disorder.

[**Table 46-4.** Some Causes of Dizziness and Vertigo]

The **most common causes of dizziness with vertigo** involve some component of the peripheral vestibular system:

• Benign positional vertigo

• Meniere's disease

• Vestibular neuronitis

• Labyrinthitis

Less often, the cause is a central vestibular disorder (most commonly migraine), a disorder with a more global effect on cerebral function, a psychiatric disorder, or a disorder affecting visual or proprioceptive input. Sometimes, no cause can be found.

The **most common causes of dizziness without vertigo** are less clear cut, but they are usually not otologic and probably are

• Drug effects

• Multifactorial or idiopathic

Nonneurologic disorders with a more global effect on cerebral function sometimes manifest as dizziness and rarely as vertigo. These disorders typically involve inadequate substrate (eg, O_2, glucose) delivery caused by hypotension, hypoxemia, anemia, or hypoglycemia; when severe, some of these disorders may manifest as syncope. Additionally, certain hormonal changes (eg, as with thyroid disease, menstruation, pregnancy) can cause dizziness. Numerous CNS-active drugs can cause dizziness independent of any toxic effect on the vestibular system.

Occasionally, dizziness and vertigo may be psychogenic. Patients with panic disorder, hyperventilation syndrome, anxiety, or depression may present with complaints of dizziness.

In elderly patients, dizziness is often multifactorial secondary to drug adverse effects and age-diminished visual, vestibular, and proprioceptive abilities. Two of the most common specific causes are disorders of the inner ear: benign paroxysmal positional vertigo and Meniere's disease.

Evaluation

History: History of present illness should cover the sensations felt; an open-ended question is best (eg, "Different people use the word 'dizziness' differently. Can you please describe as thoroughly as you can what you feel?"). Brief, specific questioning as to whether the feeling is faintness, light-headedness, loss of balance, or vertiginous may bring some clarity, but persistent efforts to categorize a patient's sensations are unnecessary. Other elements are more valuable and clear-cut:

• Severity of initial episode

• Severity and characteristics of subsequent episodes

• Symptoms continuous or episodic

• If episodic, frequency and duration

• Triggers and relievers (ie, triggered by head/body position change)

• Associated aural symptoms (eg, hearing loss, ear fullness, tinnitus)

• Severity and related disability

Is the patient having a single, sudden, acute event, or has dizziness been chronic and recurrent? Was the first episode the most severe (vestibular crisis)? How long do episodes last, and what seems to trigger and worsen them? The patient should be asked specifically about movement of the head, arising, being in anxious or stressful situations, and menses. Important associated symptoms include headache, hearing loss, tinnitus, nausea and vomiting, impaired vision, focal weakness, and difficulty walking. The severity of impact on the patient's life should be estimated: Has the patient fallen? Is the patient reluctant to drive or leave the house? Has the patient missed work days?

Review of systems should seek symptoms of causative disorders, including URI symptoms (inner ear disorders); chest pain, palpitations, or both (heart disease); dyspnea (lung disease); dark stools (anemia

caused by GI blood loss); and weight change or heat or cold intolerance (thyroid disease).

Past medical history should note presence of recent head trauma (usually obvious), migraine, diabetes, heart or lung disease, and drug and alcohol abuse. In addition to identifying all current drugs, drug history should assess recent changes in drugs, doses, or both.

Physical examination: Examination begins with a review of vital signs, including presence of fever, rapid or irregular pulse, and supine and standing BP, noting any drop in BP on standing up (orthostatic hypotension) and whether standing provokes symptoms. If standing does provoke symptoms, postural symptoms should be distinguished from those triggered by head movement by returning the patient supine until symptoms dissipate and then rotating the head.

The ENT and neurologic examinations are fundamental. Specifically, with the patient supine, the eyes are checked for presence, direction, and duration of spontaneous nystagmus (for full description of examination for nystagmus, see Sidebar 46-1). Direction and duration of nystagmus and development of vertigo are noted.

A gross bedside hearing test is done, the ear canal is inspected for discharge and foreign body, and the tympanic membrane is checked for signs of infection or perforation.

Cerebellar function is tested by assessing gait and doing a finger-nose test and Romberg's test. The remainder of the neurologic examination is done, including testing the rest of the cranial nerves.

Red flags: The following findings are of particular concern:

• Head or neck pain

• Ataxia

• Loss of consciousness

• Focal neurologic deficit

Interpretation of findings: Traditionally, differential diagnosis has been based on the exact nature of the chief complaint (ie, distinguishing dizziness from light-headedness from vertigo). However, the inconsistency of patients' descriptions and the poor specificity of symptoms make this unreliable. A better approach places more weight on the onset and timing of symptoms, the triggers, and associated symptoms and findings, particularly otologic and neurologic ones.

Some constellations of findings are highly suggestive (see Table 46-4), particularly those that help differentiate peripheral from central vestibular disorders.

• Peripheral: Ear symptoms (eg, tinnitus, fullness, hearing loss) usually indicate a peripheral disorder. They are typically associated with vertigo and not generalized dizziness (unless caused by uncompensated peripheral vestibular weakness). Symptoms are usually paroxysmal, severe, and episodic; continuous dizziness is rarely due to peripheral vertigo. Loss of consciousness is not associated with dizziness due to peripheral vestibular pathology.

• Central: Ear symptoms are rarely present, but gait/balance disturbance is common. Nystagmus is not inhibited by visual fixation.

Testing: Patients with a sudden, ongoing attack should have pulse oximetry and finger-stick glucose test. Women should have a pregnancy test. Most clinicians also do an ECG. Other tests are done based on findings (see Table 46-4), but generally gadolinium-enhanced MRI is indicated for patients with acute symptoms who have headache, neurologic abnormalities, or any other findings suggestive of a CNS etiology.

Patients with chronic symptoms should have gadolinium-enhanced MRI to look for evidence of stroke,

multiple sclerosis, or other CNS lesions.

Patients for whom results of bedside tests of hearing and vestibular function are abnormal or equivocal should undergo formal testing with audiometry and electronystagmography.

Laboratory tests are rarely helpful, except for patients with chronic vertigo and bilateral hearing loss, for whom syphilis serology is indicated.

Treatment

Treatment is directed at the cause, including stopping, reducing, or switching any causative drugs.

If a vestibular disorder is present and thought to be secondary to active Meniere's disease or vestibular neuronitis or labyrinthitis, the most effective vestibular nerve suppressants are diazepam (2 to 5 mg po q 6 to 8 h, with higher doses given under supervision for severe vertigo) or oral antihistamine/anticholinergic drugs (eg, meclizine 25 to 50 mg tid). All of these drugs can cause drowsiness, thereby limiting their use for certain patients. Nausea can be treated with prochlorperazine 10 mg IM qid or 25 mg rectally bid. Vertigo associated with benign paroxysmal positional vertigo is treated with the Epley maneuver (otolith repositioning) done by an experienced practitioner (see Fig. 48-1 on p. 443). Meniere's disease is best managed by an otolaryngologist with training in management of this chronic disorder, but initial management consists of a low-salt diet and a K-sparing diuretic.

Patients with persistent or recurrent vertigo secondary to unilateral vestibular weakness (such as secondary to vestibular neuronitis) usually benefit from vestibular rehabilitation therapy done by an experienced physical therapist. Most patients compensate well, although some, especially the elderly, have more difficulty. Physical therapy can also provide important safety information for elderly or particularly disabled patients.

Geriatrics Essentials

As people age, organs involved in balance function less well. For example, seeing in dim light becomes more difficult, inner ear structures deteriorate, proprioception becomes less sensitive, and mechanisms that control BP become less responsive (eg, to postural changes, postprandial demands). Older people also are more likely to have cardiac or cerebrovascular disorders that can contribute to dizziness. They also are more likely to be taking drugs that can cause dizziness, including those for hypertension, angina, heart failure, seizures, and anxiety, as well as certain antibiotics, antihistamines, and sleep aids. Thus, dizziness in elderly patients usually has more than one cause.

Although unpleasant at any age, the consequences of dizziness and vertigo are a particular problem for elderly patients. Those with frailty are at significant risk of falling with consequent fractures; their fear of moving and falling often significantly decreases their ability to do daily activities.

In addition to treatment of specific causes, elderly patients with dizziness or vertigo may benefit from physical therapy and exercises to strengthen muscles and help maintain independent ambulation as long as possible.

Key Points

- Vague or inconsistently described symptoms may still be associated with a serious condition.
- Cerebrovascular disease and drug effects should be sought, particularly in elderly patients.
- Peripheral vestibular system disorders should be differentiated from central vestibular system disorders.
- Immediate neuroimaging should be done when symptoms are accompanied by headache, focal neurologic abnormalities, or both.

Chapter 47. Hearing Loss

Introduction

Nearly 10% of people in the US have some degree of hearing loss. About 1/800 to 1/1000 neonates are born with severe to profound hearing loss. Two to 3 times as many are born with lesser hearing loss. During childhood, another 2 to 3/1000 children acquire moderate to severe hearing loss. Adolescents are at risk from excessive exposure to noise, head trauma, or both. Older adults typically experience a progressive decrease in hearing (presbycusis—see p. 438), which is probably related to aging and noise exposure.

Hearing deficits in early childhood can result in lifelong impairments in receptive and expressive language skills. The severity of the handicap is determined by the age at which the hearing loss occurred; the nature of the loss (its duration, the frequencies affected, and the degree); and the susceptibilities of the individual child (eg, coexisting visual impairment, intellectual disability, primary language deficits, inadequate linguistic environment). Children who have other sensory, linguistic, or cognitive deficiencies are affected most severely.

Pathophysiology

Hearing loss can be classified as conductive, sensorineural, or both (mixed loss).

Conductive hearing loss occurs secondary to lesions in the external auditory canal, tympanic membrane (TM), or middle ear. These lesions prevent sound from being effectively conducted to the inner ear.

Sensorineural hearing loss is caused by lesions of either the inner ear (sensory) or the auditory (8th) nerve (neural—see
Table 47-1). This distinction is important because sensory

[**Table 47-1.** Differences Between Sensory and Neural Hearing Losses]

hearing loss is sometimes reversible and is seldom life threatening. A neural hearing loss is rarely recoverable and may be due to a potentially life-threatening brain tumor—commonly a cerebellopontine angle tumor.

Mixed loss may be caused by severe head injury with or without fracture of the skull or temporal bone, by chronic infection, or by one of many genetic disorders. It may also occur when a transient conductive hearing loss, commonly due to otitis media, is superimposed on a sensorineural hearing loss.

Etiology

Hearing loss can be congenital (see
Table 47-2) or acquired (see
Table 47-3), progressive or sudden (see also p. 438), temporary or permanent, unilateral or bilateral, and mild or profound. Drug-induced ototoxicity is discussed elsewhere (see p. 443).

The **most common causes** overall are the following:

• Cerumen accumulation

• Noise

• Aging

• Infections (particularly among children and young adults)

Cerumen (earwax) accumulation is the most common cause of treatable hearing loss, especially in the

elderly. Foreign bodies obstructing the canal are sometimes a problem in children, both because of their presence and because of any damage inadvertently caused during their removal.

Noise can cause sudden or gradual sensorineural hearing loss. In acoustic trauma, hearing loss results from exposure to a single, extreme noise (eg, a nearby gunshot or explosion); some patients have tinnitus as well. The loss is usually temporary (unless there is also blast damage, which may destroy the TM, ossicles, or both). In noise-induced hearing loss, the loss develops over time because of chronic exposure to noise > 85 decibels (dB—see Sidebar 47-1 on p. 434). Although people vary somewhat in susceptibility to noise-induced hearing loss, nearly everyone loses some hearing if they are exposed to sufficiently intense noise for an adequate time. Repeated exposure to loud noise ultimately results in loss of hair cells in the organ of Corti. Hearing loss typically occurs first at 4 kHz and gradually spreads to the lower and higher frequencies as exposure continues. In contrast to most other causes of sensorineural hearing losses, noise-induced hearing loss may be less severe at 8 kHz than at 4 kHz.

[**Table 47-2.** Congenital Causes of Hearing Loss*]

Acute otitis media (AOM—see p. 448) is a common cause of transient mild to moderate hearing loss (mainly in children). However, without treatment, AOM sequelae and chronic otitis media (and the rarer purulent labyrinthitis) can cause permanent loss, particularly if a cholesteatoma forms.

Secretory otitis media (SOM—see p. 450) occurs in several ways. Almost all episodes of AOM are followed by a period of 2 to 4 wk of SOM. SOM can also be caused by eustachian tube dysfunction (eg, resulting from cleft palate, benign or malignant tumors of the nasopharynx, or rapid changes in external air pressure as occur during descent from high altitudes or rapid ascent while scuba diving).

Autoimmune disorders can cause sensorineural hearing loss at all ages and can cause other symptoms and signs as well.

Evaluation

Evaluation consists of detecting and quantifying hearing loss and determining etiology (particularly reversible causes).

Screening: Most adults and older children notice a sudden hearing loss, and caregivers may suspect that a neonate has a severe hearing loss within the first week of life when the neonate does not respond to voices or other sounds. However, progressive losses and nearly all losses in infants and young children must be detected by screening. Screening should begin at birth (see p. 2717) so that linguistic input can allow optimal language development. Suspected hearing loss at any time should prompt referral to a specialist. If screening is not done, severe bilateral losses may not be recognized until age 2 yr, and mild to moderate or severe unilateral losses are often not recognized until children reach school age.

History: History of present illness should note how long hearing loss has been perceived, how it began (eg, gradual, acute), whether it is unilateral or bilateral, and whether sound is distorted (eg, music is off—dull or lifeless) or there is difficulty with speech discrimination. The patient should be asked whether the loss followed any acute event (eg, head injury, barotrauma [particularly a diving injury], starting of a drug). Important accompanying symptoms include other otologic symptoms (eg, ear pain, tinnitus, ear discharge), vestibular symptoms (eg, disorientation in the dark, vertigo), and other neurologic symptoms (eg, headache, weakness or asymmetry of the face, an abnormal sense of taste, fullness of the ear). In children, important associated symptoms include presence of delays in speech or language development and delayed motor development.

Review of systems should seek to determine the impact of hearing difficulty on the patient's life.

Past medical history should note previous possibly causative disorders, including CNS infection, repeated ear infections, chronic exposure to loud noise, head trauma, rheumatic disorders (eg, RA, lupus), and a family history of hearing loss. Drug history should specifically query current or previous use of ototoxic drugs (see Table 47-3).

Physical examination: The focus is examination of the ears and hearing and the neurologic examination. The external ear is inspected for obstruction, infection, congenital malformations, and other lesions. The TM is examined for perforation, drainage, otitis media, and cholesteatoma. During the neurologic examination, particular attention needs to be paid to the 2nd through 7th cranial nerves as well as to vestibular and cerebellar function because abnormalities in these areas often occur with tumors of the brain stem and cerebellopontine angle. Weber's test and the Rinne test require a tuning fork to differentiate conductive from sensorineural hearing loss.

In **Weber's test**, the stem of a vibrating 512-Hz or 1024-Hz tuning fork is placed on the midline of the head, and the patient indicates in which ear the tone is louder. In unilateral conductive hearing loss, the tone is louder in the ear with hearing loss. In unilateral sensorineural hearing loss, the tone is louder in the normal ear because the tuning fork stimulates both inner ears equally and the patient perceives the stimulus with the unaffected ear.

In the **Rinne test**, hearing by bone and by air conduction is compared. Bone conduction bypasses the external and middle ear and tests the integrity of the inner ear, 8th cranial nerve, and central auditory pathways. The stem of a vibrating tuning fork is held against the mastoid (for bone conduction); as soon as the sound is no longer perceived, the fork is removed from the mastoid, and the still-vibrating tines are held close to the pinna (for air conduction). Normally, the fork can once more be heard, indicating that air conduction is better than bone conduction. With conductive hearing loss, the relationship is reversed; bone conduction is louder than air conduction. With sensorineural hearing loss, both air and bone conduction are reduced, but air conduction remains louder.

Red flags: Findings of particular concern are

• Unilateral sensorineural hearing loss

• Abnormalities of cranial nerves (other than hearing loss)

Interpretation of findings: Many causes of hearing loss (eg, cerumen, injury, significant noise exposure, infectious sequelae, drugs) are readily apparent based on results of the examination (see Table 47-3).

Associated findings are helpful in diagnosing the remaining small number of patients in

[**Table 47-3.** Some Causes of Acquired Hearing Loss]

whom no clear cause can be found. Those who have focal neurologic abnormalities are of particular concern. The 5th or 7th cranial nerve or both are often affected by tumors that involve the 8th nerve, so loss of facial sensation and weak jaw clench (5th) and hemifacial weakness and taste abnormalities (7th) point to a lesion in that area. Signs of autoimmune disorders, maxillofacial malformations, and renal dysfunction may suggest these disorders as a cause.

Any child with delays in speech or language development or difficulty in school should be evaluated for hearing loss. Intellectual disability, aphasia, and autism must also be considered. Delayed motor development may signal vestibular deficit, which is often associated with a sensorineural hearing loss.

Testing: Testing includes

• Audiologic tests

• Sometimes MRI or CT

Audiologic tests are required for all people who have hearing loss; these tests usually include

• Measurement of pure-tone thresholds with air and bone conduction

• Speech reception threshold

• Speech discrimination

• Tympanometry

• Acoustic reflex testing

Information gained from these tests helps determine whether more definitive differentiation of sensory from neural hearing loss is needed.

Pure-tone audiometry quantifies hearing loss. An audiometer delivers sounds of specific frequencies (pure tones) at different intensities to determine the patient's hearing threshold (how loud a sound must be to be perceived) for each frequency. Hearing in each ear is tested from 125 or 250 to 8000 Hz by air conduction (using earphones) and up to 4 kHz by bone conduction (using an oscillator in contact with the mastoid process or forehead). Test results are plotted on graphs called audiograms (see Fig. 47-1), which show the difference between the patient's hearing threshold and normal hearing at each frequency. The difference is measured in dB (see Sidebar 47-1). The normal threshold is considered 0 dB hearing level (Hl); hearing loss is considered present if the patient's threshold is > 25 dB Hl. When hearing loss is such as to require loud test tones, intense tones presented to one ear may be heard in the other ear. In such cases, a masking sound, usually narrow band noise, is presented to the ear not being tested to isolate it.

Speech audiometry includes the speech reception threshold (SRT) and the word recognition score. The SRT is a measure of the intensity at which speech is recognized. To determine the SRT, the examiner presents the patient with a list of words at specific sound intensities. These words usually have 2 equally accented syllables (spondees), such as railroad, staircase, and baseball. The examiner notes the intensity at which the patient repeats 50% of the words correctly. The SRT approximates the average hearing level at speech frequencies (eg, 500 Hz, 1000 Hz, 2000 Hz).

Sidebar 47-1 Sound Levels

Sound intensity and pressure (the physical correlates of loudness) are measured in decibels (dB). A dB is a unitless figure that compares 2 values and is defined as the logarithm of the ratio of a measured value to a reference value, multiplied by a constant:

$$dB = k \log (V_{measured}/V_{ref})$$

By convention, the reference value for sound pressure level (SPL) is taken as the quietest 1000-Hz sound detectable by young, healthy human ears.* The sound may be measured in terms of pressure (N/m^2) or intensity ($watts/m^2$).

Because sound intensity equals the square of sound pressure, the constant (k) for SPL is 20; for sound intensity, 10. Thus, each 20-dB increase represents a 10-fold increase in SPL but a 100-fold increase in sound intensity.

The dB values in the table below give only a rough idea of the risk of hearing loss. Some of them are dB SPL values (referenced to N/m^2), whereas others represent peak dB or dB on the A-scale (a scale that emphasizes the frequencies that are most hazardous to human hearing).

Db	Example
0	Faintest sound heard by human ear
30	Whisper, quiet library
60	Normal conversation, sewing machine, typewriter
90	Lawnmower, shop tools, truck traffic (8 h/day is the maximum exposure without protection†)
100	Chain saw, pneumatic drill, snowmobile (2 h/day is the maximum exposure without protection)

115 Sandblasting, loud rock concert, automobile horn (15 min/day is the maximum exposure without protection)

140 Gun muzzle blast, jet engine (noise causes pain and even brief exposure injures unprotected ears; injury may occur even with hearing protectors)

180 Rocket launching pad

*In audiometric testing, because human ears respond differently at different frequencies, the reference value changes for each frequency tested. Threshold values reported on audiograms take this into account; the normal threshold is always 0 dB, regardless of the actual SPL.

†Mandatory federal standard, but protection is recommended for more than brief exposure to sound levels > 85 db.

The word recognition score tests the ability to discriminate among the various speech sounds or phonemes. It is determined by presenting 50 phonetically balanced one-syllable words at an intensity of 35 to 40 dB above the patient's SRT. The word list contains phonemes in the same relative frequency found in conversational English. The score is the percentage of words correctly repeated by the patient and reflects the ability to understand speech

[Fig. 47-1. Audiogram of right ear in a patient with normal hearing.]

under optimal listening conditions. A normal score ranges from 90 to 100%. The word recognition score is normal with conductive hearing loss, albeit at a higher intensity level, but can be reduced at all intensity levels with sensorineural hearing loss. Discrimination is even poorer in neural than in sensory hearing loss.

Tympanometry measures the impedance of the middle ear to acoustic energy and does not require patient participation. It is commonly used to screen children for middle ear effusions. A probe containing a sound source, microphone, and air pressure regulator is placed snugly with an airtight seal into the ear canal. The probe microphone records the reflected sound from the TM while pressure in the canal is varied. Normally, maximal compliance of the middle ear occurs when the pressure in the ear canal equals atmospheric pressure. Abnormal compliance patterns suggest specific anatomic disruptions. In eustachian tube obstruction and middle ear effusion, maximal compliance occurs with a negative pressure in the ear canal. When the ossicular chain is disrupted, as in necrosis or dislocation of the long process of the incus, the middle ear is excessively compliant. When the ossicular chain is fixed, as in stapedial ankylosis in otosclerosis, compliance may be normal or reduced.

The acoustic reflex is contraction of the stapedius muscle in response to loud sounds, which changes the compliance of the TM, protecting the middle ear from acoustic trauma. The reflex is tested by presenting a tone and measuring what intensity provokes a change in middle ear impedance as noted by movement of the TM. An absent reflex could indicate middle ear disease or a tumor of the auditory nerve.

Advanced testing is sometimes needed. Gadolinium-enhanced MRI of the head to detect lesions of the cerebellopontine angle may be needed in patients with an abnormal neurologic examination or those whose audiologic testing shows poor word recognition, asymmetric sensorineural hearing loss, or a combination when the etiology is not clear.

CT is done if bony tumors or bony erosion is suspected. Magnetic resonance angiography is done if vascular abnormalities such as glomus tumors are suspected.

The auditory brain stem response uses surface electrodes to monitor brain wave response to acoustic stimulation in people who cannot otherwise respond.

Electrocochleography measures the activity of the cochlea and the auditory nerve with an electrode placed on or through the eardrum. It can be used to assess and monitor patients with dizziness, can be used in patients who are awake, and is useful in intraoperative monitoring.

Otoacoustic emissions testing measures sounds produced by outer hair cells of the cochlea in response to a sound stimulus usually placed in the ear canal. It is used to screen neonates and infants for hearing loss and to monitor the hearing of patients who are using ototoxic drugs (eg, gentamicin, cisplatin).

Certain patients, such as children with a reading or other learning problem and elderly people who seem to hear but do not comprehend, should undergo a central auditory evaluation. It measures discrimination of degraded or distorted speech, discrimination in the presence of a competing message in the opposite ear, the ability to fuse incomplete or partial messages delivered to each ear into a meaningful message, and the capacity to localize sound in space when acoustic stimuli are delivered simultaneously to both ears.

Treatment

The causes of a hearing loss should be determined and treated. Ototoxic drugs should be stopped or the dose should be lowered unless the severity of the disease being treated (usually cancer or a severe infection) requires that the risk of additional ototoxic hearing loss be accepted. Attention to peak and trough drug levels may help minimize risk.

Fluid from middle ear effusion can be drained by myringotomy and prevented with the insertion of a tympanostomy tube. Benign growths (eg, enlarged adenoids, nasal polyps) and malignant tumors (eg, nasopharyngeal cancers, sinus cancers) blocking the eustachian tube or ear canal can be removed. Hearing loss caused by autoimmune disorders may respond to corticosteroids.

Damage to the TM or ossicles or otosclerosis may require reconstructive surgery. Brain tumors causing hearing loss may in some cases be removed and hearing preserved.

Many causes of hearing loss have no cure, and treatment involves compensating for the hearing loss with hearing aids and, for severe to profound loss, a cochlear implant. In addition, various coping mechanisms may help.

Hearing aids: Amplification of sound with a hearing aid helps many people. Although hearing aids do not restore hearing to normal, they can significantly improve communication. Physicians should encourage hearing aid use and help patients overcome a sense of social stigma that continues to obstruct use of these devices, perhaps by making the analogy that a hearing aid is to hearing as eye glasses are to seeing.

All hearing aids have a microphone, amplifier, speaker, earpiece, and volume control, although they differ in the location of these components. An audiologist should be involved in selection and fitting of a hearing aid.

The best models are adjusted to a person's particular pattern of hearing loss. People with mainly high-frequency hearing loss do not benefit from simple amplification, which merely makes the garbled speech they hear sound louder. They usually need a hearing aid that selectively amplifies the high frequencies. Some hearing aids contain vents in the ear mold, which facilitate the passage of high-frequency sound waves. Some use digital sound processing with multiple frequency channels so that amplification more precisely matches hearing loss as measured on the audiogram.

Telephone use can be difficult for people with hearing aids. Typical hearing aids cause squealing when the ear is placed next to the phone handle. Some hearing aids have a phone coil with a switch that turns the microphone off and links the phone coil electromagnetically to the speaker magnet in the phone.

For moderate to severe hearing loss, a postauricular (ear-level) aid, which fits behind the pinna and is coupled to the ear mold with flexible tubing, is appropriate. An in-the-ear aid is contained entirely within the ear mold and fits less conspicuously into the concha and ear canal; it is appropriate for mild to moderate hearing loss. Some people with mild hearing loss limited to high frequencies are most comfortably fitted with postauricular aids and completely open ear canals. Canal aids are contained entirely within the ear canal and are cosmetically acceptable to many people who would otherwise refuse

to use a hearing aid, but they are difficult for some people (especially the elderly) to manipulate. The CROS aid (contralateral routing of signals) is occasionally used for severe unilateral hearing loss; a hearing-aid microphone is placed in the nonfunctioning ear, and sound is routed to the functioning ear through a wire or radio transmitter. This device enables the wearer to hear sounds from the nonfunctioning side, allowing for some limited capacity to localize sound. If the better ear also has some hearing loss, the sound from both sides can be amplified with the binaural CROS (BiCROS) aid. The body aid type is appropriate for profound hearing loss. It is worn in a shirt pocket or a body harness and connected by a wire to the earpiece (the receiver), which is coupled to the ear canal by a plastic insert (ear mold).

A bone conduction aid may be used when an ear mold or tube cannot be used, as in atresia of the ear canal or persistent otorrhea. An oscillator is held against the head, usually over the mastoid, with a spring band, and sound is conducted through the skull to the cochlea. Bone conduction hearing aids require more power, introduce more distortion, and are less comfortable to wear than air conduction hearing aids. Some bone conduction aids (bone-anchored hearing aids or BAHAs) are surgically implanted in the mastoid process, avoiding the discomfort and prominence of the spring band.

Cochlear implants: Profoundly deaf patients, including those with some hearing but who even with a hearing aid cannot understand speech without the assistance of vision (lip-reading or speech-reading), may benefit from a cochlear implant. This device provides electrical signals directly into the auditory nerve via multiple electrodes implanted in the cochlea. An external microphone and processor convert sound waves to electrical impulses, which are transmitted through the skin electromagnetically from an external induction coil to an internal coil implanted in the skull above and behind the ear. The internal coil connects to electrodes inserted in the scala tympani.

Cochlear implants help with speech-reading by providing information about the intonation of words and the rhythm of speech. Many if not most adults with cochlear implants can discriminate words without visual clues, allowing them to talk on the telephone. Cochlear implants enable deaf people to hear and distinguish environmental sounds and warning signals. They also help deaf people modulate their voice and make their speech more intelligible.

Brain stem implants: Patients who have had both acoustic nerves destroyed (eg, by bilateral temporal bone fractures or neurofibromatosis) can have some hearing restored by means of brain stem implants that have electrodes connected to sound-detecting and sound-processing devices similar to those used for cochlear implants.

Coping mechanisms: Alerting systems that use light let people know when the doorbell is ringing, a smoke detector is sounding, or a baby is crying. Special sound systems transmitting infrared or FM radio signals help people hear in theaters, churches, or other places where competing noise exists. Many television programs carry closed captioning. Telephone communication devices are also available.

Lip-reading or speech-reading is particularly important for people who can hear but have trouble discriminating sounds. Most people get useful speech information from lip-reading even without formal training. Even people with normal hearing can better understand speech in a noisy place if they can see the speaker. To use this information the listener must be able to see the speaker's mouth. Health care personnel should be sensitive to this issue and always position themselves appropriately when speaking to the hearing-impaired. Observing the position of a speaker's lips allows recognition of the consonant being spoken, thereby improving speech comprehension in patients with high-frequency hearing loss. Lip-reading may be learned in aural rehabilitation sessions in which a group of age-matched peers meets regularly for instruction and supervised practice in optimizing communication.

People can gain control over their listening environment by modifying or avoiding difficult situations. For example, people can visit a restaurant during off-peak hours, when it is quieter. They can ask for a booth, which blocks out some extraneous sounds. In direct conversations, people may ask the speaker to face them. At the beginning of a telephone conversation, they can identify themselves as being hearing-impaired. At a conference, the speaker can be asked to use an assistive listening system, which makes use of either inductive loop, infrared, or FM technology that sends sound through the microphone to a patient's hearing aid.

People with profound hearing loss often communicate by using sign language. American Sign Language (ASL) is the most common version in the US. Other forms include Signed English, Signing Exact English, and Cued Speech.

Treatment in Children

In addition to treatment of any cause and the provision of hearing aids, children with hearing loss require support of language development with appropriate therapy. Because children must hear language to learn it spontaneously, most deaf children develop language only with special training, ideally beginning as soon as the hearing loss is identified (an exception would be a deaf child growing up with deaf parents who are fluent sign language users). Deaf infants must be provided with a form of language input. For example, a visually based sign language can provide a foundation for later development of oral language if a cochlear implant is not available.

If infants as young as 1 mo have profound bilateral hearing loss and cannot benefit from hearing aids, they can be a candidate for a cochlear implant. Although cochlear implants allow auditory communication in many children with either congenital or acquired deafness, they are, in the main, more effective in children who already have developed language. Children who have postmeningitic deafness develop an ossified inner ear; they should receive cochlear implants early to maximize effectiveness. Children whose acoustic nerves have been destroyed by tumors may be helped by implantation of brain stem auditory-stimulating electrodes. Children with cochlear implants may have a slightly greater risk of meningitis than children without cochlear implants or adults with cochlear implants.

Children with unilateral deafness should be allowed to use a special system in the classroom, such as an FM auditory trainer. With these systems, the teacher speaks into a microphone that sends signals to a hearing aid in the child's nonaffected ear, improving the child's greatly impaired ability to hear speech against a noisy background.

Geriatrics Essentials

Elderly people typically experience a progressive decrease in hearing (presbycusis). The prevalence of hearing impairment is 30% in people > 65 and is 40 to 50% in those > 75. Nonetheless, hearing loss in the elderly should be evaluated and not ascribed to aging; elderly patients may have a tumor, a neurologic or autoimmune disorder, or an easily correctible conductive hearing loss. Also, hearing loss in the elderly facilitates dementia (which can be mitigated by properly correcting hearing loss).

Presbycusis: Presbycusis is sensorineural hearing loss that probably results from a combination of age-related deterioration and cell death in various components of the hearing system and the effects of chronic noise exposure.

Hearing loss usually affects the highest frequencies (18 to 20 kHz) early on and gradually affects the lower frequencies; it usually becomes clinically significant when it affects the critical 2- to 4-kHz range at about age 55 to 65 (sometimes sooner). The loss of high-frequency hearing significantly affects speech comprehension. Although the loudness of speech seems normal, certain consonant sounds (eg, C, D, K, P, S, T) become hard to hear. Consonant sounds are the most important sounds for speech recognition. For example, when "shoe," "blue," "true," "too," or "new" is spoken, many people with presbycusis can hear the "oo" sound, but most have difficulty recognizing which word has been spoken because they cannot distinguish the consonants. This inability to distinguish consonants causes affected people to often think the speaker is mumbling. A speaker attempting to speak louder usually accentuates vowel sounds (which are low frequency), doing little to improve speech recognition. Speech comprehension is particularly difficult when background noise is present.

Screening: A screening tool is often helpful for elderly people because many do not complain of hearing loss. One tool is the Hearing Handicap Inventory for the Elderly-Screening Version, which asks

• Does a hearing problem cause you to feel embarrassed when you meet people?

• Does a hearing problem cause you to feel frustrated when talking to a family member?

• Do you have difficulty hearing when someone whispers?

• Do you feel handicapped by a hearing problem?

• Does a hearing problem cause you difficulty when visiting friends, relatives, or neighbors?

• Does a hearing problem cause you to attend religious services less often than you would like?

• Does a hearing problem cause you to have arguments with family members?

• Does a hearing problem cause you difficulty when listening to the television or radio?

• Do you feel that any difficulty with your hearing hampers your personal or social life?

• Does a hearing problem cause you difficulty when in a restaurant with relatives or friends?

Scoring is "no" = 0 points, "sometimes" = 2 points, and "yes" = 4 points. Scores > 10 suggest significant hearing impairment and necessitate follow-up.

Prevention

Prevention of hearing loss consists mainly of limiting duration and intensity of noise exposure. People required to expose themselves to loud noise must wear ear protectors (eg, plastic plugs in the ear canals or glycerin-filled muffs over the ears). The Occupational Safety and Health Administration (OSHA) of the US Department of Labor and similar agencies in many other countries have standards regarding the length of time that a person can be exposed to a noise. The louder the noise, the shorter the permissible time of exposure.

Key Points

• Cerumen, genetic disorders, infections, aging, and noise exposure are the most common causes.

• All patients with hearing loss should have audiologic testing.

• Cranial nerve deficits and other neurologic deficits should raise concern and warrant imaging tests.

Sudden Deafness

Sudden deafness is severe sensorineural hearing loss that develops within a few hours or is noticed on awakening. It affects about 1/5000 people each year. Initial hearing loss is typically unilateral (unless drug-induced) and may range in severity from mild to profound. Many also have tinnitus, and some have dizziness, vertigo, or both.

Sudden deafness has some causes that differ from chronic hearing loss and must be addressed urgently.

Etiology

The following are common characteristics of sudden deafness:

• Most cases (see Table 47-4) are idiopathic.

• Some occur in the course of an obvious explanatory event.

A few represent the initial manifestation of an occult but identifiable disorder.

Idiopathic: There are numerous theories for which some evidence (although conflicting and incomplete) exists. The most promising possibilities include viral infections (particularly involving herpes simplex), autoimmune attacks, and acute microvascular occlusion.

Obvious event: Some causes of sudden deafness are readily apparent.

Blunt head trauma with temporal bone fracture or severe concussion involving the cochlea can cause sudden hearing loss.

Large ambient pressure changes (eg, caused by diving) or strenuous activities (eg, weightlifting) can induce a perilymphatic fistula between the middle and inner ear, causing sudden, severe symptoms. Perilymphatic fistula can also be congenital; it can spontaneously cause a sudden loss or loss may occur after trauma or pressure changes.

[**Table 47-4.** Some Causes of Sudden Deafness]

Ototoxic drugs can result in hearing loss occurring sometimes within a day, especially with an overdose (systemically or when applied to a large wound area, such as a burn). There is a rare genetic mitochondrial-transmitted disorder that increases the susceptibility to aminoglycoside ototoxicity.

A number of **infections** cause sudden deafness during or immediately after acute illness. Common causes include bacterial meningitis, Lyme disease, and many viral infections that affect the cochlea (and sometimes the vestibular apparatus). The most common viral causes in the developed world are mumps and herpes. Measles is a very rare cause because most of the population is immunized.

Occult disorders: Sudden deafness rarely can be an isolated first manifestation of some disorders that usually have other initial symptoms. Sudden deafness rarely may be the first manifestation of an acoustic neuroma, multiple sclerosis, Meniere's disease, or a small cerebellar stroke. Syphilis reactivation in HIV-infected patients rarely can cause sudden deafness.

Cogan's syndrome is a rare autoimmune reaction directed against an unknown common autoantigen in the cornea and inner ear; > 50% of patients present with vestibuloauditory symptoms. About 10 to 30% of patients also have a severe systemic vasculitis, which may include life-threatening aortitis.

Some vasculitic disorders can cause hearing loss, some of which is acute. Hematologic disorders, such as Waldenstrom's macroglobulinemia, sickle cell disease, and some forms of leukemia, rarely can cause sudden deafness.

Evaluation

Evaluation consists of detecting and quantifying hearing loss and determining etiology (particularly reversible causes).

History: History of present illness should verify that loss is sudden and not chronic. The history should also note whether loss is unilateral or bilateral and whether there is a current acute event (eg, head injury, barotrauma [particularly a diving injury], infectious illness). Important accompanying symptoms include other otologic symptoms (eg, tinnitus, ear discharge), vestibular symptoms (eg, disorientation in the dark, vertigo), and other neurologic symptoms (eg, headache, weakness or asymmetry of the face, abnormal sense of taste).

Review of systems should seek symptoms of possible causes, including transient, migratory neurologic deficits (multiple sclerosis) and eye irritation and redness (Cogan's syndrome).

Past medical history should ask about known HIV or syphilis infection and risk factors for them (eg, multiple sex partners, unprotected intercourse). Family history should note close relatives with hearing loss (suggesting a congenital fistula). Drug history should specifically query current or previous use of ototoxic drugs (see Table 47-4) and whether the patient has known renal insufficiency or renal failure.

Physical examination: The examination focuses on the ears and hearing and on the neurologic examination.

The tympanic membrane is inspected for perforation, drainage, or other lesions. During the neurologic examination, attention should be paid to the cranial nerves (particularly the 5th, 7th, and 8th) and to vestibular and cerebellar function because abnormalities in these areas often occur with tumors of the brain stem and cerebellopontine angle.

Weber's test and the Rinne test require a tuning fork to differentiate conductive from sensorineural hearing loss (see p. 429).

Additionally, the eyes are examined for redness and photophobia (possible Cogan's syndrome), and the skin is examined for rash (eg, viral infection, syphilis).

Red flags: Findings of particular concern are

• Abnormalities of cranial nerves (other than hearing loss)

Interpretation of findings: Traumatic, ototoxic, and some infectious causes are usually apparent clinically. A patient with perilymphatic fistula may hear an explosive sound in the affected ear when the fistula occurs and may also have sudden vertigo, nystagmus, and tinnitus.

Focal neurologic abnormalities are of particular concern. The 5th cranial nerve, 7th cranial nerve, or both are often affected by tumors that involve the 8th cranial nerve, so loss of facial sensation and weak jaw clench (5th) and hemifacial weakness and taste abnormalities (7th) point to a lesion in that area.

Unilateral hearing loss accompanied by tinnitus and vertigo also suggests Meniere's disease. Systemic symptoms suggesting inflammation (eg, fevers, rash, joint pains, mucosal lesions) should raise suspicion of an occult infection or autoimmune disorder.

Testing: Typically, patients should have an audiogram, and unless the diagnosis is clearly an acute infection or drug toxicity, most clinicians do gadolinium-enhanced MRI to diagnose inapparent causes. Patients with an acute traumatic cause also should have MRI. If a perilymphatic fistula is suspected clinically, it may be confirmed by tympanometry and electronystagmography (ENG); CT is usually done to show the bony characteristics of the inner ear.

Patients who have risk factors for or symptoms that suggest causes should have appropriate tests (eg, serologic tests for possible HIV infection or syphilis, CBC and coagulation profile for hematologic disorders, ESR and antinuclear antibodies for vasculitis).

Treatment

Treatment focuses on the causative disorder when known. Fistulas are explored and repaired surgically.

In viral and idiopathic cases, hearing returns to normal in about 50% of patients and is partially recovered in others.

In patients who recover their hearing, improvement usually occurs within 10 to 14 days.

For patients with idiopathic loss, many clinicians empirically give a short course of glucocorticoids and antiviral drugs effective against herpes simplex (eg, valacyclovir, famciclovir). Glucocorticoids can be given orally or by transtympanic injection; it is unclear which route is more effective.

Key Points

• Most cases are idiopathic.

• A few cases have an obvious cause (eg, major trauma, acute infection, drugs).

- A very few cases represent unusual manifestations of treatable disorders.

Chapter 48. Inner Ear Disorders

Introduction

(See also Hearing Loss on p. 429.)

The inner ear is in the petrous area of the temporal bone. Within the bone is the osseous labyrinth, which encases the membranous labyrinth. The osseous labyrinth includes the vestibular system (made up of the semicircular canals and the vestibule) and the cochlea. The vestibular system is responsible for balance and posture; the cochlea, for hearing.

Acoustic Neuroma

(Acoustic Neurinoma; 8th Nerve Tumor; Vestibular Schwannoma)

An acoustic neuroma is a Schwann cell-derived tumor of the 8th cranial nerve. Symptoms include unilateral hearing loss. Diagnosis is based on audiology and confirmed by MRI. Treatment is surgical removal, stereotactic radiation therapy, or both.

Acoustic neuromas almost always arise from the vestibular division of the 8th cranial nerve and account for about 7% of all intracranial tumors. As the tumor expands, it projects from the internal auditory meatus into the cerebellopontine angle and compresses the cerebellum and brain stem. The 5th cranial nerve and later the 7th cranial nerve are affected.

Bilateral acoustic neuromas are common in neurofibromatosis type 2.

Symptoms and Signs

Slowly progressive unilateral sensorineural hearing loss is the hallmark symptom. However, the onset of hearing loss may be abrupt, and the degree of impairment may fluctuate. Other early symptoms include unilateral tinnitus, dizziness and dysequilibrium, headache, sensation of pressure or fullness in the ear, otalgia, trigeminal neuralgia, and numbness or weakness of the facial nerve.

Diagnosis

• Audiogram

• If positive, gadolinium-enhanced MRI

An audiogram is the first test done (see p. 433). It usually reveals an asymmetric sensorineural hearing loss and a greater impairment of speech discrimination than would be expected for the degree of hearing loss. Acoustic reflex decay, the absence of waveforms, and increased latency of the 5th waveform in auditory brain stem response testing are further evidence of a neural lesion. Although not usually required in the routine evaluation of a patient with asymmetric sensorineural hearing loss, caloric testing shows marked vestibular hypoactivity (canal paresis). Such findings indicate the need for imaging tests, preferably gadolinium-enhanced MRI.

Treatment

• Surgical removal

• Sometimes stereotactic radiation therapy

Small tumors may be removed with microsurgery that preserves the facial nerve. A middle cranial fossa or retrosigmoid approach may preserve remaining hearing; a translabyrinthine route may be used if no useful hearing remains. Large tumors are removed with the translabyrinthine approach regardless of the remaining hearing. Stereotactic radiation therapy as the sole treatment modality is used predominantly in the management of small tumors in older patients; its long-term efficacy and adverse effects are under

study.

Benign Paroxysmal Positional Vertigo

(Benign Postural or Positional Vertigo)

In benign paroxysmal positional vertigo (BPPV), short (< 60 sec) episodes of vertigo occur with certain head positions. Nausea and nystagmus develop. Diagnosis is clinical. Treatment involves canalith repositioning maneuvers. Drugs and surgery are rarely, if ever, indicated.

BPPV is the most common cause of relapsing otogenic vertigo. It affects people increasingly as they age and can severely affect balance in the elderly, leading to potentially injurious falls.

Etiology

The condition is thought to be caused by displacement of otoconial crystals (Ca carbonate crystals normally embedded in the saccule and utricle). This displaced material stimulates hair cells in the posterior semicircular canal, creating the illusion of motion. Etiologic factors include spontaneous degeneration of the utricular otolithic membranes, labyrinthine concussion, otitis media, ear surgery, recent viral infection (eg, viral neuronitis), head trauma, prolonged anesthesia or bed rest, previous vestibular disorders (eg, Meniere's disease), and occlusion of the anterior vestibular artery.

Symptoms and Signs

Vertigo is triggered when the patient's head moves (eg, when rolling over in bed or bending over to pick up something). Acute vertigo lasts only a few seconds to minutes; episodes tend to peak in the morning and abate throughout the day. Nausea and vomiting may occur, but hearing loss and tinnitus do not.

Diagnosis

• Clinical evaluation

• Gadolinium-enhanced MRI if findings suggest CNS lesion

Diagnosis is based on characteristic symptoms, on nystagmus as determined by the Dix-Hallpike maneuver (a provocative test for positional nystagmus—see Sidebar 46-1 on p. 414), and on absence of other abnormalities on neurologic examination. Such patients require no further testing. Patients with nystagmus suggesting a CNS lesion undergo gadolinium-enhanced MRI. Unlike the positional nystagmus of BPPV, the positional nystagmus of CNS lesions lacks latency, fatigability, and severe subjective sensation and may continue for as long as the position is maintained. Nystagmus caused by a CNS lesion may be vertical or change direction and, if rotary, is likely to be in the unexpected direction.

Treatment

• Provocative maneuvers to fatigue symptoms

• Canalith repositioning maneuvers

• Drug treatment typically not recommended

BPPV usually subsides spontaneously in several weeks or months but may continue for months or years. Because the condition can be long-lasting, drug treatment (like that used in Meniere's disease—see p. 445) is not recommended. Often, the adverse effects of drugs worsen dysequilibrium.

Because BPPV is fatigable, one therapy is to have the patient perform provocative maneuvers early in the day in a safe environment. Symptoms are then minimal for the rest of the day.

Canalith repositioning maneuvers (Epley maneuver—see

Fig. 48-1—and Semont maneuver) involve moving the head through a series of specific positions intended to return the errant canalith to the utricle. After performing these maneuvers, the patient should remain erect or semi-erect for 1 to 2 days. Both maneuvers can be repeated as necessary.

[**Fig. 48-1.** The Epley maneuver.]

For the Semont maneuver, the patient is seated upright in the middle of a stretcher. The patient's head is rotated toward the unaffected ear; this rotation is maintained throughout the maneuver. Next, the torso is lowered laterally onto the stretcher so that the patient is lying on the side of the affected ear with the nose pointed up. After 3 min in this position, the patient is quickly moved through the upright position without straightening the head and is lowered laterally to the other side now with the nose pointed down. After 3 min in this position, the patient is slowly returned to the upright position, and the head is rotated back to normal.

Drug-Induced Ototoxicity

A wide variety of drugs can be ototoxic (see Table 48-1).

Factors affecting ototoxicity include dose, duration of therapy, concurrent renal failure,

[**Table 48-1.** Some Drugs that Cause Ototoxicity]

infusion rate, lifetime dose, co-administration with other drugs having ototoxic potential, and genetic susceptibility. Ototoxic drugs should not be used for otic topical application when the tympanic membrane is perforated because the drugs might diffuse into the inner ear.

Streptomycin tends to cause more damage to the vestibular portion than to the auditory portion of the inner ear. Although vertigo and difficulty maintaining balance tend to be temporary, severe loss of vestibular sensitivity may persist, sometimes permanently. Loss of vestibular sensitivity causes difficulty walking, especially in the dark, and oscillopsia (a sensation of bouncing of the environment with each step). About 4 to 15% of patients who receive 1 g/day for > 1 wk develop measurable hearing loss, which usually occurs after a short latent period (7 to 10 days) and slowly worsens if treatment is continued. Complete, permanent deafness may follow.

Neomycin has the greatest cochleotoxic effect of all antibiotics. When large doses are given orally or by colonic irrigation for intestinal sterilization, enough may be absorbed to affect hearing, particularly if mucosal lesions are present. Neomycin should not be used for wound irrigation or for intrapleural or intraperitoneal irrigation, because massive amounts of the drug may be retained and absorbed, causing deafness. Kanamycin and amikacin are close to neomycin in cochleotoxic potential and are both capable of causing profound, permanent hearing loss while sparing balance. Viomycin has both cochlear and vestibular toxicity. Gentamicin and tobramycin have vestibular and cochlear toxicity, causing impairment in balance and hearing.

Vancomycin can cause hearing loss, especially in the presence of renal insufficiency.

Chemotherapeutic (antineoplastic) drugs, particularly those containing platinum (cisplatin and carboplatin), can cause tinnitus and hearing loss. Hearing loss can be profound and permanent, occurring immediately after the first dose, or can be delayed until several months after completion of treatment. Sensorineural hearing loss strikes bilaterally, progresses decrementally, and is permanent.

Ethacrynic acid and furosemide given IV have caused profound, permanent hearing loss in patients with renal failure who had been receiving aminoglycoside antibiotics.

Salicylates in high doses (> 12 325-mg tablets of aspirin per day) cause temporary hearing loss and tinnitus. Quinine and its synthetic substitutes can also cause temporary hearing loss.

Prevention

Ototoxic antibiotics should be avoided during pregnancy. The elderly and people with preexisting hearing loss should not be treated with ototoxic drugs if other effective drugs are available. The lowest effective dosage of ototoxic drugs should be used and levels should be closely monitored. If possible before treatment with an ototoxic drug, hearing should be measured and then monitored during treatment; symptoms are not reliable warning signs.

Herpes Zoster Oticus

(Geniculate Herpes; Ramsay Hunt Syndrome; Viral Neuronitis)

Herpes zoster oticus is infection of the 8th cranial nerve ganglia and the geniculate ganglion of the facial nerve by the herpes zoster virus.

Risk factors for herpes infection include immunodeficiency secondary to cancer, chemotherapy, radiation therapy, and HIV infection.

Symptoms and Signs

Symptoms include severe ear pain, transient or permanent facial paralysis (resembling Bell's palsy), vertigo lasting days to weeks, and hearing loss (which may be permanent or which may resolve partially or completely). Vesicles occur on the pinna and in the external auditory canal along the distribution of the sensory branch of the facial nerve. Symptoms of meningoencephalitis (eg, headache, confusion, stiff neck) are uncommon. Sometimes other cranial nerves are involved.

Diagnosis

Diagnosis usually is clinical. If there is any question about viral etiology, vesicular scrapings may be collected for direct immunofluorescence or for viral cultures, and MRI is done.

Treatment

• Perhaps corticosteroids, antivirals, and surgical decompression

Although there is no reliable evidence that corticosteroids, antiviral drugs, or surgical decompression makes a difference, they are the only possibly useful treatments. Corticosteroids are started with prednisone 60 mg po once/day for 4 days, followed by gradual tapering of the dose over the next 2 wk. Acyclovir 800 mg po q 4 h 5 times/day or valacyclovir 1 g po bid for 10 days may shorten the clinical course. Vertigo is effectively suppressed with diazepam 2 to 5 mg po q 4 to 6 h. Pain may require oral opioids. Postherpetic neuralgia may be treated with amitriptyline. Surgical decompression of the fallopian canal may be indicated if the facial palsy is complete (no visible facial movement). Before surgery, however, electroneurography is done and should show a > 90% decrement.

Meniere's Disease

(Endolymphatic Hydrops)

Meniere's disease is an inner ear disorder that causes vertigo, fluctuating sensorineural hearing loss, and tinnitus. There is no diagnostic test. Vertigo and nausea are treated with anticholinergics or benzodiazepines. Diuretics and a low-salt diet may decrease frequency and severity of episodes. For severe cases, the vestibular system can be ablated with topical gentamicin or surgery.

In Meniere's disease, pressure and volume changes of the labyrinthine endolymph affect inner ear function. The etiology of endolymphatic fluid buildup is unknown. Risk factors include a family history of Meniere's disease, preexisting autoimmune disorders, allergies, trauma to the head or ear, and, rarely, syphilis (even several decades previously). Peak incidence is between ages 20 and 50.

Symptoms and Signs

Patients have sudden attacks of vertigo lasting up to 24 h, usually with nausea and vomiting. Accompanying symptoms include diaphoresis, diarrhea, and gait unsteadiness. Tinnitus may be constant or intermittent, buzzing or roaring; it is not related to position or motion. Hearing impairment, typically affecting low frequencies, may follow. Before an episode, most patients sense fullness or pressure in the affected ear. In 50% of patients, only one ear is affected.

During the early stages, symptoms remit between episodes; symptom-free interludes may last > 1 yr. As the disease progresses, however, hearing impairment persists and gradually worsens, and tinnitus may be constant.

Diagnosis

• Clinical evaluation

• Audiogram and gadolinium-enhanced MRI to rule out other causes

The diagnosis, made clinically, is primarily one of exclusion. Similar symptoms can result from viral labyrinthitis or neuritis, a cerebellopontine angle tumor (eg, acoustic neuroma), or a brain stem stroke. Patients with suggestive symptoms should have an audiogram and an MRI (with gadolinium enhancement) of the CNS with attention to the internal auditory canals to exclude other causes. Audiogram typically shows a low-frequency sensorineural hearing loss in the affected ear.

On examination during an acute attack, the patient has nystagmus and falls to the affected side. Between attacks, the Fukada stepping test (marching in place with eyes closed) can be used; a patient with Meniere's disease often turns away from the affected ear, consistent with a unilateral labyrinthine lesion. Additionally, the Rinne test and Weber's test may indicate sensorineural hearing loss (see p. 431).

Treatment

• Symptom relief with antiemetics, antihistamines, or benzodiazepines

• Diuretics and low-salt diet

• Rarely vestibular ablation by drugs or surgery

Meniere's disease tends to be self-limited. Treatment of an acute attack is aimed at symptom relief. Anticholinergics (eg, prochlorperazine or promethazine 25 mg rectally or 10 mg po q 6 to 8 h) can minimize vagal-mediated GI symptoms. Antihistamines (eg, diphenhydramine, meclizine, or cyclizine 50 mg po q 6 h) or benzodiazepines (eg, diazepam 5 mg po q 6 to 8 h) are used to sedate the vestibular system. Some physicians also use a corticosteroid burst (eg, prednisone 60 mg once/day for 1 wk, tapered over another wk) for an acute episode.

A low-salt (< 1.5 g/day) diet, avoidance of alcohol and caffeine, and a diuretic (eg, hydrochlorothiazide 25 mg po once/day) may help prevent vertigo and are useful for many patients.

Intratympanic gentamicin (chemical labyrinthectomy) may be used when medical management is unsuccessful. Typical dose is 1 mL (at a 30 mg/mL concentration, made by diluting the commercial 40 mg/mL preparation with bicarbonate) injected through the tympanic membrane. Follow-up with serial audiometry is recommended to distinguish hearing loss from cochleotoxicity. The injection can be repeated in 4 wk if vertigo persists without hearing loss.

Surgery is reserved for patients with frequent, severely debilitating episodes who are unresponsive to other modalities. Endolymphatic sac decompression relieves vertigo in some patients and poses minimal risk of hearing loss. Vestibular neurectomy (an intracranial procedure) relieves vertigo in about 95% of patients and usually preserves hearing. A surgical labyrinthectomy is done only if preexisting hearing loss is profound.

Unfortunately, there is no known way to prevent the natural progression of hearing loss. Most patients sustain moderate to severe sensorineural hearing loss in the affected ear within 10 to 15 yr.

Purulent Labyrinthitis

Purulent (suppurative) labyrinthitis is bacterial infection of the inner ear, often causing deafness and loss of vestibular function.

Purulent labyrinthitis usually occurs when bacteria spread to the inner ear during the course of severe acute otitis media, purulent meningitis, or an enlarging cholesteatoma.

Symptoms include severe vertigo and nystagmus, nausea and vomiting, tinnitus, and varying degrees of hearing loss. Pain and fever are common.

Purulent labyrinthitis is suspected if vertigo, nystagmus, sensorineural hearing loss, or a combination occurs during an episode of acute otitis media. CT of the temporal bone is done to identify erosion of the otic capsule bone or other complications of acute otitis media, such as coalescent mastoiditis. MRI may be indicated if symptoms of meningitis or brain abscess, such as altered mental status, meningismus, or high fever, are present; in such cases, a lumbar puncture and blood cultures also are done.

Treatment is with IV antibiotics appropriate for meningitis (eg, ceftriaxone 50 to 100 mg/kg IV once/day to maximum 2 g) adjusted according to results of culture and sensitivity testing. A myringotomy (and sometimes tympanostomy tube placement) is done to drain the middle ear. Mastoidectomy may be required.

Vestibular Neuronitis

Vestibular neuronitis causes a self-limited episode of vertigo, presumably due to inflammation of the vestibular division of the 8th cranial nerve; some vestibular dysfunction may persist.

Although etiology is unclear, a viral cause is suspected.

Symptoms and Signs

Symptoms include a single attack of severe vertigo, with nausea and vomiting and persistent nystagmus toward the affected side, which lasts 7 to 10 days. The nystagmus is unidirectional, horizontal, and spontaneous, with fast-beat oscillations in the direction of the unaffected ear. The absence of concomitant tinnitus or hearing loss is a hallmark of vestibular neuronitis. The condition slowly subsides after this initial episode. Some patients have residual dysequilibrium, especially with rapid head movements, probably due to permanent vestibular injury.

Diagnosis

• Audiology, electronystagmography, and MRI

Patients undergo an audiologic assessment, electronystagmography with caloric testing, and gadolinium-enhanced MRI of the head, with attention to the internal auditory canals to exclude other diagnoses, such as cerebellopontine angle tumor, brain stem hemorrhage, or infarction. MRI may show enhancement of the vestibular nerves, consistent with inflammatory neuritis.

Treatment

• Symptom relief with antiemetics, antihistamines, or benzodiazepines

Symptoms are addressed as in Meniere's disease (see p. 445), ie, with anticholinergics, antiemetics (eg, prochlorperazine or promethazine 25 mg rectally or 10 mg po q 6 to 8 h), antihistamines or benzodiazepines, and a corticosteroid burst with rapid taper. If vomiting is prolonged, IV fluids and

electrolytes may be required. Vestibular rehabilitation (usually given by a physical therapist) helps compensate for any residual vestibular deficit.

Chapter 49. Middle Ear and Tympanic Membrane Disorders

Introduction

(See also Otic Tumors on p. 493)

Middle ear disorders may be secondary to infection, eustachian tube obstruction, or trauma. Information about objects placed in the ear and symptoms such as rhinorrhea, nasal obstruction, sore throat, URI, allergies, headache, systemic symptoms, and fever aid diagnosis. The appearance of the external auditory canal and tympanic membrane (see Fig. 49-1) often yields a diagnosis. The nose, nasopharynx, and oropharynx are examined for signs of infection and allergy and for evidence of tumors. Middle ear function is evaluated with use of pneumatic otoscopy, Weber's tuning fork test and the Rinne tuning fork test, tympanometry, and audiologic tests (see p. 431).

Mastoiditis

Mastoiditis is a bacterial infection of the mastoid air cells, which typically occurs after acute otitis media. Symptoms include redness, tenderness, swelling, and fluctuation over the mastoid process, with displacement of the pinna. Diagnosis is clinical. Treatment is with antibiotics, such as ceftriaxone, and mastoidectomy if drug therapy is not effective.

In acute purulent otitis media, inflammation often extends into the mastoid antrum and air cells, resulting in fluid accumulation. In a few patients, bacterial infection develops in the collected fluid, typically with the same organism causing the otitis media; pneumococcus is most common. Mastoid infection can cause osteitis of the septae, leading to coalescence of the air cells. The infection may decompress through a perforation in the tympanic membrane or extend through the lateral mastoid cortex, forming a postauricular subperiosteal abscess. Rarely, it extends centrally, causing a temporal lobe abscess or a septic thrombosis of the lateral sinus. Occasionally, the infection may erode through the tip of the mastoid and drain into the neck (called a Bezold abscess).

Symptoms and Signs

Symptoms begin days to weeks after onset of acute otitis media and include fever and persistent, throbbing otalgia. Nearly all patients have signs of otitis media (see p. 448) and purulent otorrhea. Redness, swelling,

[**Fig. 49-1.** Tympanic membrane of right ear (A); tympanic cavity with tympanic membrane removed (B).]

tenderness, and fluctuation may develop over the mastoid process; the pinna is typically displaced laterally and inferiorly.

Diagnosis

• Clinical evaluation

• Rarely CT

Diagnosis is clinical. CT is rarely necessary but can confirm the diagnosis and show the extent of the infection. Any middle ear drainage is sent for culture and sensitivity. Tympanocentesis for culture purposes can be done if no spontaneous drainage occurs. CBC and ESR may be abnormal but are neither sensitive nor specific and add little to the diagnosis.

Treatment

• IV ceftriaxone

IV antibiotic treatment is initiated immediately with a drug that provides CNS penetration, such as

ceftriaxone 1 to 2 g (children, 50 to 75 mg/kg) once/day continued for ≥ 2 wk. Oral treatment with a quinolone may be acceptable. Subsequent antibiotic choice is guided by culture and sensitivity test results.

A subperiosteal abscess usually requires a simple mastoidectomy, in which the abscess is drained, the infected mastoid cells are removed, and drainage is established from the antrum of the mastoid to the middle ear cavity.

Myringitis

(Bullous Myringitis)

Myringitis is a form of acute otitis media in which vesicles develop on the tympanic membrane.

Myringitis can develop with viral, bacterial (particularly *Streptococcus pneumoniae*), or mycoplasmal otitis media. Pain occurs suddenly and persists for 24 to 48 h. Hearing loss and fever suggest a bacterial origin. Diagnosis is based on otoscopic visualization of vesicles on the tympanic membrane.

Because differentiation among a viral, bacterial, and mycoplasmal cause is difficult, antibiotics effective against organisms causing otitis media are prescribed (see Table 49-1). Severe, continued pain may be relieved by rupturing the vesicles with a myringotomy knife or by oral analgesics (eg, oxycodone with acetaminophen). Topical analgesics (eg, benzocaine, antipyrine) may also be beneficial.

Acute Otitis Media

Acute otitis media (AOM) is a bacterial or viral infection of the middle ear, usually accompanying a URI. Symptoms include otalgia, often with systemic symptoms (eg, fever, nausea, vomiting, diarrhea), especially in the very young. Diagnosis is based on otoscopy. Treatment is with analgesics and sometimes antibiotics.

Although AOM can occur at any age, it is most common between ages 3 mo and 3 yr. At this age, the eustachian tube is structurally and functionally immature; the angle of the eustachian tube is more horizontal; and the angle of the tensor veli palatini muscle and the cartilaginous eustachian tube renders the opening mechanism less efficient.

The etiology may be viral or bacterial. Viral infections are often complicated by secondary bacterial infection. In neonates, gram-negative enteric bacilli, particularly *Escherichia coli*, and *Staphylococcus aureus* cause AOM. In older infants and children < 14 yr, the most common organisms are *Streptococcus pneumoniae*, *Moraxella (Branhamella) catarrhalis*, and nontypeable *Haemophilus influenzae*; less common causes are group A β-hemolytic streptococci and *S. aureus*. In patients > 14 yr, *S. pneumoniae*, group A β-hemolytic streptococci, and *S. aureus* are most common, followed by *H. influenzae*.

In rare cases, bacterial middle ear infection spreads locally, resulting in acute mastoiditis, petrositis, or labyrinthitis. Intracranial spread is extremely rare and usually causes meningitis, but brain abscess, subdural empyema, epidural abscess, lateral sinus thrombosis, or otitic hydrocephalus may occur. Even with antibiotic treatment, intracranial complications are slow to resolve, especially in immunocompromised patients.

Symptoms and Signs

The usual initial symptom is earache, often with hearing loss. Infants may simply be cranky or have difficulty sleeping. Fever, nausea, vomiting, and diarrhea often occur in young children. Otoscopic examination can show a bulging, erythematous tympanic membrane (TM) with indistinct landmarks and displacement of the light reflex. Air insufflation (pneumatic otoscopy) shows poor mobility of the TM. Spontaneous perforation of the TM causes serosanguineous or purulent otorrhea.

Severe headache, confusion, or focal neurologic signs may occur with intracranial spread of infection.

Facial paralysis or vertigo suggests local extension to the fallopian canal or labyrinth.

[**Table 49-1.** Antibiotics for Otitis Media]

Diagnosis

Diagnosis usually is clinical. Except for fluid obtained during myringotomy, cultures are not generally done.

Treatment

• Analgesics

• Sometimes antibiotics

• Rarely myringotomy

Although 80% of cases resolve spontaneously, in the US, antibiotics are often given (see Table 49-1). Antibiotics relieve symptoms quicker (although results after 1 to 2 wk are similar) and may reduce the chance of residual hearing loss and labyrinthine or intracranial sequelae. However, with the recent emergence of resistant organisms, pediatric organizations have strongly recommended initial antibiotics only for those at highest risk (eg, those who are younger or more severely ill—see Table 49-2) or for those with recurrent AOM (eg, ≥ 4 episodes in 6 mo). Others, provided there is good follow-up, can safely

[**Table 49-2.** Guidelines for Using Antibiotics in Acute Otitis Media]

be observed for up to 72 h and given antibiotics only if no improvement is seen; if follow-up by phone is planned, a prescription can be given at the initial visit to save time and expense.

All patients receive analgesics (eg, acetaminophen, ibuprofen). In adults, topical intranasal vasoconstrictors, such as phenylephrine 0.25% 3 drops q 3 h, improve eustachian tube function. To avoid rebound congestion, these preparations should not be used > 4 days. Systemic decongestants (eg, pseudoephedrine 30 to 60 mg po q 6 h prn) may be helpful. Antihistamines (eg, chlorpheniramine 4 mg po q 4 to 6 h for 7 to 10 days) may improve eustachian tube function in people with allergies but should be reserved for the truly allergic. For children, neither vasoconstrictors nor antihistamines are of benefit.

Myringotomy may be done for a bulging TM, particularly if severe or persistent pain, fever, vomiting, or diarrhea is present. The patient's hearing, tympanometry, and TM appearance and movement are monitored until normal.

Prevention

Routine childhood vaccination against pneumococci (with pneumococcal conjugate vaccine), *H. influenzae* type B, and influenza decreases the incidence of AOM. Infants should not sleep with a bottle, and elimination of household smoking may decrease incidence.

Secretory Otitis Media

(Serous Otitis Media)

Secretory otitis media is an effusion in the middle ear resulting from incomplete resolution of acute otitis media or obstruction of the eustachian tube without infection. Symptoms include hearing loss and a sense of fullness or pressure in the ear. Diagnosis is based on appearance of the tympanic membrane and sometimes on tympanometry. Most cases resolve in 2 to 3 wk. If there is no improvement in 1 to 3 mo, some form of myringotomy is indicated, usually with insertion of a tympanostomy tube. Antibiotics and decongestants are not effective.

Normally, the middle ear is ventilated 3 to 4 times/min as the eustachian tube opens during swallowing, and O_2 is absorbed by blood in the vessels of the middle ear mucous membrane. If patency of the eustachian tube is impaired, a relative negative pressure develops within the middle ear, which can lead to fluid accumulation. This fluid may cause hearing loss.

Secretory otitis media is a common sequela to acute otitis media in children (often identified on routine ear recheck) and may persist for weeks to months. In other cases, eustachian tube obstruction may be secondary to inflammatory processes in the nasopharynx, allergies, hypertrophic adenoids or other obstructive lymphoid aggregations on the torus of the eustachian tube and in Rosenmuller's fossa, or benign or malignant tumors. The effusion may be sterile or (more commonly) contain pathogenic bacteria sometimes as a biofilm, although inflammation is not observed.

Symptoms and Signs

Patients may report no symptoms, but some (or their family members) note hearing loss. Patients may experience a feeling of fullness, pressure, or popping in the ear with swallowing. Otalgia is rare.

Various possible changes to the tympanic membrane (TM) include an amber or gray color, displacement of the light reflex, mild to severe retraction, and accentuated landmarks. On air insufflation, the TM may be immobile. An air-fluid level or bubbles of air may be visible through the TM.

Diagnosis

Diagnosis is clinical. Tympanometry may be done to confirm middle ear effusion. Adults and adolescents must undergo nasopharyngeal examination to exclude malignant or benign tumors.

Treatment

• Observation

• If unresolved, myringotomy with tympanostomy tube insertion

• If recurrent in childhood, sometimes adenoidectomy

For most patients, watchful waiting is all that is required. Antibiotics and decongestants are not helpful. For patients in whom allergies are clearly involved, antihistamines and topical corticosteroids may be helpful.

If no improvement occurs in 1 to 3 mo, myringotomy may be done for aspiration of fluid and insertion of a tympanostomy tube, which allows ventilation of the middle ear and temporarily ameliorates eustachian tube obstruction, regardless of cause. Tympanostomy tubes may be inserted for persistent conductive hearing loss or to help prevent recurrence of acute otitis media.

Occasionally, the middle ear is temporarily ventilated with the Valsalva maneuver or politzerization. To do the Valsalva maneuver, patients keep their mouth closed and try to forcibly blow air out through their pinched nostrils (ie, popping the ear). To do politzerization, the physician blows air with a special syringe (middle ear inflator) into one of the patient's nostrils and blocks the other while the patient swallows. This forces the air into the eustachian tube and middle ear. Neither procedure should be done if the patient has a cold and rhinorrhea.

Persistent, recurrent secretory otitis media may require correction of underlying nasopharyngeal conditions. Children may benefit from adenoidectomy, including the removal of the central adenoid mass as well as lymphoid aggregations on the torus of the eustachian tube and in Rosenmuller's fossa. Antibiotics should be given for bacterial rhinitis, sinusitis, and nasopharyngitis. Demonstrated allergens should be eliminated from the patient's environment and immunotherapy should be considered.

Chronic Otitis Media

Chronic otitis media is a persistent, chronically draining (> 6 wk), suppurative perforation of the tympanic membrane. Symptoms include painless otorrhea with conductive hearing loss. Complications include development of aural polyps, cholesteatoma, and other infections. Treatment requires complete cleaning of the ear canal several times daily, careful removal of granulation tissue, and application of topical corticosteroids and antibiotics. Systemic antibiotics and surgery are reserved for severe cases.

Chronic otitis media can result from acute otitis media, eustachian tube obstruction, mechanical trauma, thermal or chemical burns, blast injuries, or iatrogenic causes (eg, after tympanostomy tube placement). Further, patients with craniofacial abnormalities (eg, Down syndrome, cri du chat syndrome, cleft lip and/or cleft palate, velocardiofacial syndrome [Shprintzen's syndrome]) have an increased risk.

Chronic otitis media may become exacerbated after a URI or when water enters the middle ear through a tympanic membrane (TM) perforation during bathing or swimming. Infections often are caused by gram-negative bacilli or *Staphylococcus aureus*, resulting in painless, purulent, sometimes foul-smelling otorrhea. Persistent chronic otitis media may result in destructive changes in the middle ear (such as necrosis of the long process of the incus) or aural polyps (granulation tissue prolapsing into the ear canal through the TM perforation). Aural polyps are a serious sign, almost invariably suggesting cholesteatoma.

A cholesteatoma is an epithelial cell growth that forms in the middle ear, mastoid, or epitympanum after chronic otitis media (see
Plate 1). Lytic enzymes, such as collagenases, produced by the cholesteatoma can destroy adjacent bone and soft tissue. The cholesteatoma is also a nidus for infection; purulent labyrinthitis, facial paralysis, or intracranial abscess may develop.

Symptoms and Signs

Chronic otitis media usually manifests with conductive hearing loss and otorrhea. Pain is uncommon unless an associated osteitis of the temporal bone occurs. The TM is perforated and draining, and the auditory canal is macerated and littered with granulation tissue.

A patient with cholesteatoma has white debris in the middle ear, a draining polypoid mass protruding through the TM perforation, and an ear canal that appears clogged with mucopurulent granulation tissue.

Diagnosis

Diagnosis is usually clinical. Drainage is cultured. When cholesteatoma or other complications are suspected (as in a febrile patient or one with vertigo or otalgia), CT or MRI is done. These tests may reveal intratemporal or intracranial processes (eg, labyrinthitis, ossicular or temporal erosion, abscesses).

Treatment

• Irrigation and topical antibiotic drops

• Removal of granulation tissue

The ear canal is irrigated with a bulb syringe 3 times/day with a slightly warmed solution of half vinegar and half sterile water. After the ear drains, 10 drops topical ofloxacin solution are instilled in the affected ear 2 times/day for 14 days.

When granulation tissue is present, it is removed with microinstruments or cauterization with silver nitrate sticks. Ciprofloxacin 0.3% and dexamethasone 0.1% is then instilled into the ear canal for 7 to 10 days.

Severe exacerbations require systemic antibiotic therapy with amoxicillin 250 to 500 mg po q 8 h for 10 days or a 3rd-generation cephalosporin, subsequently modified by culture results and response to therapy.

Tympanoplasty is indicated for patients with marginal or attic perforations and chronic central TM

perforations. A disrupted ossicular chain may be repaired during tympanoplasty as well.

Cholesteatomas must be removed surgically. Because recurrence is common, reconstruction of the middle ear is usually deferred until a 2nd-look operation is done 6 to 8 mo later.

Otic Barotrauma

(Barotitis Media or Aerotitis Media)

Otic barotrauma is ear pain or damage to the tympanic membrane caused by rapid changes in pressure.

To maintain equal pressure on both sides of the tympanic membrane (TM), gas must move freely between the nasopharynx and middle ear. When a URI, allergy, or other mechanism interferes with eustachian tube functioning during changes in environmental pressure, the pressure in the middle ear either falls below ambient pressure, causing retraction of the TM, or rises above it, causing bulging. With negative middle ear pressure, a transudate of fluid may form in the middle ear. As the pressure differential increases, ecchymosis and subepithelial hematoma may develop in the mucous membrane of the middle ear and the TM. A very large pressure differential may cause bleeding into the middle ear, TM rupture, and the development of a perilymph fistula through the oval or round window.

Symptoms are severe pain, conductive hearing loss, and, if there is a perilymph fistula, sensory neural loss. Symptoms usually worsen during rapid increase in external air pressures, such as a rapid ascent (eg, during scuba diving) or descent (eg, during air travel). Sensorineural hearing loss or vertigo during descent suggests the development of a perilymph fistula; the same symptoms during ascent from a deep-sea dive can additionally suggest an air bubble formation in the inner ear.

Treatment

• Methods to equalize pressure (eg, yawning, swallowing, chewing gum)

Routine self-treatment of pain associated with changing pressure in an aircraft includes chewing gum, attempting to yawn and swallow, blowing against closed nostrils, and using decongestant nasal sprays.

If hearing loss is sensorineural and vertigo is present, a perilymph fistula is suspected and middle ear exploration to close a fistula is considered. If pain is severe and hearing loss is conductive, myringotomy is helpful.

Prevention

A person with nasal congestion due to URI or allergies should avoid flying and diving. When these activities are unavoidable, a topical nasal vasoconstrictor (eg, phenylephrine 0.25 to 1.0%) is applied 30 to 60 min before descent or ascent.

Otosclerosis

Otosclerosis is a disease of the bone of the otic capsule that causes an abnormal accumulation of new bone within the oval window.

In otosclerosis, the new bone traps and restricts the movement of the stapes, causing conductive hearing loss (see p. 429). Otosclerosis also may cause a sensorineural hearing loss, particularly when the foci of otosclerotic bone are adjacent to the scala media. Half of all cases are inherited. The measles virus plays an inciting role in patients with a genetic predisposition for otosclerosis.

Although about 10% of white adults have some otosclerosis (compared with 1% of blacks), only about 10% of affected people develop conductive hearing loss. Hearing loss caused by otosclerosis may manifest as early as age 7 or 8, but most cases do not become evident until the late teen or early adult years, when slowly progressive, asymmetric hearing loss is diagnosed. Fixation of the stapes may

progress rapidly during pregnancy.

A hearing aid may restore hearing. Alternatively, microsurgery to remove some or all of the stapes and to replace it with a prosthesis may be beneficial.

Traumatic Perforation of the Tympanic Membrane

Traumatic perforation of the tympanic membrane (TM) can cause pain, bleeding, hearing loss, tinnitus, and vertigo. Diagnosis is based on otoscopy. Treatment often is unnecessary. Antibiotics may be needed for infection. Surgery may be needed for perforations persisting > 2 mo, disruption of the ossicular chain, or injuries affecting the inner ear.

Traumatic causes of TM perforation include

• Insertion of objects into the ear canal purposely (eg, cotton swabs) or accidentally

• Concussion caused by an explosion or open-handed slap across the ear

• Head trauma (with or without basilar fracture)

• Sudden negative pressure (eg, strong suction applied to the ear canal)

• Barotrauma (eg, during air travel or scuba diving)

• Iatrogenic perforation during irrigation or foreign body removal

Penetrating injuries of the TM may result in dislocations of the ossicular chain, fracture of the stapedial footplate, displacement of fragments of the ossicles, bleeding, a perilymph fistula from the oval or round window resulting in leakage of perilymph into the middle ear space, or facial nerve injury.

Symptoms and Signs

Traumatic perforation of the TM causes sudden severe pain sometimes followed by bleeding from the ear, hearing loss, and tinnitus. Hearing loss is more severe if the ossicular chain is disrupted or the inner ear is injured. Vertigo suggests injury to the inner ear. Purulent otorrhea may begin in 24 to 48 h, particularly if water enters the middle ear.

Diagnosis

• Otoscopy

• Audiometry

Perforation is generally evident on otoscopy. Any blood obscuring the ear canal is carefully suctioned. Irrigation and pneumatic otoscopy are avoided. Extremely small perforations may require otomicroscopy or middle ear impedance studies for definitive diagnosis. If possible, audiometric studies are done before and after treatment to avoid confusion between trauma-induced and treatment-induced hearing loss.

Patients with marked hearing loss or severe vertigo are evaluated by an otolaryngologist as soon as possible. Exploratory tympanotomy may be needed to assess and repair damage. Patients with a large TM defect should also be evaluated, because the displaced flaps may need to be repositioned.

Treatment

• Ear kept dry

• Oral or topical antibiotics if dirty injury

Often, no specific treatment is needed. The ear should be kept dry; routine antibiotic eardrops are unnecessary. However, prophylaxis with oral broad-spectrum antibiotics or antibiotic eardrops is necessary if contaminants may have entered through the perforation as occurs in dirty injuries.

If the ear becomes infected, amoxicillin 500 mg po q 8 h is given for 7 days.

Although most perforations close spontaneously, surgery is indicated for a perforation persisting > 2 mo. Persistent conductive hearing loss suggests disruption of the ossicular chain, necessitating surgical exploration and repair.

Chapter 50. External Ear Disorders

Introduction

The external ear (pinna and external auditory canal) can be affected by congenital, dermatologic, infectious, neoplastic, obstructive, and traumatic disorders. Congenital defects are discussed on p. 2971. Ear trauma is discussed on p. 3231.

Dermatitis

Dermatitis is inflammation of the ear canal involving itching and skin changes that are caused by exposure to allergens (contact dermatitis) or are spontaneous occurrences (aural eczematoid dermatitis).

Common contact allergens include nickel-containing earrings and numerous beauty products (eg, hairsprays, lotions, hair dye). Aural eczematoid dermatitis is more common among people with a predisposition toward atopy and with other similar dermatitides (eg, seborrhea, psoriasis).

Both contact dermatitis and aural eczematoid dermatitis cause itching, redness, discharge, desquamation, hyperpigmentation, and, sometimes, fissuring. A secondary infection can occur.

Contact dermatitis requires avoidance or withdrawal of allergic triggers. Trial and error may be needed to identify the offending agent. Topical corticosteroids (eg, 1% hydrocortisone cream) can decrease inflammation and itching.

Aural eczematoid dermatitis can be treated with dilute aluminum acetate solution (Burow's solution), which can be applied as often as required for comfort. Itching and inflammation can be reduced with topical corticosteroids. If diffuse external otitis ensues, antibiotic therapy may be required (see p. 455).

External Otitis

External otitis is infection of the ear canal, typically by bacteria. Symptoms include itching, pain, and discharge. Diagnosis is based on inspection. Treatment is with topical drugs, including antibiotics, corticosteroids, and acetic acid or a combination.

External otitis may manifest as a localized furuncle or as a diffuse infection of the entire canal (generalized or diffuse external otitis). This condition is often called swimmer's ear because it sometimes afflicts people who swim. Malignant external otitis (see p. 455) is a severe *Pseudomonas* infection of the temporal bone and is especially dangerous in diabetics.

Etiology

Diffuse external otitis is usually caused by bacteria, such as *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Staphylococcus aureus*, or *Escherichia coli*. Fungal external otitis (otomycosis), typically caused by *Aspergillus niger* or *Candida albicans*, is less common. Furuncles usually are due to *S. aureus*.

Predisposing conditions include allergies, psoriasis, eczema, seborrheic dermatitis, decreased canal acidity (possibly due to the repeated presence of water), irritants (eg, hair spray, hair dye), and inadvertent injury to the canal caused by excessive cleaning with cotton swabs or other objects. Attempts to clean the ear canal may push debris and cerumen deeper into the canal; these accumulated substances tend to trap water, resulting in skin maceration that sets the stage for bacterial infection.

Symptoms and Signs

Patients have itching and pain. Sometimes, a foul-smelling discharge and hearing loss occur if the canal becomes swollen or filled with purulent debris. Exquisite tenderness accompanies traction of the pinna or pressure over the tragus. Otoscopic examination is painful and difficult to conduct. It shows the ear canal

to be red, swollen, and littered with moist, purulent debris. Otomycosis caused by *A. niger* usually manifests with grayish black or yellow dots (fungal conidiophores) surrounded by a cottonlike material (fungal hyphae). Infection caused by *C. albicans* does not show any visible fungi but usually contains a thickened, creamy white exudate.

Furuncles cause severe pain and may drain sanguineous, purulent material. They appear as a focal, erythematous swelling.

Diagnosis

• Clinical evaluation

Diagnosis is based on inspection. When discharge is copious, external otitis can be difficult to differentiate from perforated otitis media; pain with pulling on the pinna may indicate an external otitis. Fungal infection is diagnosed by appearance or culture.

Treatment

• Topical acetic acid and corticosteroids

• Sometimes topical antibiotics

In diffuse external otitis, topical antibiotics and corticosteroids are effective. First, the infected debris should be gently and thoroughly removed from the canal with suction or dry cotton wipes. Mild external otitis can be treated by altering the ear canal's pH with 2% acetic acid and by relieving inflammation with topical hydrocortisone; these are given as 5 drops tid for 7 days. Moderate external otitis requires the addition of an antibacterial solution or suspension, such as neomycin, polymyxin, ciprofloxacin, or ofloxacin. When inflammation of the ear canal is relatively severe, an ear wick should be placed into the ear canal and wetted with the necessary drugs 4 times/day. The wick is left in place for 24 to 72 h, after which time the swelling may have receded enough to allow the instillation of drops directly into the canal.

Severe external otitis or the presence of cellulitis extending beyond the ear canal may require systemic antibiotics, such as cephalexin 500 mg po tid for 10 days or ciprofloxacin 500 mg po bid for 10 days. An analgesic, such as an NSAID or even an oral opioid, may be necessary for the first 24 to 48 h. Fungal external otitis requires thorough cleaning of the ear canal and application of an antimycotic solution (eg, gentian violet, cresylate acetate, nystatin, clotrimazole). Repeated cleanings and treatments may be needed.

A furuncle, if obviously pointing, should be incised and drained. Incision is of little value, however, if the patient is seen at an early stage. Topical antibiotics are ineffective; oral antistaphylococcal antibiotics should be given. Analgesics, such as oxycodone with acetaminophen, may be necessary for pain relief. Dry heat can also lessen pain and hasten resolution.

Prevention

External otitis often can be prevented by irrigating the ears with a 1:1 mixture of rubbing alcohol and vinegar immediately after swimming. The alcohol helps remove water, and the vinegar alters the pH of the canal.

Malignant External Otitis

Malignant external otitis is typically a *Pseudomonas* osteomyelitis of the temporal bone.

Soft tissue, cartilage, and bone are all affected. The osteomyelitis spreads along the base of the skull and may cross the midline.

Malignant external otitis occurs mainly in elderly patients with diabetes or in immunocompromised patients and is often initiated by *Pseudomonas* external otitis. It is characterized by persistent and severe earache,

foul-smelling purulent otorrhea, and granulation tissue in the ear canal (usually at the junction of the bony and cartilaginous portions of the canal). Varying degrees of conductive hearing loss may occur. In severe cases, facial nerve paralysis may ensue.

Diagnosis is based on a CT scan of the temporal bone, which may show increased radiodensity in the air-cell system and middle ear radiolucency (demineralization) in some areas. Cultures are done, and the ear canal is biopsied to differentiate the granulation tissue of this disorder from a malignant tumor.

Treatment is with a 6-wk IV course of a fluoroquinolone or an aminoglycoside-semisynthetic penicillin combination. Extensive bone disease may require more prolonged antibiotic therapy. Careful control of diabetes is essential. Surgery usually is not necessary.

Obstructions

The ear canal may be obstructed by cerumen (earwax), insertion of a foreign object, or an insect. Itching, pain, and temporary conductive hearing loss may result. Most causes of obstruction are readily apparent during otoscopic examination. Treatment is manual removal.

Cerumen: Cerumen may get pushed further into the ear canal and accumulate during ill-advised attempts to clean the ear canal with cotton swabs, resulting in obstruction. Cerumen solvents (hydrogen peroxide, carbamide peroxide, glycerin, triethanolamine) may be used to soften very hard wax before irrigation or direct removal. However, the prolonged use of these agents may lead to canal skin irritation or allergic reactions. Although cerumen may be removed by irrigation, rolling the cerumen out of the ear canal with a blunt curet or loop or removing it with a suction tip (eg, Baron, size 7 French) is quicker, neater, safer, and more comfortable for the patient. Irrigation is contraindicated if the patient has a history of otorrhea or perforation of the tympanic membrane; water entering the middle ear through a perforation may exacerbate chronic otitis media.

Foreign bodies: Foreign bodies are common, particularly among children, who often insert objects, particularly beads, erasers, and beans, into the ear canal. Foreign bodies may remain unnoticed until they provoke an inflammatory response, causing pain, itching, infection, and foul-smelling, purulent drainage. A foreign body in the ear canal is best removed by reaching behind it and rolling it out with a blunt hook. Forceps tend to push smooth objects deeper into the canal. Unfortunately, a foreign body lying medial to the isthmus (the bony cartilaginous junction of the external auditory canal) is difficult to remove without injuring the tympanic membrane and ossicular chain. Metal and glass beads can sometimes be removed by irrigation, but hygroscopic foreign bodies (eg, beans or other vegetable matter) swell when water is added, complicating removal. A general anesthetic may be needed when a child cannot remain still or when removal is difficult, threatening injury to the tympanic membrane or ossicles. Further, if manipulating a presumed foreign object results in bleeding, immediate otolaryngologic consultation should be sought. Bleeding may indicate a mucosal polyp originating in the middle ear, which may be attached to the ossicles or facial nerve.

Insects in the canal are most annoying while alive. Filling the canal with viscous lidocaine kills the insect, which provides immediate relief and allows the immobilized insect to be removed with forceps.

Perichondritis

Perichondritis is infection of the perichondrium of the pinna in which pus accumulates between the cartilage and the perichondrium.

Causes of perichondritis include trauma, insect bites, body piercings, and incision of superficial infections of the pinna. Because the cartilage's blood supply is provided by the perichondrium, separation of the perichondrium from both sides of the cartilage may lead to avascular necrosis and a deformed pinna. Septic necrosis may also ensue, often with infection by gram-negative bacilli. Symptoms include redness, pain, and swelling. The course of perichondritis tends to be indolent, long-term, and destructive.

The affected area is incised, and a drain is left in place for 24 to 72 h. Systemic antibiotics are initiated with an aminoglycoside and semisynthetic penicillin. Subsequent antibiotic choice is guided by culture

and sensitivity tests. Warm compresses may help.

Chapter 51. Approach to the Patient With Nasal and Pharyngeal Symptoms

Introduction

The nose and pharynx (consisting of the nasopharynx, oropharynx, and hypopharynx) may be affected by inflammation, infection, trauma, tumors, and several miscellaneous conditions.

Anatomy

Throat: The uvula hangs in the midline at the far end of the soft palate. It varies greatly in length. A long uvula and loose or excess velopharyngeal tissue may cause snoring and occasionally contribute to obstructive sleep apnea.

Tonsils and adenoids are patches of lymphoid tissue surrounding the posterior pharynx in an area termed Waldeyer's ring. Their role is to combat infection.

The larynx is discussed in Ch. 54.

Nose: The nasal cavity is covered with a highly vascular mucosa that warms and humidifies incoming air. Each lateral wall of the cavity has 3 turbinates, which are bony shelves that increase the surface area, thereby allowing more effective heat and moisture exchange. Nasal mucus traps incoming particulate matter. The space between the middle and inferior turbinate is the middle meatus, into which the maxillary and most of the ethmoid sinuses drain. Polyps may develop between the turbinates, often in association with asthma, allergy, aspirin use, and cystic fibrosis.

Sinuses: The paranasal sinuses are mucus-lined bony cavities that connect to the nasopharynx. The 4 types are maxillary, frontal, ethmoid, and sphenoid sinuses. They are located in the facial and cranial bones (see
Fig. 51-1). The physiologic role of the sinuses is unclear.

[**Fig. 51-1.** Paranasal sinuses.]

Evaluation

Examination of the nose and pharynx is part of every general physical examination.

History: General information includes use of alcohol or tobacco (both major risk factors for head and neck cancer) and systemic symptoms, such as fever and weight loss. Oropharyngeal symptoms include pain, ulcers, and difficulty swallowing or speaking. Nasal and sinus symptoms include presence and duration of congestion, discharge, or bleeding.

Physical examination: Most physicians use a head-mounted light. However, because the light cannot be precisely aligned on the axis of vision, it is difficult to avoid shadowing in narrow areas (eg, nasal cavity). Better illumination results with a head-mounted convex mirror; the physician looks through a hole in the center of the mirror, so the illumination is always on-axis. The head mirror reflects light from a source (any incandescent light) placed behind the patient and slightly to one side and requires practice to use effectively.

The nose is examined using a nasal speculum, which is held so that the 2 blades open in an anteroposterior (or slightly oblique) direction and do not press against the septum. The physician notes crusting, discharge, septal deviation, or perforation; whether mucosa is erythematous, boggy, or swollen; and presence of polyps. The skin over the frontal and maxillary sinuses is examined for erythema and tenderness, suggesting sinus inflammation.

If necessary, the nasopharynx and hypopharynx can be examined with mirrors, which should be warmed before use to avoid fogging. A small mirror is used for the nasopharynx. It is held just below the uvula, angling upward; the tongue is pushed down with a tongue blade. A larger mirror is used for the hypopharynx and larynx. The tongue is retracted by grasping it with a gauze pad, and the mirror is placed

against the soft palate, angling downward. If patients do not tolerate mirror examination, a flexible fiberoptic nasopharyngoscope is helpful. A topical anesthetic (eg, lidocaine 4%) is sprayed in the nose and throat, and the nose is also sprayed with a decongestant (eg, phenylephrine 0.5%). After several minutes, the scope is gently passed through the nares, and the nasal cavity, hypopharynx, and larynx are inspected.

Neck examination consists of inspection and palpation for masses. If masses are found, the physician notes whether they are tender; fluctuant, firm, or stony hard; and movable or fixed. Masses caused by infection are tender and mobile; cancers tend to be nontender, hard, and fixed. Particular attention is paid to the cervical lymph nodes and thyroid and parotid glands.

Epistaxis

Epistaxis is nose bleeding. Bleeding can range from a trickle to a strong flow, and the consequences can range from a minor annoyance to life-threatening hemorrhage. Swallowed blood is a gastric irritant, so patients also may describe vomiting blood.

Pathophysiology

Most nasal bleeding is anterior, originating from a plexus of vessels in the anteroinferior septum (Kiesselbach's area).

Less common but more serious are posterior nosebleeds, which originate in the posterior septum overlying the vomer bone, or laterally on the inferior or middle turbinate. Posterior nosebleeds tend to occur in patients who have preexisting atherosclerotic vessels or bleeding disorders and have undergone nasal or sinus surgery.

Etiology

The most common causes of epistaxis are

• Local trauma (eg, nose blowing and picking)

• Drying of the nasal mucosa

There are a number of less common causes (see Table 51-1). Hypertension may contribute to the persistence of a nosebleed that has already begun but is unlikely to be the sole etiology.

Evaluation

History: History of present illness should try to determine which side began bleeding first; although major epistaxis quickly involves both nares, most patients can localize the initial flow to one side, which focuses the physical examination. Also, the duration of bleeding should be established, as well as any triggers (eg, sneezing, nose blowing, picking) and attempts by the patient to stop the bleeding. Important associated symptoms prior to onset include symptoms of a URI, sensation of nasal obstruction, and nasal or facial pain. The time and number of previous nose-bleeding episodes and their resolution should be identified.

[**Table 51-1.** Some Causes of Epistaxis]

Review of systems should ask about symptoms of excessive bleeding, including easy bruising; bloody or tarry stools; hemoptysis; blood in urine; and excess bleeding with toothbrushing, phlebotomy, or minor trauma.

Past medical history should note presence of known bleeding disorders (including a family history) and conditions associated with defects in platelets or coagulation, particularly cancer, cirrhosis, HIV, and pregnancy. Drug history should specifically query about use of drugs that may promote bleeding,

including aspirin and other NSAIDs, other antiplatelet drugs (eg, clopidogrel), heparin, and warfarin.

Physical examination: Vital signs should be reviewed for indications of intravascular volume depletion (tachycardia, hypotension) and marked hypertension. With active bleeding, treatment takes place simultaneously with evaluation.

During active bleeding, inspection is difficult, so attempts are first made to stop the bleeding as described below. The nose is then examined using a nasal speculum and a bright head lamp or head mirror, which leaves one hand free to manipulate suction or an instrument.

Anterior bleeding sites are usually apparent on direct examination. If no site is apparent and there have been only 1 or 2 minor nosebleeds, further examination is not needed. If bleeding is severe or recurrent and no site is seen, fiberoptic endoscopy may be necessary.

The general examination should look for signs of bleeding disorders, including petechiae, purpura, and perioral and oral mucosal telangiectasias as well as any intranasal masses.

Red flags: The following findings are of particular concern:

• Signs of hypovolemia or hemorrhagic shock

• Anticoagulant drug use

• Cutaneous signs of a bleeding disorder

• Bleeding not stopped by direct pressure or vasoconstrictor-soaked pledgets

• Multiple recurrences, particularly with no clear cause

Interpretation of findings: Many cases have a clear-cut trigger (particularly nose blowing or picking) as suggested by findings (see Table 51-1).

Testing: Routine laboratory testing is not required. Patients with symptoms or signs of a bleeding disorder and those with severe or recurrent epistaxis should have CBC, PT, and PTT.

CT may be done if a foreign body, a tumor, or sinusitis is suspected.

Treatment

Presumptive treatment for actively bleeding patients is that for anterior bleeding. The need for blood replacement is determined by the Hb level, symptoms of anemia, and vital signs. Any identified bleeding disorders are treated.

Anterior epistaxis: Bleeding can usually be controlled by pinching the nasal alae together for 10 min while the patient sits upright (if possible). If this maneuver fails, a cotton pledget impregnated with a vasoconstrictor (eg, phenylephrine 0.25%) and a topical anesthetic (eg, lidocaine 2%) is inserted and the nose pinched for another 10 min. The bleeding point may then be cauterized with electrocautery or silver nitrate on an applicator stick. Cauterizing 4 quadrants immediately adjacent to the bleeding vessel is most effective. Care must be taken to avoid burning the mucous membrane too deeply; therefore, silver nitrate is the preferred method. Alternatively, a nasal tampon of expandable foam may be inserted. Coating the tampon with a topical ointment, such as bacitracin or mupirocin, may help. If these methods are ineffective, various commercial nasal balloons can be used to compress bleeding sites. Alternatively, an anterior nasal pack consisting of 1/2-in petrolatum gauze may be inserted; up to 72 in of gauze may be required. This procedure is painful, and analgesics usually are needed; it should be used only when other methods fail or are not available.

Posterior epistaxis: Posterior bleeding may be difficult to control. Commercial nasal balloons are quick and convenient; a gauze posterior pack is effective but more difficult to position. Both are very

uncomfortable; IV sedation and analgesia may be needed, and hospitalization is required.

Commercial balloons are inserted according to the instructions accompanying the product.

The posterior gauze pack consists of 4-in gauze squares folded, rolled, tied into a tight bundle with 2 strands of heavy silk suture, and coated with antibiotic ointment. The ends of one suture are tied to a catheter that has been introduced through the nasal cavity on the side of the bleeding and brought out through the mouth. As the catheter is withdrawn from the nose, the postnasal pack is pulled into place above the soft palate in the nasopharynx. The 2nd suture hangs down the back of the throat and is trimmed below the level of the soft palate so that it can be used to remove the pack. The nasal cavity anterior to this pack is firmly packed with 1/2-in petrolatum gauze, and the 1st suture is tied over a roll of gauze at the anterior nares to secure the postnasal pack. The packing remains in place for 4 to 5 days. An antibiotic (eg, amoxicillin/clavulanate 875 mg po bid for 7 to 10 days) is given to prevent sinusitis and otitis media. Posterior nasal packing lowers the arterial PO_2, and supplementary O_2 is given while the packing is in place.

Rarely, the internal maxillary artery and its branches must be ligated to control the bleeding. The arteries may be ligated with clips using endoscopic or microscopic guidance and a surgical approach through the maxillary sinus. Alternatively, angiographic embolization may be done by a skilled radiologist.

Bleeding disorders: In Rendu-Osler-Weber syndrome, a split-thickness skin graft (septal dermatoplasty) reduces the number of nosebleeds and allows the anemia to be corrected. Laser (Nd:YAG) photocoagulation can be done in the operating room. Selective embolization also is very effective, particularly in patients who cannot tolerate general anesthesia or for whom surgical intervention has not been successful. New endoscopic sinus devices have made transnasal surgery more effective.

Blood may be swallowed in large amounts and, in patients with liver disease, should be eliminated promptly with enemas and cathartics to prevent hepatic encephalopathy. The GI tract should be sterilized with nonabsorbable antibiotics (eg, neomycin 1 g po qid) to prevent the breakdown of blood and the absorption of ammonia.

Key Points

• Most nosebleeds are anterior and stop with direct pressure.

• Screening (by history and physical examination) for bleeding disorders is important.

• Patients should always be asked about aspirin or ibuprofen use.

Nasal Congestion and Rhinorrhea

Nasal congestion and rhinorrhea (runny nose) are extremely common problems that commonly occur together but occasionally occur alone.

Etiology

The most common causes (see Table 51-2) are the following:

• Viral infections

• Allergic reactions

Dry air may provoke congestion. Acute sinusitis is slightly less common, and a nasal foreign body is unusual (and occurs predominantly in children).

Patients who use topical decongestants for > 1 day often experience significant rebound congestion when the effects of the drug wear off, causing them to continue using the decongestant in a vicious circle

of persistent, worsening congestion. This situation (rhinitis medicamentosa) may persist for some time and may be misinterpreted as a continuation of the original problem rather than a consequence of treatment.

Evaluation

History: History of present illness should determine the nature of the discharge (eg, watery, mucoid, purulent, bloody) and whether discharge is chronic or recurrent. If recurrent, any relation to patient location, season, or exposure to potential triggering allergens (numerous) should be determined.

Review of systems should seek symptoms of possible causes, including fever and facial pain (sinusitis); watery, itchy eyes (allergies); and sore throat, malaise, fever, and cough (viral URI).

Past medical history should seek known allergies and existence of diabetes or immunocompromise. Drug history should ask specifically about topical decongestant use.

Physical examination: Vital signs are reviewed for fever.

Examination focuses on the nose and area over the sinuses. The face is inspected for focal erythema over the frontal and maxillary sinuses; these areas are also palpated for tenderness. Nasal mucosa is inspected for color (eg, red or pale), swelling, color and nature of discharge, and (particularly in children) presence of any foreign body.

Red flags: The following findings are of particular concern:

• Unilateral discharge, particularly if purulent or bloody

• Facial pain, tenderness, or both

Interpretation of findings: Symptoms and examination are often enough to suggest a diagnosis (see Table 51-2).

In children, unilateral foul-smelling discharge suggests a nasal foreign body. If no foreign body is seen, sinusitis is suspected when purulent rhinorrhea persists for > 10 days along with fatigue and cough.

Testing: Testing is generally not indicated for acute nasal symptoms unless invasive sinusitis is suspected in a diabetic or immunocompromised patient; these patients usually should undergo CT.

[**Table 51-2.** Some Causes of Nasal Congestion and Rhinorrhea]

Treatment

Specific conditions are treated. Symptomatic relief of congestion can be achieved with topical or oral decongestants. Topical decongestants include oxymetazoline, 2 sprays each nostril once/day or bid for 3 days. Oral decongestants include pseudoephedrine 60 mg bid. Prolonged use should be avoided.

Viral rhinorrhea can be treated with oral antihistamines (eg, diphenhydramine 25 to 50 mg po bid), which are recommended because of their anticholinergic properties unrelated to their H_2-blocking properties.

Allergic congestion and rhinorrhea can be treated with antihistamines; in such cases, nonanticholinergic antihistamines (eg, fexofenadine 60 mg po bid) as needed provoke fewer adverse effects. Nasal corticosteroids (eg, mometasone 2 sprays each nostril daily) also help allergic conditions.

Antihistamines and decongestants are not recommended for children < 6 yr.

Geriatrics Essentials

Antihistamines and can have sedating and anticholinergic effects and should be given in decreased

dosage in the elderly. Similarly, sympathomimetics should be used with the lowest dosage that is clinically effective.

Key Points

• Most nasal congestion and rhinorrhea are caused by URI or allergies.

• A foreign body should be considered in children.

• Rebound from topical decongestant overuse should also be considered.

Neck Mass

Patients or their family members may notice a mass on the neck, or one may be discovered during routine examination. A neck mass may be painless or painful depending on the cause. When a neck mass is painless, much time may pass before patients seek medical care.

Etiology

There are many causes of neck mass, including infectious, cancerous, and congenital causes (see Table 51-3).

The most common causes in younger patients include the following:

• Reactive adenitis

• Primary bacterial lymph node infection

• Systemic infections

[**Table 51-3.** Some Causes of Neck Mass]

Reactive adenitis occurs in response to viral or bacterial infection somewhere in the oropharynx. Some systemic infections (eg, mononucleosis, HIV, TB) cause cervical lymph node enlargement—usually generalized rather than isolated.

Congenital disorders may cause a neck mass, typically longstanding. The most common are thyroglossal duct cysts, branchial cleft cysts, and dermoid or sebaceous cysts.

Cancerous masses are more common among older patients but may occur in younger ones. These masses may represent a local primary tumor or lymph node involvement from a local, regional, or distant primary cancer. About 60% of supraclavicular triangle masses are metastases from distant primary sites. Elsewhere in the neck, 80% of cancerous cervical adenopathy originates in the upper respiratory or alimentary tract. Likely sites of origin are the posterior-lateral border of the tongue and the floor of the mouth followed by the nasopharynx, palatine tonsil, laryngeal surface of the epiglottis, and hypopharynx, including the pyriform sinuses.

The thyroid gland may enlarge in various disorders, including simple nontoxic goiter, subacute thyroiditis, and, less often, thyroid cancer.

Evaluation

History: History of present illness should note how long the mass has been present and whether it is painful. Important associated acute symptoms include sore throat, URI symptoms, and toothache.

Review of systems should ask about difficulty swallowing or speaking and symptoms of chronic disease (eg, fever, weight loss, malaise). Regional and distant cancers causing metastases to the neck occasionally cause symptoms in their system of origin (eg, cough in lung cancer, swallowing difficulty in

esophageal cancer). Because numerous cancers can metastasize to the neck, a complete review of systems is important to help identify a source.

Past medical history should inquire about known HIV or TB and risk factors for them. Risk factors for cancer are assessed, including consumption of alcohol or use of tobacco (particularly snuff or chewing tobacco), ill-fitting dental appliances, and chronic oral candidiasis. Poor oral hygiene also may be a risk.

Physical examination: The neck mass is palpated to determine consistency (ie, whether soft and fluctuant, rubbery, or hard) and presence and degree of tenderness. Whether the mass is freely mobile or appears fixed to the skin or underlying tissue also needs to be determined.

The scalp, ears, nasal cavities, oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx are closely inspected for signs of infection and any other visible lesions. Teeth are percussed to detect the exquisite tenderness of root infection. The base of the tongue, floor of the mouth, and the thyroid and salivary glands are palpated for masses.

The breasts and prostate gland are palpated for masses, and the spleen is palpated for enlargement. Stool is checked for occult blood, suggestive of a GI cancer.

Other lymph nodes are palpated (eg, axillary, inguinal).

Red flags: The following findings are of particular concern:

• Hard, fixed mass

• Older patient

• Presence of oropharyngeal lesions (other than simple pharyngitis or dental infection)

• A history of persistent hoarseness or dysphagia

Interpretation of findings: Important differentiating factors for a neck mass (see also Table 51-3) include acuity, pain and tenderness, and consistency and mobility.

A new mass (ie, developing over only a few days), particularly after symptoms of a URI or pharyngitis, suggests benign reactive lymphadenopathy. An acute tender mass suggests lymphadenitis or an infected dermoid cyst.

A chronic mass in younger patients suggests a cyst. A non-midline mass in older patients, particularly those with risk factors, should be considered cancer until proven otherwise; a midline mass is likely of thyroid origin (benign or malignant).

Pain, tenderness, or both in the mass suggest inflammation (particularly infectious), whereas a painless mass suggests a cyst or tumor. A hard, fixed, nontender mass suggests cancer, whereas rubbery consistency and mobility suggest otherwise.

Generalized adenopathy and splenomegaly suggest infectious mononucleosis or a lymphoreticular cancer. Generalized adenopathy alone may suggest HIV infection, particularly in those with risk factors.

Red and white mucosal patches (erythroplakia and leukoplakia) in the oropharynx may be malignant lesions responsible for the neck mass.

Difficulty swallowing may be noted with thyroid enlargement or cancer originating in various sites in the neck. Difficulty speaking suggests a cancer involving the larynx or recurrent laryngeal nerve.

Testing: If the nature of the mass is readily apparent (eg, lymphadenopathy caused by recent pharyngitis) or is in a healthy young patient with a recent, tender swelling and no other findings, then no immediate testing is required. However, the patient is reexamined regularly; if the mass fails to resolve,

further evaluation is needed.

Most other patients should have a CBC and chest x-ray. Those with findings suggesting specific causes should also have testing for those disorders (see Table 51-3).

If examination reveals an oral or nasopharyngeal lesion that fails to begin resolving within 2 wk, testing may include CT or MRI and fine-needle biopsy of that lesion.

In young patients with no risk factors for head and neck cancer and no other apparent lesions, the neck mass may be biopsied.

Older patients, particularly those with risk factors for cancer, should first undergo further testing to identify the primary site; biopsy of the neck mass may simply reveal undifferentiated squamous cell carcinoma without illuminating the source. Such patients should have direct laryngoscopy, bronchoscopy, and esophagoscopy with biopsy of all suspicious areas. CT of the head, neck, and chest and possibly a thyroid scan are done. If a primary tumor is not found, fine-needle aspiration biopsy of the neck mass should be done, which is preferable to an incisional biopsy because it does not leave a transected mass in the neck. If the neck mass is cancerous and a primary tumor has not been identified, random biopsy of the nasopharynx, palatine tonsils, and base of the tongue should be considered.

Treatment

Treatment is directed at the cause.

Key Points

• An acute neck mass in younger patients is usually benign.

• Neck mass in an elderly patient raises concern of cancer.

• Thorough oropharyngeal examination is important.

Pharyngitis

Pharyngitis (sore throat) is pain in the posterior pharynx that occurs with or without swallowing. Pain can be severe; many patients refuse oral intake.

Etiology

Sore throat results from infection; the most common cause is

• Tonsillopharyngitis

Rarely, an abscess or epiglottitis is involved; although uncommon, these are of particular concern because they may compromise the airway.

Tonsillopharyngitis: Tonsillopharyngitis is predominantly a viral infection; a lesser number of cases are caused by bacteria.

The respiratory viruses (rhinovirus, adenovirus, influenza, coronavirus, respiratory syncytial virus) are the most common viral causes, but occasionally Epstein-Barr virus (the cause of mononucleosis), herpes simplex, cytomegalovirus, or primary HIV infection is involved.

The main bacterial cause is group A β-hemolytic streptococcus (GABHS), which, although estimates vary, causes perhaps 10% of cases in adults and slightly more in children. GABHS is a concern because of the possibility of the poststreptococcal sequelae of rheumatic fever, glomerulonephritis, and abscess. Uncommon bacterial causes include gonorrhea, diphtheria, mycoplasma, and chlamydia.

Abscess: An abscess in the pharyngeal area (peritonsillar, parapharyngeal, and, in children, retropharyngeal) is uncommon but causes significant throat pain. The usual causative organism is GABHS.

Epiglottitis: Epiglottitis, perhaps better termed supraglottitis, used to occur primarily in children and usually was caused by *Haemophilus influenzae* type B (HiB). Now, because of widespread childhood vaccination against HiB, supraglottitis/epiglottitis has been almost eradicated in children (more cases occur in adults). Causal organisms in children and adults include *Streptococcus pneumoniae*, *Staphylococcus aureus*, nontypeable *H. influenzae*, *Haemophilus parainfluenzae*, β-hemolytic streptococci, *Branhamella catarrhalis*, and *Klebsiella pneumoniae*. HiB is still a cause in adults and unvaccinated children.

Evaluation

History: History of present illness should note the duration and severity of sore throat.

Review of systems should seek important associated symptoms, such as runny nose, cough, and difficulty swallowing, speaking, or breathing. The presence and duration of any preceding weakness and malaise (suggesting mononucleosis) are noted.

Past medical history should seek history of previous documented mononucleosis (recurrence is highly unlikely). Social history should inquire about close contact with people with documented GABHS infection, risk factors for gonorrhea transmission (eg, recent oral-genital sexual contact), and risk factors for HIV acquisition (eg, unprotected intercourse, multiple sex partners, IV drug abuse).

Physical examination: General examination should note fever and signs of respiratory distress, such as tachypnea, dyspnea, stridor, and, in children, the tripod position (sitting upright, leaning forward with neck hyperextended and jaw thrust forward).

Pharyngeal examination should not be done in children if supraglottitis/epiglottitis is suspected, because it may trigger complete airway obstruction. Adults with no respiratory distress may be examined but with care. Erythema, exudates, and any signs of swelling around the tonsils or retropharyngeal area should be noted. Whether the uvula is in the midline or appears pushed to one side should also be noted.

The neck is examined for presence of enlarged, tender lymph nodes. The abdomen is palpated for presence of splenomegaly.

Red flags: The following findings are of particular concern:

• Stridor or other sign of respiratory distress

• Drooling

• Muffled, "hot potato" voice

• Visible bulge in pharynx

Interpretation of findings: Supraglottitis/epiglottitis and pharyngeal abscess pose a threat to the airway and must be differentiated from simple tonsillopharyngitis, which is uncomfortable but not acutely dangerous. Clinical findings help make this distinction.

With supraglottitis/epiglottitis, there is abrupt onset of severe throat pain and dysphagia, usually with no preceding URI symptoms. Children often have drooling and signs of toxicity. Sometimes (more often in children), there are respiratory manifestations, with tachypnea, dyspnea, stridor, and sitting in the tripod position. If examined, the pharynx almost always appears unremarkable.

Pharyngeal abscess and tonsillopharyngitis both may cause pharyngeal erythema, exudate, or both. However, some findings are more likely in one condition or another:

• Pharyngeal abscess: Muffled, "hot potato" voice (speaking as if a hot object is being held in the mouth); visible focal swelling in the posterior pharyngeal area (often with deviation of the uvula)

• Tonsillopharyngitis: Accompanied by URI symptoms (eg, runny nose, cough)

Although tonsillopharyngitis is easily recognized clinically, its cause is not. Manifestations of viral and GABHS infection overlap significantly, although URI symptoms are more common with a viral cause. In adults, clinical criteria that increase suspicion of GABHS as a cause include

• Tonsillar exudate

• Tender lymphadenopathy

• Fever (including history)

• Absence of cough

Those with ≤ 1 criterion reasonably may be presumed to have viral illness. If ≥ 2 criteria are present, the likelihood of GABHS is high enough to warrant testing but probably not high enough to warrant antibiotics, but this decision needs to be patient-specific (ie, threshold for testing and treatment may be lower in those at risk because of diabetes or immunocompromise). In children, testing usually is done.

Regarding rarer causes of tonsillopharyngitis, infectious mononucleosis should be considered when there is posterior cervical or generalized adenopathy, hepatosplenomegaly, and fatigue and malaise for > 1 wk. Those with no URI symptoms but recent oral-genital contact may have pharyngeal gonorrhea. A dirty-gray, thick, tough membrane on the posterior pharynx that bleeds if peeled away indicates diphtheria (rare in the US). HIV infection should be considered in patients with risk factors.

Testing: If supraglottitis/epiglottitis is considered possible after evaluation, testing is required. Patients who do not appear seriously ill and have no respiratory symptoms may have plain lateral neck x-rays to look for an edematous epiglottis. However, a child who appears seriously ill or has stridor or any other respiratory symptoms should not be transported to the x-ray suite. Such patients (and those with positive or equivocal x-ray findings) usually should have flexible fiberoptic laryngoscopy. (CAUTION: *Examination of the pharynx and larynx may precipitate complete respiratory obstruction in children, and the pharynx and larynx should not be directly examined except in the operating room, where the most advanced airway intervention is available*.)

Many abscesses are managed clinically, but if location and extent are unclear, immediate CT of the neck should be done.

In tonsillopharyngitis, throat culture is the only reliable way to differentiate viral infection from GABHS. To balance timeliness of diagnosis, cost, and accuracy, one strategy in children is to do a rapid strep screen in the office, treat if positive, and send a formal culture if negative. In adults, because other bacterial pathogens may be involved, throat culture for all bacterial pathogens is appropriate for those meeting clinical criteria described previously.

Testing for mononucleosis, gonorrhea, or HIV is done only when clinically suspected.

Treatment

Specific conditions are treated. Those with severe symptoms of tonsillopharyngitis may be started on a broad-spectrum antibiotic (eg, amoxicillin/clavulanate) pending culture results.

Symptomatic treatments such as warm saltwater gargles and topical anesthetics (eg, benzocaine, lidocaine, dyclonine) may help temporarily relieve pain in tonsillopharyngitis. Patients in severe pain (even from tonsillopharyngitis) may require short-term use of opioids.

Key Points

• Most sore throats are caused by viral tonsillopharyngitis.

• It is difficult to clinically distinguish viral from bacterial causes of tonsillopharyngitis.

• Abscess and epiglottitis are rare but serious causes.

• Severe sore throat in a patient with a normal-appearing pharynx should raise suspicion of epiglottitis.

Smell and Taste Abnormalities

Because distinct flavors depend on aromas to stimulate the olfactory chemoreceptors, smell and taste are physiologically interdependent. Dysfunction of one often disturbs the other. Disorders of smell and taste are rarely incapacitating or life threatening, so they often do not receive close medical attention, although their effect on quality of life can be severe.

Taste: Although abnormal taste sensations may be due to mental disorders, local causes should always be sought. Glossopharyngeal and facial nerve integrity can be determined by testing taste on both sides of the dorsum of the tongue with sugar, salt, vinegar (acid), and quinine (bitter).

Drying of the oral mucosa caused by heavy smoking, Sjogren's syndrome, radiation therapy of the head and neck, or desquamation of the tongue can impair taste, and various drugs (eg, those with anticholinergic properties and vincristine) alter taste. In all instances, the gustatory receptors are diffusely involved. When limited to one side of the tongue (eg, in Bell's palsy), ageusia (loss of the sense of taste) is rarely noticed.

Smell: The inability to detect certain odors, such as gas or smoke, may be dangerous, and several systemic and intracranial disorders should be excluded before dismissing symptoms as harmless. Whether brain stem disease (involvement of the nucleus solitarius) can cause disorders of smell and taste is uncertain, because other neurologic manifestations usually take precedence.

Anosmia (loss of the sense of smell) is probably the most common abnormality. Hyperosmia (increased sensitivity to odors) usually reflects a neurotic or histrionic personality but can occur intermittently with seizure disorders. Dysosmia (disagreeable or distorted sense of smell) may occur with infection of the nasal sinuses, partial damage to the olfactory bulbs, or mental depression. Some cases, accompanied by a disagreeable taste, result from poor dental hygiene. Uncinate epilepsy can produce brief, vivid, unpleasant olfactory hallucinations. Hyposmia (diminished sense of smell) and hypogeusia (diminished sense of taste) can follow acute influenza, usually temporarily.

Rarely, idiopathic dysgeusia (distorted sense of taste), hypogeusia, and dysosmia respond to zinc supplementation.

Anosmia

Anosmia is complete loss of smell. Hyposmia is partial loss of smell. Most patients with anosmia have normal perception of salty, sweet, sour, and bitter substances but lack flavor discrimination, which largely depends on olfaction. Therefore, they often complain of losing the sense of taste (ageusia) and of not enjoying food. If unilateral, anosmia is often unrecognized.

Etiology

Anosmia occurs when intranasal swelling or other obstruction prevents odors from gaining access to the olfactory area; when the olfactory neuroepithelium is destroyed; or when the olfactory nerve fila, bulbs, tracts, or central connections are destroyed (see Table 51-4).

Major causes include

• Head trauma (young adults)

• Viral infections and Alzheimer's disease (older adults)

[**Table 51-4.** Some Causes of Anosmia]

Prior URI, especially influenza infection, is implicated in 14 to 26% of all presenting cases of hyposmia or anosmia.

Drugs can contribute to anosmia in susceptible patients. Other causes include prior head and neck radiation, recent nasal or sinus surgery, nasal and brain tumors, and toxins. The role of tobacco is uncertain.

Evaluation

History: History of present illness should assess the time course of symptoms and their relation to any URI or head injury. Important associated symptoms are nasal congestion, rhinorrhea, or both. The nature of rhinorrhea should be assessed (eg, watery, mucoid, purulent, bloody).

Review of systems should assess neurologic symptoms, particularly those involving mental status (eg, difficulty with recent memory) and cranial nerves (eg, diplopia, difficulty speaking or swallowing, tinnitus, vertigo).

Past medical history should include history of sinus disorders, cranial trauma or surgery, allergies, drugs used, and exposure to chemicals or fumes.

Physical examination: The nasal passages should be inspected for swelling, inflammation, discharge, and polyps. Having the patient breathe through each nostril sequentially (while the other is manually occluded) may help identify obstruction.

A complete neurologic examination, particularly of mental status and cranial nerves, is done.

Red flags: The following findings are of particular concern:

• Previous head injury

• Neurologic symptoms or signs

• Sudden onset

Interpretation of findings: Sudden onset after significant head trauma or toxin exposure strongly implicates that event as the cause.

A history of chronic rhinosinusitis is suggestive, particularly when significant congestion, polyps, or both are visible on examination. However, because these findings are common in the population, the physician should be wary of missing another disorder. Progressive confusion and recent memory loss in an elderly patient suggest Alzheimer's disease as a cause. Waxing and waning neurologic symptoms affecting multiple areas suggest a neurodegenerative disease such as multiple sclerosis. Slowly progressive anosmia in an elderly patient with no other symptoms or findings suggests normal aging as the cause.

Testing: An in-office test of olfaction can help confirm olfactory dysfunction. Commonly, one nostril is pressed shut, and a pungent odor such as from a vial containing coffee, cinnamon, or tobacco is placed under the open nostril; if the patient can identify the substance, olfaction is presumed intact. The test is repeated on the other nostril to determine whether the response is bilateral. Unfortunately, the test is crude and unreliable.

If anosmia is present and no cause is readily apparent on clinical evaluation (see Table 51-4), patients

should have CT of the head (including sinuses) with contrast to rule out a tumor or unsuspected fracture of the floor of the anterior cranial fossa. MRI is also used to evaluate intracranial disease and may be needed as well, particularly in those patients with no nasal or sinus pathology on CT.

A psychophysical assessment of odor and taste identification and threshold detection is done as well. This assessment commonly involves use of one or several commercially available testing kits. One kit uses a scratch-and-sniff battery of odors, whereas another kit involves sequential dilutions of an odorous chemical.

Treatment

Specific causes are treated, although smell does not always recover even after successful treatment of sinusitis.

There are no treatments for anosmia. Patients who retain some sense of smell may find adding concentrated flavoring agents to food improves their enjoyment of eating. Smoke alarms, important in all homes, are even more essential for patients with anosmia. Patients should be cautioned about consumption of stored food and use of natural gas for cooking or heating, because they have difficulty detecting food spoilage or gas leaks.

Geriatrics Essentials

There is a significant loss of olfactory receptor neurons with normal aging, leading to a marked diminution of the sense of smell. Changes are usually noticeable by age 60 and can be marked after age 70.

Key Points

• Anosmia may be part of normal aging.

• Common causes include URI, sinusitis, and head trauma.

• Cranial imaging is typically required unless the cause is obvious.

Chapter 52. Oral and Pharyngeal Disorders

Introduction

Oral and pharyngeal disorders include adenoid disorders, epiglottitis, parapharyngeal abscess, peritonsillar abscess and cellulitis, retropharyngeal abscess, salivary stones, sialadenitis, submandibular space infection, tonsillopharyngitis, Tornwaldt's cyst, and velopharyngeal insufficiency. Oral, pharyngeal, and salivary gland tumors are discussed in Ch. 55.

Sialadenitis

Sialadenitis is bacterial infection of a salivary gland, usually due to an obstructing stone or gland hyposecretion. Symptoms are swelling, pain, redness, and tenderness. Diagnosis is clinical. CT, ultrasound, and MRI may help identify the cause. Treatment is with antibiotics.

Etiology

Sialadenitis usually occurs after hyposecretion or duct obstruction but may develop without an obvious cause. The major salivary glands are the parotid, submandibular, and sublingual glands. Sialadenitis is most common in the parotid gland and typically occurs in patients in their 50s and 60s, in chronically ill patients with xerostomia, in those with Sjogren's syndrome, and in those who have had radiation therapy to the oral cavity. Teenagers and young adults with anorexia are also prone to this disorder. The most common causative organism is *Staphylococcus aureus*; others include streptococci, coliforms, and various anaerobic bacteria.

Symptoms and Signs

Fever, chills, and unilateral pain and swelling develop. The gland is firm and diffusely tender, with erythema and edema of the overlying skin. Pus can often be expressed from the duct by compressing the affected gland and should be cultured. Focal enlargement may indicate an abscess.

Diagnosis

CT, ultrasound, and MRI can confirm sialadenitis or abscess that is not obvious clinically, although MRI may miss an obstructing stone.

Treatment

• Antistaphylococcal antibiotics

• Local measures (eg, sialagogues, warm compresses)

Initial treatment is with antibiotics active against *S. aureus* (eg, dicloxacillin, 250 mg po qid, a 1st-generation cephalosporin, or clindamycin), modified according to culture results. With the increasing prevalence of methicillin-resistant *S. aureus*, especially among the elderly living in extended-care nursing facilities, vancomycin is often required. Hydration, sialagogues (eg, lemon juice, hard candy, or some other substance that triggers saliva flow), warm compresses, gland massage, and good oral hygiene are also important. Abscesses require drainage. Occasionally, a superficial parotidectomy or submandibular gland excision is indicated for patients with chronic or relapsing sialadenitis.

Other Salivary Gland Infections

Mumps often cause parotid swelling (see Table 155-1 on p. 1462). Patients with HIV infection often have parotid enlargement secondary to one or more lymphoepithelial cysts. Cat-scratch disease caused by *Bartonella* infection often invades periparotid lymph nodes and may infect the parotid glands by contiguous spread. Although cat-scratch disease is self-limited, antibiotic therapy is often provided, and incision and drainage are necessary if an abscess

develops.

Atypical mycobacterial infections in the tonsils or teeth may spread contiguously to the major salivary glands. The PPD may be negative, and the diagnosis may require biopsy and tissue culture for acid-fast bacteria. Treatment recommendations are controversial. Options include surgical debridement with curettage, complete excision of the infected tissue, and use of anti-TB drug therapy (rarely necessary).

Salivary Stones

(Sialolithiasis)

Stones composed of Ca salts often obstruct salivary glands, causing pain, swelling, and sometimes infection. Diagnosis is made clinically or with CT, ultrasonography, or sialography. Treatment involves stone expression with saliva stimulants, manual manipulation, a probe, or surgery.

The major salivary glands are the paired parotid, submandibular, and sublingual glands. Stones in the salivary glands are most common among adults. Eighty percent of stones originate in the submandibular glands and obstruct Wharton's duct. Most of the rest originate in the parotid glands and block Stensen's duct. Only about 1% originate in the sublingual glands. Multiple stones occur in about 25% of patients.

Etiology

Most salivary stones are composed of Ca phosphate with small amounts of Mg and carbonate. Patients with gout may have uric acid stones. Stone formation requires a nidus on which salts can precipitate during salivary stasis. Stasis occurs in patients who are debilitated, dehydrated, have reduced food intake, or take anticholinergics. Persisting or recurrent stones predispose to infection of the involved gland (sialadenitis—see p. 469).

Symptoms and Signs

Obstructing stones cause glandular swelling and pain, particularly after eating, which stimulates saliva flow. Symptoms may subside after a few hours. Relief may coincide with a gush of saliva. Some stones cause intermittent or no symptoms. If a stone is lodged distally, it may be visible or palpable at the duct's outlet.

Diagnosis

• Clinical evaluation

• Sometimes imaging (eg, CT, ultrasonography, sialography)

If a stone is not apparent on examination, the patient can be given a sialagogue (eg, lemon juice, hard candy, or some other substance that triggers saliva flow). Reproduction of symptoms is almost always diagnostic of a stone. CT, ultrasonography, and sialography are highly sensitive and are used if clinical diagnosis is equivocal. Contrast sialography may be done through a catheter inserted into the duct and can differentiate between stone, stenosis, and tumor. This technique is occasionally therapeutic. Because 90% of submandibular calculi are radiopaque and 90% of parotid calculi are radiolucent, plain x-rays are not always accurate. MRI is not indicated.

Treatment

• Local measures (eg, sialagogues, massage)

• Sometimes manual expression or surgical removal

Analgesics, hydration, and massage can relieve symptoms. Antistaphylococcal antibiotics can be used to prevent acute sialadenitis if started early. Stones may pass spontaneously or when salivary flow is

stimulated by sialagogues; patients are encouraged to suck a lemon wedge or sour candy every 2 to 3 h. Stones right at the duct orifice can sometimes be expressed manually by squeezing with the fingertips. Dilation of the duct with a small probe may facilitate expulsion. Surgical removal of stones succeeds if other methods fail. Stones at or near the orifice of the duct may be removed transorally, whereas those in the hilum of the gland often require complete excision of the salivary gland.

Submandibular Space Infection

(Ludwig's Angina)

Submandibular space infection is acute cellulitis of the soft tissues below the mouth. Symptoms include pain, dysphagia, and potentially fatal airway obstruction. Diagnosis usually is clinical. Treatment includes airway management, surgical drainage, and IV antibiotics.

Submandibular space infection is a rapidly spreading, bilateral, indurated cellulitis occurring in the suprahyoid soft tissues, the floor of the mouth, and both sublingual and submaxillary spaces without abscess formation. Although not a true abscess, it resembles one clinically and is treated similarly.

The condition usually develops from an odontogenic infection, especially of the 2nd and 3rd mandibular molars, or as an extension of peritonsillar cellulitis. Contributing factors may include poor dental hygiene, tooth extractions, and trauma (eg, fractures of the mandible, lacerations of the floor of the mouth).

Symptoms and Signs

Early manifestations are pain in any involved teeth, with severe, tender, localized submental and sublingual induration. Board-like firmness of the floor of the mouth and brawny induration of the suprahyoid soft tissues may develop rapidly. Drooling, trismus, dysphagia, stridor caused by laryngeal edema, and elevation of the posterior tongue against the palate may be present. Fever, chills, and tachycardia are usually present as well. The condition can cause airway obstruction within hours and does so more often than do other neck infections.

Diagnosis

The diagnosis usually is obvious. If not, CT is done.

Treatment

• Maintenance of airway patency

• Surgical incision and drainage

• Antibiotics active against oral flora

Maintaining airway patency is of the highest priority. Because swelling makes oral endotracheal intubation difficult, fiberoptic nasotracheal intubation done with topical anesthesia in the operating room or ICU with the patient awake is preferable. Some patients require a tracheotomy. Patients without immediate need for intubation require intense observation and may benefit temporarily from a nasal trumpet.

Incision and drainage with placement of drains deep into the mylohyoid muscles relieve the pressure. Antibiotics should be chosen to cover both oral anaerobes and aerobes (eg, clindamycin, ampicillin/sulbactam, high-dose penicillin).

Adenoid Disorders

Hypertrophy or inflammation of the adenoids is common among children. Symptoms include nasal obstruction, sleep disturbances, and middle ear effusions with hearing loss. Diagnosis is enhanced by flexible fiberoptic nasopharyngoscopy. Treatment often includes intranasal corticosteroids, antibiotics, and, for significant nasal obstruction or persistent recurrent acute

otitis media or middle ear effusion, adenoidectomy.

The adenoids are a rectangular mass of lymphatic tissue in the posterior nasopharynx. They are largest in children 2 to 6 yr. Enlargement may be physiologic or secondary to viral or bacterial infection, allergy, irritants, and, possibly, gastroesophageal reflux. Other risk factors include ongoing exposure to bacterial or viral infection (eg, to multiple children at a child care center). Severe hypertrophy can obstruct the eustachian tubes (causing otitis media), posterior choanae (causing sinusitis), or both.

Symptoms and Signs

Although patients with adenoid hypertrophy may not complain of symptoms, they usually have chronic mouth breathing, snoring, sleep disturbance, halitosis, recurrent acute otitis media, conductive hearing loss (secondary to recurrent otitis media or persistent middle ear effusions), and a hyponasal voice quality. Chronic adenoiditis can also cause chronic or recurrent nasopharyngitis, rhinosinusitis, epistaxis, halitosis, and cough.

Diagnosis

• Flexible nasopharyngoscopy

Adenoid hypertrophy is suspected in children and adolescents with characteristic symptoms, persistent middle ear effusions, or recurrent acute otitis media or rhinosinusitis. Similar symptoms and signs in a male adolescent may result from an angiofibroma. The gold standard for office assessment of the nasopharynx is flexible nasopharyngoscopy. X-ray imaging and sleep tape recording, although also often used, are not as accurate. A sleep study may help define the severity of any sleep disturbance due to chronic obstruction.

Treatment

• Treatment of cause

• Sometimes adenoidectomy

Underlying allergy is treated with intranasal corticosteroids, and underlying bacterial infection is treated with antibiotics. In children with persistent middle ear effusions or frequent otitis media, adenoidectomy often limits recurrence. Children > 4 yr who require tympanostomy tubes often undergo adenoidectomy when tubes are placed. Surgery is also recommended for younger children with recurrent epistaxis or significant nasal obstruction (eg, sleep disturbance, voice change). Although it requires general anesthesia, adenoidectomy usually can be done on an outpatient basis with recovery in 48 to 72 h.

Retropharyngeal Abscess

Retropharyngeal abscesses, most common among young children, can cause sore throat, fever, neck stiffness, and stridor. Diagnosis requires lateral neck x-ray or CT. Treatment is with endotracheal intubation, drainage, and antibiotics.

Retropharyngeal abscesses develop in the retropharyngeal lymph nodes at the back of the pharynx, adjacent to the vertebrae. They can be seeded by infection of the pharynx, sinuses, adenoids, or nose. They occur mainly in children 1 to 8 yr, as the retropharyngeal lymph nodes begin to recede by 4 to 5 yr. However, adults may develop infection after foreign body ingestion or after instrumentation. Common organisms include aerobic (*Streptococcus* and *Staphylococcus* sp) and anaerobic (*Bacteroides* and *Fusobacterium*) bacteria and, increasingly in adults and children, HIV and TB.

The most serious consequences include airway obstruction, septic shock, rupture of the abscess into the airway resulting in aspiration pneumonia or asphyxia, mediastinitis, carotid rupture, and suppurative thrombophlebitis of the internal jugular veins (Lemierre syndrome).

Symptoms and Signs

Symptoms and signs are usually preceded in children by an acute URI and in adults by foreign body ingestion or instrumentation. Children may have odynophagia, dysphagia, fever, cervical lymphadenopathy, nuchal rigidity, stridor, dyspnea, snoring or noisy breathing, and torticollis. Adults may have severe neck pain but less often have stridor. The posterior pharyngeal wall may bulge to one side.

Diagnosis

• CT

Diagnosis is suspected in patients with severe, unexplained sore throat and neck stiffness; stridor; or noisy breathing. Lateral soft-tissue x-rays of the neck, taken in the maximum possible hyperextension and during inspiration, may show focal widening of the prevertebral soft tissues, reversal of normal cervical lordosis, air in the prevertebral soft tissues, or erosion of the adjacent vertebral body. CT can help diagnose questionable cases, help differentiate cellulitis from an abscess, and assess extent of the abscess.

Treatment

• Antibiotics (eg, ceftriaxone, clindamycin)

• Usually surgical drainage

Antibiotics, such as a broad-spectrum cephalosporin (eg, ceftriaxone 50 to 75 mg/kg IV once/day) or clindamycin, may occasionally be sufficient for children with small abscesses. However, most patients also require drainage through an incision in the posterior pharyngeal wall. Endotracheal intubation is done preoperatively and maintained for 24 to 48 h.

Tornwaldt's Cyst

(Pharyngeal Bursa)

Tornwaldt's cyst is a rare cyst in the midline of the nasopharynx that may become infected.

Tornwaldt's cyst is a remnant of the embryonal notochord superficial to the superior constrictor muscle of the pharynx and is covered by the mucous membrane of the nasopharynx. It may become infected, causing persistent purulent drainage with a foul taste and odor, eustachian tube obstruction, and sore throat.

Purulent exudate may be seen at the opening of the cyst. Diagnosis is based on nasopharyngoscopy supplemented by CT or MRI when the diagnosis is in doubt. Treatment consists of marsupialization or excision.

Velopharyngeal Insufficiency

Velopharyngeal insufficiency is incomplete closure of a sphincter between the oropharynx and nasopharynx, often resulting from anatomic abnormalities of the palate and causing hypernasal speech. Treatment is with speech therapy and surgery.

Velopharyngeal insufficiency is incomplete closure of the velopharyngeal sphincter between the oropharynx and the nasopharynx. Closure, normally achieved by the sphincteric action of the soft palate and the superior constrictor muscle, is impaired in patients with cleft palate, repaired cleft palate, congenitally short palate, submucous cleft palate, palatal paralysis, and, sometimes, enlarged tonsils. The condition may also result when adenoidectomy or uvulopalatopharyngoplasty is done in a patient with a congenital underdevelopment (submucous cleft) or paralysis of the palate.

Symptoms and Signs

Speech in a patient with velopharyngeal insufficiency is characterized by hypernasal resonant voice, nasal emission of air, nasal turbulence, and inability to produce sounds requiring oral pressure (plosives). Severe velopharyngeal insufficiency results in regurgitation of solid foods and fluids through the nose. Inspection of the palate during phonation may reveal palatal paralysis.

Diagnosis

• Direct inspection with a fiberoptic nasoendoscope

The diagnosis is suspected in patients with the typical speech abnormalities. Palpation of the midline of the soft palate may reveal an occult submucous cleft. Direct inspection with a fiberoptic nasoendoscope is the primary diagnostic technique. Multiview videofluoroscopy during connected speech and swallowing (modified barium swallow), done in conjunction with a speech pathologist, can also be used.

Treatment

• Surgical repair and speech therapy

Treatment consists of speech therapy and surgical correction by a palatal elongation pushback procedure, posterior pharyngeal wall implant, pharyngeal flap, or pharyngoplasty, depending on the mobility of the lateral pharyngeal walls, the degree of velar elevation, and the size of the defect.

Tonsillopharyngitis

(See also p. 1232.)

Tonsillopharyngitis is acute infection of the pharynx, palatine tonsils, or both. Symptoms may include sore throat, dysphagia, cervical lymphadenopathy, and fever. Diagnosis is clinical, supplemented by culture or rapid antigen test. Treatment depends on symptoms and, in the case of group A β-hemolytic streptococcus, involves antibiotics.

The tonsils participate in systemic immune surveillance. In addition, local tonsillar defenses include a lining of antigen-processing squamous epithelium that involves B- and T-cell responses.

Tonsillopharyngitis of all varieties constitutes about 15% of all office visits to primary care physicians.

Etiology

Tonsillopharyngitis is usually viral, most often caused by the common cold viruses (adenovirus, rhinovirus, influenza, coronavirus, respiratory syncytial virus), but occasionally by Epstein-Barr virus, herpes simplex virus, cytomegalovirus, or HIV.

In about 30% of patients, the cause is bacterial. Group A β-hemolytic streptococcus (GABHS) is most common (see p. 1232), but *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* are sometimes involved. Rare causes include pertussis, *Fusobacterium*, diphtheria, syphilis, and gonorrhea.

GABHS occurs most commonly between ages 5 and 15 and is uncommon before age 3.

Symptoms and Signs

Pain with swallowing is the hallmark and is often referred to the ears. Very young children who are not able to complain of sore throat often refuse to eat. High fever, malaise, headache, and GI upset are common, as are halitosis and a muffled voice. A scarlatiniform or nonspecific rash may also be present. The tonsils are swollen and red and often have purulent exudates. Tender cervical lymphadenopathy may be present. Fever, adenopathy, palatal petechiae, and exudates are somewhat more common with GABHS than with viral tonsillopharyngitis, but there is much overlap. GABHS usually resolves within 7

days. Untreated GABHS may lead to local suppurative complications (eg, peritonsillar abscess or cellulitis) and sometimes to rheumatic fever or glomerulonephritis.

Diagnosis

• Clinical evaluation

• GABHS ruled out by rapid antigen test, culture, or both

Pharyngitis itself is easily recognized clinically. However, its cause is not. Rhinorrhea and cough usually indicate a viral cause. Infectious mononucleosis is suggested by posterior cervical or generalized adenopathy, hepatosplenomegaly, fatigue, and malaise for > 1 wk; a full neck with petechiae of the soft palate; and thick tonsillar exudates. A dirty gray, thick, tough membrane that bleeds if peeled away indicates diphtheria (rare in the US).

Because GABHS requires antibiotics, it must be diagnosed early. Criteria for testing are controversial. Many authorities recommend testing with a rapid antigen test or culture for all children. Rapid antigen tests are specific but not sensitive and may need to be followed by a culture, which is about 90% specific and 90% sensitive. In adults, many authorities recommend using the following 4 criteria:

• History of fever

• Tonsillar exudates

• Absence of cough

• Tender anterior cervical lymphadenopathy

Patients who meet 1 or no criteria are unlikely to have GABHS and should not be tested. Patients who meet 2 criteria can be tested. Patients who meet 3 or 4 criteria can be tested or treated empirically for GABHS.

Treatment

• Symptomatic treatment

• Antibiotics for GABHS

• Tonsillectomy considered for recurrent GABHS

Supportive treatments include analgesia, hydration, and rest. Penicillin V is usually considered the drug of choice for GABHS tonsillopharyngitis; dose is 250 mg po bid for 10 days for patients < 27 kg and 500 mg for those > 27 kg (see also p. 1234). Amoxicillin is effective and more palatable if a liquid preparation is required. If adherence is a concern, a single dose of benzathine penicillin 1.2 million units IM (600,000 units for children ≤ 27 kg) is effective. Other oral drugs include macrolides for patients allergic to penicillin, a 1st-generation cephalosporin, and clindamycin.

Treatment may be started immediately or delayed until culture results are known. If treatment is started presumptively, it should be stopped if cultures are negative. Follow-up throat cultures are not done routinely. They are useful in patients with multiple GABHS recurrences or if pharyngitis spreads to close contacts at home or school.

Tonsillectomy: Tonsillectomy should be considered if GABHS tonsillitis recurs repeatedly (> 6 episodes/yr, > 4 episodes/yr for 2 yr, > 3 episodes/yr for 3 yr) or if acute infection is severe and persistent despite antibiotics. Other criteria for tonsillectomy include obstructive sleep disorder, recurrent peritonsillar abscess, and suspicion of cancer.

Numerous effective surgical techniques are used to perform tonsillectomy, including electrocautery,

microdebrider, radiofrequency coblation, and sharp dissection. Significant intraoperative or postoperative bleeding occurs in < 2% of patients, usually within 24 h of surgery or after 7 days, when the eschar detaches. Patients with bleeding should go to the hospital. If bleeding continues on arrival, patients generally are examined in the operating room, and hemostasis is obtained. Any clot present in the tonsillar fossa is removed, and patients are observed for 24 h. Postoperative IV rehydration is necessary in ≤ 3% of patients, possibly in fewer patients with use of optimal preoperative hydration, perioperative antibiotics, analgesics, and corticosteroids. Postoperative airway obstruction occurs most frequently in children < 2 yr who have preexisting severe obstructive sleep disorders and in patients who are morbidly obese or have neurologic disorders, craniofacial anomalies, or significant preoperative obstructive sleep apnea. Complications are generally more common and serious among adults.

Peritonsillar Abscess and Cellulitis

Peritonsillar abscess and cellulitis are acute pharyngeal infections most common among adolescents and young adults. Symptoms are severe sore throat, trismus, "hot potato" voice, and uvular deviation. Diagnosis requires needle aspiration. Treatment includes broad-spectrum antibiotics, drainage of any pus, hydration, analgesics, and, occasionally, acute tonsillectomy.

Etiology

Abscess (quinsy) and cellulitis probably represent a spectrum of the same process in which bacterial infection of the tonsils and pharynx spreads to the soft tissues. Infection is virtually always unilateral and is located between the tonsil and the superior pharyngeal constrictor muscle. It usually involves multiple bacteria. *Streptococcus* and *Staphylococcus* are the most frequent aerobic pathogens, whereas *Bacteroides* sp is the predominant anaerobic pathogen.

Symptoms and Signs

Symptoms include gradual onset of severe unilateral sore throat, dysphagia, fever, otalgia, and asymmetric cervical adenopathy. Trismus, "hot potato" voice (speaking as if a hot object was in the mouth), a toxic appearance (see Epiglottitis on p. 475), drooling, severe halitosis, tonsillar erythema, and exudates are common. Abscess and cellulitis both have swelling above the affected tonsil, but with abscess there is more of a discrete bulge, with deviation of the soft palate and uvula and pronounced trismus.

Diagnosis

• Needle aspiration

• Sometimes CT

Peritonsillar cellulitis is recognized in patients with severe sore throat who have trismus, "hot potato" voice, and uvular deviation. All such patients require needle aspiration of the tonsillar mass and cultures. Aspiration of pus differentiates abscess from cellulitis. CT or ultrasound of the neck can help confirm the diagnosis when the physical examination is difficult or the diagnosis is in doubt, particularly when the condition must be differentiated from a parapharyngeal infection or other deep neck infection.

Treatment

• Antibiotics

• Drainage of abscess

Cellulitis subsides, usually within 48 h, with hydration and high-dose penicillin (eg, 2 million units IV q 4 h or 1 g po qid); alternative drugs include a 1st-generation cephalosporin or clindamycin. Culture-directed antibiotics are then prescribed for 10 days. Abscesses are incised and drained in the emergency department using thorough local anesthesia and sometimes procedural sedation; many clinicians believe needle aspiration alone provides adequate drainage. Although most patients can be treated as

outpatients, some need brief hospitalization for parenteral antibiotics, IV hydration, and airway monitoring. Rarely, an immediate tonsillectomy is done, particularly in a young or uncooperative patient who has other indications for elective tonsillectomy (eg, history of frequently recurrent tonsillitis or obstructive sleep apnea). Otherwise, elective tonsillectomy is done 4 to 6 wk out to prevent abscess recurrence.

Parapharyngeal Abscess

A parapharyngeal abscess is a deep neck abscess treated with antibiotics and surgical drainage.

The parapharyngeal (pharyngomaxillary) space is lateral to the superior pharyngeal constrictor and medial to the masseter muscle. This space connects to every other major fascial neck space and is divided into anterior and posterior compartments by the styloid process. The posterior compartment contains the carotid artery, internal jugular vein, and numerous nerves. Infections in the parapharyngeal space usually originate in the tonsils or pharynx, although local spread from odontogenic sources and lymph nodes may occur.

Abscess swelling can compromise the airway. Posterior space abscess can erode into the carotid artery or cause septic thrombophlebitis of the internal jugular vein (Lemierre syndrome).

Symptoms and Signs

Most patients have fever, sore throat, odynophagia, and swelling in the neck down to the hyoid bone. Anterior space abscesses cause trismus and induration along the angle of the mandible, with medial bulging of the tonsil and lateral pharyngeal wall. Posterior space abscesses cause swelling that is more prominent in the posterior pharyngeal wall. Trismus is minimal. Posterior abscesses may involve structures within the carotid sheath, possibly causing rigors, high fever, bacteremia, neurologic deficits, and massive hemorrhage caused by carotid artery rupture.

Diagnosis

• CT

Diagnosis is suspected in patients with poorly defined deep neck infection or other typical symptoms and is confirmed by using contrast-enhanced CT.

Treatment

• Broad-spectrum antibiotics (eg, ceftriaxone, clindamycin)

• Surgical drainage

Treatment may require airway control. Parenteral broad-spectrum antibiotics (eg, ceftriaxone, clindamycin) and surgical drainage are generally needed. Posterior abscesses are drained externally through the submaxillary fossa. Anterior abscesses can often be drained through an intra-oral incision. Several days of parenteral culture-determined antibiotics are required after drainage, followed by 10 to 14 days of oral antibiotics. Occasionally, small abscesses can be treated with IV antibiotics alone.

Epiglottitis

(Supraglottitis)

Epiglottitis is a rapidly progressive bacterial infection of the epiglottis and surrounding tissues that may lead to sudden respiratory obstruction and death. Symptoms include severe sore throat, dysphagia, high fever, drooling, and inspiratory stridor. Diagnosis requires direct visualization of the supraglottic structures, which is not to be done until full respiratory support is available. Treatment includes airway protection and antibiotics.

Epiglottitis used to be primarily a disease of children and usually was caused by *Haemophilus influenzae* type B. Now, because of widespread vaccination, it has been almost eradicated in children (more cases occur in adults). Causal organisms in children and adults include *Streptococcus pneumoniae*, *Staphylococcus aureus*, nontypeable *H. influenzae*, *Haemophilus parainfluenzae*, β-hemolytic streptococci, *Branhamella catarrhalis*, and *Klebsiella pneumoniae*. *H. influenzae* type B is still a cause in adults and unvaccinated children.

Bacteria that have colonized the nasopharynx spread locally to cause supraglottic cellulitis with marked inflammation of the epiglottis, vallecula, aryepiglottic folds, arytenoids, and laryngeal ventricles. With *H. influenzae* type B, infection may spread hematogenously.

The inflamed supraglottic structures mechanically obstruct the airway, increasing the work of breathing, ultimately causing respiratory failure. Clearance of inflammatory secretions is also impaired.

Symptoms and Signs

In children, sore throat, odynophagia, and dysphagia develop abruptly. Fatal asphyxia may occur within a few hours of onset. Drooling is very common. Additionally, the child has signs of toxicity (poor or absent eye contact, failure to recognize parents, cyanosis, irritability, inability to be consoled or distracted) and is febrile and anxious. Dyspnea, tachypnea, and inspiratory stridor may be present, often causing the child to sit upright, lean forward, and hyperextend the neck with the jaw thrust forward and mouth open in an effort to enhance air exchange (tripod position). Relinquishing this position may herald respiratory failure. Suprasternal, supraclavicular, and subcostal inspiratory retractions may be present.

In adults, symptoms are similar to those of children, including sore throat, fever, dysphagia, and drooling, but peak symptoms usually take > 24 h to develop. Because of the larger diameter of the adult airway, obstruction is less common and less fulminant. Often, there is no visible oropharyngeal inflammation. However, severe throat pain with a normal-appearing pharynx raises suspicion of epiglottitis.

Diagnosis

• Direct inspection (typically in operating room)

• X-ray in milder cases with low suspicion

Epiglottitis is suspected in patients with severe sore throat and no pharyngitis and also in patients with sore throat and inspiratory stridor. Stridor in children may also result from croup (viral laryngotracheal bronchitis—see
Table 52-1 and p. 2879), bacterial tracheitis, and airway foreign body. The tripod position may also occur with peritonsillar or retropharyngeal abscess.

The patient is hospitalized if epiglottitis is suspected. Diagnosis requires direct examination, usually with flexible fiberoptic laryngoscopy. (CAUTION: *Examination of the pharynx and larynx may precipitate complete respiratory obstruction in children, and the pharynx and larynx should not be directly examined except in the operating room, where the most advanced airway intervention is available.*) Although plain x-rays may be helpful, a child with stridor should not be transported to the x-ray suite. Direct laryngoscopy that reveals a beefy-red, stiff, edematous epiglottis is diagnostic. Cultures from the supraglottic tissues and blood can then be taken to search for the causative organism.

[**Table 52-1.** Differentiating Epiglottitis from Croup]

Adults may, in some cases, safely undergo flexible fiberoptic laryngoscopy.

Treatment

• Adequate airway ensured

• Antibiotics (eg, ceftriaxone)

In children, the airway must be secured immediately, preferably by nasotracheal intubation. Securing the airway can be quite difficult and should, if possible, be done by experienced personnel in the operating room. An endotracheal tube is usually required until the patient has been stabilized for 24 to 48 h (usual total intubation time is < 60 h). Alternatively, a tracheotomy is done. If respiratory arrest occurs before an airway is established, bag-mask ventilation may be a life-saving temporary measure. For emergency care of children with epiglottitis, each institution should have a protocol that involves critical care, otolaryngology, anesthesia, and pediatrics.

Adults whose airway is severely obstructed can be endotracheally intubated during flexible fiberoptic laryngoscopy. Other adults may not require immediate intubation but should be observed for airway compromise in an ICU with an intubation set and cricothyrotomy tray at the bedside.

A β-lactamase-resistant antibiotic, such as ceftriaxone 50 to 75 mg/kg IV once/day (maximum 2 g), should be used empirically, pending culture and sensitivity test results.

Epiglottitis caused by *H. influenzae* type B can be effectively prevented with the *H. influenzae* type B (Hib) conjugate vaccine.

Chapter 53. Nose and Paranasal Sinus Disorders

Introduction

(See Ch. 51 for a detailed description of the anatomy of the nose and sinuses.)

Bacterial Infections

Nasal vestibulitis is bacterial infection of the nasal vestibule, typically with *Staphylococcus aureus*. It may result from nose picking or excessive nose blowing and causes annoying crusts and bleeding when the crusts slough off. Bacitracin or mupirocin ointment applied topically bid for 14 days is effective.

Furuncles of the nasal vestibule are usually staphylococcal; they may develop into spreading cellulitis of the tip of the nose. Systemic antistaphylococcal antibiotics (eg, cephalexin 500 mg po qid) are given and warm compresses and topical mupirocin are applied. Furuncles are incised and drained to prevent local thrombophlebitis and subsequent cavernous sinus thrombosis.

Foreign Bodies

Nasal foreign bodies are found occasionally in young children, the intellectually impaired, and psychiatric patients. Common objects pushed into the nose include beads, beans, seeds, nuts, insects, and button batteries (which may cause chemical burns). When mineral salts are deposited on a long-retained foreign body, the object is called a rhinolith.

A nasal foreign body is suspected in any patient with a unilateral, foul-smelling, bloody, purulent rhinorrhea. Diagnosis is often made through another party's observation of the item being pushed into the nose or through visualization with a nasal speculum.

Nasal foreign bodies can sometimes be removed in the office with a nasal speculum and Hartmann's nasal forceps. Pretreatment with topical phenylephrine may aid visualization and removal. To avoid pushing a slippery, round object deeper, it is better to reach behind the object with the bent tip of a blunt probe and pull it forward. Sometimes, general anesthesia is necessary if a rhinolith has formed or if the foreign body may be displaced dorsally and then aspirated, resulting in airway obstruction.

Nasal Polyps

Nasal polyps are fleshy outgrowths of the nasal mucosa that form at the site of dependent edema in the lamina propria of the mucous membrane, usually around the ostia of the maxillary sinuses (see Plate 2).

Allergic rhinitis, acute and chronic infections, and cystic fibrosis all predispose to the formation of nasal polyps. Bleeding polyps occur in rhinosporidiosis. Unilateral polyps occasionally occur in association with or represent benign or malignant tumors of the nose or paranasal sinuses. They can also occur in response to a foreign body. Nasal polyps are strongly associated with aspirin allergy, sinus infections, and asthma.

Symptoms include obstruction and postnasal drainage, congestion, sneezing, rhinorrhea, anosmia, hyposmia, facial pain, and ocular itching.

Diagnosis generally is based on physical examination. A developing polyp is teardrop-shaped; when mature, it resembles a peeled seedless grape.

Treatment

• Topical corticosteroid spray

• Sometimes surgical removal

Corticosteroids (eg, mometasone [30 µg/spray], beclomethasone [42 µg/spray], flunisolide [25 µg/spray] aerosols), given as 1 or 2 sprays bid in each nasal cavity, may shrink or eliminate polyps, as may a 1-wk tapered course of oral corticosteroids. Surgical removal is still required in many cases. Polyps that obstruct the airway or promote sinusitis are removed, as are unilateral polyps that may be obscuring benign or malignant tumors. However, polyps tend to recur unless the underlying allergy or infection is controlled. After removal of nasal polyps, topical beclomethasone or flunisolide therapy tends to retard recurrence. In severe recurrent cases, maxillary sinusotomy or ethmoidectomy may be indicated. These procedures are usually done endoscopically.

Rhinitis

(See also Allergic Rhinitis on p. 1117.)

Rhinitis is inflammation of the nasal mucous membrane, with resultant nasal congestion, rhinorrhea, and variable associated symptoms depending on etiology (eg, itching, sneezing, purulence, anosmia, ozena). The cause is usually viral, although irritants can cause it. Diagnosis is usually clinical. Treatment includes humidification of room air, sympathomimetic amines, and antihistamines. Bacterial superinfection requires appropriate antibiotic treatment.

There are several forms of rhinitis.

Acute rhinitis: This form of rhinitis, manifesting with edema and vasodilation of the nasal mucous membrane, rhinorrhea, and obstruction, is usually the result of a common cold (see p. 1404); other causes include streptococcal, pneumococcal, and staphylococcal infections.

Chronic rhinitis: This form of rhinitis is generally a prolongation of subacute inflammatory or infectious viral rhinitis but may also occur in syphilis, TB, rhinoscleroma, rhinosporidiosis, leishmaniasis, blastomycosis, histoplasmosis, and leprosy—all of which are characterized by granuloma formation and destruction of soft tissue, cartilage, and bone. Nasal obstruction, purulent rhinorrhea, and frequent bleeding result. Rhinoscleroma causes progressive nasal obstruction from indurated inflammatory tissue in the lamina propria. Rhinosporidiosis is characterized by bleeding polyps. Both low humidity and airborne irritants can result in chronic rhinitis.

Atrophic rhinitis: This form of rhinitis results in atrophy and sclerosis of mucous membrane; the mucous membrane changes from ciliated pseudostratified columnar epithelium to stratified squamous epithelium, and the lamina propria is reduced in amount and vascularity. Atrophic rhinitis is associated with advanced age, Wegener's granulomatosis, and iatrogenically induced excessive nasal tissue extirpation. Although the exact etiology is unknown, bacterial infection frequently plays a role. Nasal mucosal atrophy often occurs in the elderly.

Vasomotor rhinitis: This form of rhinitis is a chronic condition in which intermittent vascular engorgement of the nasal mucous membrane leads to watery rhinorrhea and sneezing. Etiology is uncertain, and no allergy can be identified. A dry atmosphere seems to aggravate the condition.

Symptoms and Signs

Acute rhinitis results in cough, low-grade fever, nasal congestion, rhinorrhea, and sneezing. Symptoms and signs of chronic rhinitis are similar but may include purulent rhinorrhea and bleeding.

Atrophic rhinitis results in abnormal patency of the nasal cavities, crust formation, anosmia, and epistaxis that may be recurrent and severe.

Vasomotor rhinitis results in sneezing and watery rhinorrhea. The turgescent mucous membrane varies from bright red to purple. The condition is marked by periods of remission and exacerbation. Vasomotor rhinitis is differentiated from specific viral and bacterial infections of the nose by the lack of purulent exudate and crusting. It is differentiated from allergic rhinitis by the absence of an identifiable allergen.

Diagnosis

The different forms of rhinitis are diagnosed clinically. Testing is unnecessary.

Treatment

• For viral rhinitis, decongestants, antihistamines, or both

• For atrophic rhinitis, topical treatment

• For vasomotor rhinitis, humidification and sometimes topical corticosteroids and oral pseudoephedrine

Viral rhinitis may be treated symptomatically with decongestants (either topical vasoconstriction with a sympathomimetic amine, such as oxymetazoline q 8 to 12 h or phenylephrine 0.25% q 3 to 4 h for not more than 7 days, or systemic sympathomimetic amines, such as pseudoephedrine 30 mg po q 4 to 6 h). Antihistamines (see
Table 127-2 on p. 1111) may be helpful. Those with anticholinergic properties dry mucous membranes and therefore may increase irritation. Decongestants also may relieve symptoms of acute bacterial rhinitis and chronic rhinitis, whereas an underlying bacterial infection requires culture or biopsy, pathogen identification, antibiotic sensitivities, and appropriate antimicrobial treatment.

Treatment of atrophic rhinitis is directed at reducing the crusting and eliminating the odor with topical antibiotics (eg, bacitracin), topical or systemic estrogens, and vitamins A and D. Occluding or reducing the patency of the nasal cavities surgically decreases the crusting caused by the drying effect of air flowing over the atrophic mucous membrane.

Treatment of vasomotor rhinitis is by trial and error and is not always satisfactory. Patients benefit from humidified air, which may be provided by a humidified central heating system or a vaporizer in the workroom or bedroom. Systemic sympathomimetic amines (eg, for adults, pseudoephedrine 30 mg po q 4 to 6 h prn) relieve symptoms but are not recommended for long-term use. Topical vasoconstrictors are avoided because they cause the vasculature of the nasal mucous membrane to lose its sensitivity to other vasoconstrictive stimuli—eg, the humidity and temperature of inspired air. Topical corticosteroids (eg, mometasone 2 sprays bid) can be of some benefit.

Septal Deviation and Perforation

Deviations of the nasal septum due to developmental abnormalities or trauma are common but often are asymptomatic and require no treatment. Symptomatic septal deviation causes nasal obstruction and predisposes the patient to sinusitis (particularly if the deviation obstructs the ostium of a paranasal sinus) and to epistaxis due to drying air currents. Other symptoms may include facial pain, headaches, and noisy night breathing. Septal deviation is usually evident on examination, although a flashlight and examination of the anterior nasal passage may not be sufficient. Treatment consists of septoplasty (septal reconstruction).

Septal ulcers and perforations may result from nasal surgery; repeated trauma, such as chronic nose picking; cosmetic piercing; toxic exposures (eg, acids, chromium, phosphorus, copper vapor); chronic cocaine use; chronic nasal spray use (including corticosteroids and OTC phenylephrine or oxymetazoline sprays); transnasal O_2 use; or diseases such as TB, syphilis, leprosy, SLE, and Wegener's granulomatosis. Crusting around the margins and repeated epistaxis, which can be severe, may result. Small perforations may whistle. Anterior rhinoscopy or fiberoptic endoscopy can be used to view septal perforations. Topical bacitracin or mupirocin ointment reduces crusting, as may saline nasal spray. Symptomatic septal perforations are occasionally repaired with buccal or septal mucous membrane flaps; closing the perforation with a silicone septal button is a reliable option.

Sinusitis

Sinusitis is inflammation of the paranasal sinuses due to viral, bacterial, or fungal infections or allergic reactions. Symptoms include nasal obstruction and congestion, purulent rhinorrhea,

cough, facial pain, malaise, and sometimes fever. Treatment is with antibiotics, such as amoxicillin, penicillin, erythromycin, or trimethoprim/sulfamethoxazole, given for 12 to 14 days for acute sinusitis and for up to 6 wk for chronic sinusitis. Decongestants and application of heat and humidity may help relieve symptoms and improve sinus drainage. Recurrent sinusitis may require surgery to improve sinus drainage.

Sinusitis may be classified as acute (completely resolved in < 30 days); subacute (completely resolved in 30 to 90 days); recurrent (multiple discrete acute episodes, each completely resolved in < 30 days but recurring in cycles, with at least 10 days between complete resolution of symptoms and initiation of a new episode); and chronic (lasting > 90 days).

Etiology

Acute sinusitis is usually precipitated by viral URI, followed by secondary bacterial colonization with streptococci, pneumococci, *Haemophilus influenzae*, *Moraxella catarrhalis*, or staphylococci. In a URI, the swollen nasal mucous membrane obstructs the ostium of a paranasal sinus, and the O_2 in the sinus is absorbed into the blood vessels of the mucous membrane. The resulting relative negative pressure in the sinus (vacuum sinusitis) is painful. If the vacuum is maintained, a transudate from the mucous membrane develops and fills the sinus; the transudate serves as a medium for bacteria that enter the sinus through the ostium or through a spreading cellulitis or thrombophlebitis in the lamina propria of the mucous membrane. An outpouring of serum and leukocytes to combat the infection results, and painful positive pressure develops in the obstructed sinus. The mucous membrane becomes hyperemic and edematous.

Chronic sinusitis may be exacerbated by gram-negative bacilli or anaerobic micro-organisms. In a few cases, chronic maxillary sinusitis is secondary to dental infection or exposure to environmental pollution. Fungal infections (*Aspergillus*, *Sporothrix*, *Pseudallescheria*) tend to strike the immunocompromised patient, whereas hospital-acquired infections complicate cystic fibrosis, nasogastric and nasotracheal intubation, and debilitated patients. Typical organisms include *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Enterobacter*.

Allergic fungal sinusitis is characterized by diffuse nasal congestion, markedly viscid nasal secretions, and, often, nasal polyps. It is an allergic response to the presence of topical fungi, often *Aspergillus*, and is not caused by an invasive infection.

Symptoms and Signs

Acute and chronic sinusitis cause similar symptoms and signs, including purulent rhinorrhea, pressure and pain in the face, nasal congestion and obstruction, hyposmia, halitosis, and productive cough (especially at night). Often the pain is more severe in acute sinusitis. The area over the affected sinus may be tender, swollen, and erythematous. Maxillary sinusitis causes pain in the maxillary area, toothache, and frontal headache. Frontal sinusitis causes pain in the frontal area and frontal headache. Ethmoid sinusitis causes pain behind and between the eyes, frontal headache often described as splitting, periorbital cellulitis, and tearing. Pain caused by sphenoid sinusitis is less well localized and is referred to the frontal or occipital area. Malaise may be present. Fever and chills suggest an extension of the infection beyond the sinuses.

The nasal mucous membrane is red and turgescent; yellow or green purulent rhinorrhea may be present. Seropurulent or mucopurulent exudate may be seen in the middle meatus with maxillary, anterior ethmoid, or frontal sinusitis and in the area medial to the middle turbinate with posterior ethmoid or sphenoid sinusitis.

Diagnosis

• Clinical evaluation

• Sometimes CT

Sinus infections are usually diagnosed clinically. Absence or dullness of light on transillumination may

suggest fluid-filled maxillary or frontal sinuses. In acute and chronic sinusitis, the swollen mucous membranes and retained exudate cause the affected sinus to appear opaque on 4-view x-rays. Plain x-rays are not as valuable as CT, which provides better definition of the extent and degree of sinusitis. X-rays of the apices of the teeth may be required in chronic maxillary sinusitis to exclude a periapical abscess. When questions persist (eg, regarding intracranial extension, treatment failure, or hospital-acquired causes of sinusitis), culture and sensitivity tests can be done on sinus secretions obtained through endoscopy or sinus puncture and aspiration.

Sinusitis in children is suspected when purulent rhinorrhea persists for > 10 days along with fatigue and cough. Fever is uncommon. Local facial pain or discomfort may be present. Nasal examination discloses purulent drainage; CT is confirmatory. CT is of limited cuts in the coronal projection to limit radiation exposure.

Treatment

• Local measures to enhance drainage (eg, steam, topical vasoconstrictors)

• Antibiotics (eg, amoxicillin, erythromycin, trimethoprim/sulfamethoxazole)

In acute sinusitis, improved drainage and control of infection are the aims of therapy. Steam inhalation; hot, wet towels over the affected sinuses; and hot beverages alleviate nasal vasoconstriction and promote drainage. Topical vasoconstrictors, such as phenylephrine 0.25% spray q 3 h, are effective but should be used for a maximum of 5 days or for a repeating cycle of 3 days on and 3 days off until the sinusitis is resolved. Systemic vasoconstrictors, such as pseudoephedrine 30 mg po (for adults) q 4 to 6 h, are less effective.

In acute and chronic sinusitis, antibiotics are given for at least 10 days and often for 14 days. In acute sinusitis, amoxicillin 500 mg po q 8 h with or without clavulanate is primary therapy. Erythromycin 250 mg po q 6 h or trimethoprim/sulfamethoxazole 80/400 mg q 6 h can be given to patients allergic to penicillin. Second-line therapy includes cefuroxime 500 mg q 12 h or moxifloxacin 400 mg once/day. For children, similar antibiotics are used, adjusted for the child's weight. Fluoroquinolones, however, are not used in children because of concerns of premature epiphyseal growth plate closure.

In exacerbations of chronic sinusitis in children or adults, a broad-spectrum antibiotic, such as amoxicillin/clavulanate 875 mg po q 12 h (12.5 to 25 mg/kg q 12 h in children), cefuroxime, or, in adults, moxifloxacin, is used. In chronic sinusitis, prolonged antibiotic therapy for 4 to 6 wk often brings complete resolution. The sensitivities of pathogens isolated from the sinus exudate and the patient's response guide subsequent therapy.

Sinusitis unresponsive to antibiotic therapy may require surgery (maxillary sinusotomy, ethmoidectomy, or sphenoid sinusotomy) to improve ventilation and drainage and to remove inspissated mucopurulent material, epithelial debris, and hypertrophic mucous membrane. These procedures usually are done intranasally with the aid of an endoscope. Chronic frontal sinusitis may be managed either with osteoplastic obliteration of the frontal sinuses or endoscopically in selected patients. The use of intraoperative computer-aided surgery to localize disease and prevent injury to surrounding contiguous structures (such as the eye and brain) has become common.

Sinusitis in Immunocompromised Patients

Aggressive and even fatal fungal or bacterial sinusitis can occur in patients who are immunocompromised because of poorly controlled diabetes, neutropenia, or HIV infection.

Mucormycosis: Mucormycosis (phycomycosis)—a mycosis due to fungi of the order Mucorales, including species of *Mucor*, *Absidia*, and *Rhizopus*—may develop in patients with poorly controlled diabetes. It is characterized by black, devitalized tissue in the nasal cavity and neurologic signs secondary to retrograde thromboarteritis in the carotid arterial system. Diagnosis is based on histopathologic demonstration of mycelia in the avascularized tissue. Treatment requires control of the underlying condition (such as reversal of ketoacidosis in diabetes) and IV amphotericin B therapy. Prompt

biopsy of intranasal tissue for histology and culture is warranted.

Aspergillosis and candidiasis: *Aspergillus* and *Candida* spp may infect the paranasal sinuses of patients who are immunocompromised secondary to therapy with cytotoxic drugs or to immunosuppressive diseases, such as leukemia, lymphoma, multiple myeloma, and AIDS. These infections can appear as polypoid tissue in the nose as well as thickened mucosa; tissue is required for diagnosis. Aggressive paranasal sinus surgery and IV amphotericin B therapy are used to control these often-fatal infections.

Chapter 54. Laryngeal Disorders

Introduction

The larynx contains the vocal cords and serves as the opening to the tracheobronchial tree. Laryngeal disorders include various benign and malignant tumors, contact ulcers, granulomas, laryngitis, laryngoceles, spasmodic dysphonia, vocal cord paralysis, and vocal cord polyps and nodules. For acute laryngotracheobronchitis, see Croup on p. 2879.

Laryngeal cancer is discussed on p. 489.

Most laryngeal disorders cause dysphonia, which is impairment of the voice (see Sidebar 54-1). A persistent change in the voice (eg, > 3 wk) requires visualization of the vocal cords, including their mobility. Although the voice changes with advancing age, becoming breathy and aperiodic, acute or prominent changes in the elderly should not be presumed to result from aging, and evaluation is required.

The voice should be assessed and recorded, particularly if surgical procedures are planned. Examination of the larynx includes external inspection and palpation of the neck and internal visualization of the epiglottis, false cords, true cords, arytenoids, pyriform sinuses, and subglottic region below the cords. Internal visualization is accomplished by either indirect mirror examination (see Fig. 54-1) or direct flexible fiberoptic laryngoscopy in an outpatient setting with a topical anesthetic. Rigid laryngoscopy with the patient under general anesthesia allows for biopsy when necessary or assessment of passive mobility of the vocal cords when immobilized by either paralysis or fixation.

Sidebar 54-1 The Professional Voice

People who use their voice professionally for public speaking and singing often experience voice disorders manifesting as hoarseness or breathiness, lowered vocal pitch, vocal fatigue, nonproductive cough, persistent throat clearing, and/or throat ache. These symptoms often have benign causes, such as vocal nodules, vocal fold edema, polyps, or granulomas. Such disorders are usually caused by vocal fold hyperfunction (excessive laryngeal muscular tension when speaking) and possibly laryngopharyngeal reflux.

Treatment in most cases includes the following:

- Voice evaluation by a speech pathologist or experienced physician, including, when available, use of a computer-assisted program to assess pitch and intensity and to determine parameters of vocal acoustics
- Behavioral treatment (decreasing musculoskeletal laryngeal tension when speaking) using the same computer program for visual and auditory biofeedback
- A vocal hygiene program to eliminate vocally abusive behaviors, such as excessive loudness, long duration, vocal tension, and habitual throat clearing
- An antireflux regimen, when appropriate
- Adequate hydration to promote an adequate glottal mucosal wave
- Diet modification before vocal performances, which may include avoidance of dairy products, caffeine, and ambient tobacco smoke and other inhaled irritants

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Benign Tumors

Benign laryngeal tumors include juvenile papillomas hemangiomas, fibromas, chondromas, myxomas, and neurofibromas. They may appear in any part of the larynx. Symptoms include hoarseness, breathy voice,

dyspnea, aspiration, dysphagia, pain, otalgia (pain referred to the ear), and hemoptysis. Diagnosis is based on direct or indirect visualization of the larynx, supplemented by CT. Removal restores the voice, the functional integrity of the laryngeal sphincter, and the airway. Smaller lesions may be excised endoscopically by using a CO_2 laser and general anesthesia. Larger lesions extending beyond the laryngeal framework often require pharyngotomy or laryngofissure.

Cancerous tumors are discussed in Ch. 55.

Contact Ulcers

Contact ulcers are unilateral or bilateral erosions of the mucous membrane over the vocal process of the arytenoid cartilage.

Contact ulcers are usually caused by voice abuse in the form of repeated sharp glottal attacks (abrupt loudness at the onset of phonation), often experienced by singers. They may also occur after endotracheal intubation if an oversized tube erodes the mucosa overlying the cartilaginous vocal processes. Gastroesophageal reflux may also cause or aggravate contact ulcers. Symptoms include varying degrees of hoarseness and mild pain with phonation and swallowing. Biopsy to exclude carcinoma or TB is important. Prolonged ulceration leads to nonspecific granulomas that also cause varying degrees of hoarseness.

Treatment consists of ≥ 6 wk of voice rest. Patients must recognize the limitations of their voice and learn to adjust their postrecovery vocal activities to avoid recurrence. Granulomas tend to recur after surgical removal. Risk of recurrence is reduced through vigorous treatment of gastroesophageal reflux (see p. 125). Suppression of bacterial flora by antibiotics during postoperative healing is also recommended.

Laryngitis

Laryngitis is inflammation of the larynx, usually the result of a virus or overuse. The result is acute change in the voice, with decreased volume and hoarseness. Diagnosis is based on clinical findings. Laryngoscopy is required for symptoms persisting > 3 wk. Viral laryngitis is self-limited. Other infectious or irritating causes may require specific treatment.

The most common cause of acute laryngitis is a viral URI. Coughing-induced laryngitis may also occur in bronchitis, pneumonia, influenza, pertussis, measles, and diphtheria.

[**Fig. 54-1.** Laryngeal disorders.]

Excessive use of the voice (especially with loud speaking or singing), allergic reactions, gastroesophageal reflux, bulimia, or inhalation of irritating substances (eg, cigarette smoke or certain aerosolized drugs) can cause acute or chronic laryngitis. Bacterial laryngitis is extremely rare. Smoking can cause Reinke's edema, which is a watery swelling of both vocal cords.

Symptoms and Signs

An unnatural change of voice is usually the most prominent symptom. Volume is typically greatly decreased; some patients have aphonia. Hoarseness, a sensation of tickling, rawness, and a constant urge to clear the throat may occur. Symptoms vary with the severity of the inflammation. Fever, malaise, dysphagia, and throat pain may occur in more severe infections. Laryngeal edema, although rare, may cause dyspnea.

Diagnosis

• Clinical evaluation

• Sometimes direct or indirect laryngoscopy

Diagnosis is based on symptoms. Indirect or direct flexible laryngoscopy is recommended for symptoms

persisting > 3 wk; findings in laryngitis include mild to marked erythema of the mucous membrane, which may also be edematous. With reflux, there is swelling of the inner lining of the larynx and redness of the vocal cords that extends above and below the edges of the back part of the cords. If a pseudomembrane is present, diphtheria is suspected.

Treatment

• Symptomatic treatment (eg, cough suppressants, voice rest, steam inhalations)

No specific treatment is available for viral laryngitis. Cough suppressants, voice rest, and steam inhalations relieve symptoms and promote resolution of acute laryngitis. Smoking cessation and treatment of acute or chronic bronchitis may relieve laryngitis. Depending on the presumed cause, specific treatments to control gastroesophageal reflux, bulimia, or drug-induced laryngitis may be beneficial.

Laryngoceles

Laryngoceles are evaginations of the mucous membrane of the laryngeal ventricle.

Internal laryngoceles displace and enlarge the false vocal cords, resulting in hoarseness and airway obstruction. External laryngoceles extend through the thyrohyoid membrane, causing a mass in the neck. Laryngoceles tend to occur in musicians who play wind instruments. Laryngoceles are filled with air and can be expanded by the Valsalva maneuver. They appear on CT as smooth, ovoid, low-density masses. Laryngoceles may become infected (laryngopyocele) or filled with mucoid fluid. Treatment is excision.

Spasmodic Dysphonia

Spasmodic dysphonia (vocal cord spasms) is intermittent spasm of laryngeal muscles that causes an abnormal voice.

Cause is unknown. Patients often describe the onset of symptoms following a URI, a period of excessive voice use, or occupational or emotional stress. As a localized form of movement disorder, spasmodic dysphonia has an onset between ages 30 and 50 yr, and about 60% of patients are women.

In the adductor type of spasmodic dysphonia, patients attempt to speak through the spasmodic closure with a voice that sounds squeezed, effortful, or strained. These spasmodic episodes usually occur when vowel sounds are being formed, particularly at the beginning of words. The less common abductor form results in sudden interruptions of sound caused by momentary abduction of the vocal cords accompanied by audible escape of air during connected speech.

Surgery has been more successful than other approaches for adductor spasmodic dysphonia. The use of botulinum toxin injection has restored a normal voice in 70% of patients for up to 3 mo. Because the effect is temporary, injections may be repeated. There is no known temporary alleviation of the abductor form of this disorder.

Vocal Cord Paralysis

Vocal cord paralysis has numerous causes and can affect speaking, breathing, and swallowing. The left vocal cord is affected twice as often as the right, and females are affected more often than males (3:2). Diagnosis is based on direct visualization. An extensive assessment may be necessary to determine the cause. Several direct surgical approaches are available if treating the cause is not curative.

Vocal cord paralysis may result from lesions at the nucleus ambiguus, its supranuclear tracts, the main trunk of the vagus, or the recurrent laryngeal nerves.

Paralysis is usually unilateral. About one third of unilateral vocal cord paralyses are neoplastic in origin, one third are traumatic, and one third are idiopathic. Intracranial tumors, vascular accidents, and demyelinating diseases cause nucleus ambiguus paralysis. Tumors at the base of the skull and trauma to

the neck cause vagus paralysis. Recurrent laryngeal nerve paralysis is caused by neck or thoracic lesions (eg, aortic aneurysm; mitral stenosis; mediastinal tuberculous adenitis; tumors of the thyroid gland, esophagus, lung, or mediastinal structures), trauma, thyroidectomy, neurotoxins (eg, lead, arsenic, mercury), neurotoxic infections (eg, diphtheria), cervical spine injury or surgery, Lyme disease, and viral illness. Viral neuronitis probably accounts for most idiopathic cases.

Bilateral vocal cord paralysis is a life-threatening disorder caused by thyroid and cervical surgery, tracheal intubation, trauma, and neurodegenerative and neuromuscular diseases.

Symptoms and Signs

Vocal cord paralysis results in loss of vocal cord abduction and adduction. Paralysis may affect phonation, respiration, and deglutition, and food and fluids may be aspirated into the trachea. The paralyzed cord generally lies 2 to 3 mm lateral to the midline. In recurrent laryngeal nerve paralysis, the cord may move with phonation but not with inspiration. In unilateral paralysis, the voice may be hoarse and breathy, but the airway is usually not obstructed because the normal cord abducts sufficiently. In bilateral paralysis, both cords generally lie within 2 to 3 mm of the midline, and the voice is of good quality but of limited intensity. The airway, however, is inadequate, resulting in stridor and dyspnea with moderate exertion as each cord is drawn to the midline glottis by an inspiratory Bernoulli effect. Aspiration is also a danger.

Diagnosis

• Laryngoscopy

• Various tests for possible causes

Diagnosis is based on laryngoscopy. The cause must always be sought. Evaluation is guided by abnormalities identified on history and physical examination. During the history, the physician asks about all possible causes of peripheral neuropathy, including chronic heavy metal exposure (arsenic, lead, mercury), drug effects from phenytoin and vincristine, and history of connective tissue disorders, Lyme disease, sarcoidosis, diabetes, and alcoholism. Further evaluation may include enhanced CT or MRI of the head, neck, and chest; thyroid scan; barium swallow or bronchoscopy; and esophagoscopy. Cricoarytenoid arthritis, which may cause fixation of the cricoarytenoid joint, must be differentiated from a neuromuscular etiology. Fixation is best documented by absence of passive mobility during rigid laryngoscopy under general anesthesia. Cricoarytenoid arthritis may complicate such conditions as RA, external blunt trauma, and prolonged endotracheal intubation.

Treatment

• For unilateral paralysis, surgical procedures to move cords closer together

• For bilateral paralysis, surgical procedures and measures to maintain airway

In unilateral paralysis, treatment is directed at improving voice quality through augmentation, medialization, or reinnervation.

Augmentation involves injecting a paste of plasticized particles, collagen, micronized dermis, or autologous fat into the paralyzed cord, bringing the cords closer together to improve the voice and prevent aspiration.

Medialization is shifting the vocal cord toward the midline by inserting an adjustable spacer laterally to the affected cord. This can be done with a local anesthetic, allowing the position of the spacer to be "tuned" to the patient's voice. Unlike augmentation with plasticized particles, which permanently fixes the cord, the spacer is both adjustable and removable.

Reinnervation has only rarely been successful.

In bilateral paralysis, an adequate airway must be reestablished. Tracheotomy may be needed permanently or temporarily during a URI. An arytenoidectomy with lateralization of the true vocal cord opens the glottis and improves the airway but may adversely affect voice quality. Posterior laser cordectomy opens the posterior glottis and may be preferred to endoscopic or open arytenoidectomy. Successful laser establishment of a posterior glottic airway usually obviates the need for long-term tracheotomy while preserving a serviceable voice quality.

Vocal Cord Polyps and Nodules

Acute trauma or chronic irritation causes changes in the vocal cords that can lead to polyps or nodules. Both cause hoarseness and a breathy voice. Persistence of these symptoms for > 3 wk dictates visualization of the vocal cords. Diagnosis is based on laryngoscopy and on biopsy to rule out cancer. Surgical removal restores the voice, and removal of the irritating source prevents recurrence.

Etiology

Polyps and nodules result from injury to the lamina propria of the true vocal cords. Polyps may occur at the mid third of the membranous cords and are more often unilateral. They frequently result from an initiating acute phonatory injury. Nodules usually occur bilaterally at the junction of the anterior and middle third of the cords. Their main cause is chronic voice abuse—yelling, shouting, singing loudly, or using an unnaturally low frequency. Polyps may have several other causes, including gastric reflux, untreated hypothyroid states, chronic laryngeal allergic reactions, or chronic inhalation of irritants, such as industrial fumes or cigarette smoke. Polyps tend to be larger and more protuberant than nodules and often have a dominant surface blood vessel.

Symptoms and Signs

Both result in slowly developing hoarseness and a breathy voice.

Diagnosis

• Laryngoscopy

• Sometimes biopsy

Diagnosis is based on direct or indirect visualization of the larynx with a mirror or laryngoscope. Biopsy of discrete lesions to exclude carcinoma is done by microlaryngoscopy.

Treatment

• Avoidance of cause

• For polyps, usually surgical removal

Correction of the underlying voice abuse cures most nodules and prevents recurrence. Removal of the offending irritants allows healing, and voice therapy with a speech therapist reduces the trauma to the vocal cords caused by improper singing or protracted loud speaking. Nodules usually regress with voice therapy alone.

Most polyps must be surgically removed to restore a normal voice. Cold-knife microsurgical excision during direct microlaryngoscopy is preferable to laser excision, which is more likely to cause collateral thermal injury if improperly applied.

In microlaryngoscopy, an operating microscope is used to examine, biopsy, and operate on the larynx. Images can be recorded on video as well. The patient is anesthetized, and the airway is secured by high-pressure jet ventilation through the laryngoscope, endotracheal intubation, or, for an inadequate upper airway, tracheotomy. Because the microscope allows observation with magnification, tissue can be

removed precisely and accurately, minimizing damage (possibly permanent) to the vocal mechanism. Laser surgery can be done through the optical system of the microscope to allow for precise cuts. Microlaryngoscopy is preferred for almost all laryngeal biopsies, for procedures involving benign tumors, and for many forms of phonosurgery.

Chapter 55. Tumors of the Head and Neck

Introduction

The most common noncutaneous tumor of the head and neck is squamous cell carcinoma of the larynx, followed by squamous cell carcinomas of the tongue, palatine tonsil, and floor of the mouth. Less common are tumors of the salivary glands, jaw, nose and paranasal sinuses, and ear. Tumors of the thyroid gland, eye, and skin are discussed elsewhere in THE MANUAL.

Excluding the skin and thyroid gland, > 90% of head and neck cancers are squamous cell (epidermoid) carcinomas, and 5% are melanomas, lymphomas, and sarcomas. Patients with sarcomas or carcinomas of the salivary glands or paranasal sinuses are often younger than patients with squamous cell carcinoma, who are more commonly in their mid-50s and older.

Etiology

The vast majority of patients, 85% or more, with cancer of the head and neck have a history of alcohol use, smoking, or both. Other suspected causes include use of snuff or chewing tobacco, sunlight exposure, previous x-rays of the head and neck, certain viral infections, ill-fitting dental appliances, chronic candidiasis, and poor oral hygiene. In India, oral cancer is extremely common, probably because of chewing betel quid (a mixture of substances, also called paan). Long-term exposure to sunlight and the use of tobacco products are the primary causes of squamous cell carcinoma of the lower lip.

Patients who in the past were treated with radiation for acne, excess facial hair, enlarged thymus, or hypertrophic tonsils and adenoids are predisposed to thyroid and salivary gland cancers and benign salivary tumors.

Epstein-Barr virus plays a role in the pathogenesis of nasopharyngeal cancer, and serum measures of certain Epstein-Barr virus proteins may be biomarkers of recurrence. Human papillomavirus seems to be associated with head and neck squamous cell carcinoma, particularly oropharyngeal cancer. The mechanism for viral-mediated tumor genesis may be distinct from tobacco-related pathways and seem to have a different, better, prognosis.

Symptoms and Signs

Most head and neck cancers first manifest as an asymptomatic neck mass, painful mucosal ulceration, or visible mucosal lesion (eg, leukoplakia, erythroplakia). Subsequent symptoms depend on location and extent of the tumor and include pain, paresthesia, nerve palsies, trismus, and halitosis. Otalgia is an often overlooked symptom usually representing referred pain from the primary tumor. Weight loss caused by perturbed eating and odynophagia is also common.

Diagnosis

• Clinical evaluation

• Biopsy

• Imaging tests and endoscopy to evaluate extent of disease

Routine physical examination (including a thorough oral examination) is the best way to detect cancers early before they become symptomatic. Commercially available brush biopsy kits help screen for oral cancers. Any head and neck symptom (eg, sore throat, hoarseness, otalgia) lasting > 2 to 3 wk should prompt referral to a head and neck specialist.

Definitive diagnosis usually requires a biopsy. Additional important information is obtained from a combination of imaging tests (eg, CT, MRI, PET/CT), endoscopy, and fine-needle aspiration of any neck mass.

Staging

Head and neck cancers may remain localized for months to years. Local tissue invasion eventually is followed by metastasis to regional lymph nodes, related in large part to tumor size and extent, and reduces overall survival by nearly half. Distant metastases tend to occur late, usually in patients with advanced tumor and nodal stages. Metastases occur more commonly among immunocompromised patients. Common sites of distant metastases are the lungs, liver, bone, and brain.

Head and neck cancers are staged (see Table 55-1) according to size and site of the primary tumor (T), number and size of metastases to the cervical lymph nodes (N), and evidence of distant metastases (M). Staging usually requires imaging with CT, MRI, or both, and often PET.

Prognosis

Prognosis is favorable if diagnosis is early and treatment is timely and appropriate. In general, the more poorly differentiated the cancer, the greater the chance of regional and distant metastases. The presence of regional nodal spread reduces overall survival by nearly half. Distant metastasis greatly reduces survival, having only rare cures. Local invasion, a criterion for advanced T stage, with invasion of muscle, bone, or cartilage, also significantly decreases cure rate. Perineural spread, as evidenced by pain, paralysis, or numbness, indicates a highly aggressive tumor, is associated with nodal metastasis, and has a less favorable prognosis than a similar lesion without perineural invasion.

With appropriate treatment, 5-yr survival can be as high as 90% for stage I, 75 to 80% for stage II, 45 to 75% for stage III, and up to 40% for stage IV. The survival rates vary greatly depending on the primary site. Stage I laryngeal cancers have an excellent survival rate when compared to other sites.

Treatment

• Surgery, radiation therapy, or both

• Sometimes chemotherapy

Many stage I tumors, regardless of location, respond similarly to surgery and to radiation therapy, allowing other factors (eg, patient preference) to determine choice of therapy. Thus, the treating physician should carefully review risks and benefits with the patient. However, at certain locations, there is clear superiority of one modality over another. For

[**Table 55-1.** Staging of Head and Neck Cancer]

example, surgery is the better treatment for early-stage disease involving the oral cavity. In select head and neck cancers, endoscopic surgery has cure rates similar to those of open surgery or radiation, and morbidity is significantly less. However, many physicians still recommend radiation for early-stage laryngeal cancer.

If radiation therapy is chosen for primary therapy, it is delivered to the primary site and sometimes bilaterally to the cervical lymph nodes. The treatment of lymphatics, whether by radiation or surgery, is determined by the primary site, histologic criteria, and risk of nodal disease.

Advanced-stage disease (stages III and IV) often requires multimodality treatment, incorporating some combination of chemotherapy, radiation therapy, and surgery. Bone or cartilage invasion requires surgical resection of the primary site and usually regional lymph nodes because of the high risk of nodal spread. If the primary site is treated surgically, then postoperative radiation to the cervical lymph nodes is delivered if there are high-risk features, such as multiple lymph nodes with cancer or extracapsular extension. Postoperative radiation usually is preferred over preoperative radiation, because radiated tissues heal poorly. Recent studies have shown that adding chemotherapy to adjuvant radiation therapy to the neck improves regional control of the cancer and improves survival. There are significant risks to this approach, so the decision to add chemotherapy should be carefully considered.

Advanced squamous cell carcinoma without bony invasion often is treated with concomitant chemotherapy and radiation therapy. Although advocated as organ-sparing, combining chemotherapy with radiation therapy doubles the rate of acute toxicities, particularly severe dysphagia. Radiation may be used alone for debilitated patients with advanced disease who cannot tolerate the sequelae of chemotherapy and are too high a risk for general anesthesia.

Primary chemotherapy is reserved for chemosensitive tumors, such as Burkitt's lymphoma, or for patients who have widespread metastases (eg, hepatic or pulmonary involvement). Several drugs—cisplatin, fluorouracil, bleomycin, and methotrexate—provide palliation for pain and shrink the tumor in patients who cannot be treated with other methods. Response may be good initially but is not durable, and the cancer will return.

Tumor recurrence: Managing recurrent tumors after therapy is complex and has potential complications. A palpable mass or ulcerated lesion with edema or pain at the primary site after therapy strongly suggests a persistent tumor. Such patients require CT (with thin cuts) or MRI. For local recurrence after surgical treatment, all scar planes and reconstructive flaps are excised along with residual cancer. Radiation therapy, chemotherapy, or both may be done but have limited effectiveness. Patients with recurrence after radiation therapy should not receive additional radiation and are best treated with surgery.

Symptom control: Pain is a common symptom in patients with head and neck cancer and must be adequately addressed. Palliative surgery or radiation may temporarily alleviate pain, and in 30 to 50% of patients, chemotherapy can produce improvement that lasts a mean of 3 mo. A stepwise approach to pain management, as recommended by the WHO, is critical to controlling pain. Severe pain is best managed in association with a pain and palliative care specialist.

Pain, difficulty eating, choking on secretions, and other problems make adequate symptomatic treatment essential. Patient directives regarding such care should be clarified early (see p. 3471).

Adverse effects of treatment: All cancer treatments have potential complications and expected sequelae. Because many treatments have similar cure rates, the choice of modality is based largely on real, or perceived, differences in sequelae.

Although it is commonly thought that surgery requires rehabilitation for swallowing and speaking, many procedures do not require such rehabilitation. Increasingly complex reconstructive procedures and techniques, including prostheses, grafts, regional pedicle flaps, and complex free flaps, can restore function and appearance often to near normal.

Toxic effects of chemotherapy include malaise, severe nausea and vomiting, mucositis, transient hair loss, gastroenteritis, hematopoietic and immune suppression, and infection.

Therapeutic radiation for head and neck cancers has several adverse effects. The function of any salivary gland within the beam is permanently destroyed by a dose of about 40 Gy, resulting in xerostomia, which markedly increases the risk of dental caries. Newer radiation techniques, such as intensity-modulated radiation therapy, can minimize or eliminate toxic doses to the parotid glands in certain patients. Radioprotectant drugs (eg, amifostine) also can help protect salivary function. In addition, the blood supply of bone, particularly in the mandible, is compromised by doses of > 60 Gy, and osteoradionecrosis may occur (see also p. 505). In this condition, tooth extraction sites break down, sloughing bone and soft tissue. Therefore, any needed dental treatment, including scaling, fillings, and extractions, should be done before radiation therapy. Any teeth in poor condition that cannot be rehabilitated should be extracted. Radiation therapy may also cause oral mucositis and dermatitis in the overlying skin, which may result in dermal fibrosis. Loss of taste (ageusia) and impaired smell (dysosmia) often occur but are usually transient.

Prevention

Removing risk factors is critical, and all patients should cease tobacco use and limit alcohol consumption. Removing risk factors also helps prevent disease recurrence in those treated for cancer. A new primary

cancer develops in about 5% of patients/yr (to a maximum risk of about 20%); risk is lower in those who stop.

Cancer of the lower lip may be prevented by sunscreen use and tobacco cessation. Because 60% of head and neck cancers are well advanced (stage III or IV) at the time of diagnosis, the most promising strategy for reducing morbidity and mortality is diligent routine examination of the oral cavity.

Jaw Tumors

Numerous tumor types, both benign and malignant, originate in the jaw. Symptoms are swelling, pain, tenderness, and unexplained tooth mobility; some tumors are discovered on routine dental x-rays, whereas others are found on routine examinations of the oral cavity and teeth. Treatment depends on location and tumor type. Benign tumors may be observed and may not need surgical excision, although most tumors require resection with possible reconstruction.

If not initially detected on x-ray, jaw tumors are diagnosed clinically because their growth causes swelling of the face, palate, or alveolar ridge (the part of the jaw supporting the teeth). They can also cause bone tenderness and severe pain.

Bony outgrowths (torus palatinus, torus mandibularis) may develop on the palate or mandible. These are common growths and may prompt concerns about cancer, although they are benign and of concern only if they interfere with dental care or function of the submandibular gland. When on the palate, they are in the midline and have intact, smooth mucosa. Multiple osteomas seen on dental x-ray may suggest Gardner's syndrome.

The most common tumor of the mandible and maxilla is squamous cell carcinoma invading the bone through dental sockets. These can involve any portion of the intraoral mandible or maxilla.

Ameloblastoma, the most common epithelial odontogenic tumor, usually arises in the posterior mandible. It is slowly invasive and rarely metastatic. On x-ray, it typically appears as multiloculated or soap-bubble radiolucency. Treatment is wide surgical excision and reconstruction if appropriate.

Odontoma, the most common odontogenic tumor, affects the dental follicle or the dental tissues and usually appears in the mandibles of young people. Odontomas include fibrous odontomas and cementomas. A clinically absent molar tooth suggests a composite odontoma. Typically, no treatment is indicated. These tumors may be excised when the diagnosis is in doubt.

Osteosarcoma, giant cell tumor, Ewing's tumor, multiple myeloma, and metastatic tumors may affect the jaw. Treatment is the same as for those tumors in other bony sites.

Laryngeal Cancer

Ninety percent of laryngeal cancer is squamous cell carcinoma. Smoking, alcohol abuse, lower socioeconomic status, and being male and > 60 yr increase risk. Early diagnosis is common with vocal cord tumors because vocal, swallowing, or respiratory symptoms develop early. However, supraglottic tumors (above the vocal cords) and subglottic tumors (below the vocal cords) are often very large and at an advanced stage when diagnosed because they are asymptomatic until obstructive symptoms develop. Diagnosis is based on laryngoscopy and biopsy. Treatment of early-stage tumors is with surgery or radiation. Advanced-stage tumors are most often treated with chemotherapy and radiation therapy. Surgery is reserved for salvage treatment or lesions with significant extralaryngeal extension or cartilage destruction. Reestablishment of speaking ability is needed if a total laryngectomy is done.

Squamous cell carcinoma is the most common cancer of the larynx. In the US, it is 4 times more common among men and is more common among those of lower socioeconomic status. Over 95% of patients are smokers; 15 pack-years of smoking increase the risk 30-fold. The incidence of larynx cancer is decreasing, particularly among men, most likely due to changes in smoking habits.

Sixty percent of patients present with localized disease alone; 25% present with local disease and regional nodal metastatic disease; and 15% present with advanced disease, distant metastases, or both. Distant metastases occur most frequently in the lungs and liver.

Common sites of origin are the true vocal cords (glottis) and the supraglottic larynx. The least common site is the subglottic larynx, where only 1% of primary laryngeal cancers originate. Verrucous carcinoma, a rare variant of squamous cell carcinoma, usually arises in the glottic area and has a better survival rate than standard squamous cell carcinoma.

Symptoms and Signs

Symptoms and signs differ based on the involved portion of the larynx. Hoarseness is common early in glottic cancers but is a late symptom for supraglottic and subglottic cancers. Supraglottic cancer is often asymptomatic until it manifests as a mass lesion (eg, with airway obstruction, dysphagia, otalgia, or a "hot potato" voice) or with weight loss. Such patients should be referred for indirect laryngoscopy without delay.

Diagnosis

• Laryngoscopy

• Operative endoscopy and biopsy

• Imaging tests for staging

All patients who have hoarseness for > 2 to 3 wk should have their larynx examined by a head and neck specialist. Any lesions discovered require further evaluation, usually with operative endoscopy and biopsy, with concomitant evaluation of the upper airway and GI tract for coexisting cancers. The incidence of a synchronous second primary tumor may be as high as 10%.

Patients with confirmed carcinoma typically have neck CT with contrast and a chest x-ray or chest CT. Most clinicians also do PET of the neck and chest at the time of diagnosis.

Treatment

• Early-stage: Surgery or radiation therapy

• Advanced: Radiation therapy and sometimes chemotherapy

For early-stage glottic carcinoma, laser excision, radiation therapy, or occasionally open laryngeal surgery results in a 5-yr survival rate of 85 to 95%. Endoscopic laser resection and radiation therapy usually preserve a normal voice and post-treatment function and have similar cure rates.

For advanced glottic carcinoma, defined by a lack of vocal cord mobility, thyroid cartilage invasion, or extension into the tongue, most patients are treated with chemotherapy and radiation therapy. Surgery (followed by radiation therapy) is reserved for salvage situations; most such cases require total laryngectomy, although endoscopic or open partial laryngectomy may sometimes be used. Extensive local invasion, however, usually requires an initial total laryngectomy rather than nonsurgical therapy.

Early supraglottic carcinoma can be effectively treated with radiation therapy or partial laryngectomy. Laser resection has shown considerable success on early-stage supraglottic squamous cell carcinomas and minimizes functional changes after surgery. If the carcinoma is more advanced but does not affect the true vocal cords, a supraglottic partial laryngectomy can be done to preserve the voice and glottic sphincter. If the true vocal cords also are affected, a supracricoid laryngectomy or a total laryngectomy is required if surgery is chosen. As with glottic carcinoma, most advanced-stage supraglottic cancers initially are treated with chemotherapy and radiation therapy.

Treatment of hypopharyngeal carcinomas is similar to that of laryngeal cancer. Early-stage lesions usually are treated with radiation alone, although endoscopic resection is an option. However, the majority of patients with hypopharyngeal cancer have advanced-stage disease, because of the silent nature of the disease and frequent regional lymphatic spread; such patients are treated with chemotherapy and radiation therapy primarily, with surgical salvage.

Rehabilitation: Rehabilitation may be required after either surgical or nonsurgical treatment. Significant swallowing problems are common after chemotherapy and radiation therapy and may require esophageal dilation, swallowing therapy, or, in severe cases, surgical replacement of the pharynx or gastrostomy tube feedings. Swallowing also is affected by surgery and may require swallowing therapy or dilation as well.

Speech, on the other hand, is more significantly affected by surgery. After total laryngectomy, the patient requires creation of a new voice by way of

• Esophageal speech

• A tracheoesophageal puncture

• An electrolarynx

In all 3 techniques, sound is articulated into speech by the pharynx, palate, tongue, teeth, and lips.

Esophageal speech involves taking air into the esophagus during inspiration and gradually eructating the air through the pharyngoesophageal junction to produce a sound.

A tracheoesophageal puncture involves placement of a one-way valve between the trachea and esophagus to facilitate phonation. This valve forces air into the esophagus during expiration to produce a sound. Patients receive physical rehabilitation, speech therapy, and appropriate training in the maintenance and use of this valve and must be cautioned against the possible aspiration of food, fluids, and secretions.

An electrolarynx is a battery-powered sound source that is held against the neck to produce sound. Although it carries a great deal of social stigma for many patients, it has the advantage of being functional immediately with little or no training.

Nasopharyngeal Cancer

Nasopharyngeal cancers are rare in the US but common in the South China Sea region. Symptoms develop late, including unilateral bloody nasal discharge, nasal obstruction, facial swelling, and numbness. Diagnosis is based on inspection and biopsy, with CT, MRI, or PET to evaluate extent. Treatment is with radiation, chemotherapy, and, rarely, surgery.

Squamous cell carcinoma is the most common malignant tumor of the nasopharynx. It can occur in any age group and is rare in North America. It is one of the most common cancers among people of Chinese, especially southern Chinese, and Southeast Asian ancestry, including Chinese immigrants to North America. Over several generations, the prevalence among Chinese-Americans gradually decreases to that among non-Chinese Americans, suggesting an environmental component to etiology. Dietary exposure to nitrites and salted fish also is thought to increase risk. Epstein-Barr virus is a significant risk factor, and there is hereditary predisposition. Other nasopharyngeal cancers include adenoid cystic and mucoepidermoid carcinomas, malignant mixed tumors, adenocarcinomas, lymphomas, fibrosarcomas, osteosarcomas, chondrosarcomas, and melanomas.

Symptoms and Signs

The first symptom is often nasal or eustachian tube obstruction causing hearing loss due to a middle ear effusion. Other symptoms include purulent bloody rhinorrhea, frank epistaxis, cranial nerve palsies, and cervical lymphadenopathy. Cranial nerve palsies most often involve the 6th, 4th, and 3rd cranial nerves due to their location in the cavernous sinus, in close proximity to the foramen lacerum, which is the most

common route of intracranial spread for these tumors. Because lymphatics of the nasopharynx communicate across the midline, bilateral metastases are common.

Diagnosis

• Nasopharyngeal endoscopy and biopsy

• Imaging tests for staging

Patients suspected of having nasopharyngeal cancer must undergo examination with a nasopharyngeal mirror or endoscope, and lesions are biopsied. Open cervical node biopsy should not be done as the initial procedure (see Neck Mass on p. 461), although a needle biopsy is acceptable and often recommended. Gadolinium-enhanced MRI (with fat suppression) of the head with attention to the nasopharynx and skull base is done; the skull base is involved in about 25% of patients. CT also is required to accurately assess skull base bony changes, which are less visible on MRI. A PET scan also commonly is done to assess the extent of disease as well as the cervical lymphatics.

Treatment

• Chemotherapy plus radiation therapy

Because of the location and extent of involvement, nasopharyngeal cancers often are not amenable to surgical resection. They are typically treated with chemotherapy and radiation therapy, which are often followed by adjuvant chemotherapy.

Recurrent tumors can be treated with another course of radiation, commonly with brachytherapy; radionecrosis of the skull base is a risk. An alternative to radiation is skull base resection.

Oral Squamous Cell Carcinoma

Oral squamous cell carcinoma affects about 30,000 Americans each year. Over 95% smoke, drink alcohol, or both. Early, curable lesions are rarely symptomatic; thus, preventing fatal disease requires early detection by screening. Treatment is with surgery, radiation, or both. The overall 5-yr survival rate (all sites and stages combined) is > 50%.

In the US, 3% of cancers in men and 2% in women are oral squamous cell carcinomas, most of which occur after age 50. Squamous cell carcinoma is the most common oral or pharyngeal cancer (and the most common at head and neck sites in general).

The chief risk factors for oral squamous cell carcinoma are smoking (especially > 2 packs/day) and alcohol use. Risk increases dramatically when alcohol use exceeds 6 oz of distilled liquor, 6 oz of wine, or 12 oz of beer/day. The combination of heavy smoking and alcohol abuse is estimated to raise the risk 100-fold in women and 38-fold in men. Squamous cell carcinoma of the tongue may also result from any chronic irritation, such as dental caries, overuse of mouthwash, chewing tobacco, or the use of betel quid. Oral human papillomavirus (HPV), typically acquired via oral-genital contact, may have a role in etiology.

About 40% of intraoral squamous cell carcinomas begin on the floor of the mouth or on the lateral and ventral surfaces of the tongue. About 38% of all oral squamous cell carcinomas occur on the lower lip; these are usually solar-related cancers on the external surface. About 11% begin in the palate and tonsillar area. Squamous cell carcinoma of the tonsil (an oropharyngeal cancer), 2nd in frequency only to carcinoma of the larynx among cancers of the upper respiratory tract, occurs predominantly in males.

Symptoms and Signs

Oral lesions are asymptomatic initially, highlighting the need for oral screening. Most dental professionals carefully examine the oral cavity and oropharynx during routine care and may do a brush biopsy of abnormal areas. The lesions may appear as areas of erythroplakia or leukoplakia and may be exophytic

or ulcerated. Cancers are often indurated and firm with a rolled border. Tonsillar carcinoma usually manifests as an asymmetric swelling and sore throat, with pain often radiating to the ipsilateral ear. A metastatic mass in the neck may be the first symptom, particularly in tonsillar cancer.

Diagnosis

• Biopsy

• Endoscopy to detect second primary cancer

• Chest x-ray and CT of head and neck

Biopsy of suspect areas is done. Direct laryngoscopy, bronchoscopy, and esophagoscopy are done to exclude a simultaneous second primary cancer. Head and neck CT usually is done. Chest x-ray is done; chest CT is done if an advanced stage is suspected or confirmed.

Prognosis

If carcinoma of the tongue is localized (no lymph node involvement), 5-yr survival is > 50%. For localized carcinoma of the floor of the mouth, 5-yr survival is 65%. Lymph node metastasis decreases survival rate by about 50%. Metastases reach the regional lymph nodes first and later the lungs.

For lower lip lesions, 5-yr survival is 90%, and metastases are rare. Carcinoma of the upper lip tends to be more aggressive and metastatic. For carcinoma of the palate and tonsillar area, 5-yr survival is 68% if patients are treated before lymph node involvement but only 17% after involvement. The prognosis for tonsillar carcinoma is often better stage for stage than that for oral cancers. Oropharyngeal cancer associated with HPV infection may have a better prognosis.

Treatment

• Surgery or radiation therapy

Surgery and radiation therapy are the treatments of choice. Regional or distant disease necessitates a more radical treatment approach.

For tongue lesions, surgery is usually the initial treatment, particularly for early-stage disease. Selective neck dissection is indicated if the risk of nodal disease exceeds 15 to 20%. Routine surgical reconstruction is the key to reducing postoperative oral disabilities; procedures range from local tissue flaps to free tissue transfers. Speech and swallowing therapy may be required after significant resections. Radiation therapy is an alternative treatment. Chemotherapy is not used routinely but is recommended on an individual basis; rare distant metastases are present in sites where chemotherapy may be of some palliative value (eg, lung, bone, heart, pericardium).

Treatment of squamous cell carcinoma of the lip is surgical excision with reconstruction to maximize postoperative function. When large areas of the lip exhibit premalignant change, the lip can be surgically shaved, or a laser can remove all affected mucosa. Thereafter, appropriate sunscreen application is recommended.

Treatment of tonsillar carcinoma usually consists of concomitant chemotherapy and radiation therapy. Another option includes radical resection of the tonsillar fossa, sometimes with partial mandibulectomy and neck dissection.

Otic Tumors

A number of malignant and benign otic tumors occur, usually manifesting with hearing loss. They may also manifest with dizziness, vertigo, or imbalance. These tumors are rare and can be difficult to diagnose.

Malignant otic tumors: Basal cell and squamous cell carcinomas may arise in the ear canal. Persistent inflammation caused by chronic otitis media may predispose to the development of squamous cell carcinoma. Extensive resection is indicated, followed by radiation therapy. En bloc resection of the ear canal with sparing of the facial nerve is done when lesions are limited to the canal and have not invaded the middle ear. Deeper invasion requires a more significant temporal bone resection.

Rarely, squamous cell carcinoma originates in the middle ear. The persistent otorrhea of chronic otitis media may be a predisposing factor. Resection of the temporal bone and postoperative radiation therapy are necessary.

Nonchromaffin paragangliomas (chemodectomas) arise in the temporal bone from glomus bodies in the jugular bulb (glomus jugulare tumors) or the medial wall of the middle ear (glomus tympanicum tumors). They appear as a pulsatile red mass in the middle ear. The first symptom often is tinnitus that is synchronous with the pulse. Hearing loss develops, followed by vertigo. Cranial nerve palsies of the 9th, 10th, or 11th nerve may accompany glomus jugulare tumors that extend through the jugular foramen. Excision is the treatment of choice, and radiation is used for nonsurgical candidates.

Benign otic tumors: Sebaceous cysts, osteomas, and keloids may arise in and occlude the ear canal, causing retention of cerumen and conductive hearing loss. Excision is the treatment of choice for all benign otic tumors.

Ceruminomas occur in the outer third of the ear canal. These tumors appear benign histologically and do not metastasize regionally or distantly but they are locally invasive and potentially destructive and should be excised widely.

Salivary Gland Tumors

Most salivary gland tumors are benign and occur in the parotid glands. A painless salivary mass is the most common sign and is evaluated by fine-needle aspiration biopsy. Imaging with CT and MRI can be helpful. For malignant tumors, treatment is with excision and radiation. Long-term results are related to the grade of the cancer.

About 85% of salivary gland tumors occur in the parotid glands, followed by the submandibular and minor salivary glands, and about 1% occur in the sublingual glands. About 75 to 80% are benign, slow-growing, movable, painless, usually solitary nodules beneath normal skin or mucosa. Occasionally, when cystic, they are soft but most often they are firm.

Benign tumors: The most common type is a pleomorphic adenoma (mixed tumor). Malignant transformation is possible, resulting in carcinoma ex mixed tumor, but this usually occurs only after the benign tumor has been present for 15 to 20 yr. If malignant transformation occurs, the cure rates are very low, despite adequate surgery and adjuvant therapy.

Other benign tumors include monomorphic adenoma, oncocytoma, and papillary cystadenoma lymphomatosum (previously known as cylindroma). These tumors rarely recur and rarely become malignant.

Malignant salivary gland tumors: Malignant tumors are less common and are characterized by rapid growth or a sudden growth spurt. They are firm, nodular, and can be fixed to adjacent tissue, often with a poorly defined periphery. Pain and neural involvement are common. Eventually, the overlying skin or mucosa may become ulcerated or the adjacent tissues may become invaded. Surgery, followed by radiation therapy, is the treatment of choice for resectable disease. Currently, there is no effective chemotherapy for salivary cancer.

Mucoepidermoid carcinoma is the most common salivary gland cancer, typically occurring in people in their 20s to 50s. It can manifest in any salivary gland, often in a minor salivary gland of the palate, or it can occur deep within the bone, such as in the wall of a dentigerous cyst. Intermediate and high-grade mucoepidermoid carcinomas may metastasize to the regional lymphatics, which must be addressed with surgical dissection or postoperative radiation therapy.

Adenoid cystic carcinoma is the most common malignant tumor of minor salivary glands (and of the trachea). It is a slowly growing malignant transformation of a much more common benign cylindroma. Its peak incidence is between ages 40 and 60, and symptoms include severe pain and, often, facial nerve paralysis. It has a propensity for perineural invasion and spread, with disease potentially extending many centimeters from the main tumor mass. Lymphatic spread is not a common feature of this tumor, so elective nodal treatment is less common. Although the 5- and 10-yr survival rates are quite good, the 15- and 20-yr rates are quite poor, with most patients developing distant metastases. Pulmonary metastases are common, although patients can live quite long with them.

Acinic cell carcinoma, a common parotid tumor, occurs in people in their 40s and 50s. This carcinoma has a more indolent course, as well as an incidence of multifocality.

Carcinoma ex mixed tumor is adenocarcinoma arising in a preexisting benign carcinoma ex mixed tumor. Only the carcinomatous element metastasizes.

Symptoms and Signs

Most benign and malignant tumors manifest as a painless mass. However, malignant tumors may invade nerves, causing localized or regional pain, numbness, paresthesia, causalgia, or a loss of motor function.

Diagnosis

• Biopsy

• CT and MRI for extent of disease

CT and MRI locate the tumor and describe its extent. Biopsy confirms the cell type. A search for spread to regional nodes or distant metastases in the lung, liver, bone, or brain may be indicated before treatment is selected.

Treatment

• Surgery, sometimes plus radiation therapy

Treatment of benign tumors is surgery. The recurrence rate is high when excision is incomplete.

Treatment of mucoepidermoid carcinoma consists of wide excision and postoperative radiation. The 5-yr survival rate is 95% with the low-grade type, primarily affecting mucus cells, and 50% with the high-grade type, primarily affecting epidermoid cells. Treatment of adenoid cystic carcinoma is wide surgical excision, but local recurrence is common. Lung metastases and death are likely, although many years, to a decade or more, after the initial diagnosis and treatment. The prognosis for acinic cell carcinoma is favorable after wide excision. All surgeries are designed to spare the facial nerve, which is sacrificed only in cases of direct tumor involvement with the nerve.

Chapter 56. Approach to Dental and Oral Symptoms

Introduction

A physician should always examine the mouth and be able to recognize major oral disorders, particularly possible cancers. However, consultation with a dentist is needed to evaluate nonmalignant changes as well as patients with tooth problems. Likewise, patients with xerostomia or unexplained swelling or pain in the mouth, face, or neck require a dental consultation. Children with abnormal facies (who also may have dental malformations requiring correction) should be evaluated by a dentist. In FUO or a systemic infection of unknown cause, a dental disorder should be considered. A dental consultation is necessary before head and neck radiation therapy and is advisable before chemotherapy.

Clues suggesting systemic disease may be found in the mouth and adjacent structures (see Table 56-1). A dentist should consult a physician when a systemic disorder is suspected, when the patient is taking certain drugs (eg, warfarin, bisphosphonates), and when a patient's ability to withstand general anesthesia or extensive oral surgery must be evaluated. Patients with certain heart valve abnormalities may require antibiotic prophylaxis to help prevent bacterial endocarditis before undergoing certain dental procedures (see Tables 215-3 and 215-4 on pp. 2199 and 2200).

Common dental disorders are discussed in Ch. 57. Dental emergencies, including toothache, are discussed in Ch. 58.

Anatomy and Development

Teeth: The teeth are categorized as incisors, canines, premolars, and molars and conventionally are numbered beginning with the maxillary right 3rd molar (see Fig. 56-1).

Each tooth has a crown and a root. The canines have the largest and strongest roots. An inner pulp contains blood vessels, lymphatics, and nerves, surrounded by the hard but porous dentin, a very hard enamel coating that covers the crown. The bonelike cementum is over the root, which, when healthy, is covered by gingiva (see Fig. 56-2). Twenty deciduous

[**Table 56-1.** Oral Findings in Systemic Disorders]

teeth normally begin appearing at close to age 6 mo and should all be in place by age 30 mo (see Table 271-1 on p. 2757). These teeth are followed by 32 permanent teeth that begin to appear by about age 6. The period from age 6 to 11 is called the mixed dentition stage, in which both deciduous and permanent teeth are present. Timing of tooth eruption is one indicator of skeletal age and may identify growth retardation or establish age for forensic purposes.

Supporting tissues: The gingiva surrounds the teeth at the base of their crown. The alveolar ridges are trabecular bone containing sockets for the teeth. The periodontium consists of the tissues that support the teeth—the gingiva, epithelial attachment, connective tissue attachment, periodontal ligament, and alveolar bone. The mandible and maxilla support the alveolar ridges and house the teeth. Saliva from the salivary glands bathes and protects the teeth. The tongue directs food between the grinding surfaces and helps clean the teeth. The maxilla receives innervation from the maxillary nerve, the 2nd division of the trigeminal nerve (the 5th cranial nerve). The mandibular nerve, which is the 3rd and most inferior division of the trigeminal nerve, innervates the mandible.

In the elderly, or in some periodontal diseases, gingival recession exposes the dental root adjacent to the crown, making root caries common. If tooth destruction results and the tooth must be removed, the mechanical stimulation necessary for maintaining bone integrity ceases. Consequently, atrophy of the alveolar ridge (senile atrophy) begins when teeth are absent.

Mouth: Normally, keratinized epithelium occurs on the facial aspect of the lips, dorsum of the tongue, hard palate, and gingiva around the teeth. When healthy, the gingiva extends

[Fig. 56-1. Identifying the teeth.]

5 to 7 mm from the tooth. Nonkeratinized mucosa occurs over alveolar bone further from the teeth, inside the lips and cheeks, on the sides and undersurface of the tongue, on the soft palate, and covering the floor of the mouth. The skin and mucosa of the lips are demarcated by the vermilion border.

The buccal mucosa, including the vestibule and nonkeratinized alveolar mucosa, is usually smooth, moist, and more red than pink (as compared to healthy gingiva). Innocuous entities in this region include linea alba (a thin white line, typically bilateral, on the level of the occlusal plane, where the cheek is bitten), Fordyce's granules (aberrant sebaceous glands appearing as < 1 mm light yellow spots that also may occur on the lips), and white sponge nevus (bilateral thick white folds over most of the buccal mucosa). Recognizing these avoids needless biopsy and apprehension. The orifices of the parotid (Stensen's) ducts are opposite the maxillary 1st molar on the inside of each cheek and should not be mistaken for an abnormality.

The dorsal surface of the tongue is covered with numerous whitish elevations called the filiform papillae. Interspersed among them are isolated reddish prominences called the fungiform papillae, occurring mostly on the anterior part of the tongue. The circumvallate papillae, numbering 8 to 12, are considerably larger and lie posteriorly in a V pattern. The circumvallate papillae do not project from the tongue but instead are surrounded by a trench. The foliate papillae appear as a series of parallel, slitlike folds on the lateral borders of the tongue, near the anterior pillars of the fauces. They vary in length and can easily be confused with malignant lesions, as may the foramen cecum, median rhomboid glossitis, and, rarely, a lingual thyroid nodule. Lingual tonsils are components of Waldeyer's ring, are at the back of the tongue, and should not be mistaken for lesions. If an apparent abnormality is bilateral, it is almost always a normal variant.

Innervation is supplied by the lingual nerves (branches of the 5th cranial nerves), for general sensory innervation, and the chorda tympani fibers (of the 7th cranial nerve), which innervate the taste buds of the anterior two thirds of the tongue. Behind the circumvallate papillae, the glossopharyngeal nerves (9th cranial nerves) provide the sensations of touch and taste. The tongue has taste receptors for sweet, salty, sour, bitter, and umami (a savory

[Fig. 56-2. Section of a canine tooth.]

taste triggered by natural glutamic acid and glutamates such as the flavoring agent monosodium glutamate). Although previously thought to be isolated to particular portions of the tongue, these receptors are now known to be distributed over the surface of the tongue. The hypoglossal nerves (12th cranial nerves) control movement of the tongue.

The major salivary glands are the paired parotid, submandibular, and sublingual glands. Most oral mucosal surfaces contain many minor mucus-secreting salivary glands. Anteriorly and near the midline on each side of the floor of the mouth are the openings of Wharton's ducts, which drain the ipsilateral submandibular and sublingual glands. The parotid glands drain into the cheeks via Stensen's ducts.

Evaluation

The first routine dental examination should take place by age 1 yr or when the first tooth erupts. Subsequent evaluations should take place at 6-mo intervals or whenever symptoms develop. Examination of the mouth is part of every general physical examination. Oral findings in many systemic diseases are unique, sometimes pathognomonic, and may be the first sign of disease. Oral cancer may be detected at an early stage.

History: Important dental symptoms include bleeding, pain, malocclusion, new growths, numbness or paresthesias, and chewing problems (which may lead to weight loss—see Table 56-2). General information includes use of alcohol or tobacco (both major risk factors for head and

neck cancer) and systemic symptoms, such as fever and weight loss.

Physical examination: A thorough inspection requires good illumination, a tongue blade, gloves, and a gauze pad. Complete or partial dentures are removed so that underlying soft tissues can be seen.

Most physicians use a head-mounted light. However, because the light cannot be precisely aligned on the axis of vision, it is difficult to avoid shadowing in narrow areas. Better illumination results with a head-mounted convex mirror; the physician looks through a hole in the center of the mirror, so the illumination is always on-axis. The head mirror reflects light from a source (any incandescent light) placed behind the patient and slightly to one side and requires practice to use effectively.

The examiner initially looks at the face for asymmetry, masses, and skin lesions. Slight facial asymmetry is universal, but more marked asymmetry may indicate an underlying disorder, either congenital or acquired (see
Table 56-3).

Teeth are inspected for shape, alignment, defects, mobility, color, and presence of adherent plaque, materia alba (dead bacteria, food debris, desquamated epithelial cells), and calculus (tartar).

Teeth are gently tapped with a tongue depressor or mirror handle to assess tenderness (percussion sensitivity). Tenderness to percussion suggests deep caries that has caused a necrotic pulp with periapical abscess or severe periodontal disease. Percussion sensitivity or pain on biting also can indicate an incomplete (green stick) fracture of a tooth. Percussion tenderness in multiple adjacent maxillary teeth may result from maxillary sinusitis. Tenderness to palpation around the apices of the teeth also may indicate an abscess.

Loose teeth usually indicate severe periodontal disease but can be caused by bruxism (clenching or grinding of teeth—see p. 506) or trauma that damages periodontal tissues. Rarely, teeth become loose when alveolar bone is eroded by an underlying mass (eg, ameloblastoma, eosinophilic granuloma). A tumor or systemic cause of alveolar bone loss (eg, diabetes mellitus, hyperparathyroidism, osteoporosis, Cushing's syndrome) is suspected when teeth are loose and heavy plaque and calculus are absent.

Calculus is mineralized bacterial plaque—a concretion of bacteria, food residue, saliva,

[**Table 56-2.** Some Oral Symptoms and Possible Causes]

and mucus with Ca and phosphate salts. After a tooth is cleaned, a mucopolysaccharide coating (pellicle) is deposited almost immediately. After about 24 h, bacterial colonization turns the pellicle into plaque. After about 72 h, the plaque starts calcifying, becoming calculus. When present, calculus is deposited most heavily on the lingual (inner, or tongue) surfaces of the mandibular anterior teeth near the submandibular and sublingual duct orifices (Wharton's ducts) and on the buccal (cheek) surfaces of the maxillary molars near the parotid duct orifices (Stensen's ducts).

Caries (tooth decay—see p. 516) first appears as defects in the tooth enamel. Caries then appears as white spots, later becoming brown.

Attrition (wearing of biting surfaces) can result from chewing abrasive foods or tobacco or from the wear that accompanies aging, but it usually indicates bruxism. Another common cause is abrasion of a porcelain crown occluding against opposing enamel, because porcelain is considerably harder than enamel. Attrition makes chewing less effective and causes noncarious teeth to become

[**Table 56-3.** Some Disorders of the Oral Region by Predominant Site of Involvement]

painful when the eroding enamel exposes the underlying dentin. Dentin is sensitive to touch and to temperature changes. A dentist can desensitize such teeth or restore the dental anatomy by placing crowns or onlays over badly worn teeth. In minor cases of root sensitivity, the exposed root may be desensitized by fluoride application or dentin-bonding agents.

Deformed teeth may indicate a developmental or endocrine disorder. In Down syndrome, teeth are small. In congenital syphilis, the incisors may be small at the incisal third, causing a pegged or screwdriver shape with a notch in the center of the incisal edge (Hutchinson's incisors), and the 1st molar is small, with a small occlusal surface and roughened, lobulated, often hypoplastic enamel (mulberry molar). In ectodermal dysplasia, teeth are absent or conical, so that dentures are needed from childhood. Dentinogenesis imperfecta, an autosomal dominant disorder, causes abnormal dentin that is dull bluish brown and opalescent and does not cushion the overlying enamel adequately. Such teeth cannot withstand occlusal stresses and rapidly become worn. People with pituitary dwarfism or with congenital hypoparathyroidism have small dental roots; people with gigantism have large ones. Acromegaly causes excess cementum in the roots as well as enlargement of the jaws, so teeth may become widely spaced. Acromegaly also can cause an open bite to develop in adulthood. Congenitally narrow lateral incisors occur in the absence of systemic disease. The most commonly congenitally absent teeth are the 3rd molars, followed in frequency by the maxillary lateral incisors and 2nd mandibular premolars.

Defects in tooth color must be differentiated from the darkening or yellowing that is caused by food pigments, aging, and, most prominently, smoking. A tooth may appear gray because of pulpal necrosis, usually due to extensive caries penetrating the pulp or because of hemosiderin deposited in the dentin after trauma, with or without pulpal necrosis. Children's teeth darken appreciably and permanently after even short-term use of tetracyclines by the mother during the 2nd half of pregnancy or by the child during odontogenesis (tooth development), specifically calcification of the crowns, which lasts until age 9. Tetracyclines rarely cause permanent discoloration of fully formed teeth in adults. However, minocycline darkens bone, which can be seen in the mouth when the overlying gingiva and mucosa are thin. Affected teeth fluoresce with distinctive colors under ultraviolet light corresponding to the specific tetracycline taken. In congenital porphyria, both the deciduous and permanent teeth may have red or brownish discoloration but always fluoresce red from the pigment deposited in the dentin. Congenital hyperbilirubinemia causes a yellowish tooth discoloration. Teeth can be whitened (see Table 56-4).

Defects in tooth enamel may be caused by rickets, which results in a rough, irregular band in the enamel. Any prolonged febrile illness during odontogenesis can cause a permanent narrow zone of chalky, pitted enamel or simply white discoloration visible after the tooth erupts. Thus, the age at which the disease occurred and its duration can be estimated from the location and height of the band. Amelogenesis imperfecta, an autosomal dominant disease, causes severe enamel hypoplasia. Chronic vomiting and esophageal reflux can decalcify the dental crowns, primarily the lingual surfaces of the maxillary anterior teeth. Chronic snorting of cocaine can result in widespread decalcification of teeth, because the drug dissociates in saliva into a base and HCl. Chronic use of methamphetamines markedly increases dental caries ("meth mouth").

Swimmers who spend a lot of time in over-chlorinated pools may lose enamel from the outer facial/buccal side of the teeth, especially the maxillary incisors, canines, and 1st premolars. If Na carbonate has been added to the pool water to correct pH, then brown calculus develops but can be removed by a dental cleaning.

Fluorosis is mottled enamel that may develop in children who drink water containing > 1 ppm of fluoride during tooth development. Fluorosis depends on the amount of fluoride ingested. Enamel changes range from irregular whitish opaque areas to severe brown discoloration of the entire crown with a roughened surface. Such teeth are highly resistant to dental caries.

The lips are palpated. With the patient's mouth open, the buccal mucosa and vestibules are examined with a tongue blade; then the hard and soft palates, uvula, and oropharynx are viewed. The patient is asked to extend the tongue as far as possible, exposing the dorsum, and to move the extended tongue as far as possible to each side, so that its posterolateral surfaces can be seen. If a patient does not extend the tongue far enough to expose the circumvallate papillae, the examiner grasps the tip of the tongue with a gauze pad and extends it. Then the tongue is raised to view the ventral surface and the floor of the mouth. The teeth and gingiva are viewed. An abnormal distribution of keratinized or nonkeratinized oral mucosa demands attention. Keratinized tissue that occurs in normally nonkeratinized areas appears white. This abnormal condition, called leukoplakia, requires a biopsy because it may be cancerous or precancerous. More ominous, however, are thinned areas of mucosa. These

[Table 56-4. Tooth Whitening Procedures]

red areas, called erythroplakia, if present for at least 2 wk, especially on the ventral tongue and floor of the mouth, suggest dysplasia, carcinoma in situ, or cancer.

With gloved hands, the examiner palpates the vestibules and the floor of the mouth, including the sublingual and submandibular glands. To make palpation more comfortable, the examiner asks the patient to relax the mouth, keeping it open just wide enough to allow access.

The temporomandibular joint (TMJ) is assessed by looking for jaw deviation on opening and by palpating the head of the condyle anterior to the external auditory meatus. Examiners then place their little fingers into the external ear canals with the pads of the fingertips lightly pushing anteriorly while patients open widely and close 3 times. Patients also should be able to comfortably open wide enough to fit 3 of their fingers vertically between the incisors (typically 4 to 5 cm). Trismus, the inability to open the mouth, may indicate temporomandibular disease (the most common cause), pericoronitis, scleroderma, arthritis, ankylosis of the TMJ, dislocation of the temporomandibular disk, tetanus, or peritonsillar abscess. Unusually wide opening suggests subluxation or type III Ehlers-Danlos syndrome.

Testing: For a new patient or for someone who requires extensive care, the dentist takes a full mouth x-ray series. This series consists of 14 to 16 periapical films to show the roots and bone plus 4 bite-wing films to detect early caries between posterior teeth. Modern techniques reduce radiation exposure to a near-negligible level. Patients at high risk of caries (ie, those who have had caries detected during the clinical examination, have many restorations, or have recurrent caries on teeth previously restored) should undergo bite-wing x-rays every 12 mo. Otherwise, bite-wings are indicated every 2 to 3 yr. A panoramic x-ray can yield useful information about tooth development, cysts or tumors of the jaws, supernumerary or congenitally absent teeth, 3rd molar impaction, Eagle's syndrome (less frequently), and carotid plaques.

Geriatrics Essentials

With aging, resting salivary secretion diminishes and can be further diminished by drugs, although meal-stimulated salivary flow is usually adequate. The flattened cusps of worn teeth and weakness of the masticatory muscles may make chewing tiresome, impairing food intake. Loss of bone mass in the jaws (particularly the alveolar portion), dryness of the mouth, thinning of the oral mucosa, and impaired coordination of lip, cheek, and tongue movements may make denture retention difficult. The taste buds become less sensitive, so the elderly may add abundant seasonings, particularly salt (which is harmful for some), or they may desire very hot foods for more taste, sometimes burning the often atrophic oral mucosa. Gingival recession and xerostomia contribute to development of root caries. Despite these changes, improved dental hygiene has greatly decreased the prevalence of tooth loss, and most older people can expect to retain their teeth.

Poor oral health contributes to poor nutritional intake, which impairs general health. Dental disease (particularly periodontitis) is associated with a 2-fold increased risk of coronary artery disease. Edentulous patients cannot have periodontitis (because they do not have a periodontium), although periodontitis may have resulted in their tooth loss. Aspiration pneumonia in patients with periodontitis can involve anaerobic organisms and has a high mortality rate. Severe bacteremias secondary to acute or chronic dental infection may contribute to brain abscesses, cavernous sinus thrombosis, endocarditis, prosthetic joint infections, and unexplained fevers.

Dental Care of Patients With Systemic Disorders

Certain medical conditions (and their treatment) predispose patients to dental problems or affect dental care.

Hematologic disorders: People who have disorders that interfere with coagulation (eg, hemophilia, acute leukemia, thrombocytopenia) require medical consultation before undergoing dental procedures that might cause bleeding (eg, extraction, mandibular block). Hemophiliacs should have clotting factors

given before, during, and after an extraction. Such oral surgery should be done in the hospital in consultation with a hematologist. All patients with bleeding disorders should maintain a lifelong routine of regular dental visits, which includes cleanings, fillings, topical fluoride, and preventative sealants, to avoid the need for extractions.

Cardiovascular disorders: After an MI, dental procedures should be avoided for 6 mo, if possible, to allow damaged myocardium to become less electrically labile. Patients with pulmonary or cardiac disease who require inhalation anesthesia for dental procedures should be hospitalized.

Endocarditis prophylaxis is required before dental procedures only in patients with

• Prosthetic cardiac valves

• Previous history of bacterial endocarditis

• Cyanotic congenital defects of the heart or great vessels (if unrepaired, if completely repaired during first 6 mo after surgery, or if repaired but with residual defects)

• Cardiac transplantation recipients with a valvulopathy

The heart is better protected against low-grade bacteremias, which occur in chronic dental conditions, when dental treatment is received (with prophylaxis) than when it is not received. Patients who are to undergo cardiac valve surgery or repair of congenital heart defects should have any necessary dental treatment completed before surgery.

Although probably of marginal benefit, antibiotic prophylaxis is sometimes recommended for patients with hemodialysis shunts and within 2 yr of receipt of a major prosthetic joint (hip, knee, shoulder, elbow). The organisms causing infections at these sites are almost invariably of dermal rather than oral origin.

Epinephrine and levonordefrin are added to local anesthetics to increase the duration of anesthesia. In some cardiovascular patients, excess amounts of these drugs cause arrhythmias, myocardial ischemia, or hypertension. Plain anesthetic can be used for procedures requiring < 45 min, but in longer procedures or where hemostasis is needed, up to 0.04 mg epinephrine (2 dental cartridges with 1:100,000 epinephrine) is considered safe. Generally, no healthy patient should receive > 0.2 mg epinephrine at any one appointment. Absolute contraindications to epinephrine (any dose) are uncontrolled hyperthyroidism; pheochromocytoma; BP > 200 mm Hg systolic or > 115 mm Hg diastolic; uncontrolled arrhythmias despite drug therapy; and unstable angina, MI, or stroke within 6 mo.

Some electrical dental equipment, such as an electrosurgical cautery, a pulp tester, or an ultrasonic scaler, can interfere with early-generation pacemakers.

Cancer: Extracting a tooth adjacent to a carcinoma of the gingiva, palate, or antrum facilitates invasion of the alveolus (tooth socket) by the tumor. Therefore, a tooth should be extracted only during the course of definitive treatment. In patients with leukemia or agranulocytosis, infection may follow an extraction despite the use of antibiotics.

Immunosuppression: People with impaired immunity are prone to severe mucosal and periodontal infections by fungi, herpes and other viruses, and, less commonly, bacteria. The infections may cause hemorrhage, delayed healing, or sepsis. Dysplastic or neoplastic oral lesions may develop after a few years of immunosuppression. People with AIDS may develop Kaposi's sarcoma, non-Hodgkin lymphoma, hairy leukoplakia, candidiasis, aphthous ulcers, or a rapidly progressive form of periodontal disease.

Endocrine disorders: Dental treatment may be complicated by some endocrine disorders. For example, people with hyperthyroidism may develop tachycardia and excessive anxiety as well as thyroid storm if given epinephrine. Insulin requirements may be reduced on elimination of oral infection in diabetics; insulin dose may require reduction when food intake is limited because of pain after oral surgery. In people with diabetes, hyperglycemia with resultant polyuria may lead to dehydration, resulting in decreased salivary flow (xerostomia), which, along with elevated salivary glucose levels, contributes to

caries.

Patients receiving corticosteroids and those with adrenocortical insufficiency may require supplemental corticosteroids during major dental procedures. Patients with Cushing's syndrome or who are taking corticosteroids may have alveolar bone loss, delayed wound healing, and increased capillary fragility.

Neurologic disorders: Patients with seizures who require dental appliances should have nonremovable appliances that cannot be swallowed or aspirated. Patients unable to brush or floss effectively may use chlorhexidine 12% rinses in the morning and at bedtime.

Obstructive sleep apnea: Patients with obstructive sleep apnea who are unable to tolerate treatment with a positive airway pressure (CPAP, biPAP) mask are sometimes treated with an intraoral device that expands the oropharynx. This treatment is not as effective as CPAP, but more patients tolerate using it.

Drugs: Certain drugs, such as corticosteroids, immunosuppressants, and antineoplastics, compromise healing and host defenses. When possible, dental procedures should not be done while these drugs are being given.

Some antineoplastics (eg, doxorubicin, 5-fluorouracil, bleomycin, dactinomycin, cytosine, arabinoside, methotrexate) cause stomatitis, which is worse in patients with preexisting periodontal disease. Before such drugs are prescribed, oral prophylaxis should be completed, and patients should be instructed in proper toothbrushing and flossing.

Drugs that interfere with clotting may need to be reduced or stopped before oral surgery. Patients taking aspirin, NSAIDs, or clopidogrel should stop doing so 4 days before undergoing dental surgery and can resume taking these drugs after bleeding stops. Warfarin should be stopped 2 to 3 days before oral surgery. PT is obtained; INR of 1.5 is considered safe for surgery. For people receiving hemodialysis, dental procedures should be done the day after dialysis, when heparinization has subsided.

Phenytoin and Ca channel blockers, particularly nifedipine, contribute to gingival hyperplasia; however, this hyperplasia is minimized with excellent oral hygiene and frequent oral prophylaxes (cleanings).

Bisphosphonates, primarily when given parenterally for treatment of bone cancer, and to a much lesser degree when used orally to prevent osteoporosis, can result in osteonecrosis after an extraction (see Sidebar 39-1 on p. 363).

Radiation therapy: (CAUTION: *Extraction of teeth from irradiated tissues [particularly if the total dose was > 65 Gy, especially in the mandible] is commonly followed by osteoradionecrosis of the jaw. This is a catastrophic complication in which extraction sites break down, frequently sloughing bone and soft tissue.*) Thus, if possible, patients should have any necessary dental treatment completed before undergoing radiation therapy of the head and neck region, with time allowed for healing. Teeth that may not survive should be extracted. Necessary sealants and topical fluoride should be applied. After radiation, extraction should be avoided, if possible, by using dental restorations and root canal treatment instead.

Head and neck radiation often damages salivary glands, causing xerostomia, which promotes caries. Patients must therefore practice lifelong good oral hygiene. A fluoride gel and fluoride mouth rinse should be used daily. Rinsing with 0.12% chlorhexidine for 30 to 60 sec, if tolerated, can be done in the morning and at bedtime. Viscous lidocaine may enable a patient with sensitive oral tissues to brush and floss the teeth and eat. A dentist must be seen at 3-, 4-, or 6-mo intervals, depending on findings at the last examination. Irradiated tissue under dentures is likely to break down, so dentures should be checked and adjusted whenever discomfort is noted. Early caries may also be reversed by Ca phosphopeptides and amorphous Ca phosphate, which can be applied by a dentist or prescribed to a patient for at-home use.

Patients who undergo radiation therapy may develop oral mucosal inflammation and diminished taste as well as trismus due to fibrosis of the masticatory muscles. Trismus may be minimized by such exercises as opening and closing the mouth widely 20 times 3 or 4 times/day. Extractions of teeth in irradiated bone

should be avoided (because of possible osteoradionecrosis). Sometimes root canal therapy is done, and the tooth is ground down to the gum line. If extraction is required after radiation, 10 to 20 treatments in a hyperbaric O_2 chamber may forestall or prevent osteoradionecrosis.

Bruxism

Bruxism is clenching or grinding of teeth. Bruxism can abrade and eventually wear down dental crowns and loosen teeth. In many people, headaches, jaw pain, or both actually are the result of bruxism. The most severe and extensive grinding and clenching occurs during sleep, so the person may be oblivious to it, but family members might notice.

Treatment requires that the patient consciously try to reduce bruxism while awake. Plastic oral appliances (night guards) that prevent occlusal contact by fitting between the teeth can be used while sleeping. When symptoms are severe, a guard can be used also during the day. Usually, such devices are made by dentists. However, if the only problem is tooth wear, OTC heat-moldable devices, fitted at home, are available. Mild anxiolytics, particularly benzodiazepines, may help until a night guard is available but should not be used for extended periods.

Halitosis

(Fetor Oris; Oral Malodor)

Halitosis is a frequent or persistent unpleasant odor to the breath.

Pathophysiology

Halitosis most often results from fermentation of food particles by anaerobic gram-negative bacteria in the mouth, producing volatile sulfur compounds such as hydrogen sulfide and methyl mercaptan. Causative bacteria may be present in areas of gingival or periodontal disease, particularly when ulceration or necrosis is present. The causative organisms reside deep in periodontal pockets around teeth. In patients with healthy periodontal tissue, these bacteria may deposit on the dorsal posterior tongue.

Factors contributing to the overgrowth of causative bacteria include decreased salivary flow (eg, due to parotid disease, Sjogren's syndrome, use of anticholinergics—see p. 513), salivary stagnation, and increased salivary pH.

Certain foods or spices, after digestion, release the odor of that substance to the lungs; the exhaled odor may be unpleasant to others. For example, the odor of garlic is noted on the breath by others 2 or 3 h after consumption, long after it is gone from the mouth.

Etiology

About 85% of cases result from oral conditions. A variety of systemic and extraoral conditions account for the remainder (see
Table 56-5).

The **most common causes** overall are the following:

• Gingival or periodontal disease

• Smoking

• Ingested foods that have a volatile component

GI disorders rarely cause halitosis because the esophagus is normally collapsed. It is a fallacy that breath odor reflects the state of digestion and bowel function.

Other breath odors: Several systemic diseases produce volatile substances detectable on the breath,

although not the particularly foul, pungent odors typically considered halitosis. Diabetic ketoacidosis produces a sweet or fruity odor of acetone; liver failure produces a mousy or sometimes faintly sulfurous odor; and renal failure produces an odor of urine or ammonia.

Evaluation

History: History of present illness should ascertain duration and severity of halitosis (including whether other people have noticed or complained), adequacy of patient's oral hygiene, and the relationship of halitosis to ingestion of causative foods (see Table 56-5).

Review of systems should seek symptoms of causative disorders, including nasal discharge and face or head pain (sinusitis, nasal foreign body); productive cough and fevers (pulmonary infection); and regurgitation of undigested food when lying down or bending over (Zenker's diverticulum). Predisposing factors such as dry mouth, dry eyes, or both (Sjogren's syndrome) should be noted.

Past medical history should ask about duration and amount of use of alcohol and tobacco. Drug history should specifically ask about use of those that can cause dry mouth.

[**Table 56-5.** Some Causes of Halitosis]

Physical examination: Vital signs are reviewed, particularly for presence of fever.

The nose is examined for discharge and foreign body.

The mouth is examined for signs of gum disease, dental infection, and cancer. Signs of apparent dryness are noted (eg, whether the mucosa is dry, sticky, or moist; whether saliva is foamy, stringy, or normal in appearance).

The pharynx is examined for signs of infection and cancer.

Sniff test: A sniff test of exhaled air is conducted. In general, oral causes result in a putrefying, pungent smell, whereas systemic conditions result in a more subtle, abnormal odor. Ideally, for 48 h before the examination, the patient avoids eating garlic or onions, and for 2 h before, the patient abstains from eating, chewing, drinking, gargling, rinsing, or smoking. During the test, the patient exhales 10 cm away from the examiner's nose, first through the mouth and then with the mouth closed. A worse odor through the mouth suggests an oral etiology. A worse odor through the nose suggests a nasal or sinus etiology. Similar odor through both nose and mouth suggests a systemic or pulmonary cause. If site of origin is unclear, the posterior tongue is scraped with a plastic spoon. After 5 sec, the spoon is sniffed 5 cm from the examiner's nose.

Red flags: The following findings are of particular concern:

• Fever

• Purulent nasal discharge or sputum

• Visible or palpable oral lesions

Interpretation of findings: Because oral causes are by far the most common, any visible oral disease may be presumed to be the cause in patients with no extraoral symptoms or signs. When other disorders are involved, clinical findings often suggest a diagnosis (see Table 56-5).

In patients whose symptoms seem to be related to intake of certain substances and who have no other findings, a trial of avoidance may clarify the diagnosis.

Testing: Extensive diagnostic evaluation should not be undertaken unless the history and physical examination suggest an underlying disease (see Table 56-5). Portable sulfur monitors, gas chromatography, and chemical tests of tongue scrapings are available but best left to research protocols

or the occasional dental office that focuses on halitosis.

Treatment

Underlying diseases are treated.

If the cause is oral, the patient should see a dentist for professional cleaning and treatment of gingival disease and caries. Home treatment involves enhanced oral hygiene, including thorough flossing, toothbrushing, and brushing of the tongue with the toothbrush or a scraper. Mouthwashes are of limited benefit except to mask odor for about 20 min. Psychogenic halitosis may require psychiatric consultation.

Geriatrics Essentials

Elderly patients are more likely to take drugs that cause dry mouth, which leads to difficulties with oral hygiene and hence to halitosis, but are otherwise not more likely to have halitosis. Also, oral cancers are more common with aging and are more of a concern among elderly than younger patients.

Key Points

- Most halitosis comes from fermentation of food particles by anaerobic gram-negative bacteria in the mouth.
- Extraoral disorders may cause halitosis but are often accompanied by suggestive findings.
- It is a fallacy that breath odor reflects the state of digestion and bowel function.
- Mouthwashes provide only brief benefit.

Malocclusion

Malocclusion is abnormal contact between the maxillary and mandibular teeth.

Normally, each dental arch consists of teeth in side-by-side contact, forming a smooth curve, with the maxillary anterior teeth overlying the upper third of the mandibular anterior teeth. The buccal (outer) cusps of the maxillary posterior teeth are external to the corresponding cusps of the mandibular posterior teeth. On each side of the mouth, the anterior buccal cusp of the maxillary 1st permanent molar fits into the anterior buccal groove of the mandibular 1st molar. Because the outer parts of all maxillary teeth are normally external to the mandibular teeth, the lips and cheeks are displaced from between the teeth so that they are not bitten. The lingual (inner) surfaces of the lower teeth form a smaller arc than those of the upper teeth, confining the tongue and minimizing the likelihood of its being bitten. All the maxillary teeth should contact the corresponding mandibular teeth, so that the masticatory forces (which may be > 150 lb in the molar region and 250 lb when clenching during sleep) are widely distributed. If these forces are applied to only a few teeth, those teeth will eventually loosen.

Etiology

Malocclusion often results from jaw and tooth size discrepancies (ie, the jaw is too small or the teeth are too large for the jaw to accommodate them in proper alignment) but may be caused by a number of congenital deformities and disorders or by tooth loss. When permanent teeth are lost, adjacent teeth shift and opposing teeth extrude, causing malocclusion unless a bridge, implant, or partial denture is worn to prevent these movements. When children lose deciduous teeth prematurely, the teeth more posterior in the arch or the permanent 1st molars often drift forward, leaving insufficient space for other permanent teeth to erupt. Malocclusion after facial trauma may indicate tooth displacement or jaw fracture. In ectodermal dysplasia, malocclusion results from having too few teeth.

Evaluation

Occlusion is checked on both sides of the mouth by retracting each cheek with a tongue depressor while

telling the patient to close on the back teeth. Malocclusion sometimes is identified as early as the first dental visit. Early identification may make later treatment easier and more effective.

Treatment

Malocclusions are corrected primarily for aesthetic and psychologic reasons. However, in some cases, treatment may increase resistance to caries (in specific teeth), to anterior tooth fracture, and, possibly, to periodontal disease or stripping of the gingiva on the palate. Treatment may improve speech and mastication as well. Occlusion can be improved by aligning teeth properly, by selectively grinding teeth and restorations that contact prematurely, and by inserting crowns or onlays to build up tooth surfaces that are below the plane of occlusion.

Orthodontic appliances (braces) apply a continuous mild force to teeth to gradually remodel the surrounding alveolar bone. Extraction of one or more permanent teeth (usually a 1st premolar) may be needed to allow other teeth to be repositioned or to erupt into a stable alignment. After the teeth are properly aligned, the patient wears a plastic-and-wire retainer 24 h/day initially, then only at night for 2 to 3 yr.

When orthodontic treatment alone is insufficient, surgical correction of jaw abnormalities contributing to malocclusion (orthognathic surgery) may be indicated.

Stomatitis

Oral inflammation and ulcers, known as stomatitis, may be mild and localized or severe and widespread. They are invariably painful. Stomatitis may involve swelling and redness of the oral mucosa or discrete, painful ulcers (single or multiple). Less commonly, whitish lesions form, and, rarely, the mouth appears normal (burning mouth syndrome) despite significant symptoms. Symptoms hinder eating, sometimes leading to dehydration and malnutrition. Secondary infection occasionally occurs. Some conditions are recurrent.

Etiology

Stomatitis may be caused by local infection, systemic disease, a physical or chemical irritant, or an allergic reaction (see
Table 56-6); many cases are idiopathic. Because the normal flow of saliva protects the mucosa against many insults, xerostomia predisposes the mouth to stomatitis of any cause.

The **most common specific causes** overall include

• Recurrent aphthous stomatitis (RAS)—also called recurrent aphthous ulcers (RAU)

• Viral infections, particularly herpes simplex and herpes zoster

• Other infectious agents (*Candida albicans* and bacteria)

• Trauma

• Tobacco

• Chemotherapy and radiation therapy

Evaluation

History: History of present illness should ascertain the duration of symptoms and whether the patient ever had them previously. Presence and severity of pain should be noted. The relation of symptoms to food, drugs, and other substances (particularly occupational exposure to chemicals, metals, fumes, or dust) is sought.

Review of systems seeks symptoms of possible causes, including chronic diarrhea and weakness (inflammatory bowel disease, celiac sprue); genital lesions (Behcet's syndrome, syphilis); eye irritation (Behcet's syndrome); and weight loss, malaise, and fever (nonspecific chronic illness).

Past medical history should ascertain known conditions that cause oral lesions, including herpes simplex, Behcet's syndrome, inflammatory bowel disease, and risk factors for oral lesions, including immunocompromised state (eg, cancer, diabetes, organ transplant, use of immunosuppressants, HIV infection). Whether chemotherapy or radiation therapy has ever been used to manage cancer needs to be determined. Drug history should note all recent drugs used. History of tobacco use should be noted. Social history should include sexual contact, particularly oral sex, unprotected sex, and sex with multiple partners.

Physical examination: Vital signs are reviewed for fever. The patient's general appearance is noted for lethargy, discomfort, or other signs of significant systemic illness.

The mouth is inspected for the location and nature of any lesions.

The skin and other mucosal surfaces (including the genitals) are inspected for any lesions,

[Table 56-6. Some Causes of Stomatitis]

rash, petechiae, or desquamation. Any bullous lesions are rubbed for Nikolsky's sign (peeling of epithelium with lateral pressure).

Red flags: The following findings are of particular concern:

• Fever

• Cutaneous bullae

• Ocular inflammation

• Immunocompromise

Interpretation of findings: Occasionally, causes are obvious in the history (eg, cytotoxic chemotherapy; significant occupational exposure to chemicals, fumes, or dust). Recurrent episodes of oral lesions occur with RAS, herpes simplex, and Behcet's syndrome. History of diabetes, HIV infection or other immunocompromise, or recent antibiotic use should increase suspicion of *Candida* infection. Recent drug use (particularly sulfa drugs, other antibiotics, and antiepileptics) should increase suspicion of Stevens-Johnson syndrome (SJS).

Some causes typically have **extraoral, noncutaneous findings**, some of which suggest a cause. Recurrent GI symptoms suggest inflammatory bowel disease or celiac sprue. Ocular symptoms can occur with Behcet's syndrome and SJS. Genital lesions may occur with Behcet's syndrome and primary syphilis.

Some causes usually also have **extraoral, cutaneous findings**.

Cutaneous bullae suggest SJS, pemphigus vulgaris, or bullous pemphigoid. Prodrome of malaise, fever, conjunctivitis, and generalized macular target lesions suggests SJS. Pemphigus vulgaris starts with oral lesions, then progresses to flaccid cutaneous bullae. Bullous pemphigoid has tense bullae on normal-appearing skin. Nikolsky's sign is usually positive in SJS and pemphigus vulgaris.

Cutaneous vesicles are typical with chickenpox or herpes zoster. Unilateral lesions in a band after a dermatome suggest herpes zoster. Diffuse, scattered vesicular and pustular lesions in different stages suggest chickenpox.

Kawasaki disease usually has a macular rash, desquamation of hands and feet, and conjunctivitis; it occurs in children, usually those < 5 yr. Oral findings include erythema of the lips and oral mucosa.

Other cutaneous lesions may implicate erythema multiforme, hand-foot-and-mouth disease (from coxsackievirus), or secondary syphilis.

Some causes have **isolated oral findings**, including RAS, most viral infections, acute necrotizing ulcerative gingivitis, primary syphilis, gonorrhea, and *Candida*.

Location of oral lesions may help identify the cause. Interdental ulcers occur with primary herpes simplex or acute necrotizing ulcerative gingivitis. Lesions on keratinized surfaces suggest herpes simplex, RAS, or physical injury. Physical injury typically has an irregular appearance and occurs near projections of teeth, dental appliances, or where biting can injure the mucosa. An aspirin burn next to a tooth and pizza burn on the palate are common.

Primary herpes simplex infection causes multiple vesicular lesions on the intraoral mucosa on both keratinized and nonkeratinized surfaces and always includes the gingiva. These lesions rapidly ulcerate. Clinical manifestation occurs most often in children. Subsequent reactivations (secondary herpes simplex, cold sore) usually appear starting in puberty on the lip at the vermilion border and, rarely, on the hard palate.

Acute necrotizing ulcerative gingivitis causes severe inflammation and punched-out ulcers on the dental papillae and marginal gingivae. A severe variant called noma (gangrenous stomatitis) can cause full-thickness tissue destruction (sometimes involving the lips or cheek), typically in a debilitated patient. It begins as a gingival, buccal, or palatal (midline lethal granuloma) ulcer that becomes necrotic and spreads rapidly. Tissue sloughing may occur.

Isolated oral gonorrhea very rarely causes burning ulcers and erythema of the gingiva and tongue, as well as the more common pharyngitis. Primary syphilis chancres may appear in the mouth. Tertiary syphilis may cause oral gummas or a generalized glossitis and mucosal atrophy. The site of a gumma is the only time that squamous cell carcinoma develops on the dorsum of the tongue. A common sign of HIV becoming AIDS is hairy leukoplakia (vertical white lines on the lateral border of the tongue).

C. albicans and related species, which are normal oral flora, can overgrow in people who have taken antibiotics or corticosteroids or who are immunocompromised, such as patients with AIDS. *C. albicans* can cause whitish, cheesy plaques that leave erosions when wiped off. Sometimes only flat, erythematous areas appear (erosive form of *Candida*).

Testing: Patients with acute stomatitis and no symptoms, signs, or risk factors for systemic illness probably require no testing.

If stomatitis is recurrent, viral and bacterial cultures, CBC, serum iron, ferritin, vitamin B_{12}, folate, zinc, and endomysial antibody (for sprue) are done. Biopsy at the periphery of normal and abnormal tissue can be done for persistent lesions that do not have an obvious etiology.

Systematically eliminating foods from the diet can be useful, as can changing brands of toothpaste, chewing gum, or mouthwash.

Treatment

Specific disorders are treated, and any causative substances or drugs are avoided.

Meticulous oral hygiene (using a soft toothbrush) may help prevent secondary infection. A soft diet that does not include acidic or salty foods is followed.

Topical measures: Numerous topical treatments, alone or in combination, are used to ease symptoms. These treatments include

• Anesthetics

• Protective coatings

• Corticosteroids

• Antibiotics

• Physical measures (eg, cautery)

For topical anesthesia of discomfort that may interfere with eating and drinking, the following may be effective:

• Lidocaine rinse

• Sucralfate plus aluminum-magnesium antacid rinse

A 2-min rinse is done with 15 mL (1 tbsp) 2% viscous lidocaine q 3 h prn; patient expectorates when done (no rinsing with water and no swallowing unless the pharynx is involved). A soothing coating may be prepared with sucralfate (1-g pill dissolved in 15 mL water) plus 30 mL of aluminum-magnesium liquid antacid; the patient should rinse with or without swallowing. Many institutions and pharmacies have their own variation of this formulation (magic mouthwash), which sometimes also contains an antihistamine.

If the physician is certain the inflammation is not caused by an infectious organism, the patient can

• Rinse and expectorate after meals with dexamethasone elixir 0.5 mg/5 mL (1 tsp)

• Apply a paste of 0.1% triamcinolone in an oral emollient

• Wipe amlexanox over the ulcerated area with the tip of a finger

Chemical or physical cautery can ease pain of localized lesions. Silver nitrate sticks are not as effective as low-power (2- to 3-watt), defocused, pulsed-mode CO_2 laser treatments, after which pain relief is immediate and lesions tend not to recur locally.

Key Points

• Isolated stomatitis in patients with no other symptoms and signs or risk factors for systemic illness is usually caused by a viral infection or RAS.

• Extraoral symptoms, skin rash, or both suggest more immediate need for diagnosis.

Recurrent Aphthous Stomatitis

Recurrent aphthous stomatitis is a common condition in which round or ovoid painful ulcers recur on the oral mucosa. Etiology is unclear. Diagnosis is clinical. Treatment is symptomatic and usually includes topical corticosteroids.

Recurrent aphthous stomatitis (RAS) affects 20 to 30% of adults and a greater percentage of children at some time in their life.

Etiology

Etiology is unclear, but RAS tends to run in families. The damage is predominately cell-mediated. Cytokines, such as IL-2, IL-10, and, particularly, tumor necrosis factor-α, play a role.

Predisposing factors include

• Oral trauma

- Stress
- Foods, particularly chocolate, coffee, peanuts, eggs, cereals, almonds, strawberries, cheese, and tomatoes

Allergy does not seem to be involved.

Factors that may, for unknown reasons, be *protective* include oral contraceptives, pregnancy, and tobacco, including smokeless tobacco and nicotine-containing tablets.

Symptoms and Signs

Symptoms and signs usually begin in childhood (80% of patients are < 30 yr) and decrease in frequency and severity with aging. Symptoms may involve as few as one ulcer 2 to 4 times/yr or almost continuous disease, with new ulcers forming as old ones heal. A prodrome of pain or burning for 1 to 2 days precedes ulcers, but there are no antecedent vesicles or bullae. Severe pain, disproportionate to the size of the lesion, can last from 4 to 7 days.

Ulcers are well-demarcated, shallow, ovoid, or round and have a necrotic center with a yellow-gray pseudomembrane, a red halo, and slightly raised red margins.

Minor aphthae (Mikulicz's disease) account for 85% of cases. They occur on the floor of the mouth, lateral and ventral tongue, buccal mucosa, and pharynx; are < 8 mm (typically 2 to 3 mm); and heal in 10 days without scarring.

Major aphthae (Sutton's disease, periadenitis mucosa necrotica recurrens) constitute 10% of cases. Appearing after puberty, the prodrome is more intense and the ulcers are deeper, larger (> 1 cm), and longer lasting (weeks to months) than minor aphthae. They appear in the lips, soft palate, and throat. Fever, dysphagia, malaise, and scarring may occur.

Herpetiform ulcers (morphologically resembling but unrelated to herpesvirus) account for 5% of cases. They begin as multiple (up to 100) 1- to 3-mm crops of small, painful clusters of ulcers on an erythematous base. They coalesce to form larger ulcers that last 2 wk. They tend to occur in women and at a later age of onset than do other forms of RAS.

Diagnosis

- Clinical evaluation

Evaluation proceeds as described previously under stomatitis (see p. 509). Diagnosis is based on appearance and on exclusion, because there are no definitive histologic features or laboratory tests.

Primary oral herpes simplex may mimic RAS but usually occurs in younger children, always involves the gingiva and may affect any keratinized mucosa (hard palate, attached gingiva, dorsum of tongue), and is associated with systemic symptoms. Viral culture can be done to identify herpes simplex. Recurrent herpetic lesions are usually unilateral.

Similar recurrent episodes can occur with Behcet's syndrome, inflammatory bowel disease, sprue, HIV infection, and nutritional deficiencies; these conditions generally have systemic symptoms and signs. Isolated recurrent oral ulcers can occur with herpes infection, HIV, and, rarely, nutritional deficiency. Viral testing and serum hematologic tests can identify these conditions.

Drug reactions may mimic RAS but are usually temporally related to ingestion. However, reactions to foods or dental products may be difficult to identify; sequential elimination may be necessary.

Treatment

- Topical chlorhexidine and corticosteroids

General treatments for stomatitis (see p. 512) may help patients with RAS. Chlorhexidine gluconate mouthwashes and topical corticosteroids, the mainstays of therapy, should be used during the prodrome, if possible. The corticosteroid can be dexamethasone 0.5 mg/5 mL tid used as a rinse and then expectorated or clobetasol ointment 0.05% or fluocinonide ointment 0.05% in carboxymethylcellulose mucosal protective paste (1:1) applied tid. Patients using these corticosteroids should be monitored for candidiasis. If topical corticosteroids are ineffective, prednisone (eg, 40 mg po once/day) may be needed for ≤ 5 days. Continuous or particularly severe RAS is best treated by a specialist in oral medicine. Treatment may require prolonged use of systemic corticosteroids, azathioprine or other immunosuppressants, pentoxifylline, or thalidomide. Intralesional injections can be done with betamethasone, dexamethasone, or triamcinolone. Supplemental B_1, B_2, B_6, B_{12}, folate, or iron lessens RAS in some patients.

Xerostomia

Xerostomia is dry mouth caused by reduced or absent flow of saliva. This condition can result in discomfort, interfere with speech and swallowing, make wearing dentures difficult, cause halitosis, and impair oral hygiene by causing a decrease in oral pH and an increase in bacterial growth. Longstanding xerostomia can result in severe tooth decay and oral candidiasis. Xerostomia is a common complaint among older adults, affecting about 20% of the elderly.

Pathophysiology

Stimulation of the oral mucosa signals the salivatory nuclei in the medulla, triggering an efferent response. The efferent nerve impulses release acetylcholine at salivary gland nerve terminals, activating muscarinic receptors (M_3), which increase saliva production and flow. Medullary signals responsible for salivation may also be modulated by cortical inputs from other stimuli (eg, taste, smell, anxiety).

Etiology

Xerostomia is usually caused by the following:

• Drugs

• Radiation to the head and neck (for cancer treatment)

Systemic disorders are less commonly the cause, but xerostomia is common in Sjogren's syndrome and may occur in HIV/AIDS, uncontrolled diabetes, and certain other disorders.

Drugs: Drugs are the most common cause (see Table 56-7); about 400 prescription drugs

[**Table 56-7.** Some Causes of Xerostomia]

and many OTC drugs cause decreased salivation. The most common include the following:

• Anticholinergics

• Antiparkinsonians

• Antineoplastics (chemotherapy)

Chemotherapy drugs cause severe dryness and stomatitis while they are being taken; these problems usually end after therapy is stopped.

Other common drug classes that cause xerostomia include antihypertensives, anxiolytics, and antidepressants (less severe with SSRIs than with tricyclics).

The rise of illicit methamphetamine use has resulted in an increasing incidence of meth mouth, which is severe tooth decay caused by methamphetamine-induced xerostomia. The damage is exacerbated by the bruxing and clenching caused by the drug. This combination causes very rapid destruction of teeth. Tobacco use usually causes a decrease of saliva.

Radiation: Incidental radiation to the salivary glands during radiation therapy for head and neck cancer often causes severe xerostomia (5200 cGy causes severe, permanent dryness, but even low doses can cause temporary drying).

Evaluation

History: History of present illness should include acuity of onset, temporal patterns (eg, constant vs intermittent, presence only on awakening), provoking factors, including situational or psychogenic factors (eg, whether xerostomia occurs only during periods of psychologic stress or certain activities), assessment of fluid status (eg, fluid intake habits, recurrent vomiting or diarrhea), and sleeping habits. Use of recreational drugs should be specifically elicited.

Review of systems should seek symptoms of causative disorders, including dry eyes, dry skin, rashes, and joint pain (Sjogren's syndrome).

Past medical history should inquire about conditions associated with xerostomia, including Sjogren's syndrome, history of radiation treatment, head and neck trauma, and a diagnosis of or risk factors for HIV infection. Drug profiles should be reviewed for potential offending drugs (see Table 56-7).

Physical examination: Physical examination is focused on the oral cavity, specifically any apparent dryness (eg, whether the mucosa is dry, sticky, or moist; whether saliva is foamy, stringy, or normal in appearance), the presence of any lesions caused by *Candida albicans*, and the condition of the teeth.

The presence and severity of xerostomia can be assessed at the bedside in several ways. For example, a tongue blade can be held against the buccal mucosa for 10 sec. If the tongue blade falls off immediately when released, salivary flow is normal. The more difficulty encountered removing the tongue blade, the more severe the xerostomia. In women, the lipstick sign, where lipstick adheres to the front teeth, may be a useful indicator of xerostomia.

If there appears to be dryness, the submandibular, sublingual, and parotid glands should be palpated while observing the ductal openings for saliva flow. The openings are at the base of the tongue anteriorly for the submandibular glands and on the middle of the inside of the cheek for the parotid glands. Drying the duct openings with a gauze square before palpation aids observation. If a graduated container is available, the patient can expectorate once to empty the mouth and then expectorate all saliva into the container. Normal production is 0.3 to 0.4 mL/min. Significant xerostomia is 0.1 mL/min.

Dental caries may be sought at the margins of restorations or in unusual places (eg, at the neck or tip of the tooth).

The most common manifestation of *C. albicans* infection is areas of erythema and atrophy (eg, on the dorsum of the tongue). Less common is the better-known white, cheesy curd that bleeds when wiped off.

Red flags: The following findings are of particular concern:

• Extensive tooth decay

• Concomitant dry eyes, dry skin, rash, or joint pain

• Risk factors for HIV

Interpretation of findings: Xerostomia is diagnosed by symptoms, appearance, and absence of salivary flow when massaging the salivary glands.

No further assessment is required when xerostomia occurs after initiation of a new drug and stops after cessation of that drug or when symptoms appear within several weeks of irradiation of the head and neck. Xerostomia that occurs with abrupt onset after head and neck trauma is caused by nerve damage.

Concomitant presence of dry eyes, dry skin, rash, or joint pain, particularly in a female patient, suggests a diagnosis of Sjogren's syndrome. Severe tooth decay, out of proportion to expected findings, may be indicative of illicit drug use, particularly methamphetamines. Xerostomia that occurs only during nighttime or that is noted only on awakening may be indicative of excessive mouth breathing in a dry environment.

Testing: For those in whom the presence of xerostomia is unclear, sialometry can be conducted by placing collection devices over the major duct orifices and then stimulating salivary production with citric acid or by chewing paraffin. Normal parotid flow is 0.4 to 1.5 mL/min/gland. Flow monitoring can also help determine response to therapy.

The cause of xerostomia is often apparent, but if the etiology is unclear and systemic disease is considered possible, further assessment should be pursued with biopsy of a minor salivary gland (for detection of Sjogren's syndrome, sarcoidosis, amyloidosis, TB, or cancer) and HIV testing.

Treatment

When possible, the cause of xerostomia should be addressed and treated.

For patients with drug-related xerostomia whose therapy cannot be changed to another drug, drug schedules should be modified to achieve maximum drug effect during the day, because nighttime xerostomia is more likely to cause caries. For all drugs, easy-to-take formulations, such as liquids, should be considered, and sublingual dosage forms should be avoided. The mouth and throat should be lubricated with water before swallowing capsules and tablets or before using sublingual nitroglycerin. Patients should avoid decongestants and antihistamines.

Patients using continuous positive airway pressure for obstructive sleep apnea may benefit from humidifying the source air (room humidifier for those using oral appliance therapy).

Symptom control: Symptomatic treatment consists of measures that do the following:

• Increase existing saliva

• Replace lost secretions

• Control caries

Drugs that augment saliva production include cevimeline and pilocarpine, both cholinergic agonists. Cevimeline (30 mg po tid) has less M_2 (cardiac) receptor activity than pilocarpine and a longer half-life. The main adverse effect is nausea. Pilocarpine (5 mg po tid) may be given after ophthalmologic and cardiorespiratory contraindications are excluded; adverse effects include sweating, flushing, and polyuria.

Sipping sugarless fluids frequently, chewing xylitol-containing gum, and using an OTC saliva substitute containing carboxymethylcellulose or hydroxyethylcellulose may help. Petroleum jelly can be applied to the lips and under dentures to relieve drying, cracking, soreness, and mucosal trauma. A cold-air humidifier may aid mouth breathers who typically have their worst symptoms at night.

Meticulous oral hygiene is essential. Patients should brush and floss regularly and use fluoride rinses or gels daily; using newer toothpastes with added Ca and phosphorous also may help avoid rampant caries. An increased frequency of preventive dental visits with plaque removal is advised. The most effective way to prevent caries is to sleep with individually fitted carriers containing 1.1% Na fluoride or 0.4% stannous fluoride. If 2 carriers cannot be worn at once, then each arch should be covered every other night. In addition, a dentist can apply a 5% Na fluoride varnish 2 to 4 times/yr.

Patients should avoid sugary or acidic foods and beverages and any irritating foods that are dry, spicy,

astringent, or excessively hot or cold.

Geriatrics Essentials

Although dry mouth becomes more common among the elderly, this is probably due to the many drugs typically used by the elderly rather than aging itself.

Key Points

- Drugs are the most common cause, but systemic diseases (most commonly Sjogren's syndrome or HIV) and radiation therapy also can cause xerostomia.
- Symptomatic treatment includes increasing existing saliva flow with stimulants or drugs, and artificial saliva replacement. Xylitol-containing gum and candy may be useful.
- Patients with xerostomia are at high risk of tooth decay; meticulous oral hygiene and professionally applied fluorides are essential.

Chapter 57. Common Dental Disorders

Introduction

Common dental disorders include caries, gingivitis, periodontitis, and pulpitis. Dental emergencies, such as toothache, fractured or avulsed teeth, and postextraction complications, are discussed in Ch. 58.

Caries

Caries is tooth decay, commonly called cavities. The symptoms—tender, painful teeth—appear late. Diagnosis is based on inspection, probing of the enamel surface with a fine metal instrument, and dental x-rays. Treatment involves removing affected tooth structure and restoring it with various materials. Fluoride, diligent dental hygiene, sealants, and proper diet can prevent virtually all caries.

Etiology

Caries is caused by acids produced by bacteria in dental plaque. Plaque is, at first, a soft, thin film of bacteria, mucin, dead epithelial cells, and food debris that develops on the tooth surface within about 24 h after the tooth is cleaned. *Mutans streptococci* is a group of related bacteria that grow in plaque and can cause caries. Some strains are more cariogenic than others. Eventually (commonly, after 72 h), soft plaque mineralizes, mainly with Ca, phosphate, and other minerals, becoming calculus (hard plaque or tartar), which cannot easily be removed with a toothbrush.

Risk factors: There are several risk factors for caries:

• Dental defects

• High-acid or low-fluoride environment

• Reduced salivary flow

Many teeth have open enamel pits, fissures, and grooves, which may extend from the surface to the dentin. These defects may be wide enough to harbor bacteria but too narrow to clean effectively. They predispose teeth to caries. Large amounts of sugar in the diet provide nutrients for plaque-forming bacteria.

A tooth surface is more susceptible to caries when it is poorly calcified, has low fluoride exposure, or is in an acidic environment. Typically, decalcification begins when the pH at the tooth falls below 5.5 (eg, when lactic acid-producing bacteria colonize the area or when people drink cola beverages, which contain phosphoric acid).

Rampant caries in deciduous teeth suggests prolonged contact with infant formula, milk, or juice, typically when an infant goes to bed with a bottle (baby or nursing bottle caries). Thus, bedtime bottles should contain only water.

The elderly often take drugs that reduce salivary flow, predisposing to caries. The elderly also have a higher incidence of root caries because of gingival recession, exposure of root surfaces, and declining manual dexterity.

Complications: Untreated caries leads to tooth destruction, infections, and the need for extractions and replacement prostheses. Premature loss of deciduous teeth may shift the adjacent teeth, hindering eruption of their permanent successors.

Symptoms and Signs

Caries initially involves only the enamel and causes no symptoms. A cavity that invades the dentin causes pain, first when hot, cold, or sweet foods or beverages contact the involved tooth, and later with chewing

or percussion. Pain can be intense and persistent when the pulp is severely involved (see Pulpitis on p. 522).

Diagnosis

• Direct inspection

• Sometimes use of x-rays or special testing instruments

Routine, frequent (q 6 to 12 mo) clinical evaluation identifies early caries at a time when minimal intervention prevents its progression. A thin probe, sometimes special dyes, and transillumination by fiberoptic lights are used, frequently supplemented by new devices that detect caries by changes in electrical conductivity or laser reflectivity. However, x-rays are still important for detecting caries, determining the depth of involvement, and identifying caries under existing restorations.

Treatment

• Restorative therapy

• Sometimes a root canal and crown

Incipient caries (which is confined to the enamel) should be remineralized through improved home care (brushing and flossing), cleanings, prescriptions for high-fluoride toothpastes, and multiple fluoride applications at the dental office.

The primary treatment of caries that has entered dentin is removal by drilling, followed by filling of the resultant defect. For very deep cavities, a temporary filling may be left in place 6 to 10 wk in the hope that a tooth will deposit reparative dentin, preventing exposure of the pulp, which necessitates root canal treatment.

Fillings for occlusal surfaces of posterior teeth, which bear the brunt of mastication, must be composed of strong materials. The most common material has been silver amalgam, which combines silver, mercury, copper, tin, and, occasionally, zinc, palladium, or indium. Amalgam is inexpensive and lasts an average of 14 yr. However, if oral hygiene is good and if amalgam was placed using a rubber dam for isolation from saliva, many amalgam fillings last > 40 yr. Although concern has been raised about mercury poisoning, the number of amalgam fillings a person has bears no relationship to blood mercury levels. Replacing amalgam is not recommended because it is expensive, damages tooth structure, and actually increases patient exposure to mercury.

Composite resins, which have a more acceptable appearance, have long been used in anterior teeth, where aesthetics are primary and the forces of chewing are minimal. Some patients request them in posterior teeth as well, and they are becoming common there. However, composite resins under high occlusal stress generally last less than half as long as amalgam and tend to develop recurrent decay because the composite resin shrinks when it hardens and expands and contracts with heat and cold more than the tooth or other filling materials. The current generation of composites also closely resemble enamel but do not appear to have the same incidence of recurrent caries as earlier materials and may also last longer. However, although long-term results with these newer amalgam substitutes appear good, data equivalent in numbers and duration to those with amalgam are not yet available.

If decay leaves too little dentin to hold a restoration, a dentist replaces the missing dentin with cement, amalgam, composite, or other materials. Sometimes a post must be inserted into one or more roots to support a gold, silver, or composite core, which replaces the coronal dentin. This procedure necessitates a root canal filling, in which an opening is made in the tooth and the pulp is removed. The root canal system is thoroughly debrided, shaped, and then filled with gutta-percha. The outer tooth surfaces (what would have been the enamel) are then reduced so that an artificial crown, usually made of gold, porcelain, or both, can be placed. Crowns for anterior teeth consist of, or are covered with, porcelain.

Prevention

• Regular brushing and flossing

• Fluoride in water, toothpaste, or both

• Regular professional cleanings

• Rarely chlorhexidine rinses and topical fluoride applications

For most people, caries is preventable. Cavities first form on permanent teeth in the early teens to late 20s. Caries-prone people typically have low exposure to fluoride and a relatively cariogenic microflora acquired from their mothers and through social contact. Maintaining good oral hygiene and minimizing sugar intake are especially important.

Removal of plaque at least q 24 h, usually by brushing and flossing, helps prevent dental caries. The gingival third of the tooth is the most important area to clean but is the area most often neglected. Electric and electronic toothbrushes are excellent, but a manual soft toothbrush, used for an average of 3 to 4 min, suffices. Using excess toothpaste, particularly an abrasive type, may erode the teeth. Dental floss is placed between each of the teeth, curved against the side of each tooth, and moved up and down 3 times, going just beneath the gingival margin. Flosses that are very thin (dental tape) or coated with wax or polytetraethylene can be used for exceptionally tight contacts between teeth or rough filling margins.

Teeth with fluoride incorporated into their enamel are more resistant to acidic decalcification and more readily recalcify when pH increases. If drinking water is not adequately fluoridated, fluoride supplements are recommended for children from shortly after birth through age 8 yr and for pregnant women beginning at 3 mo gestation (when teeth are forming in the fetus). The dose must be selected according to the amount of fluoride present in the drinking water and the age of the child. The total dose should not be so high as to cause dental fluorosis (see p. 52). Fluoridated toothpaste should also be used by people of all ages.

Fluoridation offers less protection against caries in pits and fissures than against those on smooth surfaces. Pits and fissures require use of sealants (plastic materials that adhere tightly to the surface of the enamel) to prevent nutrients from reaching bacteria, reducing their growth and acid production.

If these measures do not decrease cavity formation, more intensive therapy is aimed at changing the flora. After cavities are treated, pits and fissures, which can harbor *M. streptococci*, are sealed. This treatment is followed by 60-sec mouth rinses using 0.12% chlorhexidine bid for 2 wk, which may reduce the cariogenic bacteria in plaque and allow repopulation with less cariogenic strains of *M. streptococci*. To encourage this repopulation, xylitol in the form of hard candy or chewing gum is used for 5 min tid. Additionally, topical fluoride may be applied by a dentist or used at night in a custom-made fluoride carrier.

For pregnant women with a history of severe caries, the above regimen may be used before the child's teeth erupt. If this is not feasible, the mother can use xylitol, as mentioned above, from the time of the baby's birth to the age at which the mother no longer samples the child's food (the hypothesized mode of transfer).

For prevention of caries in deciduous teeth (once they have erupted) in infants, bedtime bottles should contain only water.

Gingivitis

Gingivitis is inflammation of the gingivae, causing bleeding with swelling, redness, exudate, a change of normal contours, and, occasionally, discomfort. Diagnosis is based on inspection. Treatment involves professional teeth cleaning and intensified home dental hygiene. Advanced cases may require antibiotics or surgery.

Normally, the gingivae are firm, tightly adapted to the teeth, and contoured to a point. Keratinized gingiva near the crowns is pink stippled tissue. This tissue should fill the entire space between the crowns. The

gingiva farther from the crowns, called alveolar mucosa, is nonkeratinized, highly vascular, red, movable, and continuous with the buccal mucosa. A tongue depressor should express no blood or pus from normal gingiva.

Inflammation, or gingivitis, the most common gingival problem, may evolve into periodontitis (see p. 520).

Etiology

The most common cause of gingivitis is poor oral hygiene.

Poor oral hygiene allows plaque to accumulate between the gingiva and the teeth; gingivitis does not occur in edentulous areas. Irritation due to plaque deepens the normal crevice between the tooth and gingiva, creating gingival pockets. These pockets contain bacteria that may cause both gingivitis and root caries. Other local factors, such as malocclusion, dental calculus, food impaction, faulty dental restorations, and xerostomia, play a secondary role.

Systemic causes: Gingivitis also commonly occurs at puberty, during menstruation and pregnancy, and at menopause, presumably because of hormonal changes. Similarly, oral contraceptives may exacerbate inflammation.

Gingivitis may be an early sign of a systemic disorder, particularly those that affect the response to infection (eg, diabetes, AIDS, vitamin deficiency, leukopenia), particularly if it occurs in patients with minimal dental plaque. Some patients with Crohn's disease have a cobblestone area of granulomatous gingival hypertrophy when intestinal flare-ups occur. Exposure to heavy metals (eg, lead, bismuth) may cause gingivitis and a dark line at the gingival margin. Severe deficiency of niacin or vitamin C can cause gingivitis.

Symptoms and Signs

Simple gingivitis first causes a deepening of the sulcus (gingival crevice) between the tooth and the gingiva, followed by a band of red, inflamed gingiva along one or more teeth, with swelling of the interdental papillae and easy bleeding. Pain is usually absent. It may resolve, remain superficial for years, or occasionally progress to periodontitis.

Pericoronitis is acute, painful inflammation of the gingival flap over a partly erupted tooth, usually around mandibular 3rd molars (wisdom teeth). Infection is common, and an abscess may develop. Pericoronitis often recurs as food gets trapped beneath the flap. The gingival flap disappears when the tooth is fully erupted.

Desquamative gingivitis may occur during menopause. It is characterized by deep red, painful gingival tissue that bleeds easily. Vesicles may precede desquamation. The gingivae are soft because the keratinized cells that resist abrasion by food particles are absent. A similar gingival lesion may be associated with pemphigus vulgaris, bullous pemphigoid, benign mucous membrane pemphigoid, or atrophic lichen planus.

During pregnancy, swelling, especially of the interdental papillae, is likely to occur. Pedunculated gingival growths often arise in the interdental papillae during the 1st trimester, may persist throughout pregnancy, and may or may not subside after delivery. Pregnancy tumors are soft reddish masses that are, histologically, pyogenic granulomas. They develop rapidly and then remain static. An underlying irritant is common, such as calculus or a restoration with a rough margin.

Uncontrolled diabetes can exaggerate the effects of gingival irritants, making secondary infections and acute gingival abscesses common.

In leukemia, the gingivae may become engorged with a leukemic infiltrate, exhibiting clinical symptoms of edema, pain, and easily induced bleeding.

In scurvy (vitamin C deficiency), the gingivae are inflamed, hyperplastic, and engorged, bleeding easily.

Petechiae and ecchymoses may appear throughout the mouth.

In pellagra (niacin deficiency), the gingivae are inflamed, bleed easily, and are susceptible to secondary infection. Additionally, the lips are reddened and cracked, the mouth feels scalded, the tongue is smooth and bright red, and the tongue and mucosa may have ulcerations.

Diagnosis

• Clinical evaluation

Finding erythematous, friable tissue at the gum lines confirms the diagnosis. To detect early gingival disease, some dentists frequently measure the depth of the pocket around each tooth. Depths < 3 mm are normal; deeper pockets are at high risk of gingivitis and periodontitis.

Treatment

• Regular oral hygiene and professional cleaning

Simple gingivitis is controlled by proper oral hygiene with or without an antibacterial mouth rinse. Thorough scaling (professional cleaning with hand or ultrasonic instruments) should be done. If appropriate, poorly contoured restorations are reshaped or replaced and local irritants are removed. Excess gingiva, if present, can be excised. Drugs causing gingival hyperplasia should be stopped if possible; if not, improved home care and more frequent professional cleanings (at least every 3 mo) usually reduce the hyperplasia. Pregnancy tumors are excised.

Treatment of pericoronitis consists of

• Removal of debris from under the gingival flap

• Irrigation with saline, 1.5% hydrogen peroxide, or 0.12% chlorhexidine

• Particularly when episodes recur, extraction

If severe infection develops, antibiotics may be given for a day before extraction and continued during healing. A common regimen is amoxicillin 500 mg po q 6 h for 10 days (or until 3 days after all inflammation has subsided). Abscesses associated with pericoronitis require localized incision and drainage, a periodontal flap and root debridement, or extraction.

In gingivitis caused by systemic disorders, treatment is directed at the cause. In desquamative gingivitis during menopause, sequential administration of estrogens and progestins may be beneficial, but adverse effects of this therapy (see p. 2519) limit recommendations for its use. Otherwise, dentists may prescribe a corticosteroid rinse or a corticosteroid paste that is applied directly to the gums. Gingivitis caused by pemphigus vulgaris (see p. 658) and similar mucocutaneous conditions may require systemic corticosteroid therapy.

Prevention

Daily removal of plaque with dental floss and a toothbrush and routine cleaning by a dentist or hygienist at 6-mo to 1-yr intervals can help minimize gingivitis. Patients with systemic disorders predisposing to gingivitis require more frequent professional cleanings (from q 2 wk to 4 times/yr).

Acute Necrotizing Ulcerative Gingivitis

(Fusospirochetosis; Trench Mouth; Vincent's Infection or Angina)

Acute necrotizing ulcerative gingivitis is a painful infection of the gums. Symptoms are acute pain, bleeding, and foul breath. Diagnosis is based on clinical findings. Treatment is gentle debridement, improved oral hygiene, mouth rinses, supportive care, and, if debridement must

be delayed, antibiotics.

Acute necrotizing ulcerative gingivitis occurs most frequently in smokers and debilitated patients who are under stress. Other risk factors are poor oral hygiene, nutritional deficiencies, and sleep deprivation.

Symptoms and Signs

The usually abrupt onset may be accompanied by malaise or fever. The chief manifestations are acutely painful, bleeding gingivae; excessive salivation; and overwhelmingly foul breath (fetor oris). Ulcerations, which are pathognomonic, are present on the dental papillae and marginal gingiva; these have a characteristically punched-out appearance and are covered by a gray pseudomembrane. Similar lesions on the buccal mucosa and tonsils are rare. Swallowing and talking may be painful. Regional lymphadenopathy often is present.

Diagnosis

• Clinical evaluation

Rarely, tonsillar or pharyngeal tissues are affected, and diphtheria or infection due to agranulocytosis must be ruled out by throat culture and CBC.

Treatment

• Debridement

• Rinses (eg, hydrogen peroxide, chlorhexidine)

• Improved oral hygiene

• Sometimes oral antibiotics

Treatment consists of gentle debridement with a hand scaler or ultrasonic device. Debridement is done over several days. The patient uses a soft toothbrush to wipe the teeth. Rinses at hourly intervals with warm normal saline or twice/day with 1.5% hydrogen peroxide or 0.12% chlorhexidine may help during the first few days after initial debridement. Essential supportive measures include improved oral hygiene (done gently at first), adequate nutrition, high fluid intake, rest, analgesics as needed, and avoiding irritation (eg, caused by smoking or hot or spicy foods). Marked improvement usually occurs within 24 to 48 h, after which debridement can be completed. If debridement is delayed (eg, if a dentist or the instruments necessary for debridement are unavailable), oral antibiotics (eg, amoxicillin 500 mg, erythromycin 250 mg, or tetracycline 250 mg q 6 h) provide rapid relief and can be continued until 72 h after symptoms resolve. If the gingival contour inverts (ie, if the tips of papillae are lost) during the acute phase, surgery is eventually required to prevent subsequent periodontitis.

Other Gingival Disorders

Hyperplasia of gingival tissues may occur without inflammation in response to various drugs, particularly phenytoin, cyclosporine, and nifedipine or, less commonly, other Ca channel blockers. Hyperplasia is characterized by diffuse, relatively avascular smooth or nodular enlargement of the gingiva, which may almost cover some teeth. The hypertrophied tissue is often excised. If possible, substitutions are made for the offending drugs. Scrupulous oral hygiene may minimize recurrence.

Carcinoma can also originate in the gingiva and spread to regional lymph nodes.

Periodontitis

Periodontitis is an infection of the periodontium—causing inflammation of the periodontal ligament, gingiva, cementum, and alveolar bone. It usually manifests as a worsening of gingivitis. Symptoms are rare except with HIV or when abscesses develop, in which case pain

and swelling are common. Diagnosis is based on inspection, periodontal probing, and x-rays. Treatment involves dental cleaning that extends under the gums and a vigorous home hygiene program. Advanced cases may require antibiotics and surgery.

Etiology

Periodontitis usually develops when gingivitis, usually with abundant plaque and calculus beneath the gingival margin, has not been adequately treated. In periodontitis, the deep pockets can harbor anaerobic organisms that do more damage than those usually present in simple gingivitis. The gingiva progressively loses its attachment to the teeth, periodontal pockets deepen, and bone loss begins. With progressive bone loss, teeth may loosen, and gingiva recedes. Tooth migration is common in later stages.

Systemic causes: Systemic diseases that predispose patients to periodontitis include diabetes (especially type 1); acquired, familial, and cyclic neutropenia; leukemia; Down syndrome; leukocyte adhesion deficiency syndromes; Papillon-Lefevre syndrome; Crohn's disease; histiocytosis syndromes; agranulocytosis; lazy leukocyte syndrome; hypogammaglobulinemia; Chediak-Higashi syndrome; glycogen storage disease; infantile genetic agranulocytosis; Ehlers-Danlos syndrome (types IV and VIII); vitamin C deficiency (scurvy); and hypophosphatasia. Faulty occlusion, causing an excessive functional load on teeth, may contribute to progression of a particular type of periodontitis characterized by angular bony defects.

Pathophysiology

Periodontitis is usually chronic and characterized by periods of exacerbation and remission. Chronic periodontitis (formerly adult periodontitis) occurs in localized and generalized forms, and people with significant disease tend to be > 35 yr. About 85% of the population is affected to a mild degree, but the most advanced cases are seen in less than 5% of the population.

Aggressive periodontitis: Several more rapidly progressive subtypes of chronic periodontitis exist, collectively known as aggressive periodontitis. Aggressive periodontitis may develop as early as childhood, sometimes before age 3 yr. Patients may have severe bone loss, even tooth loss, by age 20. Neutrophil function may be defective in aggressive periodontitis; its clinical significance is unknown.

In one type of aggressive periodontitis that occurs in healthy adolescents (formerly called localized juvenile periodontitis), patients often have significant colonization of *Actinobacillus actinomycetemcomitans*. Typically, the signs of inflammation are minor. The disease is detected by periodontal probing or x-rays, which show localized, deep (vertical) bone loss, commonly limited to the 1st molars and incisors. Bone loss progresses faster than in adult periodontitis, often at a rate of 3 to 4 µm/day.

An uncommon type of aggressive periodontitis (formerly called prepubertal periodontitis) affects deciduous teeth, usually shortly after eruption. Generalized acute proliferative gingivitis and rapid alveolar bone destruction are its hallmarks. Patients also have frequent bouts of otitis media and are usually diagnosed by age 4 yr. In some patients, the disease resolves before the permanent teeth erupt. Treatment regimens are under study.

Prototypical aggressive periodontitis (formerly called rapidly progressive periodontitis) occurs in patients aged 20 to 35 yr. It is often associated with *A. actinomycetemcomitans*, *Porphyromonas gingivalis*, *Eikenella corrodens*, and many gram-negative bacilli, but cause and effect are not clear. Some cases result from undiagnosed localized juvenile periodontitis or prepubertal periodontitis, but others appear independently.

HIV-associated periodontitis is a particularly virulent, rapidly progressing disease. Clinically, it resembles acute necrotizing ulcerative gingivitis (see p. 520) combined with rapidly progressive periodontitis. Patients may lose 9 to 12 mm of attachment in as little as 6 mo.

Symptoms and Signs

Pain is usually absent unless an acute infection forms in one or more periodontal pockets or if HIV-associated periodontitis is present. Impaction of food in the pockets can cause pain at meals. Abundant plaque along with redness, swelling, and exudate are characteristic. Gums may be tender and bleed easily, and breath may be foul.

Diagnosis

• Clinical evaluation

• Sometimes dental x-rays

Inspection of the teeth and gingiva combined with probing of the pockets and measurement of their depth are usually sufficient for diagnosis. Pockets deeper than 4 mm indicate periodontitis. Dental x-rays reveal alveolar bone loss adjacent to the periodontal pockets.

Treatment

• Scaling and root planing

• Sometimes oral antibiotics, antibiotic packs, or both

• Surgery or extraction

For all forms of periodontitis, the first phase of treatment consists of thorough scaling and root planing (ie, removal of diseased or toxin-affected cementum and dentin followed by smoothing of the root) to remove plaque and calculus deposits. Thorough home oral hygiene is necessary. The patient is reevaluated after 3 wk. If pockets are no deeper than 4 mm at this point, the only treatment needed is regular cleanings.

If deeper pockets persist, systemic antibiotics can be used. A common regimen is amoxicillin 500 mg po qid for 10 days. In addition, a gel containing doxycycline or microspheres of minocycline can be placed into isolated recalcitrant pockets. These are resorbed in 2 wk.

Another approach is to surgically eliminate the pocket and recontour the bone so that the patient can clean the depth of the sulcus (pocket reduction/elimination surgery). In selected situations, regenerative surgery and bone grafting are done to encourage alveolar bone growth. Splinting of loose teeth and selective reshaping of tooth surfaces to eliminate traumatic occlusion may be necessary. Extractions are often necessary in advanced disease. Contributing systemic factors should be controlled before initiating periodontal therapy.

Ninety percent of patients with HIV-associated periodontitis respond to irrigation of the sulcus with povidone-iodine (which the dentist applies with a syringe), regular use of chlorhexidine mouth rinses, and systemic antibiotics, usually metronidazole 250 mg po tid for 14 days.

Localized juvenile periodontitis requires periodontal surgery plus oral antibiotics (eg, amoxicillin 500 mg qid or metronidazole 250 mg tid for 14 days).

Pulpitis

Pulpitis is inflammation of the dental pulp resulting from untreated caries, trauma, or multiple restorations. Its principal symptom is pain. Diagnosis is based on clinical findings and is confirmed by x-ray. Treatment involves removing decay, restoring the damaged tooth, and sometimes doing root canal therapy or extracting the tooth.

Pulpitis can occur when

• Caries progresses deeply into the dentin

• A tooth requires multiple invasive procedures

• Trauma disrupts the lymphatic and blood supply to the pulp

Pulpitis begins as a reversible condition in which the tooth can be saved by a simple filling. It becomes irreversible as swelling inside the rigid encasement of the dentin compromises circulation, making the pulp necrotic, which predisposes to infection.

Complications: Infectious sequelae of pulpitis include apical periodontitis, periapical abscess, cellulitis, and osteomyelitis of the jaw. Spread from maxillary teeth may cause purulent sinusitis, meningitis, brain abscess, orbital cellulitis, and cavernous sinus thrombosis. Spread from mandibular teeth may cause Ludwig's angina, parapharyngeal abscess, mediastinitis, pericarditis, empyema, and jugular thrombophlebitis.

Symptoms and Signs

In reversible pulpitis, pain occurs when a stimulus (usually cold or sweet) is applied to the tooth. When the stimulus is removed, the pain ceases within 1 to 2 sec.

In irreversible pulpitis, pain occurs spontaneously or lingers minutes after the stimulus is removed. A patient may have difficulty locating the tooth from which the pain originates, even confusing the maxillary and mandibular arches (but not the left and right sides of the mouth). The pain may then cease for several days because of pulpal necrosis. As infection develops and extends through the apical foramen, the tooth becomes exquisitely sensitive to pressure and percussion. A periapical (dentoalveolar) abscess elevates the tooth from its socket and feels "high" when the patient bites down.

Diagnosis

• Clinical evaluation

• Sometimes dental x-rays

Diagnosis is based on the history and physical examination, which makes use of provoking stimuli (application of heat, cold, percussion). X-rays help determine whether inflammation has extended beyond the tooth apex and help exclude other conditions.

Treatment

• Drilling and filling for reversible pulpitis

• Root canal and crown or extraction for irreversible pulpitis

• Antibiotics (eg, amoxicillin) for infection

In reversible pulpitis, pulp vitality can be maintained if the tooth is treated, usually by caries removal, and then restored.

Irreversible pulpitis and its sequelae require endodontic (root canal) therapy or tooth extraction. In endodontic therapy, an opening is made in the tooth and the pulp is removed. The root canal system is thoroughly debrided, shaped, and then filled with gutta-percha. After root canal therapy, adequate healing is manifested clinically by resolution of symptoms and radiographically by bone filling in the radiolucent area at the root apex over a period of months. If patients have systemic signs of infection (eg, fever), an oral antibiotic is prescribed (amoxicillin 500 mg q 8 h; for patients allergic to penicillin, clindamycin 150 mg or 300 mg q 6 h). If symptoms persist or worsen, root canal therapy is usually repeated in case a root canal was missed, but alternative diagnoses (eg, temporomandibular disorder, occult tooth fracture, neurologic disorder) should be considered.

Very rarely, subcutaneous or mediastinal emphysema develops after compressed air or a high-speed air turbine dental drill has been used during root canal therapy or extraction. These devices can force air into

the tissues around the tooth socket that dissects along fascial planes. Acute onset of jaw and cervical swelling with characteristic crepitus of the swollen skin on palpation is diagnostic. Treatment usually is not required, although prophylactic antibiotics are sometimes given.

Dental Appliances

Teeth may be lost to dental caries, periodontal disease, or trauma or may be removed when treatment fails. Missing teeth may cause cosmetic, phonation, and occlusal problems and may allow movement of remaining teeth.

Types: Dental appliances include fixed bridges, removable partial or complete dentures, and osseo-integrated implants.

A **bridge** (fixed partial denture) is composed of false teeth cast or soldered to each other and, at each end, to a crown that is cemented to natural (abutment) teeth, which bear all stress of biting. A bridge is not removed. A bridge is smaller than a removable partial denture, but one or multiple bridges can be made to replace many of the teeth in a dental arch.

A **removable partial denture**, typically an appliance with clasps that snap over abutment teeth, may be removed for cleaning and during sleep. Part of the occlusal stress may be borne by the soft tissues under the denture, often on both sides of the jaw. This appliance commonly is used when many teeth have to be replaced and bridges or implants are not feasible or affordable.

Complete dentures are removable appliances used when no teeth remain. They help a patient chew and improve speech and appearance but do not provide the efficiency or sensation of natural dentition. When teeth are absent, the mandible slowly resorbs, resulting in ill-fitting dentures that require revision (called reline or rebase) or replacement. Alternatives are oral surgical procedures to enlarge the alveolar ridge or dental implants to replace missing teeth.

An **implant** is typically a titanium cylinder or screw that replaces a tooth root. One or more implants are placed into the alveolar bone, where they ankylose. After 4 to 6 mo, artificial teeth are attached to the implants. Implants are not readily removable, although the prostheses they support can be. The potential for infection at these sites warrants scrupulous attention to oral hygiene.

Dental appliances and surgery: Generally, all removable dental appliances are removed before general anesthesia, throat surgery, or convulsive therapy to prevent their breakage or aspiration. They are stored in water to prevent changes in shape. However, some anesthesiologists believe that leaving appliances in place aids the passage of an airway tube, keeps the face in a more normal shape so that the anesthetic mask fits better, prevents natural teeth from injuring the opposing gingiva of a completely edentulous jaw, and does not interfere with laryngoscopy.

Denture problems: Occasionally, the mucosa beneath a denture becomes inflamed (denture sore mouth, inflammatory papillary hyperplasia). Contributing factors to this usually painless condition include candidal infections, poor denture fit, poor hygiene, excessive movement of the denture, and, most frequently, wearing a denture 24 h/day. The mucosa appears red and velvety. Candidal overgrowth may be indicated by adherent cottonlike patches or, more commonly, erosive lesions on the mucosa. The presence of *Candida* can be confirmed by the microscopic appearance of typical branching hyphae. Without *Candida,* inflammatory papillary hyperplasia is unlikely.

A new well-made denture almost always improves the situation. Other treatments consist of improving oral and denture hygiene, refitting the existing denture, removing the denture for extended periods, and using anti-fungal therapy (nystatin rinses for the mouth and overnight nystatin soaks for the denture). Soaking the denture in a commercial cleanser is sometimes helpful. Other options are applying nystatin suspension to the tissue surface of the denture and clotrimazole troches 10 mg 5 times/day. Ketoconazole 200 mg po once/day may be required. If inflammation persists, biopsy is indicated, and systemic conditions should be ruled out.

Chapter 58. Dental Emergencies

Introduction

Emergency dental treatment by a physician is sometimes required when a dentist is unavailable.

Oral analgesics effective for most dental problems include acetaminophen 650 to 1000 mg q 6 h and NSAIDs such as ibuprofen 400 to 800 mg q 6 h. For severe pain, these drugs may be combined with opioids such as codeine 60 mg; hydrocodone 5 mg, 7.5 mg, or 10 mg; or oxycodone 5 mg.

Antibiotics for dental infections include penicillin VK 500 mg po q 6 h and clindamycin 300 mg po q 8 h.

Prophylactic antibiotics: Current American Heart Association guidelines (2007) recommend far fewer people use prophylactic antibiotics for prevention of infective endocarditis (IE—see p. 2199).

Coverage for dental procedures is recommended only for patients with prosthetic cardiac valves, previous IE, specific congenital heart diseases, and for cardiac transplant recipients with heart valve problems (valvulopathy). Dental procedures requiring prophylaxis are those that require manipulation or perforation of gingival or oral mucosa or that involve the root end area of the teeth (ie, those most likely to cause bacteremia). The preferred drug is amoxicillin 2 g po 30 to 60 min before the procedure. For those who cannot tolerate penicillins, alternatives include clindamycin 600 mg or cephalexin 2 g.

Fractured and Avulsed Teeth

Tooth fracture: Fractures are divided by depth into those that

• Affect only the enamel

• Expose the dentin

• Expose the pulp

If the fracture involves only the enamel, patients notice rough or sharp edges but are asymptomatic. Dental treatment to smooth the edges and improve appearance is elective.

If dentin is exposed but not the dental pulp, patients usually exhibit sensitivity to cold air and water. Treatment is a mild analgesic and referral to a dentist. Dental treatment consists of restoration of the tooth by a composite (white filling) or, if the fracture is extensive, a dental crown, to cover the exposed dentin.

If the pulp is exposed (indicated by bleeding from the tooth) or if the tooth is mobile, dental referral is urgent. Dental treatment usually involves a root canal.

Root fractures and alveolar fractures are not visible, but the tooth (or several teeth) may be mobile. Dental referral is also urgent for stabilization by bonding an orthodontic arch wire or polyethylene line onto several adjacent teeth.

Tooth avulsion: Avulsed primary teeth are not replaced because they typically become necrotic, then infected. They may also become ankylosed and do not exfoliate, thereby interfering with the eruption of the permanent tooth.

If a secondary tooth is avulsed, the patient should replace it in its socket immediately and seek dental care to stabilize it. If this cannot be done, the tooth should be kept immersed in milk or wrapped in a moistened paper towel and brought to a dentist for replacement and stabilization. The tooth should not be scrubbed, because scrubbing may remove viable periodontal ligament fibers, which aid in reattachment. A patient with an avulsed tooth should take an antibiotic for several days. If the avulsed tooth cannot be found, it may have been aspirated, embedded in soft tissue, or swallowed. A chest x-ray may be needed to rule out aspiration, but a swallowed tooth is harmless.

A partially avulsed tooth that is repositioned and stabilized quickly usually is permanently retained. A completely avulsed tooth may be permanently retained if replaced in the socket with minimal handling within 30 min to 1 h. Both partial and complete avulsions usually ultimately require root canal therapy because the pulp tissue becomes necrotic. When replacement of the tooth is delayed, the long-term retention rate drops, and root resorption eventually occurs. Nevertheless, a patient may be able to use the tooth for several years.

Mandibular Dislocation

Spontaneous mandibular dislocation usually occurs in people with a history of such dislocations. Although a dislocated mandible is occasionally caused by trauma, the initiating episode is typically a wide opening followed by biting pressure (eg, biting into a large

[
Fig. 58-1. Mandibular reduction.]

sandwich with hard bread), a wide yawn, or a dental procedure. People prone to dislocation may have naturally loose temporomandibular joint (TMJ) ligaments.

Patients present with a wide-open mouth that they are unable to close. Pain is secondary to patients' attempts to close the mouth. If the mandibular midline deviates to one side, the dislocation is unilateral. Although rarely used, a local anesthetic (eg, 2% lidocaine 2 to 5 mL) injected into the ipsilateral joint and into the adjacent area of insertion of the lateral pterygoid muscle may allow the mandible to reduce spontaneously.

Manual reduction may be necessary (see Fig. 58-1). Premedication may be used (eg, diazepam 5 to 10 mg IV at 5 mg/min or midazolam 3 to 5 mg IV at 2 mg/min and an opioid such as meperidine 25 mg IV or fentanyl 0.5 to 1 µg/kg IV) but is usually unnecessary, especially if time will be lost preparing the IV. The longer the mandible is dislocated, the more difficult it is to reduce and the greater the likelihood that dislocation will recur.

Barton's bandage may be needed for 2 or 3 days. Most importantly, the patient must avoid opening the mouth wide for at least 6 wk. When anticipating a yawn, the patient should place a fist under the chin to prevent wide opening. Food must be cut into small pieces. If the patient suffers from chronic dislocations and more conservative treatment modalities have been exhausted, an oral and maxillofacial surgeon may be consulted. As last-resort treatments, the ligaments around the TMJ can be surgically tightened (shortened) in an attempt to stabilize the joint or the articular eminence can be reduced (eminectomy).

Postextraction Problems

Pain and swelling: Swelling is normal after oral surgery and is proportional to the degree of manipulation and trauma. If swelling does not begin to subside by the 3rd postoperative day, infection is likely and an antibiotic may be given (eg, penicillin VK 500 mg po q 6 h until 72 h after symptoms subside).

Postoperative pain varies from moderate to severe and is treated with analgesics (see p. 1623).

Alveolitis and osteomyelitis: Postextraction alveolitis (dry socket) is pain emanating from bare bone if the socket's clot lyses. Although assumed to be due to bacterial action, it is much more common among smokers and oral contraceptive users. It is peculiar to the removal of mandibular molars, usually wisdom teeth. Typically, the pain begins on the 2nd or 3rd postoperative day, is referred to the ear, and lasts from a few days to many weeks. Alveolitis is best treated with topical analgesics: a 1- to 2-in iodoform gauze strip saturated in eugenol or coated with an anesthetic ointment, such as lidocaine 2.5% or tetracaine 0.5%, is placed in the socket. The gauze is changed every 1 to 3 days until symptoms do not return after the gauze is left out for a few hours. This procedure eliminates the need for systemic analgesics.

Osteomyelitis, which in rare cases is confused with alveolitis, is differentiated by fever, local tenderness,

and swelling. If symptoms last a month, a sequestrum, which is diagnostic of osteomyelitis, should be sought by x-ray. Osteomyelitis requires long-term treatment with antibiotics effective against both gram-positive and gram-negative organisms and referral for definitive care.

Osteonecrosis of the jaw (ONJ): ONJ (see also Sidebar 39-1 on p. 363) is an oral lesion involving persistent exposure of mandibular or maxillary bone, which usually manifests with pain, loosening of teeth, and purulent discharge. ONJ may occur after dental extraction but also may develop after trauma or radiation therapy to the head and neck. Recently, an association has been discovered between IV bisphosphonate (BP) use and ONJ. However, oral BP therapy seems to pose very low risk of ONJ. Stopping oral BP therapy is unlikely to reduce this already low rate of ONJ, and maintaining good oral hygiene is a more effective preventative measure than stopping oral BP before dental procedures. Management of ONJ is challenging and typically involves limited debridement, antibiotics, and oral rinses.

Bleeding: Postextraction bleeding usually occurs in the small vessels. Any clots extending out of the socket are removed with gauze, and a 4-in gauze pad (folded) or a tea bag is placed over the socket. Then the patient is instructed to apply continuous pressure by biting for 1 h. The procedure may have to be repeated 2 or 3 times. Patients are told to wait at least 1 h before checking the site so as not to disrupt clot formation. They also are informed that a few drops of blood diluted in a mouth full of saliva appear to be more blood than is actually present. If bleeding continues, the site may be anesthetized by nerve block or local infiltration with 2% lidocaine containing 1:100,000 epinephrine. The socket is then curetted to remove the existing clot and to freshen the bone and is irrigated with normal saline. Then the area is sutured under gentle tension. Local hemostatic agents, such as oxidized cellulose, topical thrombin on a gelatin sponge, or microfibrillar collagen, may be placed in the socket before suturing.

If possible, patients taking low-dose anticoagulants (eg, aspirin, clopedigrol, warfarin) should stop therapy 3 to 4 days before surgery. Therapy can be reinstated that evening. If these measures fail, a systemic cause (eg, bleeding diathesis) is sought.

Toothache and Infection

Pain in and around the teeth is a common problem, particularly among those with poor oral hygiene. Pain may be constant, felt after stimulation (eg, heat, cold, sweet food or drink, chewing, brushing), or both.

Etiology

The most common causes of toothache (see Table 58-1) are

- Dental caries
- Pulpitis
- Trauma
- Erupting wisdom tooth (causing pericoronitis)

Toothache is usually caused by dental caries and its consequences.

Caries causes pain when the lesion extends through the enamel into dentin. Pain usually occurs after stimulation from cold, heat, sweet food or drink, or brushing; these stimuli cause fluid to move along dentinal tubules to the pulp. As long as the discomfort does not persist after the stimulus is removed, the pulp is likely healthy enough to be maintained. This is referred to as normal dentinal sensitivity, reversible pulpalgia, or reversible pulpitis.

Pulpitis is inflammation of the pulp, typically due to advancing caries, cumulative minor pulp damage from previous large restorations, a defective restoration, or trauma. It may be reversible or irreversible. Pressure necrosis frequently results from pulpitis, because the pulp is encased in a rigid compartment. Pain may be spontaneous or in response to stimulation. In both cases, pain lingers for a minute or longer.

Once the pulp becomes necrotic, pain ends briefly (hours to weeks). Subsequently, periapical inflammation (apical periodontitis) or an abscess develops. The tooth is exquisitely sensitive to percussion (tapped with a metal dental probe or tongue blade) and chewing.

Periapical abscess may follow untreated caries or pulpitis. The abscess may point intraorally and eventually drain or may become a cellulitis.

Tooth trauma can damage the pulp. The damage may manifest soon after the injury or up to decades later.

Pericoronitis is inflammation and infection of the tissue between the tooth and its overlying flap of gingiva (operculum). It usually occurs in an erupting wisdom tooth (almost always a lower one).

Complications: Rarely, sinusitis results from untreated maxillary dental infection. More commonly, pain from a sinus infection is perceived as originating in the (unaffected) teeth, mistakenly creating the impression of a dental origin.

Rarely, cavernous sinus thrombosis (see p. 624) or Ludwig's angina (submandibular space infection—see p. 470) develops; these conditions are life threatening and require immediate intervention.

[**Table 58-1.** Some Causes of Toothache]

Evaluation

History: History of present illness should identify the location and duration of the pain and whether it is constant or present only after stimulation. Specific triggering factors to review include heat, cold, sweet food or drink, chewing, and brushing. Any preceding trauma or dental work should be noted.

Review of systems should seek symptoms of complications, including face pain, swelling, or both (dental abscess, sinusitis); pain below the tongue and difficulty swallowing (submandibular space infection); pain with bending forward (sinusitis); and retro-orbital headache, fever, and vision symptoms (cavernous sinus thrombosis).

Past medical history should note previous dental problems and treatment.

Physical examination: Vital signs are reviewed for fever.

The examination focuses on the face and mouth. The face is inspected for swelling and is palpated for induration and tenderness.

The oral examination includes inspection for gum inflammation and caries and any localized swelling at the base of a tooth that may represent a pointing apical abscess. If no tooth is clearly involved, teeth in the area of pain are percussed for tenderness with a tongue depressor. Also, an ice cube can be applied briefly to each tooth, removing it immediately once pain is felt. In healthy teeth, the pain stops almost immediately. Pain lingering more than a few seconds indicates pulp damage (eg, irreversible pulpitis, necrosis). The floor of the mouth is palpated for induration and tenderness, suggesting a deep space infection.

Neurologic examination, concentrating on the cranial nerves, should be done in those with fever, headache, or facial swelling.

Red flags: Findings of particular concern are

• Headache

• Fever

• Swelling or tenderness of floor of the mouth

• Cranial nerve abnormalities

Interpretation of findings: Red flag finding of headache suggests sinusitis, particularly if multiple upper molar and premolar (back) teeth are painful. However, presence of vision symptoms or abnormalities of the pupils or of ocular motility suggests cavernous sinus thrombosis.

Fever is unusual with routine dental infection unless there is significant local extension. Bilateral tenderness of the floor of the mouth suggests Ludwig's angina.

[
Table 58-2. Characteristics of Pain in Toothache]

Difficulty opening the mouth (trismus) can occur with any lower molar infection but is common only with pericoronitis.

Isolated dental condition: Patients without red flag findings or facial swelling likely have an isolated dental condition, which, although uncomfortable, is not serious. Clinical findings, particularly the nature of the pain, help suggest a cause (see Tables 58-1 and 58-2). Because of its innervation, the pulp can perceive stimuli (eg, heat, cold, sweets) only as pain. An important distinction is whether there is continuous pain or pain only on stimulation and, if pain is only on stimulation, whether the pain lingers after the stimulus is removed.

Swelling at the base of a tooth, on the cheek, or both indicates infection, either cellulitis or abscess. A tender, fluctuant area at the base of a tooth suggests a pointing abscess.

Testing: Dental x-rays are the mainstay of testing but can be deferred to a dentist.

The rare cases in which cavernous sinus thrombosis or Ludwig's angina are suspected require imaging studies, typically CT or MRI.

Treatment

Analgesics (see p. 1623) are given pending dental evaluation and definitive treatment. A patient who is seen frequently for emergencies but who never receives definitive dental treatment despite availability may be seeking opioids.

Antibiotics directed at oral flora are given for most disorders beyond irreversible pulpitis (eg, necrotic pulp, apical periodontitis, abscess, cellulitis). The patient with pericoronitis also should receive an antibiotic. However, antibiotics can be deferred if the patient can be seen the same day by a dentist, who may be able to treat the infection by removing the source (eg, by extraction, pulpectomy, or curettage). When antibiotics are used, penicillin is preferred, with clindamycin the alternative.

An **abscess** associated with well-developed (soft) fluctuance is typically drained through an incision with a #15 scalpel blade at the most dependent point of the swelling. A rubber drain, held by a suture, is often placed.

Pericoronitis or erupting 3rd molars are treated with chlorhexidine 0.12% rinses or hypertonic saltwater soaks (1 tbsp salt mixed in a glass of hot water—no hotter than the coffee or tea a patient normally drinks). The salt water is held in the mouth on the affected side until it cools and then is expectorated and immediately replaced with another mouthful. Three or 4 glasses of salt water a day usually control inflammation and pain pending dental evaluation.

Teething pain in young children may be treated with weight-based doses of acetaminophen or ibuprofen. Topical treatments can include chewing hard crackers (eg, biscotti), applying 7.5% or 10% benzocaine gel qid (provided there is no family history of methemoglobinemia), and chewing on anything cold (eg, gel-containing teething rings).

The rare patient with cavernous sinus thrombosis or Ludwig's angina requires immediate hospitalization, removal of the infected tooth, and culture-guided parenteral antibiotics.

Geriatrics Essentials

The elderly are more prone to caries of the root surfaces, usually because of gingival recession. Periodontitis often begins in young adulthood; if untreated, tooth pain and loss are common in old age.

Key Points

- Most toothache involves dental caries or its complications (eg, pulpitis, abscess).
- Symptomatic treatment and dental referral are usually adequate.
- Antibiotics are given if signs of a necrotic pulp or more severe conditions are present.
- Very rare but serious complications include extension of dental infection to the floor of the mouth or to the cavernous sinus.
- Dental infections rarely cause sinusitis, but sinus infection may cause pain perceived as originating in the teeth.

Chapter 59. Temporomandibular Disorders

Introduction

(See also Mandibular Dislocation on p. 524, Temporal Bone Fractures on p. 3234, and Jaw Tumors on p. 489.)

The term temporomandibular disorders is an umbrella term for conditions causing dysfunction of the jaw joint or pain in the jaw and face, often in or around the temporomandibular joint (TMJ), including masticatory and other muscles of the head and neck, the fascia, or both. A person is considered to have a temporomandibular disorder only if pain or limitation of motion is severe enough to require professional care.

Temporomandibular disorders typically are multifactorial, but most are related to problems with muscles or joints. Internal derangements of the TMJ cause disturbed movement of the mandibular condyle in the glenoid fossa or against the cartilaginous articular disk (see Fig. 59-1). This disk, shaped like a donut with a closed hole or like a mature red blood cell, serves as a cushion between joint surfaces. Causes for this disturbed movement include clenching and grinding of the teeth, trauma, arthritis, and malocclusion and missing teeth. Even the trauma of persistent gum chewing can be enough to damage the joint.

Diagnosis

Disorders of the TMJ must be distinguished from the many conditions that mimic them (see Table 59-1). Pain exacerbated by finger pressure on the joint when the mouth is opened implicates the TMJ.

Patients are asked to describe the pain and designate painful areas. The cervical and occipital muscles and each of the major muscle groups involved in mastication are palpated for general tenderness and trigger points (spots

[**Fig. 59-1.** The temporomandibular joint.]

that radiate pain to another area). Patients are observed opening the mouth as wide as is comfortable. When patients open and close their mouth with the junction of the maxillary and mandibular central incisors (normally in the midline) lined up against a vertical straight edge, the mandibular midline typically deviates toward the painful side. Palpation and auscultation of the joint during opening and closing may reveal tenderness, catching, clicking, or popping. Condylar motion can best be palpated by placing the 5th fingers into the external ear canals and exerting very gentle forward pressure as patients move the jaw. The average-sized patient can open the mouth at least 40 to 45 mm (measured between upper and lower central incisors). To account for differences in patient size, a patient should be able to fit 3 fingers (index, middle, ring) in the mouth on top of each other.

Ankylosis of the Temporomandibular Joint

Ankylosis of the TMJ is immobility or fusion of the joint.

Ankylosis of the TMJ most often results from trauma or infection, but it may be congenital or a result of RA. Chronic, painless limitation of motion occurs. When ankylosis leads to arrest of condylar growth, facial asymmetry is common (see Condylar Hyperplasia on p. 532). Intra-articular (true) ankylosis must be distinguished from extra-articular (false) ankylosis, which may be caused by enlargement of the coronoid process, depressed fracture of the zygomatic arch, or scarring resulting from surgery, irradiation, or infection. In most cases of true ankylosis, x-rays of the joint show loss of normal bony architecture.

Treatment may include a condylectomy if the ankylosis is intra-articular or an ostectomy of part of the ramus if the coronoid process and zygomatic arch are also affected. Jaw-opening exercises must be done for months to years to maintain the surgical correction, but forced opening of the jaws without surgery is generally ineffective because of bony fusion.

Arthritis of the Temporomandibular Joint

Infectious arthritis, traumatic arthritis, osteoarthritis, RA, and secondary degenerative arthritis can affect the TMJ.

Infectious arthritis: Infection of the TMJ may result from direct extension of adjacent infection or hematogenous spread of blood-borne organisms (see also Acute Infectious Arthritis on p. 365). The area is inflamed, and jaw movement is limited. Local signs of infection associated with evidence of a systemic disease or with an adjacent infection suggest the diagnosis. X-ray results are negative in the early stages but may show bone destruction later. If suppurative arthritis is suspected, the joint is aspirated to confirm the diagnosis and to identify the causative organism. Diagnosis must be made rapidly to prevent permanent joint damage.

[Table 59-1. Some Conditions that Mimic Temporomandibular Disorders]

Treatment includes antibiotics, proper hydration, pain control, and motion restriction. Parenteral penicillin G is the drug of choice until a specific bacteriologic diagnosis can be made on the basis of culture and sensitivity testing. Suppurative infections are aspirated or incised. Once the infection is controlled, jaw-opening exercises help prevent scarring and limitation of motion.

Traumatic arthritis: Rarely, acute injury (eg, due to difficult tooth extraction or endotracheal intubation) may lead to arthritis of the TMJ. Pain, tenderness, and limitation of motion occur. Diagnosis is based primarily on history. X-ray results are negative except when intra-articular edema or hemorrhage widens the joint space. Treatment includes NSAIDs, application of heat, a soft diet, and restriction of jaw movement.

Osteoarthritis: The TMJ may be affected, usually in people > 50 yr. Occasionally, patients complain of stiffness, grating, or mild pain. Crepitus results from a hole worn through the disk, causing bone to grate on bone. Joint involvement is generally bilateral. X-rays or CT may show flattening and lipping of the condyle, suggestive of dysfunctional change. Treatment is symptomatic.

Rheumatoid arthritis: The TMJ is affected in > 17% of adults and children with RA, but it is usually among the last joints involved. Pain, swelling, and limited movement are the most common findings. In children, destruction of the condyle results in mandibular growth disturbance and facial deformity. Ankylosis may follow. X-rays of the TMJ are usually negative in early stages but later show bone destruction, which may result in an anterior open-bite deformity. The diagnosis is suggested by TMJ inflammation associated with polyarthritis and is confirmed by other findings typical of the disease.

Treatment is similar to that of RA in other joints. In the acute stage, NSAIDs may be given, and jaw function should be restricted. A night guard or splint is often helpful. When symptoms subside, mild jaw exercises help prevent excessive loss of motion. Surgery is necessary if ankylosis develops but should not be done until the condition is quiescent.

Secondary degenerative arthritis: This type of arthritis usually develops in people aged 20 to 40 after trauma or in people with persistent myofascial pain syndrome (see p. 533). It is characterized by limited opening of the mouth, unilateral pain during jaw movement, joint tenderness, and crepitus. When it is associated with the myofascial pain syndrome, symptoms wax and wane. Diagnosis is based on x-rays, which generally show condylar flattening, lipping, spurring, or erosion. Unilateral joint involvement helps distinguish secondary degenerative arthritis from osteoarthritis.

Treatment is conservative, as it is for myofascial pain syndrome, although arthroplasty or high condylectomy may be necessary. An occlusal splint (mouth guard) usually relieves symptoms. The splint is worn constantly, except during meals, oral hygiene, and appliance cleaning. When symptoms resolve, the length of time that the splint is worn each day is gradually reduced. Intra-articular injection of corticosteroids may relieve symptoms but may harm the joint if repeated often.

Condylar Hyperplasia

Condylar hyperplasia is a disorder of unknown etiology characterized by persistent or accelerated growth of the condyle when growth should be slowing or ended. Growth eventually stops without treatment.

Slowly progressive unilateral enlargement of the head and neck of the condyle causes crossbite malocclusion, facial asymmetry, and shifting of the midpoint of the chin to the unaffected side. The patient may appear prognathic. The lower border of the mandible is often convex on the affected side. Chondroma and osteochondroma may cause similar symptoms and signs, but they grow more rapidly and may cause even greater asymmetric condylar enlargement.

Diagnosis

• Plain x-rays

• Usually CT

On x-ray, the temporomandibular joint may appear normal, or the condyle may be proportionally enlarged and the mandibular neck elongated. CT is usually done to determine whether bone growth is generalized, which confirms the diagnosis, or localized to part of the condylar head. If growth is localized, a biopsy may be necessary to distinguish between tumor and hyperplasia.

Treatment

• During active growth, usually condylectomy

• After growth cessation, orthodontics or surgical mandibular repositioning

Treatment usually includes condylectomy during the period of active growth. If growth has stopped, orthodontics and surgical mandibular repositioning are indicated. If the height of the mandibular body is greatly increased, facial symmetry can be further improved by reducing the inferior border.

Condylar Hypoplasia

Condylar hypoplasia is facial deformity caused by a short mandibular ramus.

This condition usually results from trauma, infection, or irradiation occurring during the growth period but may be idiopathic. The deformity involves fullness of the face, deviation of the chin to the affected side, an elongated mandible, and flatness of the face on the unaffected side. (The side to which the ramus is short causes muscles to appear fuller; the muscles on the unaffected side are stretched so that side appears flatter.) Mandibular deviation causes malocclusion.

Diagnosis is based on a history of progressive facial asymmetry during the growth period, x-ray evidence of condylar deformity and antegonial notching (a depression in the inferior border of the mandible just anterior to the angle of the mandible), and, frequently, a causative history.

Treatment consists of surgical shortening of the unaffected side of the mandible or lengthening of the affected side. Presurgical orthodontic therapy helps optimize results.

Internal Joint Derangement

The most common form of internal joint derangement is anterior misalignment or displacement of the articular disk above the condyle. Symptoms are localized joint pain and popping on jaw movement. Diagnosis is based on history and physical examination. Treatment is with analgesics, jaw rest, muscle relaxation, physical therapy, and bite splinting. If these methods fail, surgery may be necessary. Early treatment greatly improves results.

The superior head of the lateral pterygoid muscle may pull the articular disk out of place when abnormal

jaw mechanics place unusual stress on the joint. Abnormal jaw mechanics can be due to congenital or acquired asymmetries or to the sequelae of trauma or arthritis. If the disk remains anterior, the derangement is said to be without reduction. Restricted jaw opening (locked jaw) and pain in the ear and around the temporomandibular joint result. If at some point in the joint's excursion the disk returns to the head of the condyle, it is said to be with reduction. Derangement with reduction occurs in about one third of the population at some point. All types of derangement can cause capsulitis (or synovitis), which is inflammation of the tissues surrounding the joint (eg, tendons, ligaments, connective tissue, synovium). Capsulitis can also occur spontaneously or result from arthritis, trauma, or infection.

Symptoms and Signs

Derangement with reduction often causes a clicking or popping sound when the mouth is opened. Pain may be present, particularly when chewing hard foods. Patients are often embarrassed because they think others can hear noise when they chew. Indeed, although the sound seems louder to the patient, others can sometimes hear it.

Derangement without reduction usually causes no sound, but maximum opening between the tips of the upper and lower incisors is reduced from the normal 40 to 45 mm to ≤ 30 mm. Pain and a change in the patients' perception of their bite generally result.

Capsulitis results in localized joint pain, tenderness, and, sometimes, restricted opening.

Diagnosis

• Clinical evaluation

Diagnosis of derangement with reduction requires observation of the jaw when the mouth is opened. When the jaw is opened > 10 mm (measured between upper and lower incisors), a click or pop is heard or a catch is felt as the disk pops back over the head of the condyle. The condyle remains on the disk during further opening. Usually, another click is heard during closing when the condyle slips over the posterior rim of the disk and the disk slips forward (reciprocal clicking).

Diagnosis of derangement without reduction requires that the patient open as wide as possible. The opening is measured, and gentle pressure is then exerted to open the mouth a little wider. Normally, the jaw opens about 45 to 50 mm; if the disk is deranged, it will open about 20 mm. Closing or protruding the jaw against resistance worsens the pain.

MRI is usually done to confirm presence of derangement or to determine why a patient is not responding to treatment.

Capsulitis is often diagnosed based on a history of injury or infection along with exquisite tenderness over the joint and by exclusion when pain remains after treatment for myofascial pain syndrome, disk derangement, arthritis, and structural asymmetries. However, capsulitis may be present with any of these conditions.

Treatment

• Analgesics as needed

• Sometimes repositioning splint or surgery

• Sometimes corticosteroid injection for capsulitis

Derangement with reduction does not require treatment if the patient can open reasonably wide (about 40 mm or the width of the index, middle, and ring fingers) without discomfort. If pain occurs, mild analgesics, such as NSAIDs (ibuprofen 400 mg po q 6 h), can be used. If onset is < 6 mo, an anterior repositioning splint may be used to position the mandible forward and on the disk. The splint is a horseshoe-shaped appliance of hard, transparent acrylic (plastic) made to fit snugly over the teeth of one arch. Its chewing

surface is designed to hold the mandible forward when the patient closes on the splint. In this position, the disk is always on the head of the condyle. The splint is gradually adjusted to allow the mandible to move posteriorly. If the disk stays with the condyle as the superior head of the external pterygoid stretches, the disk is said to be captured. The longer the disk is displaced, the more deformed it becomes and the less likely repositioning will succeed. Surgical plication of the disk may be done, with variable success.

Derangement without reduction may not require treatment other than analgesics. Splints may help if the articular disk has not been significantly deformed, but long-term use may result in irreversible changes in oral architecture. In some cases, the patient is instructed to slowly stretch the disk out of position, which allows the jaw to open normally. Various arthroscopic and open surgical procedures are available when conservative treatment fails.

Capsulitis is initially treated with NSAIDs, jaw rest, and muscle relaxation. If these treatments are unsuccessful, corticosteroids may be injected into the joint, or arthroscopic joint lavage and debridement are used.

Myofascial Pain Syndrome

Myofascial pain syndrome can occur in patients with a normal temporomandibular joint. It is caused by tension, fatigue, or spasm in the masticatory muscles (medial or internal and lateral or external pterygoids, temporalis, and masseter). Symptoms include bruxism, pain and tenderness in and around the masticatory apparatus or referred to other locations in the head and neck, and, often, abnormalities of jaw mobility. Diagnosis is based on history and physical examination. Conservative treatment, including analgesics, muscle relaxation, habit modification, and bite splinting, usually is effective.

This syndrome is the most common disorder affecting the temporomandibular region. It is more common among women and has a bimodal age distribution in the early 20s and around menopause. The muscle spasm causing the disorder usually is the result of nocturnal bruxism (clenching or grinding of the teeth). Whether bruxism is caused by irregular tooth contacts, emotional stress, or sleep disorders is controversial. Bruxism usually has a multifactorial etiology. Myofascial pain syndrome is not limited to the muscles of mastication. It can occur anywhere in the body, most commonly involving muscles in the neck and back.

Symptoms and Signs

Symptoms include pain and tenderness of the masticatory muscles and often pain and limitation of jaw excursion. Nocturnal bruxism may lead to headache that is more severe on awakening and that gradually subsides during the day. Such pain should be distinguished from temporal arteritis. Daytime symptoms, including headache, may worsen if bruxism continues throughout the day.

The jaw deviates when the mouth opens but usually not as suddenly or always at the same point of opening as it does with internal joint derangement (see p. 532). Exerting gentle pressure, the examiner can open the patient's mouth another 1 to 3 mm beyond unaided maximum opening.

Diagnosis

• Clinical evaluation

A simple test may aid the diagnosis: Tongue blades of 2 or 3 thicknesses are placed between the rear molars on each side, and the patient is asked to bite down gently. The distraction produced in the joint space may ease the symptoms. X-rays usually do not help except to rule out arthritis. If temporal arteritis is suspected, ESR is measured.

Treatment

• Mild analgesics

- Splint or mouth guard
- An anxiolytic at bedtime considered
- Physical therapy modalities considered

A plastic splint or mouth guard from the dentist can keep teeth from contacting each other and prevent the damages of bruxism. Comfortable, heat-moldable splints are available from many sporting goods stores or drugstores. Low doses of a benzodiazepine at bedtime are often effective for acute exacerbations and temporary relief of symptoms. Mild analgesics, such as NSAIDs or acetaminophen, are indicated. Cyclobenzaprine may help muscle relaxation in some people. Because the condition is chronic, opioids should not be used, except perhaps briefly for acute exacerbations. The patient must learn to stop clenching the jaw and grinding the teeth. Hard-to-chew foods and chewing gum should be avoided. Physical therapy, biofeedback to encourage relaxation, and counseling help some patients. Physical modalities include transcutaneous electric nerve stimulation and "spray and stretch," in which the jaw is stretched open after the skin over the painful area has been chilled with ice or sprayed with a skin refrigerant, such as ethyl chloride. Botulinum toxin has recently been used successfully to relieve muscle spasm in myofascial pain syndrome. Most patients, even if untreated, stop having significant symptoms within 2 to 3 yr.

6 - Eye Disorders

Chapter 60. Approach to the Ophthalmologic Patient

Introduction

The eye can be examined with routine equipment, including a standard ophthalmoscope; thorough examination requires special equipment and evaluation by an ophthalmologist. (See Fig. 60-1 for a cross-section of the eye.)

History

History includes location, speed of onset, and duration of current symptoms and history of previous ocular symptoms; the presence and nature of pain, discharge, or redness; and changes in visual acuity. Worrisome symptoms besides vision loss and eye pain include flashing lights, showers of floaters (both of which may be symptoms of retinal detachment), diplopia, and loss of peripheral vision.

Physical Examination

Visual acuity: The first step is to record visual acuity. Many patients do not give a full effort. Providing adequate time and coaxing patients tend to yield more accurate results. Visual acuity is measured with and without the patient's own glasses. If patients do not have their glasses, a pinhole refractor is used. If a commercial pinhole refractor is unavailable, one can be made at the bedside by poking holes through a piece of cardboard using an 18-gauge needle and varying the diameter of each hole slightly. Patients choose the hole that corrects vision the most. If acuity corrects with pinhole refraction, the problem is a refractive error. Pinhole refraction is a rapid, efficient way to diagnose refractive errors, which are the most common cause of blurred vision. However, with pinhole refraction, best correction is usually to only about 20/30, not 20/20.

[**Fig. 60-1.** Cross-section of the eye.]

Visual acuity in each eye is tested as the opposite eye is covered with a solid object (not the patient's fingers, which may separate during testing). Patients look at an eye chart 20 ft (6 m) away. If this test cannot be done, acuity can be measured using a chart held about 36 cm (14 in) from the eye. Normal and abnormal vision is quantified by Snellen notation. A Snellen notation of 20/40 (6/12) indicates that the smallest letter that can be read by someone with normal vision at 40 ft (12 m) has to be brought to 20 ft (6 m) before it is recognized by the patient. Vision is recorded as the smallest letter patients read correctly, even if patients feel that the letter is blurry or they have to guess. If the patient cannot read the top line of the Snellen chart at 20 ft (6 m), acuity is tested at 10 ft (3 m). If nothing can be read from a chart even at the closest distance, the examiner holds up different numbers of fingers to see whether the patient can accurately count them. If not, the examiner tests whether the patient can perceive hand motion. If not, a light is shined into the eye to see whether light is perceived.

Near vision is checked by asking patients to read a standard near card or newsprint at 14 in (35 cm); patients > 40 yr who require corrective lenses (reading glasses) should wear them during near vision testing.

Refractive error can be estimated roughly with a handheld ophthalmoscope by noting the lens necessary for the examiner to focus on the retina; this procedure requires examiners to use their own corrective lenses and is never a substitute for a comprehensive assessment of refraction. More commonly, refractive error is measured with a standard phoropter or an automated refractor (a device that measures changes in light projected and reflected by the patient's eye). These devices also measure astigmatism (see p. 571).

Eyelid and conjunctival examination: Eyelid margins and periocular cutaneous tissues are examined under a focal light and magnification (eg, provided by loupe, slit lamp, or ophthalmoscope focused at the examiner's working distance). In cases of suspected dacryocystitis or canaliculitis, the lacrimal sacs are palpated and an attempt is made to express any contents through the canaliculi and puncta. After eyelid

eversion, the palpebral and bulbar conjunctivae and the fornices can be inspected for foreign bodies, signs of inflammation (eg, follicular hypertrophy, exudate, hyperemia, edema), or other abnormalities.

Corneal examination: Indistinct or blurred edges of the corneal light reflex (reflection of light from the cornea when illuminated) suggest the corneal surface is not intact or is roughened, as occurs with a corneal abrasion or keratitis. Fluorescein staining reveals abrasions and ulcers. Before staining, a drop of topical anesthetic (eg, proparacaine 0.5%, tetracaine 0.5%) may be added to facilitate examination if the patient is in pain or if it is necessary to touch the cornea or conjunctiva (eg, to remove a foreign body or measure intraocular pressure). A sterile, individually packaged fluorescein strip is moistened with 1 drop of sterile saline or topical anesthetic and, with the patient's eye turned upward, is touched momentarily to the inside of the lower eyelid. The patient blinks several times to spread the dye into the tear film, and then the eye is examined under magnification and cobalt blue illumination. Areas where corneal or conjunctival epithelium is absent (abraded or ulcerated) fluoresce green.

Pupil examination: The size and shape of the pupils are noted, and pupillary reaction to light is tested in each eye, one at a time, while the patient looks in the distance. Then the swinging flashlight test is done with a penlight to compare direct and consensual pupillary response. There are 3 steps:

1. One pupil is maximally constricted by being exposed to light from the penlight for 1 to 3 sec.

2. The penlight is rapidly moved to the other eye for 1 to 3 sec.

3. The light is moved back to the first eye.

Normally, a pupil constricts similarly when light is shone on it (direct response) and when light is shone on the other eye (consensual response). However, if one eye has less light perception than the other, as caused by dysfunction of the afferent limb (from the optic nerve to the optic chiasm) or extensive retinal disease, then the *consensual* response in the affected eye is stronger than the *direct* response. Thus, on step 3 of the swinging light test, when the light is shined back on the affected eye, it paradoxically appears to dilate. This finding indicates a relative afferent pupillary defect (RAPD, or Marcus Gunn pupil).

Extraocular muscles: The examiner guides the patient to look in 8 directions (up, up and right, right, down and right, down, down and left, left, left and up) with a moving finger, penlight, or transillumination light, observing for gaze deviation, limitation of movement, disconjugate gaze, or a combination consistent with cranial nerve palsy, orbital disease, or other abnormalities that restrict movement.

Ophthalmoscopy: Ophthalmoscopy can be done directly by using a handheld ophthalmoscope or indirectly by using a head-mounted ophthalmoscope with a handheld lens. With handheld ophthalmoscopy, the examiner dials the ophthalmoscope to zero diopters, then increases or decreases the setting until the fundus comes into focus. The view of the retina is limited with a handheld ophthalmoscope, whereas indirect ophthalmoscopy gives a 3-dimensional view and is better for visualizing the peripheral retina, where retinal detachment most commonly occurs. The view of the fundus can be improved by dilating the pupils. Before dilation, the anterior chamber depth is estimated because mydriasis can precipitate an attack of acute angle-closure glaucoma if the anterior chamber is shallow. Depth can be estimated with a slit lamp (see below) or less accurately with a penlight held at the temporal limbus parallel to the plane of the iris and pointed toward the nose. If the medial iris is in shadow, the chamber is shallow and dilation should be avoided. Other contraindications to dilation include head trauma, suspicion of a ruptured globe, a narrow angle, and angle-closure glaucoma.

Pupils can be dilated using 1 drop of tropicamide 1%, phenylephrine 2.5%, or both (repeated in 5 to 10 min if necessary); for longer action, a larger dilated pupil, or both, cyclopentolate 1% can be substituted for tropicamide.

Ophthalmoscopy can detect lens or vitreous opacities, assess the optic cup-to-disk ratio, and identify retinal and vascular changes. The optic cup is the central depression, and the optic disk is the entire area of the optic nerve head. The normal ratio of the cup-to-nerve diameters is 0 to 0.4. A ratio of ≥ 0.5 may signify loss of ganglion cells and may be a sign of glaucoma. Retinal changes include hemorrhage, manifested as small or large areas of blood, and drusen (small subretinal yellow-white spots that may

signify dry age-related macular degeneration). Vascular changes include arteriovenous nicking, a sign of chronic hypertension in which retinal veins are compressed by arteries where the two cross; copper wiring, a sign of arteriosclerosis in which thickened arteriolar walls increase the thickness of the light reflex; silver wiring, a sign of hypertension in which thin, fibrotic arteriolar walls decrease the thickness of the light reflex; and loss of venous pulsations, a sign of increased intracranial pressure in patients known to have had pulsations.

Slit-lamp examination: A slit lamp focuses the height and width of a beam of light for a precise stereoscopic view of the eyelids, conjunctiva, cornea, anterior chamber, iris, lens, and anterior vitreous. It is especially useful for the following:

- Identifying corneal foreign bodies and abrasions
- Measuring depth of the anterior chamber
- Detecting cells (RBCs or WBCs) and flare (evidence of protein) in the anterior chamber
- Identifying ciliary flush (dilation of blood vessels localized to the limbal region overlying the ciliary body), which occurs with uveitis
- Identifying scleral edema, which is seen as a bowing forward of the slit beam when it is focused beneath the conjunctiva and which is usually a sign of scleritis

Tonometry (see p. 540) and gonioscopy, which quantifies the iridocorneal angle and requires the use of a special lens, may be done.

Visual field testing: Visual fields may be impaired by lesions anywhere in the neural visual pathways from the optic nerves to the occipital lobes (see Table 60-1 and Fig. 69-1 on p. 620). Glaucoma causes loss of peripheral vision. Fields can be assessed grossly by direct confrontation testing or by more precise, detailed testing.

In **direct confrontation**, patients maintain a fixed gaze at the examiner's eye or nose. The examiner brings a small target (eg, a match or a finger) from the patients' visual periphery into each of the 4 visual quadrants and asks patients to indicate when they first see the object. Wiggling the small target helps patients separate and define it. Another method of direct confrontation visual field testing is to hold a number of fingers in each quadrant and ask patients how many they see. For both methods, each eye is tested separately. Abnormalities in target detection should prompt detailed testing with more precise instruments.

More detailed methods include use of a tangent screen, Goldmann perimeter, or computerized automated perimetry (in which the visual field is mapped out in detail based on patient response to a series of flashing lights in different locations controlled by a standardized computer program). The Amsler grid is used to test central vision. Distortion of the grid (metamorphopsia) or a missing area (central scotoma) may indicate disease of the macula (eg, choroidal neovascularization), as occurs in age-related macular degeneration.

Color vision testing: Twelve to 24 Ishihara color plates, which have colored numbers or symbols hidden in a field of colored dots, are commonly used to test color vision. Colorblind patients or patients with acquired color deficiency (eg, in optic nerve diseases) cannot see some or all of the hidden numbers. Most

[**Table 60-1.** Types of Field Defects]

congenital color blindness is red-green; most acquired (eg, caused by glaucoma or optic nerve disease) is blue-yellow.

Testing

Tonometry: Tonometry measures intraocular pressure by determining the amount of force needed to indent the cornea. Handheld pen-type tonometers are used for screening. This test requires topical anesthesia (eg, proparacaine 0.5%). Office-based screening with noncontact air-puff tonometry also can be used; it requires less training because it makes no direct corneal contact. Goldmann applanation tonometry is the most accurate method but requires more training and typically is used only by ophthalmologists. Measurement of intraocular pressure alone is not adequate screening for glaucoma; the optic nerve also should be examined.

Fluorescein angiography: After IV injection of fluorescein solution, the retinal, choroidal, optic disk, or iris vasculature is photographed in rapid sequence. Fluorescein angiography is used to investigate underperfusion and neovascularization in conditions such as diabetes, age-related macular degeneration, retinal vascular occlusion, and ocular histoplasmosis. It is also useful in preoperative assessment for retinal laser procedures.

Electroretinography: Electrodes are placed on each cornea and on the surrounding skin, and electrical activity in the retina is recorded. This technique evaluates retinal function in patients with retinal degeneration. It does not evaluate vision.

Ultrasonography: B-mode ultrasonography provides 2-dimensional structural information even in the presence of opacities of the cornea and lens. Examples of ophthalmologic applications include assessment of retinal tumors, detachments, and vitreous hemorrhages; location of foreign bodies; detection of posterior scleral edema characteristic of posterior scleritis; and distinction of choroidal melanoma from metastatic carcinoma and subretinal hemorrhage.

A-mode ultrasonography is 1-dimensional ultrasonography used to determine the axial length of the eye, a measurement needed to calculate the power of an intraocular lens for implantation as a part of cataract surgery.

Ultrasonic pachymetry is use of ultrasonography to measure the thickness of the cornea before refractive surgery (eg, LASIK) and in patients with corneal dystrophies.

CT and MRI: These imaging techniques most often are used for evaluation of ocular trauma, particularly if an intraocular foreign body is suspected, and in the evaluation of orbital tumors, optic neuritis, and optic nerve tumors. MRI should not be done when there is suspicion of a metallic intraocular foreign body.

Electronystagmography: See p. 414.

Acute Vision Loss

Loss of vision is usually considered acute if it develops within a few minutes to a couple of days. It may affect one or both eyes and all or part of a visual field. Patients with small visual field defects (eg, caused by a small retinal detachment) may describe their symptoms as blurred vision.

Pathophysiology

Acute loss of vision has 3 general causes:

- Opacification of normally transparent structures through which light rays pass to reach the retina (eg, cornea, vitreous)
- Retinal abnormalities
- Abnormalities affecting the optic nerve or visual pathways

Etiology

The most common causes of acute loss of vision are

• Vascular occlusions of the retina (central retinal artery occlusion, central retinal vein occlusion)

• Ischemic optic neuropathy (often in patients with temporal arteritis)

• Vitreous hemorrhage (caused by diabetic retinopathy or trauma)

• Trauma

In addition, sudden recognition of loss of vision (pseudo-sudden loss of vision) may manifest initially as sudden onset. For example, a patient with long-standing reduced vision in one eye (possibly caused by a dense cataract) suddenly is aware of the reduced vision in the affected eye when covering the unaffected eye.

Presence or absence of pain helps categorize loss of vision (see Table 60-2).

Most disorders that cause total loss of vision when they affect the entire eye may affect only part of the eye and cause only a visual field defect (eg, branch occlusion of the retinal artery or retinal vein, focal retinal detachment).

Less common causes of acute loss of vision include

• Anterior uveitis (a common disorder, but one that usually causes eye pain severe enough to trigger evaluation before vision is lost)

• Highly aggressive retinitis

• Certain drugs (eg, methanol, salicylates, ergot alkaloids, quinine)

Evaluation

History: History of present illness should describe loss of vision in terms of onset, duration, progression, and location (whether it is monocular or binocular and whether it involves the entire visual field or a specific part and which part). Important associated visual symptoms include floaters, flashing lights, halos around lights, distorted color vision,

[**Table 60-2.** Some Disorders that Cause Acute Vision Loss]

and jagged or mosaic patterns (scintillating scotomata). The patient should be asked about eye pain and whether it is constant or occurs only with eye movement.

Review of systems should seek extraocular symptoms of possible causes, including jaw or tongue claudication, temporal headache, proximal muscle pain, and stiffness (giant cell arteritis); and headaches (ocular migraine).

Past medical history should seek known risk factors for eye disorders (eg, contact lens use, severe myopia, recent eye surgery or injury), risk factors for vascular disease (eg, diabetes, hypertension), and hematologic disorders (eg, sickle cell anemia or disorders such as Waldenstrom's macroglobulinemia or multiple myeloma that could cause a hyperviscosity syndrome).

Family history should note any family history of migraine headaches.

Physical examination: Vital signs, including temperature, are measured.

If the diagnosis of a transient ischemic attack is under consideration, a complete neurologic examination is done. The facial skin is inspected for vesicles or ulcers in the V_1 distribution (ophthalmic division of the trigeminal nerve), and the temples are palpated for pulses, tenderness, or nodularity over the course of

the temporal artery. However, most of the examination focuses on the eye.

Eye examination includes the following:

• Visual acuity is measured.

• Peripheral visual fields are assessed by confrontation.

• Central visual fields are assessed by Amsler grid.

• Direct and consensual pupillary light reflexes are examined using the swinging flashlight test.

• Ocular motility is assessed.

• Color vision is tested with color plates.

• The eyelids, sclera, and conjunctiva are examined using a slit lamp if possible.

• The cornea is examined with fluorescein staining.

• The anterior chamber is examined for cells and flare in patients who have eye pain or conjunctival injection.

• The lens is checked for cataracts using a direct ophthalmoscope, slit lamp, or both.

• Intraocular pressure is measured.

• Ophthalmoscopy is done, preferably after dilating the pupil with a drop of a sympathomimetic (eg, 2.5% phenylephrine), cycloplegic (eg, 1% cyclopentolate or 1% tropicamide), or both; dilation is nearly full after about 20 min. The entire fundus, including the retina, macula, fovea, vessels, and optic disk and its margins, is examined.

• If pupillary light responses are normal and functional loss of vision is suspected (rarely),

[
Fig. 60-2. Evaluation of acute vision loss.]

optokinetic nystagmus is checked. If an optokinetic drum is unavailable, a mirror can be held near the patient's eye and slowly moved. If the patient can see, the eyes usually track movement of the mirror.

Red flags: Acute loss of vision is itself a red flag; most causes are serious.

Interpretation of findings: Diagnosis can be begun systematically. Fig. 60-2 describes a simplified, general approach. Specific patterns of visual field deficit help suggest a cause (see Table 60-1). Other clinical findings also help suggest a cause (see Table 60-2):

• Difficulty seeing the red reflex during ophthalmoscopy suggests opacification of transparent structures (eg, caused by corneal ulcer, vitreous hemorrhage, or severe endophthalmitis).

• Retinal abnormalities that are severe enough to cause acute loss of vision are detectable during ophthalmoscopy, particularly if the pupils are dilated. Retinal detachment may show retinal folds; retinal vein occlusion may show marked retinal hemorrhages; and retinal artery occlusion may show a pale retina with cherry-red fovea.

• An afferent pupillary defect (absence of a direct pupillary light response but a normal consensual response) with an otherwise normal examination (except sometimes an abnormal optic disk) suggests an abnormality of the optic nerve or retina (ie, anterior to the chiasm).

In addition, the following facts may help:

- Monocular symptoms suggest a lesion anterior to the optic chiasm.
- Bilateral, symmetric visual field defects suggest a lesion posterior to the chiasm.
- Constant eye pain suggests a corneal lesion (ulcer or abrasion), anterior chamber inflammation, or increased intraocular pressure, whereas eye pain with movement suggests optic neuritis.
- Temporal headaches suggest giant cell arteritis or migraine.

Testing: ESR is done for all patients with symptoms (eg, temporal headaches, jaw claudication, proximal myalgias, stiffness) or signs (eg, temporal artery tenderness or induration, pale retina, papilledema) suggesting optic nerve or retinal ischemia to exclude giant cell arteritis.

Other testing is listed in Table 60-2. The following are of particular importance:

- Ultrasonography is done to view the retina if the retina is not clearly visible with pupillary dilation and indirect ophthalmoscopy done by an ophthalmologist.
- Gadolinium-enhanced MRI is done for patients who have eye pain with movement or afferent pupillary defect, particularly with optic nerve swelling on ophthalmoscopy, to diagnose multiple sclerosis.

Treatment

Causative disorders are treated. Treatment should usually commence immediately if the cause is treatable. In many cases (eg, vascular disorders), treatment is unlikely to salvage the affected eye but can decrease the risk of the same process occurring in the contralateral eye.

Key Points

- Diagnosis and treatment should occur as rapidly as possible.
- Acute monocular loss of vision with an afferent pupillary defect indicates a lesion of the eye or of the optic nerve anterior to the optic chiasm.
- Optic nerve lesion, particularly ischemia, is considered in patients with acute monocular loss of vision or afferent pupillary defect and in those with or without optic nerve abnormalities on ophthalmoscopy but no other abnormalities on eye examination.
- Corneal ulcer, acute angle-closure glaucoma, endophthalmitis, or severe anterior uveitis is considered in patients with acute monocular loss of vision, afferent pupillary defect, eye pain, and conjunctival injection.

Anisocoria

(Unequal Pupils)

Anisocoria is unequal pupil sizes. Anisocoria itself does not cause symptoms.

Etiology

The most common cause of anisocoria is

- Physiologic (present in about 20% of people)

See Table 60-3 for other causes of anisocoria.

Many disorders are accompanied by anisocoria due to iris or neurologic dysfunction but usually manifest with other, more bothersome symptoms (eg, uveitis, optic neuritis, stroke, subarachnoid hemorrhage, acute angle-closure glaucoma).

Evaluation

The goal of evaluation is to elucidate the physiologic mechanism of anisocoria. By identifying certain mechanisms (eg, Horner's syndrome, 3rd cranial nerve palsy), clinicians can diagnose the occasional serious occult disorder (eg, tumor, aneurysm) manifesting with anisocoria.

History: History of present illness includes the presence, nature, and duration of symptoms. Any history of head or ocular trauma is noted.

Review of systems seeks symptoms that may suggest a cause, such as birth defects or chromosomal abnormalities (congenital defects); droopy eyelid, cough, chest pain, or dyspnea (Horner's syndrome); genital lesions, adenopathy, rashes, or fever (syphilis); and headaches or other neurologic symptoms (Horner's syndrome or 3rd cranial nerve palsy).

Past medical history includes known ocular disorders and surgeries and exposure to drugs.

[Table 60-3. Some Common Causes of Anisocoria]

Physical examination: Pupillary size and light responses should be examined in lighted and dark rooms. Accommodation and extraocular movements should be tested. Ocular structures are inspected by using a slit lamp or other magnification to identify structural abnormalities and ptosis. Other ocular symptoms are evaluated by eye examination as clinically indicated. An old photograph of the patient or the patient's driver's license should be examined (under magnification if possible) to see whether anisocoria was present previously.

Testing: Testing is usually unnecessary but is indicated for clinically suspected disorders. Patients with Horner's syndrome or 3rd cranial nerve palsy usually require brain MRI or CT.

Red flags: The following findings are of particular concern:

• Ptosis

• Anhidrosis

• Pupils that respond more to accommodation than light

• Impaired extraocular movements

Interpretation of findings: If the difference in size is greater in the dark, the smaller pupil is abnormal. Common causes include Horner's syndrome and physiologic anisocoria. An ophthalmologist can differentiate them because the small pupil in Horner's syndrome does not dilate after instillation of an ocular dilating drop (eg, 10% cocaine).

If the difference in pupillary sizes is greater in light, the larger pupil is abnormal. If extraocular movements are impaired, particularly with ptosis, 3rd cranial nerve palsy is likely. If extraocular movements are intact, an ophthalmologist can further differentiate among causes by instilling a drop of a pupillary constrictor (eg, 0.1% pilocarpine). If the large pupil constricts, the cause is probably Adie's tonic pupil; if the large pupil does not constrict, the cause is probably drugs or structural (eg, traumatic, surgical) damage to the iris.

Treatment

Treatment of anisocoria is unnecessary.

Key Points

• Physiologic anisocoria is very common and causes < 1 mm of difference between the pupils in size.

• Examining the pupils in light and dark and inspecting an old photograph or the driver's license of the patient provide a great deal of diagnostic information.

• Serious disorders should be considered in patients with Horner's syndrome or 3rd cranial nerve palsy.

Blurred Vision

Blurred vision is the most common visual symptom. It usually refers to decreased visual acuity of gradual onset. For sudden, complete loss of vision in one or both eyes (blindness), see p. 541. Patients with small visual field defects (eg, caused by a small retinal detachment) may describe their symptoms as blurring.

Etiology

The most common causes of blurred vision (see Table 60-4) include

• Refractive errors (the most common cause overall)

• Age-related macular degeneration

• Cataracts

• Diabetic retinopathy

• Glaucoma

Blurred vision has 4 general mechanisms:

• Opacification of normally transparent ocular structures (cornea, lens, vitreous) through which light rays must pass to reach the retina

• Disorders affecting the retina

• Disorders affecting the optic nerve or its connections

• Refractive errors

Certain disorders can have more than one mechanism. For example, refraction can be impaired by early cataracts or the reversible lens swelling caused by poorly controlled diabetes.

Patients with certain disorders that cause blurred vision (eg, acute corneal lesions [such as abrasions], ulcers, herpes simplex keratitis, herpes zoster ophthalmicus, acute angle-closure glaucoma) are more likely to present with other symptoms such as eye pain and red eye.

Rare disorders that can cause blurred vision include hereditary optic neuropathies (eg, dominant optic atrophy, Leber's hereditary optic neuropathy) and corneal scarring due to vitamin A deficiency or amiodarone toxicity.

Evaluation

History: History of present illness should ascertain the onset, duration, and progression of symptoms, as well as whether they are bilateral or unilateral. The symptom should be defined as precisely as possible by asking an open-ended question or request (eg, "Please describe what you mean by blurred

vision"). For example, loss of detail is not the same as loss of contrast. Also, visual field defects may not be recognized as such by patients, who may instead describe symptoms such as missing steps or the inability to see words when reading. Important associated symptoms include eye redness, photophobia, floaters, sensation of lightning-like flashes of light (photopsias), and pain at rest or with eye movement. The effects of darkness (night vision), bright lights (ie, causing blur, star bursts, halos, photophobia), distance from an object, and corrective lenses and whether central or peripheral vision seems to be more affected should be ascertained.

Review of systems includes questions about symptoms of possible causes, such as increased thirst and polyuria (diabetes).

Past medical history should note previous eye injury or other diagnosed eye disorders and ask about disorders known to be risk factors for eye disorders (eg, hypertension, diabetes, HIV/AIDS, SLE, sickle cell anemia, disorders that could cause hyperviscosity syndrome such as multiple myeloma or Waldenstrom's macroglobulinemia). Drug history should include questions about use of drugs that could affect vision (eg, amiodarone, corticosteroids) and treatments for disorders affecting vision (eg, diabetic retinopathy).

Physical examination: Nonvisual symptoms are evaluated as needed; however, examination of the eyes may be all that is necessary.

Testing **visual acuity** is key. Many patients do not give a full effort. Providing adequate time and coaxing patients tend to yield more accurate results.

Acuity ideally is measured while the patient stands 6 m (about 20 ft) from a Snellen chart posted on a wall. If this test cannot be done, acuity can be measured using a chart held about 36 cm (14 in) from the eye. Measurement of near vision should be done with reading correction in place for patients > age 40. Each eye is measured separately while the other eye is covered with a solid object (not the patient's fingers, which may separate during testing). If the patient cannot read the top line of the Snellen chart at 6 m, acuity is tested at 3 m. If nothing can be read from a chart even at the closest distance, the examiner holds up different numbers of fingers to see whether the patient can accurately count them. If not, the examiner tests whether the patient can perceive hand motion. If not, a light is shined into the eye to see whether light is perceived.

Visual acuity is measured with and without the patients' own glasses. If acuity is corrected

[Table 60-4. Some Causes of Blurred Vision]

with glasses, the problem is a refractive error. If patients do not have their glasses, a pinhole refractor is used. If a commercial pinhole refractor is unavailable, one can be made at the bedside by poking holes through a piece of cardboard using an 18-gauge needle and varying the diameter of each hole slightly. Patients choose the hole that corrects vision the most. If acuity corrects with pinhole refraction, the problem is a refractive error. Pinhole refraction is a rapid, efficient way to diagnose refractive errors, which are the most common cause of blurred vision. However, with pinhole refraction, best correction is usually to only about 20/30, not 20/20.

Eye examination is also important. Direct and consensual pupillary light responses are examined using the swinging flashlight test. Visual fields are checked using confrontation and an Amsler grid.

The cornea is examined for opacification, ideally using a slit lamp. The anterior chamber is examined for cells and flare using a slit lamp if possible, although results of this examination are unlikely to explain visual blurring in patients without eye pain or redness.

The lens is examined for opacities using an ophthalmoscope, slit lamp, or both.

Ophthalmoscopy is done using a direct ophthalmoscope. More detail is visible if the eyes are dilated for ophthalmoscopy with a drop of a sympathomimetic (eg, 2.5% phenylephrine), cycloplegic (eg, 1% tropicamide or 1% cyclopentolate), or both; dilation is nearly full after about 20 min. As much of the fundus

as is visible, including the retina, macula, fovea, vessels, and optic disk and its margins, is examined. To see the entire fundus (ie, to see a peripheral retinal detachment), the examiner, usually an ophthalmologist, must use an indirect ophthalmoscope.

Intraocular pressure is measured.

Red flags: The following findings are of particular concern:

- Sudden change in vision
- Eye pain (with or without eye movement)
- Visual field defect (by history or examination)
- Visible abnormality of the retina or optic disk
- HIV/AIDS or other immunosuppressive disorder
- A systemic disorder that could cause retinopathy (eg, sickle cell anemia, possible hyperviscosity syndrome, diabetes, hypertension)

Interpretation of findings: Symptoms and signs help suggest a cause (see Table 60-4).

If visual acuity is corrected with glasses or a pinhole refractor, simple refractive error is the cause of blurring. Loss of contrast or glare may still be caused by cataract, which should be considered.

However, red flag findings suggest a more serious ophthalmologic disorder (see Table 60-5) and need for a complete examination, including slit-lamp examination, tonometry, ophthalmoscopic examination with pupillary dilation, and, depending on findings, possibly immediate or urgent ophthalmologic referral.

Specific retinal findings help suggest a cause (see Table 60-6).

[**Table 60-5.** Interpretation of Some Red Flag Findings]

[**Table 60-6.** Interpretation of Retinal Findings]

Testing: If acuity corrects appropriately with refraction, patients are referred to an optometrist or ophthalmologist for routine formal refraction. If visual acuity is not corrected with refraction but there are no red flag findings, patients are referred to an ophthalmologist for routine evaluation. With certain red flag findings, patients are referred for immediate or urgent ophthalmologic evaluation.

Patients with symptoms or signs of systemic disorders should have appropriate testing:

- Diabetes: Fingerstick or random glucose measurement
- Poorly controlled hypertension and acute hypertensive retinopathy (hemorrhages, exudates, or papilledema): Urinalysis, renal function testing, BP monitoring, and possibly ECG
- HIV/AIDS and retinal abnormalities: HIV serology and CD4+ count
- SLE and retinal abnormality: Antinuclear antibodies, ESR, and CBC
- Waldenstrom's macroglobulinemia, multiple myeloma, or sickle cell anemia: CBC with differential count and other testing (eg, serum protein electrophoresis) as clinically indicated

Treatment

Underlying disorders are treated. Corrective lenses may be used to improve visual acuity, even when the disorder causing blurring is not purely a refractive error (eg, early cataract).

Geriatrics Essentials

Although some decrease in visual acuity normally occurs with aging, acuity normally is correctable to 20/20 with refraction, even in very elderly patients.

Key Points

- If visual acuity is corrected with pinhole refraction, refractive error is the problem.
- Because glaucoma is common, intraocular pressure should be measured.
- If pinhole refraction does not correct acuity and there is no obvious cataract or corneal abnormality, ophthalmoscopy should be done after pupillary dilation.
- Many abnormalities on ophthalmoscopy, particularly if symptoms are recently worsening, require urgent or immediate ophthalmologic referral.

Diplopia

(Double Vision)

Diplopia is the perception of 2 images of a single object. Diplopia may be monocular or binocular. Monocular diplopia is present when only one eye is open. Binocular diplopia disappears when either eye is closed.

Etiology

Monocular diplopia can occur when something distorts light transmission through the eye to the retina. There may be > 2 images. One of the images is of normal quality (eg, brightness, contrast, clarity); the rest are of inferior quality. The most common causes of monocular diplopia are

- Cataract
- Corneal shape problems, such as keratoconus or surface irregularity
- Uncorrected refractive error, usually astigmatism

Other causes include corneal scarring and dislocated lens. Complaints also may represent malingering.

Binocular diplopia suggests disconjugate alignment of the eyes. There are only 2 images, and they are of equal quality. There are many possible causes of binocular diplopia (see Table 60-7). The most common are

- Cranial nerve (3rd, 4th, or 6th) palsy
- Myasthenia gravis
- Orbital infiltration (eg, thyroid infiltrative ophthalmopathy, orbital pseudotumor)

Most commonly, the eyes are misaligned because of a disorder affecting the cranial nerves innervating the extraocular muscles (3rd, 4th, or 6th cranial nerves). These palsies may be isolated and idiopathic or the result of various disorders involving the cranial nerve nuclei or the infranuclear nerve or nerves. Other causes involve mechanical interference with ocular motion or a generalized disorder of neuromuscular transmission.

Evaluation

History: History of present illness should determine whether diplopia involves one or both eyes, whether diplopia is intermittent or constant, and whether the images are separated vertically, horizontally, or both. Any associated pain is noted, as well as whether it occurs with or without eye movement.

Review of systems should seek symptoms of other cranial nerve dysfunction, such as vision abnormalities (2nd cranial nerve); numbness of forehead and cheek (5th cranial nerve); facial weakness (7th cranial nerve); dizziness, hearing loss, or gait difficulties (8th cranial nerve); and swallowing or speech difficulties (9th and 12th cranial nerves). Other neurologic symptoms, such as weakness and sensory abnormalities, should be sought noting whether these are intermittent or constant. Nonneurologic symptoms of potential causes are ascertained; they include nausea, vomiting, and diarrhea (botulism); palpitations, heat sensitivity, and weight loss (Graves' disease); and difficulty with bladder control (multiple sclerosis).

Past medical history should seek presence of known hypertension, diabetes, or both; atherosclerosis, particularly including cerebrovascular disease; and alcohol abuse.

Physical examination: Examination begins with a review of vital signs for fever and general appearance for signs of toxicity (eg, prostration, confusion).

Eye examination begins with measuring visual acuity (with correction) in each eye and both together, which also helps determine whether diplopia is monocular or binocular. Eye examination should note presence of bulging of one or both eyes, eyelid droop, pupillary abnormalities, and disconjugate eye movement and nystagmus during ocular motility testing. Ophthalmoscopy should be done, particularly noting any abnormalities of the lens (eg, cataract, displacement) and retina (eg, detachment).

Ocular motility is tested by having the patient hold the head steady and track the examiner's finger, which is moved to extreme gaze to the right, left, upward, downward, diagonally to either side, and finally inward toward the patient's nose (convergence). However, mild paresis of ocular motility sufficient to cause diplopia may escape detection by such examination.

If diplopia occurs in one direction of gaze, the eye that produces each image can be determined by repeating the examination with a red glass placed over one of the patient's eyes. The image that is more peripheral originates in the paretic eye; ie, if the more peripheral image is red, the red glass is covering the paretic eye. If a red glass is not available, the paretic eye can sometimes be identified by having the patient close each eye. The paretic eye is the eye that when closed eliminates the more peripheral image.

The other cranial nerves are tested, and the remainder of the neurologic examination, including strength, sensation, reflexes, cerebellar function, and observation of gait, is completed.

Relevant nonneurophthalmologic components of the examination include palpation of the neck for goiter and inspection of the shins for pretibial myxedema (Graves' disease).

Red flags: The following findings are of particular concern:

- More than one cranial nerve deficit
- Pupillary involvement of any degree
- Any neurologic symptoms or signs besides diplopia
- Pain
- Proptosis

Interpretation of findings: Findings sometimes suggest which nerve is involved.

• Nerve III: Eyelid droop, eye deviated laterally and down, sometimes pupillary dilation

[**Table 60-7.** Some Causes of Binocular Diplopia]

• Nerve IV: Vertical diplopia worse on downward gaze (patient tilts head to improve vision)

• Nerve VI: Eye deviated medially, diplopia worse on lateral gaze (patient turns head to improve vision)

Other findings help suggest a cause (see Table 60-7).

Intermittent diplopia suggests a waxing and waning neurologic disorder, such as myasthenia gravis or multiple sclerosis, or unmasking of a latent phoria (eye deviation). Patients with latent phoria do not have any other neurologic manifestations.

Internuclear ophthalmoplegia (INO) results from a brain stem lesion in the medial longitudinal fasciculus (MLF). INO manifests on horizontal gaze testing with diplopia, weak adduction on the affected side (usually cannot adduct eye past midline), and nystagmus of the contralateral eye. However, the affected eye adducts normally on convergence testing (which does not require an intact MLF).

Pain suggests a compressive lesion or inflammatory disorder.

Testing: Patients with monocular diplopia are referred to an ophthalmologist to evaluate for ocular pathology; no other tests are required beforehand.

For binocular diplopia, patients with a unilateral, single cranial nerve palsy, a normal pupillary light response, and no other symptoms or signs can usually be observed without testing for a few weeks. Many cases resolve spontaneously. Ophthalmologic evaluation may be done to monitor the patient and help further delineate the deficit.

Most other patients require neuroimaging with MRI to detect orbital, cranial, or CNS abnormalities. CT may be substituted if there is concern about a metallic intraocular foreign body or if MRI is otherwise contraindicated or unavailable. Imaging should be done immediately if findings suggest infection, aneurysm, or acute (< 3 h) stroke.

Patients with manifestations of Graves' disease should have thyroid tests (serum thyroxine [T_4] and thyroid-stimulating hormone [TSH] levels). Testing for myasthenia gravis and multiple sclerosis should be strongly considered for those with intermittent diplopia.

Treatment

Treatment is management of the underlying disorder.

Key Points

• Isolated, pupil-sparing nerve palsy in patients with no other symptoms may resolve spontaneously.

• Imaging is required for those with red flag findings.

• Focal weakness (in any muscle) may indicate a disorder of neuromuscular transmission.

Eyelid Swelling

Eyelid swelling can be unilateral or bilateral. It may be asymptomatic or accompanied by itching or pain.

Etiology

Eyelid swelling has many causes (see

Table 60-8). It usually results from an eyelid disorder but may result from disorders in and around the orbit or from systemic disorders that cause generalized edema.

The most common causes are allergic, including

• Local allergy (contact sensitivity)

• Systemic allergy (eg, angioedema, systemic allergy accompanying allergic rhinitis)

Focal swelling of one eyelid is most often caused by a chalazion.

The most immediately dangerous causes are orbital cellulitis and cavernous sinus thrombosis (rare).

[**Table 60-8.** Some Causes of Eyelid Swelling]

In addition to the disorders listed in Table 60-8, eyelid swelling may result from the following:

• Disorders that may involve the eyelid but do not cause swelling unless very advanced (eg, eyelid tumors, including squamous cell carcinomas and melanoma)

• Disorders (eg, dacryocystitis, canaliculitis) that cause swelling that begins and is usually most severe in structures near, but not part of, the eyelids

• Disorders in which swelling occurs but is not the presenting symptom (eg, basilar skull fracture, burns, trauma, postsurgery)

Evaluation

History: History of present illness should ascertain how long swelling has been present, whether it is unilateral or bilateral, and whether it has been preceded by any trauma (including insect bites). Important accompanying symptoms to identify include itching, pain, headache, change in vision, fever, and eye discharge.

Review of systems should seek symptoms of possible causes, including runny nose, itching, rash, and wheezing (systemic allergic reaction); headache, nasal congestion, and purulent nasal discharge (sinusitis); toothache (dental infection); dyspnea, orthopnea, and paroxysmal nocturnal dyspnea (heart failure); cold intolerance and changes in skin texture (hypothyroidism); and heat intolerance, anxiety, and weight loss (hyperthyroidism).

Past medical history should include recent eye injury or surgery; known heart, liver, renal, or thyroid disease; and allergies and exposure to possible allergens. Drug history should specifically include use of ACE inhibitors.

Physical examination: Vital signs should be assessed for fever and tachycardia.

Eye inspection should assess the location and color of swelling (erythematous or pale), including whether it is present on one eyelid, both eyelids, or both eyes and whether it is tender, warm, or both. The examiner should observe whether the finding represents edema of the eyelids, protrusion of the globe (proptosis), or both. Eye examination should particularly note visual acuity and range of extraocular motion (full or limited). This examination can be difficult when swelling is marked but is important because deficits suggest an orbital or retro-orbital disorder rather than an eyelid disorder; an assistant may be required to hold the eyelids open. Conjunctivae are examined for injection and discharge. Any eyelid or eye lesions are evaluated using a slit lamp.

General examination should assess signs of toxicity, suggesting a serious infection, and signs of a causative disorder. Facial skin is inspected for dryness and scales (which may suggest hypothyroidism) and greasy scales or other signs of seborrheic dermatitis. Extremities and the presacral area are examined for edema, which suggests a systemic cause. If a systemic cause is suspected, see p. 2031 for

further discussion of the evaluation.

Red flags: The following findings are of particular concern:

• Fever

• Loss of visual acuity

• Impaired extraocular movements

• Proptosis

Interpretation of findings: Some findings help distinguish among categories of disorders. The first important distinction is between inflammation or infection and allergy or fluid overload. Pain, redness, warmth, and tenderness suggest inflammation or infection. Painless, pale swelling suggests angioedema. Itching suggests allergic reaction, and absence of itching suggests cardiac or renal dysfunction.

Swelling localized to one eyelid in the absence of other signs is rarely caused by a dangerous disorder. Massive swelling of the eyelids of one or both eyes should raise suspicion of a serious problem. Signs of inflammation, proptosis, loss of vision, and impaired extraocular movements suggest an orbital disorder (eg, orbital cellulitis, cavernous sinus thrombosis) that may be pushing the globe forward or affecting the nerves or muscles. Other suggestive and specific findings are listed in Table 60-8.

Testing: In most cases, diagnosis can be established clinically and no testing is necessary. If orbital cellulitis or cavernous sinus thrombosis is suspected, diagnosis and treatment should proceed as rapidly as possible. Immediate imaging with CT or MRI should be done. If cardiac, liver, renal, or thyroid dysfunction is suspected, organ function is evaluated with laboratory tests and imaging as appropriate for that system.

Treatment

Treatment is directed at the underlying disorder. There is no specific treatment for the swelling.

Key Points

• Proptosis with impaired vision or extraocular movements suggests orbital cellulitis or cavernous sinus thrombosis, and diagnosis and treatment should proceed as rapidly as possible.

• Eyelid disorders should be differentiated from orbital and systemic causes of swelling.

Eye Pain

Eye pain may be described as sharp, aching, or throbbing and should be distinguished from superficial irritation or a foreign body sensation. In some disorders, pain is worsened by bright light. Eye pain may be caused by a serious disorder and requires prompt evaluation. Many causes of eye pain also cause a red eye.

Pathophysiology

The cornea is richly innervated and highly sensitive to pain. Many disorders that affect the cornea or anterior chamber (eg, uveitis) also cause pain via ciliary muscle spasm; when such spasm is present, bright light causes muscle contraction, worsening pain.

Etiology

Disorders that cause eye pain can be divided into those that affect primarily the cornea, other ocular disorders, and disorders that cause pain referred to the eye (see Table 60-9).

The most common causes overall are

• Corneal abrasion

• Foreign bodies

However, most corneal disorders can cause eye pain.

A feeling of scratchiness or of a foreign body may be caused by either a conjunctival or a corneal disorder.

Evaluation

History: History of present illness should address the onset, quality, and severity of pain and any history of prior episodes (eg, daily episodes in clusters). Important associated symptoms include true photophobia (shining a light into the unaffected eye causes pain in the affected eye when the affected eye is shut), decreased visual acuity, foreign body sensation and pain when blinking, and pain when moving the eye.

Review of systems should seek symptoms suggesting a cause, including presence of an aura (migraine); fever and chills (infection); and pain when moving the head, purulent rhinorrhea, productive or nocturnal cough, and halitosis (sinusitis).

Past medical history should include known disorders that are risk factors for eye pain, including autoimmune disorders, multiple sclerosis, migraine, and sinus infections. Additional risk factors to assess include use (and overuse) of contact lenses (contact lens keratitis), exposure to excessive sunlight or to welding (UV keratitis), hammering or drilling metal (foreign body), and recent eye injury or surgery (endophthalmitis).

Physical examination: Vital signs are checked for the presence of fever. The nose is inspected for purulent rhinorrhea, and the face is palpated for tenderness. If the eye is red, the preauricular region is checked for adenopathy. Hygiene during examination must be scrupulous when examining patients who have chemosis, preauricular adenopathy, punctate corneal staining, or a combination; these findings suggest epidemic keratoconjunctivitis, which is highly contagious.

Eye examination should be as complete as possible for patients with eye pain. Best corrected visual acuity is checked. Visual fields are typically tested by confrontation in patients with eye pain, but this test can be insensitive (particularly for small defects) and unreliable because of poor patient cooperation. A light is moved from one eye to the other to check for pupillary size and direct and consensual pupillary light responses. In patients who have unilateral eye pain, a light is shined in the unaffected eye while the affected eye is shut; pain in the affected eye represents true photophobia. Extraocular movements are checked. The orbital and periorbital structures are inspected. Conjunctival injection that seems most intense and confluent around the cornea and limbus is called ciliary flush.

Slit-lamp examination is done if possible. The cornea is stained with fluorescein and examined under magnification with cobalt blue light. If a slit lamp is unavailable, the cornea can be examined after fluorescein staining with a Wood's light using magnification. Ophthalmoscopy is done, and ocular pressures are measured (tonometry). In patients with a foreign body sensation or unexplained corneal abrasions, the eyelids are everted and examined for foreign bodies.

Red flags: The following findings are of particular concern:

• Vomiting, halos around lights, or corneal edema

• Signs of systemic infection (eg, fever, chills)

• Decreased visual acuity

• Proptosis

• Impaired extraocular motility

Interpretation of findings: Suggestive findings are listed in Table 60-9. Some findings suggest categories of disorders.

Scratchiness or a foreign body sensation is most often caused by disorders of the eyelids, conjunctivae, or superficial cornea. Photosensitivity is possible.

Surface pain with photophobia is often accompanied by a foreign body sensation and pain when blinking; it suggests a corneal lesion, most often a foreign body or abrasion.

Deeper pain—often described as aching or throbbing—usually indicates a serious disorder such as glaucoma, uveitis, scleritis, endophthalmitis, orbital cellulitis, or orbital pseudotumor. Within this group, eyelid swelling, proptosis, or both and impaired extraocular movements or visual acuity suggest orbital pseudotumor, orbital cellulitis, or possibly severe endophthalmitis. Fever, chills, and tenderness suggest infection (eg, orbital cellulitis, sinusitis).

A red eye suggests that the disorder causing pain is ocular rather than referred.

If pain develops in the affected eye in response to shining light in the unaffected eye when the affected eye is shut (true photophobia), the cause is most often a corneal lesion or uveitis.

If topical anesthetic drops (eg, proparacaine) abolish pain in a red eye, the cause is probably a corneal disorder.

Some findings are more suggestive of particular disorders. Pain and photophobia days after blunt eye trauma suggest uveitis. Hammering or drilling metal is a risk factor for occult metal intraocular foreign body. Pain with movement of extraocular muscles and loss of pupillary light response that is disproportionate to loss of visual acuity suggest optic neuritis.

Testing: Testing is not usually necessary, with some exceptions (see Table 60-9). Gonioscopy is done if glaucoma is suspected based on increased intraocular pressure. Imaging, usually with CT or MRI, is done if orbital pseudotumor or orbital cellulitis is suspected or if sinusitis is suspected but the diagnosis is not clinically clear. MRI is often done when optic neuritis is suspected, looking for demyelinating lesions in the brain suggesting multiple sclerosis.

Intraocular fluids (vitreous and aqueous humor) may be cultured for suspected endophthalmitis. Viral cultures can be used to confirm herpes zoster ophthalmicus or herpes

[**Table 60-9.** Some Causes of Eye Pain]

simplex keratitis if the diagnosis is not clear clinically.

Treatment

The cause of pain is treated. Pain itself is also treated. Systemic analgesics are used as needed. Pain caused by uveitis and many corneal lesions is also relieved with cycloplegic eye drops (eg, homatropine 5% qid).

Key Points

• Most diagnoses can be made by clinical evaluation.

• Infection precautions should be maintained when examining patients with bilateral red eyes.

- Important danger signs are vomiting, halos around lights, fever, decreased visual acuity, proptosis, and impaired extraocular motility.

- Pain in the affected eye in response to shining light in the unaffected eye when the affected eye is shut (true photophobia) suggests a corneal lesion or uveitis.

- If a topical anesthetic (eg, proparacaine) relieves pain, the cause of pain is a corneal lesion.

- Hammering or drilling on metal is a risk factor for occult intraocular foreign body.

Proptosis

(Exophthalmos)

Proptosis is protrusion of the eyeball. Exophthalmos means the same thing, and this term is usually used when describing proptosis due to Grave's disease. Disorders that may cause changes in the appearance of the face and eyes that resemble proptosis but are not include hyperthyroidism without infiltrative eye disease, Cushing's disease, and severe obesity.

Etiology

The **most common cause** is Graves' disease (see Table 60-10), which causes edema and lymphoid infiltration of the orbital tissues.

Evaluation

Rate of onset may provide a clue to diagnosis. Sudden unilateral onset suggests intraorbital hemorrhage (which can occur after surgery, retrobulbar injection, or trauma) or inflammation of the orbit or paranasal sinuses. A 2- to 3-wk onset suggests chronic inflammation or orbital inflammatory pseudotumor (non-neoplastic cellular infiltration and proliferation); slower onset suggests an orbital tumor.

Ocular examination findings typical of hyperthyroidism but unrelated to infiltrative eye disease include eyelid retraction, eyelid lag, temporal flare of the upper eyelid, and staring. Other signs include eyelid erythema and conjunctival hyperemia. Prolonged exposure of larger-than-usual areas of the eyeball to air causes corneal drying and can lead to infection and ulceration.

Testing: Proptosis can be confirmed with exophthalmometry, which measures the distance between the lateral angle of the bony orbit and the cornea; normal values are < 20 mm in whites and < 22 mm in blacks. CT or MRI is often useful to confirm the diagnosis and to identify structural causes of unilateral proptosis. Thyroid function testing is indicated when Graves' disease is suspected.

[**Table 60-10.** Some Causes of Proptosis]

Treatment

Lubrication to protect the cornea is required in severe cases. When lubrication is not sufficient, surgery to provide better coverage of the eye surface or to reduce proptosis may be required. Systemic corticosteroids (eg, prednisone 1 mg/kg po once/day for 1 wk, tapered over ≥ 1 mo) are often helpful in controlling edema and orbital congestion due to thyroid eye disease or inflammatory orbital pseudotumor. Other interventions vary by etiology. Graves' exophthalmos is not affected by treatment of the thyroid condition but may lessen over time. Tumors must be surgically removed. Selective embolization or, rarely, trapping procedures may be effective in cases of arteriovenous fistulas involving the cavernous sinus.

Floaters

Floaters are opacities that move across the visual field and do not correspond to external visual objects.

Pathophysiology

With aging, the vitreous humor can contract and separate from the retina. The age at which this change occurs varies but most often is between 50 and 75 yr. During this separation, the vitreous can intermittently tug on the retina. The mechanical traction stimulates the retina, which sends a signal that is perceived by the brain and interpreted as light. Complete separation of the vitreous leads to an increase in floaters, which may last for years.

However, traction on the retina may create a hole (retinal tear), and if fluid leaks behind the tear, the retina may detach. Retinal detachment may also be caused by other factors (eg, trauma, primary retinal disorders). Lightning-like flashes, common in retinal detachment, are called **photopsias**. Photopsias can also occur when rubbing the eyes or when looking around after awakening.

Etiology

The most common cause of vitreous floaters is

• Contraction of the vitreous humor that occurs for unknown reasons (idiopathic)

Less common causes are listed in
Table 60-11.

Rare causes of floaters include intraocular tumors (eg, lymphoma). Intraocular foreign bodies can cause floaters but usually manifest with other symptoms, such as loss of vision, eye pain, or redness.

Evaluation

The most important goal is to identify serious vitreous and retinal disorders. If these disorders cannot be ruled out, patients should be examined by an ophthalmologist using an indirect ophthalmoscope after pupillary dilation. Recognizing ocular migraine is also helpful.

History: History of present illness should ascertain onset and duration of symptoms and the shape and volume of floaters, as well as whether they are unilateral or bilateral and whether they have been preceded by trauma. The patient should try to distinguish floaters from lightning-like flashes of light (as in photopsias) or jagged lines across the visual field (as in migraine). Important associated symptoms include loss of vision (and its distribution in the visual field) and eye pain.

Review of systems should seek symptoms of possible causes, such as headaches (ocular migraine) and eye redness (vitreous inflammation).

Past medical history should note diabetes (including diabetic retinopathy), migraine headaches, eye surgery, severe myopia, and any disorders that could affect the immune system (eg, AIDS).

Physical examination: Eye examination should be reasonably complete. Best corrected visual acuity is measured. The eyes are inspected for redness. Visual fields are assessed in all patients. However, recognition of visual field defects by bedside examination is very insensitive, so inability to show such a defect is not evidence that the patient has full visual fields. Extraocular movements and pupillary light responses are assessed. If patients have a red eye or eye pain, the corneas are examined under magnification after fluorescein staining, and slit-lamp examination is done if possible. Ocular pressure is measured (tonometry).

Ophthalmoscopy is the most important part of the examination. It is done using a direct ophthalmoscope and after dilating the pupils. To dilate the pupils, the physician first makes sure to record pupillary size and light responses, then instills drops, usually 1 drop each of a short-acting α-adrenergic agonist (eg, 2.5% phenylephrine) and a cycloplegic (eg, 1% tropicamide or 1% cyclopentolate). The pupils are fully dilated about 20 min after these drops are instilled.

Red flags: The following findings are of particular concern:

[Table 60-11. Some Causes of Floaters]

- Sudden increase in floaters
- Lightning-like flashes (photopsias)
- Loss of vision, diffuse or focal (visual field defect)
- Recent eye surgery or eye trauma
- Eye pain
- Loss of red reflex
- Abnormal retinal findings

Interpretation of findings: Retinal detachment is suggested by sudden increases in floaters, photopsias, or any of its other, more specific characteristics (eg, visual field defects, retinal abnormalities). Bilateral synchronous symptoms suggest ocular migraine, although patients often have difficulty deciphering the laterality of their symptoms (eg, they often interpret scintillating scotoma of the left field of both eyes as left-eyed). Loss of red reflex suggests opacification of the vitreous (eg, vitreous hemorrhage or inflammation), but it also can be caused by advanced cataracts. Loss of vision suggests a serious disorder causing dysfunction of the vitreous or retina.

Testing: Patients who require evaluation by an ophthalmologist may need testing. However, tests can be selected by or in conjunction with the ophthalmologist. For example, patients suspected of having chorioretinitis may require microbiologic testing.

Treatment

Idiopathic vitreous floaters require no treatment. Other disorders causing symptoms are treated.

Key Points

- Floaters by themselves rarely indicate a serious disorder.
- Patients with any abnormal findings on examination require ophthalmologic referral.
- If floaters are accompanied by any other symptoms (eg, persistent flashing lights, visual deficit, sensation of a moving curtain of vision loss), patients require ophthalmologic referral, regardless of examination findings.

Red Eye

(Pink Eye)

Red eye refers to a red appearance of the opened eye, reflecting dilation of the superficial ocular vessels.

Pathophysiology

Dilation of superficial ocular vessels can result from

- Infection
- Allergy
- Inflammation (noninfectious)

• Elevated intraocular pressure

Several ocular components may be involved, most commonly the conjunctiva, but also the uveal tract, episclera, and sclera.

Etiology

The most common causes of red eye include

• Infectious conjunctivitis

• Allergic conjunctivitis

Corneal abrasions and foreign bodies are common causes (see Table 60-12). Although the eye is red, patients usually present with a complaint of injury, eye pain, or both. However, in young children and infants, this information may be unavailable.

Evaluation

Most disorders can be diagnosed by a general health care practitioner.

History: History of present illness should note the onset and duration of redness and presence of any change in vision, itching, scratchy sensation, pain, or discharge. Nature and severity of pain, including whether pain is worsened by light (photophobia), are noted. The clinician should determine whether discharge is watery or purulent. Other questions assess history of injury, including exposure to irritants and use of contact lenses (eg, possible overuse, such as wearing them while sleeping). Prior episodes of eye pain or redness and their time patterns are elicited.

Review of systems should seek symptoms suggesting possible causes, including headache, nausea, vomiting, and halos around lights (acute angle-closure glaucoma); runny nose and sneezing (allergies, URI); and cough, sore throat, and malaise (URI).

Past medical history includes questions about known allergies and autoimmune disorders. Drug history should specifically ask about recent use of topical ophthalmic drugs (including OTC drugs), which might be sensitizing.

Physical examination: General examination should include head and neck examination for signs of associated disorders (eg, URI, allergic rhinitis, zoster rash).

Eye examination involves a formal measure of visual acuity and usually requires a penlight, fluorescein stain, and slit lamp.

Best corrected visual acuity is measured. Pupillary size and reactivity to light are assessed. True photophobia (sometimes called

[**Table 60-12.** Some Causes of Red Eye]

consensual photophobia) is present if shining light into an unaffected eye causes pain in the affected eye when the affected eye is shut. Extraocular movements are assessed, and the eye and periorbital tissues are inspected for lesions and swelling. The tarsal surface is inspected for follicles. The corneas are stained with fluorescein and examined with magnification. If a corneal abrasion is found, the eyelid is everted and examined for hidden foreign bodies. Inspection of the ocular structures and cornea is best done using a slit lamp. A slit lamp is also used to examine the anterior chamber for cells, flare, and pus (hypopyon). Ocular pressure is measured using tonometry, although it may be permissible to omit this test if there are no symptoms or signs suggesting a disorder other than conjunctivitis.

Red flags: The following findings are of particular concern:

• Sudden, severe pain and vomiting

• Zoster skin rash

• Decreased visual acuity

• Corneal crater

• Branching, dendritic corneal lesion

• Ocular pressure > 40 mm Hg

• Failure to blanch with phenylephrine eye drop

Interpretation of findings: Conjunctival disorders and **episcleritis** are differentiated from other causes of red eye by the absence of pain, photophobia, and corneal staining. Among these disorders, episcleritis is differentiated by its focality, and subconjunctival hemorrhage is usually differentiated by the absence of lacrimation, itching, and photosensitivity. Clinical criteria do not accurately differentiate viral from bacterial conjunctivitis.

Corneal disorders are differentiated from other causes of red eye (and usually from each other) by fluorescein staining. These disorders also tend to be characterized by pain and photophobia. If instillation of an ocular anesthetic drop (eg, proparacaine 0.5%), which is done before tonometry and ideally before fluorescein instillation, completely relieves pain, the cause is probably limited to the cornea. If pain is present and is not relieved by an ocular anesthetic, the cause may be anterior uveitis, glaucoma, or scleritis. Because patients may have anterior uveitis secondary to corneal lesions, persistence of pain after instillation of the anesthetic does not exclude a corneal lesion.

Anterior uveitis, glaucoma, acute angle-closure glaucoma, and **scleritis** can usually be differentiated from other causes of red eye by the presence of pain and the absence of corneal staining. Anterior uveitis is likely in patients with pain, true photophobia, absence of corneal fluorescein staining, and normal intraocular pressure; it is definitively diagnosed based on the presence of cells and flare in the anterior chamber. However, these findings may be difficult for general health care practitioners to discern. Acute angle-closure glaucoma can usually be recognized by the sudden onset of its severe and characteristic symptoms, but tonometry is definitive.

Instillation of phenylephrine 2.5% causes blanching in a red eye unless the cause is scleritis. Phenylephrine is instilled to dilate the pupil in patients needing a thorough retinal examination. However, it should not be used in patients who have the following:

• Suspected acute angle-closure glaucoma

• A history of angle-closure glaucoma

• A narrow anterior chamber

Testing: Testing is usually unnecessary. Viral cultures may help if herpes simplex or herpes zoster is suspected and the diagnosis is not clear clinically. Corneal ulcers are cultured by an ophthalmologist. Gonioscopy is done in patients with glaucoma. Testing for autoimmune disorders may be worthwhile in patients with uveitis and no obvious cause (eg, trauma). Patients with scleritis undergo further testing as directed by an ophthalmologist.

Treatment

The cause is treated. Red eye itself does not require treatment. Topical vasoconstrictors are not recommended.

Key Points

• Most cases are caused by conjunctivitis.

• Pain and true photophobia suggest other, more serious diagnoses.

• In patients with pain, slit-lamp examination with fluorescein staining and tonometry are key.

• Persistence of pain despite an ocular anesthetic in a patient with a normal fluorescein examination suggests anterior uveitis, scleritis, or acute angle-closure glaucoma. These diagnoses should not be missed.

Tearing

(Epiphora)

Excess tearing may cause a sensation of watery eyes or result in tears falling down the cheek (epiphora).

Pathophysiology

Tears are produced in the lacrimal gland and drain through the upper and lower puncta into the canaliculi and then into the lacrimal sac and nasolacrimal duct (see Fig. 60-3). Obstruction of tear drainage can lead to stasis and infection. Recurrent infection of the lacrimal sac (dacryocystitis) can sometimes spread, potentially leading to orbital cellulitis.

Etiology

Overall, the most common causes of tearing are

• URI

• Allergic rhinitis

Tearing can be caused by increased tear production or decreased nasolacrimal drainage.

Increased tear production: The most common causes are

• URI

• Allergic rhinitis

• Allergic conjunctivitis

• Dry eyes (reflex tearing produced in response to dryness of the ocular surface)

• Trichiasis

Any disorder causing conjunctival or corneal irritation can increase tear production (see Table 60-13). However, most patients with corneal disorders that cause excess tearing (eg, corneal abrasion, corneal ulcer, corneal foreign body, keratitis) or with primary angle-closure glaucoma or anterior uveitis present with eye symptoms other than tearing (eg, eye pain, redness). Most people who have been crying do not present for evaluation of tearing.

Decreased nasolacrimal drainage: The most common causes are

• Idiopathic age-related nasolacrimal duct stenosis

• Dacryocystitis

• Ectropion

[Fig. 60-3. Anatomy of the lacrimal system.]

Nasolacrimal drainage system obstruction may be caused by strictures, tumors, or foreign bodies (eg, stones, often associated with subclinical infection by *Actinomyces*). Obstruction can also be a congenital malformation. Many disorders and drugs can cause stricture or obstruction of nasolacrimal drainage.

Other causes of nasolacrimal drainage stricture or obstruction include

• Burns

• Chemotherapy drugs

• Eye drops (particularly echothiophate iodide, epinephrine, and pilocarpine)

• Infection, including canaliculitis (eg, caused by *Staphylococcus aureus*, *Actinomyces*, *Streptococcus*, *Pseudomonas*, herpes zoster virus, herpes simplex conjunctivitis, infectious mononucleosis, human papillomavirus, *Ascaris*, leprosy, TB)

• Inflammatory disorders (sarcoidosis, Wegener's granulomatosis)

• Injuries (eg, nasoethmoid fractures; nasal, orbital, or endoscopic sinus surgery)

• Obstruction of nasal outlet despite an intact nasolacrimal system (eg, URI, allergic rhinitis, sinusitis)

• Radiation therapy

• Stevens-Johnson syndrome

• Tumors (eg, primary lacrimal sac tumors, benign papillomas, squamous and basal cell carcinoma, transitional cell carcinoma, fibrous histiocytomas, midline granuloma, lymphoma)

Evaluation

History: History of present illness addresses the duration, onset, and severity of symptoms, including whether tears drip down the cheek (true epiphora). The effects of weather, environmental humidity, and cigarette smoke are ascertained.

Review of symptoms should seek symptoms of possible causes, including itching, rhinorrhea, or sneezing, particularly when occurring perennially or after exposure to specific potential allergens (allergic reaction); eye irritation or pain (blepharitis, corneal abrasion, irritant chemicals); and pain near the medial canthus (dacryocystitis). Other symptoms are of lower yield but should be sought; they include positional headache, purulent rhinorrhea, nocturnal cough, and fever (sinusitis, Wegener's granulomatosis); rash (Stevens-Johnson syndrome); cough, dyspnea, and chest pain (sarcoidosis); and epistaxis, hemoptysis, polyarthralgias, and myalgias (Wegener's granulomatosis).

Past medical history asks about known disorders that can cause tearing, including Wegener's granulomatosis, sarcoidosis, and

[Table 60-13. Some Causes of Tearing]

cancer treated with chemotherapy drugs; disorders that cause dry eyes (eg, RA, sarcoidosis, Sjogren's syndrome); and drugs, such as echothiophate, epinephrine, and pilocarpine. Previous ocular and nasal history, including infections, injuries, surgical procedures, and radiation exposure, is ascertained.

Physical examination: Examination focuses on the eye and surrounding structures.

The face is inspected; asymmetry suggests congenital or acquired obstruction of nasolacrimal duct drainage. When available, a slit lamp should be used to examine the eyes. The conjunctivae and corneas are inspected for lesions, including punctate spots, and redness. The cornea is stained with fluorescein and examined. The lids are everted to detect hidden foreign bodies. The eyelids, including the lacrimal puncta, are closely inspected for foreign bodies, blepharitis, hordeola, ectropion, entropion, and trichiasis. The lacrimal sac (near the medial canthus) is palpated for warmth, tenderness, and swelling. Any swellings are palpated for consistency and to see whether pus is expressed.

The nose is examined for congestion, purulence, and bleeding.

Red flags: The following findings are of particular concern:

• Repeated, unexplained episodes of tearing

• Hard mass in or near the nasolacrimal drainage structures

Interpretation of findings: Findings that suggest obstruction of nasolacrimal drainage include

• Tears running down the cheek (true epiphora)

• Absence of signs of a specific cause

A cause is often evident from the clinical evaluation (see Table 60-14).

[**Table 60-14.** Findings that Suggest the Cause of Nasolacrimal Obstruction]

Testing: Testing is often unnecessary because the cause is usually evident from the examination.

Schirmer's test with a large amount of wetting (eg, > 25 mm) suggests an evaporative dry eye as the etiology of tearing. Schirmer's test with very little wetting (< 5.5 mm) suggests an aqueous teardeficient dry eye. Usually, Schirmer's test is done by an ophthalmologist to ensure it is done and interpreted correctly.

Probing and saline irrigation of the lacrimal drainage system can help detect anatomic obstruction of drainage, as well as stenosis due to complete obstruction of the nasolacrimal drainage system. Irrigation is done with and without fluorescein dye. Reflux through the opposite punctum or canaliculus signals fixed obstruction; reflux and nasal drainage signify stenosis. This test is considered adjunctive and is done by ophthalmologists.

Imaging tests and procedures (dacryocystography, CT, nasal endoscopy) are sometimes useful to delineate abnormal anatomy when surgery is being considered or occasionally to detect an abscess.

Treatment

Underlying disorders (eg, allergies, foreign bodies, conjunctivitis) are treated.

The use of artificial tears lessens tearing when dry eyes or corneal epithelial defects are the cause.

Congenital nasolacrimal duct obstruction often resolves spontaneously. In patients < 1 yr, manual compression of the lacrimal sac 4 or 5 times/day may relieve the distal obstruction. After 1 yr, the nasolacrimal duct may need probing with the patient under general anesthesia. If obstruction is recurrent, a temporary drainage tube may be inserted.

In acquired nasolacrimal duct obstruction, irrigation of the nasolacrimal duct may be therapeutic when underlying disorders do not respond to treatment. As a last resort, a passage between the lacrimal sac and the nasal cavity can be created surgically (dacryocystorhinostomy).

In cases of punctal or canalicular stenosis, dilation is usually curative. If canalicular stenosis is severe and bothersome, a surgical procedure that places a glass tube leading from the caruncle into the nasal cavity can be considered.

Geriatrics Essentials

Idiopathic age-related nasolacrimal duct stenosis is the most common cause of unexplained epiphora in elderly patients; however, tumors should also be considered.

Key Points

• If tears do not run down the cheek, dry eyes is often the cause.

• If tears run down the cheek, obstruction of nasolacrimal drainage is likely.

• Testing is often unnecessary but is needed in cases of recurrent infectious dacryocystitis, which can progress to more serious conditions such as orbital cellulitis.

Other Eye Symptoms

Dry eyes are discussed under Keratoconjunctivitis sicca (see p. 592) The disorder is most often idiopathic or associated with older age but can also be caused by connective tissue diseases (eg, Sjogren's syndrome, RA, SLE).

Eye discharge: Discharge is often accompanied by a red eye (see p. 563) and commonly is caused by allergic or infectious conjunctivitis, blepharitis, and, in infants, ophthalmia neonatorum (neonatal conjunctivitis). Infectious discharge may be purulent in bacterial infection, such as staphylococcal conjunctivitis or gonorrhea. Less common causes include dacryocystitis and canaliculitis.

Diagnosis is usually made clinically. Allergic conjunctivitis can often be distinguished from infectious by predominance of itching, clear discharge, and presence of other allergic symptoms (eg, runny nose, sneezing). Clinical differentiation between viral and bacterial conjunctivitis is difficult. Cultures are not usually done, but are indicated for patients with the following:

• Clinically suspected gonococcal or chlamydial conjunctivitis

• Severe symptoms

• Immunocompromise

• A vulnerable eye (eg, after a corneal transplant, in exophthalmos due to Graves' disease)

• Ineffective initial therapy

Halos: Halos around light may result from cataracts; conditions that result in corneal edema, such as acute angle-closure glaucoma or disorders that cause bullous keratopathy; corneal haziness; mucus on the cornea; or drugs, such as digoxin or chloroquine.

Blue hues: Certain conditions may cause a blue tint to the visual field (cyanopsia). Cyanopsia may occur for a few days after cataract removal or as an adverse effect of sildenafil and possibly other phosphodiesterase-5 (PDE5) inhibitors.

Scotomata: Scotomata are visual field deficits and are divided into

• Negative scotomata (blind spots)

• Positive scotomata (light spots or scintillating flashes)

Negative scotomata may not be noticed by patients unless they involve central vision and interfere significantly with visual acuity; the complaint is most often decreased visual acuity (see p. 541). Negative scotomata have multiple causes that can sometimes be distinguished by the specific type of field deficit (see Table 60-1) as identified by use of a tangent screen, Goldmann perimeter, or computerized automated perimetry (in which the visual field is mapped out in detail based on patient response to a series of flashing lights in different locations controlled by a standardized computer program).

Positive scotomata represent a response to abnormal stimulation of some portion of the visual system, as occurs in migraines.

Chapter 61. Refractive Error

Introduction

In the emmetropic (normally refracted) eye, entering light rays are focused on the retina by the cornea and the lens, creating a sharp image that is transmitted to the brain. The lens is elastic, more so in younger people. During accommodation, the ciliary muscles adjust lens shape to properly focus images. Refractive errors are failure of the eye to focus images sharply on the retina, causing blurred vision (see Fig. 61-1).

In **myopia** (nearsightedness), the point of focus is in front of the retina because the cornea is too steeply curved, the axial length of the eye is too long, or both. Distant objects are blurred, but near objects can be seen clearly. To correct myopia, a concave (minus) lens is used. Myopic refractive errors in children frequently increase until the child stops growing.

In **hyperopia** (farsightedness), the point of focus is behind the retina because the cornea is too flatly curved, the axial length is too short, or both. In adults, both near and distant objects are blurred. Children and young adults with mild hyperopia may be able to see clearly because of their ability to accommodate. To correct hyperopia, a convex (plus) lens is used.

[**Fig. 61-1.** Errors of refraction.]

In **astigmatism,** nonspherical (variable) curvature of the cornea or lens causes light rays of different orientations (eg, vertical, oblique, horizontal) to focus at different points. To correct astigmatism, a cylindric lens (a segment cut from a cylinder) is used. Cylindric lenses have no refractive power along one axis and are concave or convex along the other axis.

Presbyopia is loss of the lens' ability to change shape to focus on near objects due to aging. Typically, presbyopia becomes noticeable by the time a person reaches the early or mid 40s. A convex (plus) lens is used for correction when viewing near objects. These lenses may be supplied as separate glasses or built into a lens as bifocals or variable focus lenses.

Anisometropia is a significant difference between the refractive errors of the 2 eyes (usually > 3 diopters). When corrected with eyeglasses, a difference in image size (aniseikonia) is produced; it can lead to difficulties with fusion of the 2 differently sized images and even to suppression of one of the images.

Symptoms and Signs

The primary symptom of refractive errors is blurred vision for distant objects, near objects, or both. Sometimes the excessive ciliary muscle tone can cause headaches. Occasionally, excessive staring can lead to ocular surface desiccation, causing eye irritation, itching, visual fatigue, foreign body sensation, and redness. Frowning when reading and excessive blinking or rubbing of the eyes are symptoms in children.

Diagnosis

Refraction should be checked every 1 or 2 yr. Screening children helps detect refractive errors before they interfere with learning. A comprehensive eye examination (see p. 537) should accompany refraction testing, whether done by an ophthalmologist or an optometrist.

Contact Lenses

Contact lenses often provide better visual acuity and peripheral vision than do eyeglasses and can be prescribed to correct myopia, hyperopia, astigmatism, anisometropia, aniseikonia, aphakia (absence of the lens) after cataract removal, and keratoconus (a conical-shaped cornea). Either soft or rigid lenses are used to correct myopia and hyperopia. Toric soft contact lenses (which have different curvatures molded onto the front lens surface) or rigid lenses are used to correct significant astigmatism; they are

satisfactory in many cases but require expert fitting.

Presbyopia can also be corrected with contact lenses. In one approach, termed monovision, the nondominant eye is corrected for reading and the dominant eye is corrected for distant vision. Rigid and soft bifocal and multifocal contact lenses can also be successful, but the fitting procedure is time-consuming because precise alignment is essential.

Neither rigid nor soft contact lenses offer the eyes the protection against blunt or sharp injury that eyeglasses do.

Care and Complications

Instructions for hygiene and handling lenses must be strictly observed. Poor contact lens hygiene may lead to persistent inflammation or infection of the cornea.

Contact lenses occasionally cause painless superficial corneal changes. Contact lenses can be painful when

- The corneal epithelium is abraded (see p. 3236); the cornea becomes red and inflamed and stains with fluorescein.
- The lenses fit poorly (eg, too tight, too loose, poorly centered).
- There is too little moisture to keep the lens floating above the cornea.
- The lenses are worn in a nonideal environment (eg, O_2-poor, smoky, windy).
- A lens is improperly inserted or removed.
- A small foreign particle (eg, soot, dust) becomes trapped between the lens and the cornea.
- The lenses are worn for a long time (overwear syndrome).

In overwear syndrome, spontaneous healing may occur in a day or so if lenses are not worn. In some cases, active treatment is required—eg, topical antibiotic eyedrops or ointments and dilation of the pupil with a mydriatic to ease photophobia. (Mydriatics work by paralyzing the muscles of the iris and ciliary body [movement of the inflamed muscles causes pain].) Recovery is usually rapid, complete, and without vision impairment. An ophthalmologist should be consulted before lenses are worn again.

Risk factors for contact lens-related corneal infection (keratitis) include the following:

- Poor lens hygiene
- Overnight or extended wear
- Use of tap water in the cleaning regimen
- Eyes with a compromised ocular surface (eg, dryness, poor corneal sensation)

Infections require rapid management by an ophthalmologist.

Corneal ulcer: A corneal ulcer, which is a potentially vision-threatening infection of the cornea, is suspected when a contact lens wearer experiences intense eye pain (both foreign body sensation and ache), redness, photophobia, and tearing (see also p. 588).

Diagnosis is by slit-lamp examination and fluorescein staining. A corneal infiltrate (collection of WBCs in the corneal stroma) is present. At times, the corneal infiltrate is large and dense enough to be seen with handheld magnification or even with the naked eye as a white spot on the cornea. Microbiologic analysis

of cultures and smears of the corneal infiltrate, contact lens, and contact lens case is indicated.

Treatment includes cessation of contact lens wear and antibiotic drops. Initial therapy includes broad-spectrum antibiotic coverage using a fluoroquinolone antibiotic drop q 15 to 60 min around the clock for 24 to 72 h, then at gradually longer intervals. Drops of an additional antibiotic, such as cefazolin, vancomycin, or concentrated tobramycin, are used if the ulcer is large, deep, or close to the visual axis. The antibiotic may be changed later based on culture results. Neglected cases may respond poorly or not at all to treatment, and severe vision loss may result.

Rigid Corneal Contact Lenses

Older polymethyl methacrylate rigid contact lenses have been replaced by gas-permeable contact lenses (GPCLs) made of fluorocarbon and polymethyl methacrylate admixtures. GPCLs are 6.5 to 10 mm in diameter and cover part of the cornea, floating on the tear layer overlying it.

Rigid contact lenses can improve vision for people with myopia, hyperopia, and astigmatism. If the corneal surface is irregular, rigid lenses often provide a smooth refracting surface and thus improve visual acuity noticeably more than soft contact lenses or eyeglasses.

For complete wearing comfort, rigid contact lenses require an adaptation period, sometimes as long as 1 wk. During this time, the wearer gradually increases the number of hours the lenses are worn each day. Importantly, no pain should occur at any time. Pain is a sign of an ill-fitting contact lens or corneal irritation. Wearers usually experience temporary (< 2 h) blurred vision (spectacle blur) when wearing eyeglasses after removing rigid contact lenses.

Soft Hydrophilic Contact Lenses

Soft contact lenses are made of poly-2-hydroxyethyl methacrylate and other flexible plastics and are 30 to 79% water. They are 13 to 15 mm in diameter and cover the entire cornea. Soft contact lenses can improve vision for people with myopia and hyperopia. Because soft contact lenses mold to the existing corneal curvature, anything greater than minimal astigmatism cannot be treated unless a special toric lens, which has different curvatures molded onto the front lens surface, is used. Weighting the lower aspect of the lens maintains its orientation.

Soft contact lenses are also prescribed for treatment of recurrent corneal erosions and other corneal disorders (called bandage or therapeutic contact lenses). Prophylactic antibiotic eyedrops (eg, fluoroquinolone qid) may be advisable with a bandage lens. Extended wearing of contact lenses, especially in aphakia after cataract surgery, is practical, but an ophthalmologist should examine the patient at least 4 times/yr. The patient should clean the lenses once/wk.

Because of their larger size, soft contact lenses are easier to handle, are not as likely as rigid lenses to eject spontaneously, and are less likely to allow foreign bodies to lodge beneath them. Immediate wearing comfort allows for a brief adaptation period.

Soft contact lenses have a higher incidence of corneal infections, which increases for every night a person wears them during sleep. When dry, soft contact lenses are brittle and break easily. They absorb a certain amount of moisture (based on the water content) from the tear film to retain adequate shape and pliability. Therefore, patients with dry eye are usually more comfortable wearing lenses that have a low water content.

Refractive Surgery

Corneal refractive surgery alters the curvature of the cornea to focus light more precisely on the retina. The goal of refractive surgery is to decrease dependence on eyeglasses or contact lenses. Most people who undergo refractive surgery achieve this goal; about 95% do not need corrective lenses for distance vision. Ideal candidates for refractive surgery are people with healthy eyes who are not satisfied wearing eyeglasses or contact lenses. Preoperative examination excludes people with active ocular diseases, including severe dry eye. Candidates should not have a history of autoimmune or connective tissue

disease because of potential problems with wound healing. Latent herpes simplex virus may be reactivated after surgery; patients should be advised accordingly. Refraction should be stable for at least 1 yr, and candidates should be > 18 yr. Another contraindication is use of isotretinoin or amiodarone.

Adverse effects of refractive surgery include temporary foreign body sensation, glare, halos, and dryness; occasionally, these symptoms persist. Potential complications include overcorrection and undercorrection, infection, and irregular astigmatism. In excimer laser procedures performed on the superficial corneal stroma, haze formation is possible. If infection, irregular astigmatism, or haze formation causes permanent changes in the central cornea, best-corrected acuity could be lost. The overall complication rate is low; chance of vision loss is < 1% if the patient is considered a good candidate for refractive surgery preoperatively.

Laser In Situ Keratomileusis

In laser in situ keratomileusis (LASIK), a flap of corneal tissue is created with a laser or mechanical microkeratome and turned back, the underlying stromal bed is sculpted (photo-ablated) with the excimer laser, and the flap is replaced without suturing. Because surface epithelium is not disrupted centrally, vision returns rapidly. Most people notice a significant improvement the next day. LASIK can be used to treat myopia, astigmatism, and hyperopia.

Advantages of LASIK over photorefractive keratectomy (PRK) include the desirable lack of healing response (the central corneal epithelium is not removed, thereby decreasing the risk of central haze formation that occurs during healing), the shorter visual rehabilitation period, and minimal postoperative pain. Disadvantages include possible intraoperative and postoperative flap-related complications, such as irregular flap formation, flap dislocation, and the need for adequate corneal thickness to prevent long-term corneal ectasia. Ectasia occurs when the cornea has become so thin that intraocular pressure causes instability and bulging of the thinned and weakened corneal stroma. Blurring, increasing myopia, and irregular astigmatism can result.

Photorefractive Keratectomy

In PRK, the excimer laser is used to sculpt (photoablate) the anterior curvature of the corneal stromal bed to treat myopia, hyperopia, and astigmatism. The corneal epithelium is removed before photoablation and generally takes 3 to 4 days to regenerate; during this time a bandage contact lens is worn. Unlike LASIK, no corneal flap is created.

PRK may be more suitable for patients with thin corneas or anterior basement membrane dystrophy.

Advantages of PRK include an overall thicker residual stromal bed (thereby reducing risk of ectasia) and lack of flap-related complications. Disadvantages include potential for corneal haze formation if a large amount of corneal tissue is ablated and the need for postoperative corticosteroid drops for 3 to 4 mo. More than 95% of patients see 20/40 or better without eyeglasses after surgery.

Intracorneal Ring Segments

Intracorneal ring segments (INTACS) are thin arc-shaped segments of biocompatible plastic that are inserted in pairs through a small radial corneal incision into the peripheral corneal stroma at two-thirds depth. After INTACS are inserted, the central corneal curvature is flattened, reducing myopia. INTACS are used for mild myopia (< 3 diopters) and minimal astigmatism (< 1 diopter). INTACS maintain a central, clear, optical zone because the 2 segments are placed in the corneal periphery. INTACS can be replaced or removed if desired.

Risks include induced astigmatism, undercorrection and overcorrection, infection, glare, halo, and incorrect depth placement. Vision results are very good; in US clinical studies, 97% of patients saw 20/40 or better and 74% of patients saw 20/20 or better.

Conductive Keratoplasty

Conductive keratoplasty (CK) is a thermal technique that can treat spherical hyperopia (ie, hyperopia without associated astigmatism) and presbyopia. CK uses radiofrequency energy applied with a fine probe in a ring pattern to the peripheral cornea to contract the periphery and steepen the center, thereby increasing the refractive power of the cornea. For presbyopic patients who wear only reading glasses, CK is typically done in the nondominant eye (monovision) to induce myopia in that eye and enable the patient to regain reading vision. As the presbyopia progresses, additional rings of treatment are added. Risks of CK include induced astigmatism and regression of effect.

Phakic Intraocular Lenses

Phakic intraocular lenses (IOLs) are lens implants that are used to treat severe myopia in patients who are not suitable candidates for laser vision correction. Unlike in cataract surgery, the patient's natural lens is not removed. The phakic IOL is inserted directly anterior or posterior to the iris through an incision in the eye. This procedure is intraocular surgery and must be done in an operating room.

Risks include cataract formation, glaucoma, infection, and loss of corneal endothelial cells.

Because phakic IOLs do not correct astigmatism, patients can undergo subsequent laser vision correction to refine refractive results in a technique known as bioptics. Because the bulk of the myopia is corrected with the phakic IOL, less corneal tissue is removed with LASIK, and the risk of ectasia is thus low.

Clear Lensectomy

Clear lensectomy can be considered in patients with high hyperopia who are already presbyopic. This procedure is identical to cataract surgery except the patient's lens is clear and not cataractous. A multifocal intraocular lens, which allows the patient to focus over a wide range of distances without external lens correction, can be inserted.

The main risks of clear lensectomy are infection and rupture of the posterior capsule of the lens, which would necessitate further surgery. Clear lensectomy should be done with great caution in young myopic patients because they have an increased risk of retinal detachment.

Radial and Astigmatic Keratotomy

Radial and astigmatic keratotomy procedures change the shape of the cornea by making deep corneal incisions using a diamond blade.

Radial keratotomy has been replaced by laser vision correction and is rarely used because it offers no clear advantages over laser vision correction, has a greater need for subsequent retreatment, leads to visual and refractive results that change through the day, and tends to cause hyperopia in the long term.

Astigmatic keratotomy is used to treat astigmatism at the time of cataract surgery or after corneal transplantation.

Chapter 62. Eyelid and Lacrimal Disorders

Introduction

Common eyelid and lacrimal disorders include blepharitis, blepharospasm, canaliculitis, chalazion and hordeolum, dacryocystitis, dacryostenosis, entropion and ectropion, trichiasis, and tumors.

Blepharitis

Blepharitis is inflammation of the eyelid margins that may be acute or chronic. Symptoms and signs include itching and burning of the eyelid margins with redness and edema. Diagnosis is by history and examination. Acute ulcerative blepharitis is usually treated with topical antibiotics or systemic antivirals. Acute nonulcerative blepharitis is occasionally treated with topical corticosteroids. Chronic disease is treated with tear supplements, warm compresses, and occasionally oral antibiotics (eg, a tetracycline) for meibomian gland dysfunction or with eyelid hygiene and tear supplements for seborrheic blepharitis.

Etiology

Blepharitis may be acute (ulcerative or nonulcerative) or chronic (meibomian gland dysfunction, seborrheic blepharitis).

Acute: Acute ulcerative blepharitis is usually caused by bacterial infection (usually staphylococcal) of the eyelid margin at the origins of the eyelashes; the lash follicles and meibomian glands are also involved. It may also be due to a virus (eg, herpes simplex, varicella zoster).

Acute nonulcerative blepharitis is usually caused by an allergic reaction involving the same area (eg, atopic blepharodermatitis and seasonal allergic blepharoconjunctivitis, which cause intense itching, rubbing, and a rash; contact sensitivity [dermatoblepharo-conjunctivitis]).

Chronic: Chronic blepharitis is noninfectious inflammation of unknown cause. Meibomian glands in the eyelid produce lipids (meibum) that reduce tear evaporation by forming a lipid layer on top of the aqueous tear layer. In meibomian gland dysfunction, the lipid composition is abnormal, and gland ducts and orifices become inspissated with hard, waxy plugs. Many patients have rosacea (see p. 654) and recurrent hordeola or chalazia.

Many patients with seborrheic blepharitis have seborrheic dermatitis of the face and scalp (see p. 671) or acne rosacea. Secondary bacterial colonization often occurs on the scales that develop on the eyelid margin. Meibomian glands can become obstructed.

Most patients with meibomian gland dysfunction or seborrheic blepharitis have increased tear evaporation and secondary keratoconjunctivitis sicca.

Symptoms and Signs

Symptoms common to all forms of blepharitis include itching and burning of the eyelid margins and conjunctival irritation with lacrimation, photosensitivity, and foreign body sensation.

Acute: In acute ulcerative blepharitis, small pustules may develop in eyelash follicles and eventually break down to form shallow marginal ulcers. Tenacious adherent crusts leave a bleeding surface when removed. During sleep, eyelids can become glued together by dried secretions. Recurrent ulcerative blepharitis can cause eyelid scars and loss of eyelashes.

In acute nonulcerative blepharitis, eyelid margins become edematous and erythematous; eyelashes may become crusted with dried serous fluid.

Chronic: In meibomian gland dysfunction, examination reveals dilated, inspissated gland orifices that, when pressed, exude a waxy, thick, yellowish secretion with pressure. In seborrheic blepharitis, greasy,

easily removable scales develop on eyelid margins. Most patients with seborrheic blepharitis and meibomian gland dysfunction have symptoms of keratoconjunctivitis sicca, such as foreign body sensation, grittiness, eye strain and fatigue, and blurring with prolonged visual effort.

Diagnosis

Diagnosis is usually by slit-lamp examination. Chronic blepharitis that does not respond to treatment may require biopsy to exclude eyelid tumors that can simulate the condition.

Prognosis

Acute blepharitis most often responds to treatment but may recur, develop into chronic blepharitis, or both. Chronic blepharitis is indolent, recurrent, and resistant to treatment. Exacerbations are inconvenient, uncomfortable, and cosmetically unappealing but do not usually result in corneal scarring or vision loss.

Treatment

Acute: Acute ulcerative blepharitis is treated with an antibiotic ointment (eg, bacitracin/polymyxin B, erythromycin, or gentamicin 0.3% qid for 7 to 10 days). Acute viral ulcerative blepharitis is treated with systemic antivirals (eg, for herpes simplex, acyclovir 400 mg po tid for 7 days; for varicella zoster, famciclovir 500 mg po tid or valacyclovir 1 g po tid for 7 days).

Treatment of acute nonulcerative blepharitis begins with avoiding the offending action (eg, rubbing) or substance (eg, new eye drops). Warm compresses over the closed eyelid may relieve symptoms and speed resolution. If swelling persists > 24 h, topical corticosteroids (eg, fluorometholone ophthalmic ointment 0.1% tid for 7 days) can be used.

Chronic: The initial treatment for both meibomian gland dysfunction and seborrheic blepharitis is directed toward the secondary keratoconjunctivitis sicca (see p. 592). Tear supplements, bland ointments at night, and, if necessary, punctal plugs (inserts that obstruct the puncta and thus decrease tear drainage) are effective in most patients.

If needed, additional treatment for meibomian gland dysfunction includes warm compresses to melt the waxy plugs and occasionally eyelid massage to extrude trapped secretions and coat the ocular surface. A tetracycline (eg, doxycycline 100 mg po bid tapered over 3 to 4 mo) may also be effective because it changes the composition of meibomian gland secretions.

If needed, additional treatment for seborrheic blepharitis includes gentle cleansing of the eyelid margin 2 times a day with a cotton swab dipped in a dilute solution of baby shampoo (2 to 3 drops in 1/2 cup of warm water). A topical antibiotic ointment (bacitracin/polymyxin B or sulfacetamide 10% bid for up to 3 mo) may be added to reduce bacterial counts on the eyelid margin when cases are unresponsive to weeks of eyelid hygiene.

Blepharospasm

Blepharospasm is spasm of muscles around the eye causing involuntary blinking and eye closing.

The cause of blepharospasm is most often unknown. It affects women more than men and tends to occur in families. Blepharospasm may be secondary to eye disorders, including those that cause ocular irritation (eg, trichiasis, corneal foreign body, keratoconjunctivitis sicca) and systemic neurologic diseases that cause spasm (eg, Parkinson's disease).

Symptoms are involuntary blinking and closing of the eyes; in severe cases, people cannot open their eyes. Spasms may be made worse by fatigue, bright light, and anxiety.

Treatment involves injecting botulinum toxin type A into the eyelid muscles; treatment must be repeated in

most instances. Anxiolytics may help. Surgery to cut the periorbital muscles is also effective but, because of potential complications, is considered only if botulinum toxin is ineffective. Sunglasses help decrease the light sensitivity that may cause or accompany blepharospasm.

Canaliculitis

Canaliculitis is inflammation of the canaliculus (see Fig. 60-3 on p. 567).

The most common cause is infection with *Actinomyces israelii*, a gram-positive bacillus with fine branching filaments, but other bacteria, fungi (eg, *Candida albicans*), and viruses (eg, herpes simplex) may be causative. Symptoms and signs are tearing, discharge, red eye (especially nasally), and mild tenderness over the involved side.

Diagnosis is suspected based on symptoms and signs, expression of turbid secretions with pressure over the lacrimal sac, and a gritty sensation caused by necrotic material that can be felt during probing of the lacrimal system. Canaliculitis can be differentiated from dacryocystitis. In canaliculitis, the punctum and canaliculus are red and swollen; in dacryocystitis, the punctum and canaliculus are normal, but a red, swollen, tender mass is located in or near the lacrimal sac.

Treatment is warm compresses, irrigation of the canaliculus with antibiotic solution (by an ophthalmologist), and removal of any concretions, which usually requires surgery. Antibiotic selection is usually empiric with a 1st-generation cephalosporin or penicillinase-resistant synthetic penicillin but may be guided by irrigation samples.

Chalazion and Hordeolum

Chalazia and hordeola are sudden-onset localized swellings of the eyelid. A chalazion is caused by noninfectious meibomian gland occlusion, whereas a hordeolum is caused by infection. Both conditions initially cause eyelid hyperemia and edema, swelling, and pain. With time, a chalazion becomes a small nontender nodule in the eyelid center, whereas a hordeolum remains painful and localizes to an eyelid margin. Diagnosis is clinical. Treatment is with hot compresses. Both conditions improve spontaneously, but incision or, for chalazia, intralesional corticosteroids may be used to hasten resolution.

Chalazion: A chalazion is noninfectious obstruction of a meibomian gland causing extravasation of irritating lipid material in the eyelid soft tissues with focal secondary granulomatous inflammation (see Plate 7). Disorders that cause abnormally thick meibomian gland secretions (eg, meibomian gland dysfunction, acne rosacea) increase the risk of meibomian gland obstruction.

Hordeolum: A hordeolum (stye) is an acute, localized, pyogenic (usually staphylococcal) infection or abscess of the eyelid that may be external or internal (see Plate 16). Most hordeola are external and result from obstruction and infection of an eyelash follicle and adjacent glands of Zeis or Moll's glands. Follicle obstruction may be associated with blepharitis. An internal hordeolum, which is very rare, results from infection of a meibomian gland. Sometimes cellulitis accompanies hordeola.

Symptoms and Signs

Chalazia and hordeola each cause eyelid redness, swelling, and pain.

Chalazion: After 1 or 2 days, a chalazion localizes to the body of the eyelid. Typically, a small nontender nodule or lump develops. A chalazion usually drains through the inner surface of the eyelid or is absorbed spontaneously over 2 to 8 wk; rarely, it persists longer. Vision may be slightly blurred.

Hordeolum: After 1 to 2 days, an external hordeolum localizes to the eyelid margin. There may be tearing, photophobia, and a foreign body sensation. Typically, a small yellowish pustule develops at the base of an eyelash, surrounded by hyperemia, induration, and diffuse edema. Within 2 to 4 days, the

lesion ruptures and discharges pus, thereby relieving pain and resolving the lesion.

Symptoms of an internal hordeolum are the same as those of a chalazion, with pain, redness, and edema localized to the posterior tarsal conjunctival surface. Inflammation may be severe, sometimes with fever or chills. Inspection of the tarsal conjunctivae shows a small elevation or yellow area at the site of the affected gland. Later, an abscess forms. Spontaneous rupture is rare; however, when it does occur, it usually occurs on the conjunctival side of the eyelid and sometimes erupts through the skin side. Recurrence is common.

Diagnosis

• Clinical assessment

Diagnosis of chalazion and both kinds of hordeola is clinical; however, during the first 2 days, they may be clinically indistinguishable. Because internal hordeola are so rare, they are not usually suspected unless inflammation is severe or fever or chills are present. If the chalazion or hordeolum lies near the inner canthus of the lower eyelid, it must be differentiated from dacryocystitis (see below), which can usually be excluded by noting the location of maximum induration and tenderness (eg, eyelid for a chalazion, under the medial canthus near the side of the nose for dacryocystitis). Chronic chalazia that do not respond to treatment require biopsy to exclude tumor of the eyelid.

Treatment

• Hot compresses

• Sometimes drainage or drug therapy

Hot compresses for 5 to 10 min 2 or 3 times a day can be used to hasten resolution of chalazia and external hordeola.

Chalazion: Incision and curettage or intrachalazion corticosteroid therapy (0.05 to 0.2 mL triamcinolone 25 mg/mL) may be indicated if chalazia are large, unsightly, and persist for more than several weeks despite conservative therapy.

Hordeolum: An external hordeolum that does not respond to hot compresses can be incised with a sharp, fine-tipped blade. Systemic antibiotics (eg, dicloxacillin or erythromycin 250 mg po qid) are indicated when cellulitis accompanies a hordeolum.

Treatment of internal hordeola is oral antibiotics and incision and drainage if needed. Topical antibiotics are usually ineffective.

Dacryocystitis

Dacryocystitis is infection of the lacrimal sac, usually with staphyloccocal or streptococcal species and usually as a consequence of nasolacrimal duct obstruction.

In acute dacryocystitis, the patient presents with pain, redness, and edema around the lacrimal sac. Diagnosis is suspected based on symptoms and signs and when pressure over the lacrimal sac causes reflux of mucoid material through the puncta. Initial treatment is with warm compresses and oral antibiotics for mild cases or IV antibiotics for more severe cases. The antibiotic is usually a 1st-generation cephalosporin or penicillinase-resistant synthetic penicillin. If the infection does not respond as expected, consideration should be given to methicillin-resistant *Staphylococcus aureus* (MRSA), and antibiotics changed accordingly. The abscess can be drained and the antibiotics can be changed based on culture results if the initial antibiotic proves ineffective.

Patients with chronic dacryocystitis usually present with a mass under the medial canthal tendon and chronic conjunctivitis. Definitive treatment for resolved acute dacryocystitis or chronic conjunctivitis is usually surgery that creates a passage between the lacrimal sac and the nasal cavity

(dacryocystorhinostomy).

Dacryostenosis

Dacryostenosis is obstruction or stenosis of the nasolacrimal duct, causing excess tearing.

Nasolacrimal obstruction may be congenital or acquired. One cause of congenital obstruction is inadequate development of any part of the nasolacrimal ducts. Typically, a membrane at the distal end of the nasolacrimal duct persists. There is tearing and purulent discharge; the condition may manifest as chronic conjunctivitis, usually beginning after the age of 2 wk (most often at age 3 to 12 wk).

Causes of acquired nasolacrimal duct obstruction are listed in Table 62-1. The cause is most often age-related stenosis of the nasolacrimal duct. Other causes include past nasal or facial bone fractures and sinus surgery, which disrupt the nasolacrimal duct; inflammatory diseases (eg, sarcoidosis, Wegener's granulomatosis); and dacryocystitis.

Causes of punctal or canalicular stenosis include chronic conjunctivitis (especially herpetic), certain types of chemotherapy, adverse reactions to eye drops (especially topical echothiophate iodide), and radiation.

Diagnosis

Diagnosis is usually based on clinical criteria. Sometimes ophthalmologists probe and irrigate the lacrimal drainage system with saline, with or without fluorescein dye. Reflux indicates stenosis.

Treatment

Congenital nasolacrimal duct obstruction often resolves spontaneously by about age 6 to 9 mo; before 1 yr, manual compression of the lacrimal sac 4 or 5 times/day may relieve the obstruction. After 1 yr, the nasolacrimal duct may need probing, usually under general anesthesia; if obstruction is recurrent, a temporary silastic tube may be inserted.

[**Table 62-1.** Causes of Acquired Nasolacrimal Duct Obstruction]

In acquired nasolacrimal duct obstruction, the underlying disorder is treated when possible. If treatment is not possible or is ineffective, a passage between the lacrimal sac and the nasal cavity can be created surgically (dacryocystorhinostomy).

In cases of punctal or canalicular stenosis, dilation is usually curative. If canalicular stenosis is severe and bothersome, a surgical procedure that places a glass tube (Jones tube) leading from the caruncle into the nasal cavity can be considered.

Entropion and Ectropion

Entropion is inversion of an eyelid. Ectropion is eversion of the lower eyelid.

Entropion: Entropion (inversion of an eyelid) is caused by age-related tissue relaxation, postinfectious or posttraumatic changes, or blepharospasm. Eyelashes rub against the eyeball and may lead to corneal ulceration and scarring. Symptoms can include foreign body sensation, tearing, and red eye. Diagnosis is clinical. Definitive treatment is surgery.

Ectropion: Ectropion (eversion of the lower eyelid—see Plate 12) is caused by age-related tissue relaxation, cranial nerve VII palsy, and posttraumatic or postsurgical changes. Symptoms are tearing (due to poor drainage of tears through the nasolacrimal system, which may no longer contact the eyeball) and symptoms of dry eyes (see p. 592), possibly due to inadequate blinking. Diagnosis is clinical. Symptomatic treatment can include tear supplements and, at night, ocular lubricants; definitive treatment is surgery.

Trichiasis

Trichiasis is an anatomic misalignment of eyelashes, which rub against the eyeball, in a patient with no entropion.

Trichiasis is most often idiopathic, but known causes include blepharitis, posttraumatic and postsurgical changes, conjunctival scarring (eg, secondary to cicatricial pemphigoid, atopic keratoconjunctivitis, Stevens-Johnson syndrome, or chemical injury), epiblepharon (an extra lower eyelid skinfold that directs lashes into a vertical position), and distichiasis (a congenital extra row of eyelashes). Corneal ulceration and scarring can occur in chronic cases. Symptoms are foreign body sensation, tearing, and red eye. Diagnosis is usually clinical. Trichiasis differs from entropion in that the eyelid position is normal. Evaluation includes fluorescein staining to exclude corneal abrasion or ulceration. Treatment is eyelash removal with forceps. If eyelashes grow back, electrolysis or cryosurgery is more effective at permanently preventing recurrence.

Tumors

The skin of the eyelids is a common site for growth of benign and malignant tumors.

Xanthelasma: Xanthelasma is a common, benign deposit of yellow-white flat plaques of lipid material that occur subcutaneously on the upper and lower eyelids. Although some people with xanthelasmas have dyslipidemias, most do not. Diagnosis is by appearance. No treatment is necessary, although xanthelasmas can be removed for cosmetic reasons, and underlying dyslipidemias should be treated.

Basal cell carcinoma: This skin cancer frequently occurs at the eyelid margins, at the inner canthus, and on the upper cheek (see also p. 749). Metastasis is rare. Biopsy establishes the diagnosis. Treatment is surgical excision using conventional techniques or by Mohs' surgery.

Other malignant tumors: These types of tumors are less common; they include squamous cell carcinoma, meibomian gland carcinoma, and melanomas. Eyelid tumors may simulate chronic blepharitis or chronic chalazion. Therefore, chronic blepharitis, chronic chalazion, or similar lesions should be biopsied if unresponsive to initial treatment.

Chapter 63. Conjunctival and Scleral Disorders

Introduction

The conjunctiva lines the back of the eyelids (palpebral or tarsal conjunctiva), crosses the space between the lid and the globe (forniceal conjunctiva), then folds back on itself as it spreads over the sclera to the cornea (bulbar conjunctiva). The conjunctiva helps maintain the tear film and protect the eye from foreign objects and infection.

The sclera is the thick white sphere of dense connective tissue that encloses the eye and maintains its shape. Anteriorly, the sclera fuses with the cornea, and posteriorly it blends with the meninges where the optic nerve penetrates the globe.

The episclera is a thin vascular membrane between the conjunctiva and the sclera.

The most common disorders are inflammatory (eg, conjunctivitis, episcleritis, scleritis). Conjunctivitis can be acute or chronic and is infectious, allergic, or irritant in origin. Scleritis usually results from immune-mediated disease and episcleritis often does as well. Episcleritis usually does not threaten vision, but scleritis can destroy vision and the eye. Major symptoms of conjunctivitides (eg, conjunctival hyperemia) are similar. Early, accurate diagnosis is important.

Select eye findings in conjunctival disorders: Edema of the bulbar conjunctiva results in a translucent, bluish, thickened conjunctiva. Gross edema with ballooning of the conjunctiva, often leading to prolapse of conjunctiva, is known as chemosis.

Edema of the tarsal conjunctiva (typical of allergic conjunctivitis) results in fine, minute projections (papillae), giving the conjunctiva a velvety appearance.

Hyperplasia of lymphoid follicles in the conjunctiva can occur in viral or chlamydial conjunctivitis. It appears as small bumps with pale centers, resembling cobblestones. It occurs most commonly in the inferior tarsal conjunctiva.

Cicatricial Pemphigoid

(Benign Mucous Membrane Pemphigoid; Mucous Membrane Pemphigoid; Ocular Cicatricial Pemphigoid)

Cicatricial pemphigoid is a chronic, bilateral, progressive scarring and shrinkage of the conjunctiva with opacification of the cornea. Early symptoms are hyperemia, discomfort, itching, and discharge; progression leads to eyelid and corneal damage and sometimes blindness. Diagnosis may be confirmed by biopsy, but biopsy is often not necessary. Treatment may require systemic immunosuppression.

Cicatricial pemphigoid is an autoimmune disease in which binding of anticonjunctival basement membrane antibodies results in conjunctival inflammation. It is unrelated to bullous pemphigoid.

Symptoms and Signs

Usually beginning as a chronic conjunctivitis, the condition progresses to symblepharon (adhesion between the tarsal and bulbar conjunctiva); trichiasis (in-turning eyelashes); keratoconjunctivitis sicca; corneal neovascularization, opacification, and keratinization; and conjunctival shrinkage and keratinization. Chronic corneal epithelial defects can lead to secondary bacterial ulceration, scarring, and blindness. Oral mucous membrane involvement with ulceration and scarring is common, but skin involvement, characterized by scarring bullae and erythematous plaques, is uncommon.

Diagnosis

• Unexplained symblepharon or biopsy findings

Diagnosis is suspected clinically in patients with conjunctival scarring plus corneal changes, symblepharon, or both. The differential diagnosis of progressive conjunctival scarring includes postradiation and atopic disease. Therefore, the clinical diagnosis of cicatricial pemphigoid is made when there is progression of symblepharon without a history of local radiation or severe perennial allergic conjunctivitis. Diagnosis can be confirmed by conjunctival biopsy showing antibody deposition on the basement membrane.

Treatment

• Epilation of in-turning lashes

• Sometimes systemic immunosuppression

Tear substitutes and epilation, cryoepilation, or electroepilation of the in-turning eyelashes may increase patient comfort and reduce the risk of ocular infection and secondary scarring. For progressive scarring or corneal opacification or for nonhealing corneal epithelial defects, systemic immunosuppression with dapsone or cyclophosphamide is indicated.

Conjunctivitis

Conjunctival inflammation typically results from infection, allergy, or irritation. Symptoms are conjunctival hyperemia and ocular discharge and, depending on the etiology, discomfort and itching. Diagnosis is clinical; sometimes cultures are indicated. Treatment depends on etiology and may include topical antibiotics, antihistamines, mast cell stabilizers, and corticosteroids.

Infectious conjunctivitis is most commonly viral or bacterial and is contagious. Rarely, mixed or unidentifiable pathogens are present. Numerous allergens can cause allergic conjunctivitis (see p. 584). Nonallergic conjunctival irritation can result from foreign bodies; wind, dust, smoke, fumes, chemical vapors, and other types of air pollution; and intense ultraviolet light of electric arcs, sunlamps, and reflection from snow.

Conjunctivitis is typically acute, but both infectious and allergic conditions can be chronic. Conditions that cause chronic conjunctivitis include ectropion, entropion, blepharitis, and chronic dacryocystitis.

Symptoms and Signs

Any source of inflammation causes lacrimation or discharge and diffuse conjunctival vascular dilation. Discharge may cause the eyes to crust overnight. Thick discharge may blur vision, but once discharge is cleared, visual acuity should be unaffected.

Itching and watery discharge predominate in allergic conjunctivitis. Chemosis and papillary hyperplasia also suggest allergic conjunctivitis. Irritation or foreign body sensation, photophobia, and discharge suggest infectious conjunctivitis; purulent discharge suggests a bacterial cause. Severe eye pain suggests scleritis (see p. 587).

Diagnosis

• Clinical evaluation

• Sometimes culture

Usually, diagnosis is made by history and examination (see also Table 63-1), usually including slit-lamp examination with fluorescein staining of the cornea and, if glaucoma is suspected, measurement of intraocular pressure.

Other disorders can cause a red eye (see p. 563). Deep pain in the affected eye when a light is shone in the unaffected eye (true photophobia) does not occur in uncomplicated conjunctivitis and suggests a disorder of the cornea or anterior uveal tract. Circumcorneal conjunctival hyperemia (sometimes

described as ciliary flush) is caused by dilated, fine, straight, deep vessels that radiate out 1 to 3 mm from the limbus, without significant hyperemia of the bulbar and tarsal conjunctivae. Ciliary flush occurs with uveitis, acute glaucoma, and some types of keratitis.

The cause of conjunctivitis is suggested by clinical findings. However, cultures are indicated for patients with severe symptoms, immunocompromise, a vulnerable eye (eg, after a corneal transplant, in exophthalmos due to Graves' disease), or ineffective initial therapy.

Clinical differentiation between viral and bacterial infectious conjunctivitis is not highly accurate. However, temporarily missing some cases of mild bacterial conjunctivitis is not likely to be harmful because the infection often resolves spontaneously and antibiotics can be prescribed if symptoms persist.

Treatment

• Prevention of spread

• Treatment of symptoms

Most infectious conjunctivitis is highly contagious and spreads by droplet, fomites, and hand-to-eye inoculation. To avoid transmitting infection, physicians must wash their hands thoroughly and disinfect equipment after examining patients. Patients should wash their hands thoroughly after touching their eyes or nasal secretions, avoid touching the noninfected eye after touching the infected eye, avoid sharing towels or pillows, and avoid swimming in pools. Eyes should be kept free of discharge and should not be patched. Small children with conjunctivitis should be kept home from school to avoid spread. Cool wash-cloths applied to the eyes may help relieve local burning and itching. Antimicrobials are used for certain infections.

Viral Conjunctivitis

Viral conjunctivitis is a highly contagious acute conjunctival infection usually caused by adenovirus. Symptoms include irritation, photophobia, and watery discharge. Diagnosis is clinical. Infection is self-limited, but severe cases sometimes require topical corticosteroids.

Etiology

Conjunctivitis may accompany the common cold and other systemic viral infections (especially measles, but also chickenpox, rubella, and mumps). Isolated viral conjunctivitis usually results from adenoviruses and sometimes enteroviruses.

Epidemic keratoconjunctivitis usually results from adenovirus serotypes Ad 5, 8, 11, 13, 19, and 37. Pharyngoconjunctival fever usually results from serotypes Ad 3, 4, and 7. Outbreaks of acute hemorrhagic conjunctivitis, a rare conjunctivitis associated with infection by enterovirus type 70, have occurred in Africa and Asia.

Symptoms and Signs

After an incubation period of about 5 to 12 days, conjunctival hyperemia, watery discharge, and ocular irritation usually begin in one eye and spread rapidly to the other. Follicles may be present on the palpebral conjunctiva. A preauricular lymph node is often enlarged and painful. Many patients have had contact with someone with conjunctivitis, a recent URI, or both.

[Table 63-1. Differentiating Features in Acute Conjunctivitis]

In severe adenoviral conjunctivitis, patients may have photophobia and foreign body sensation. Chemosis may be present. Pseudomembranes of fibrin and inflammatory cells on the tarsal conjunctiva, focal corneal inflammation, or both may blur vision. Even after conjunctivitis has resolved, residual corneal subepithelial opacities (multiple, coin-shaped, 0.5 to 1.0 mm in diameter) may be visible with a slit lamp for up to 2 yr. Corneal opacities occasionally result in decreased vision and significant glare.

Diagnosis

• Clinical evaluation

Diagnosis of conjunctivitis and differentiation between bacterial, viral, and noninfectious conjunctivitis are usually clinical; special tissue cultures are necessary for growth of the virus but are rarely indicated. Features that may help differentiate between viral and bacterial conjunctivitis can include purulence of eye discharge, presence of preauricular lymphadenopathy, and, in epidemic keratoconjunctivitis, chemosis. Patients with photophobia are stained with fluorescein and examined with a slit lamp. Epidemic keratoconjunctivitis may cause punctate corneal staining. Secondary bacterial infection of viral conjunctivitis is rare. However, if any signs suggest bacterial conjunctivitis (eg, purulent discharge), smears from the eye may be examined microscopically and cultured for bacteria.

Treatment

• Supportive measures

Viral conjunctivitis is highly contagious, and transmission precautions must be followed (as described previously). Children should generally be kept out of school until resolution.

Viral conjunctivitis is self-limiting, lasting 1 wk in mild cases to up to 3 wk in severe cases. It requires only warm or cool compresses for symptomatic relief. However, patients who have severe photophobia or whose vision is affected may benefit from topical corticosteroids (eg, 1% prednisolone acetate q 6 to 8 h). Corticosteroids, if prescribed, are usually prescribed by an ophthalmologist. Herpes simplex keratitis (see p. 589) must be ruled out first (by fluorescein staining and slit-lamp examination) because corticosteroids can exacerbate it.

Acute Bacterial Conjunctivitis

Acute conjunctivitis can be caused by numerous bacteria. Symptoms are hyperemia, lacrimation, irritation, and discharge. Diagnosis is clinical. Treatment is with topical antibiotics, augmented by systemic antibiotics in more serious cases.

Most bacterial conjunctivitis is acute; chronic bacterial conjunctivitis may be caused by *Chlamydia* and rarely *Moraxella*. Chlamydial conjunctivitis includes trachoma and adult or neonatal inclusion conjunctivitis.

Etiology

Bacterial conjunctivitis is usually caused by *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus* sp, or, less commonly, *Chlamydia trachomatis* (see p. 583). *Neisseria gonorrhoeae* causes gonococcal conjunctivitis, which usually results from sexual contact with a person who has a genital infection.

Ophthalmia neonatorum (see also p. 2824) is conjunctivitis that occurs in 20 to 40% of neonates delivered through an infected birth canal. It can be caused by maternal gonococcal or chlamydial infection.

Symptoms and Signs

Symptoms are typically unilateral but frequently spread to the opposite eye within a few days. Discharge is typically purulent.

The bulbar and tarsal conjunctivae are intensely hyperemic and edematous. Petechial subconjunctival hemorrhages, chemosis, photophobia, and an enlarged preauricular lymph node are typically absent. Eyelid edema is often moderate.

With adult gonococcal conjunctivitis, symptoms develop 12 to 48 h after exposure. Severe eyelid edema, chemosis, and a profuse purulent exudate are typical. Rare complications include corneal ulceration, abscess, perforation, panophthalmitis, and blindness.

Ophthalmia neonatorum caused by gonococcal infection appears 2 to 5 days after delivery. With ophthalmia neonatorum caused by a chlamydial infection, symptoms appear within 5 to 14 days. Symptoms of both are bilateral, intense papillary conjunctivitis with lid edema, chemosis, and mucopurulent discharge.

Diagnosis

• Clinical evaluation

Diagnosis of conjunctivitis and differentiation between bacterial, viral, and noninfectious conjunctivitis are usually clinical. Smears and bacterial cultures should be done in patients with severe symptoms, immunocompromise, ineffective initial therapy, or a vulnerable eye (eg, after a corneal transplant, in exophthalmos due to Graves' disease). Smears and conjunctival scrapings should be examined microscopically and stained with Gram stain to identify bacteria and stained with Giemsa stain to identify the characteristic epithelial cell basophilic cytoplasmic inclusion bodies of chlamydial conjunctivitis.

Treatment

• Antibiotics (topical for all causes except gonococcal)

Bacterial conjunctivitis is very contagious, and standard infection control measures (see p. 581) should be followed.

If neither gonococcal nor chlamydial infection is suspected, most clinicians treat presumptively with moxifloxacin 0.5% drops tid for 7 to 10 days or another fluoroquinolone or trimethoprim/polymyxin B qid. A poor clinical response after 2 or 3 days indicates that the cause is resistant bacteria, a virus, or an allergy. Culture and sensitivity studies determine subsequent treatment.

Adult gonococcal conjunctivitis requires a single dose of ceftriaxone 1 g IM. Fluoroquinolones are no longer recommended because resistance is now widespread. Bacitracin 500 U/g or gentamicin 0.3% ophthalmic ointment instilled into the affected eye q 2 h may be used in addition to systemic treatment. Sex partners should also be treated. Because chlamydial genital infection is often present in patients with gonorrhea, patients should also receive a single dose of azithromycin 1 g or doxycycline 100 mg po bid for 7 days.

Ophthalmia neonatorum is prevented by the routine use of silver nitrate eye drops or erythromycin ointment at birth. Infections that develop despite this treatment require systemic treatment. For gonococcal infection, ceftriaxone 25 to 50 mg/kg IV or IM is given once/day for 7 days. Chlamydial infection is treated with erythromycin 12.5 mg/kg po or IV qid for 14 days. The parents should also be treated.

Adult Inclusion Conjunctivitis

(Adult Chlamydial Conjunctivitis; Swimming Pool Conjunctivitis)

Adult inclusion conjunctivitis is caused by sexually transmitted *Chlamydia trachomatis*. Symptoms include chronic unilateral hyperemia and mucopurulent discharge. Diagnosis is clinical. Treatment is with systemic antibiotics.

Adult inclusion conjunctivitis is caused by *Chlamydia trachomatis* serotypes D through K. In most instances, adult inclusion conjunctivitis results from sexual contact with a person who has a genital infection. Usually, patients have acquired a new sex partner in the preceding 2 mo. Rarely, adult inclusion conjunctivitis is acquired from contaminated, incompletely chlorinated swimming pool water.

Symptoms and Signs

Adult inclusion conjunctivitis has an incubation period of 2 to 19 days. Most patients have a unilateral mucopurulent discharge. The tarsal conjunctiva is often more hyperemic than the bulbar conjunctiva. Characteristically, there is a marked tarsal follicular response. Occasionally, superior corneal opacities and vascularization occur. Preauricular lymph nodes may be swollen on the side of the involved eye. Often, symptoms have been present for many weeks or months and have not responded to topical antibiotics.

Diagnosis

• Clinical evaluation

• Laboratory testing

Chronicity, mucopurulent discharge, marked tarsal follicular response, and failure of topical antibiotics differentiate adult inclusion conjunctivitis from other bacterial conjunctivitides. Smears, bacterial cultures, and chlamydial studies should be done. Immunofluorescent staining techniques, PCR, and special cultures are used to detect *C. trachomatis*. Smears and conjunctival scrapings should be examined microscopically and stained with Gram stain to identify bacteria and stained with Giemsa stain to identify the characteristic epithelial cell basophilic cytoplasmic inclusion bodies of chlamydial conjunctivitis.

Treatment

• Antibiotics

Azithromycin 1 g po once only or either doxycycline 100 mg po bid or erythromycin 500 mg po qid for 1 wk cures the conjunctivitis and concomitant genital infection. Sex partners also require treatment.

Trachoma

(Egyptian Ophthalmia; Granular Conjunctivitis)

Trachoma is a chronic conjunctivitis caused by *Chlamydia trachomatis* and is characterized by progressive exacerbations and remissions. It is the leading cause of preventable blindness worldwide. Initial symptoms are conjunctival hyperemia, eyelid edema, photophobia, and lacrimation. Later, corneal neovascularization and scarring of the conjunctiva, cornea, and eyelids occur. Diagnosis is usually clinical. Treatment is with topical or systemic antibiotics.

Trachoma is endemic in poverty-stricken parts of North Africa, the Middle East, the Indian subcontinent, Australia, and Southeast Asia. The causative organism is *Chlamydia trachomatis* (serotypes A, B, Ba, and C). In the US, trachoma is rare, occurring occasionally among Native Americans and immigrants. The disease occurs mainly in children, particularly those between the ages of 3 and 6. Older children and adults are much less susceptible because of increased immunity and better personal hygiene. Trachoma is highly contagious in its early stages and is transmitted by eye-to-eye contact, hand-to-eye contact, eye-seeking flies, or the sharing of contaminated articles (eg, towels, handkerchiefs, eye makeup).

Symptoms and Signs

Trachoma usually affects both eyes. After an incubation period of about 7 days, conjunctival hyperemia, eyelid edema, photophobia, and lacrimation gradually appear, usually bilaterally. Small follicles develop in the upper tarsal conjunctiva 7 to 10 days later and gradually increase in size and number for 3 or 4 wk (see
Plate 20). Inflammatory papillae appear on the upper tarsal conjunctiva, and corneal neovascularization begins during this stage, with invasion of the upper half of the cornea by loops of vessels from the limbus (called pannus). The stage of follicular/papillary hypertrophy and corneal neovascularization may last from several months to > 1 yr, depending on response to therapy. The entire cornea may ultimately be involved, reducing vision.

Without treatment, a cicatricial (scarring) stage follows. The follicles and papillae gradually shrink and are replaced by scar tissue that often causes entropion and lacrimal duct obstruction. Entropion leads to further corneal scarring and neovascularization. Secondary bacterial infection is common, contributing to scarring and disease progression. The corneal epithelium becomes dull and thickened, and lacrimation is decreased. Small corneal ulcers may appear at the site of peripheral corneal infiltrates, stimulating further neovascularization.

With treatment and healing, the conjunctiva becomes smooth and grayish white. Rarely, corneal neovascularization regresses completely without treatment, and corneal transparency is restored. Impaired vision or blindness occurs in about 5% of people with trachoma.

Diagnosis

• Clinical findings (eg, tarsal lymphoid follicles, linear conjunctival scars, corneal pannus)

Diagnosis is usually clinical because testing is rarely available in endemic areas. Lymphoid follicles on the tarsal plate or along the corneal limbus, linear conjunctival scarring, and corneal pannus are considered diagnostic in the appropriate clinical setting. If diagnosis is uncertain, *C. trachomatis* can be isolated in culture or identified by PCR and immunofluorescence techniques. In the early stage, minute basophilic cytoplasmic inclusion bodies within conjunctival epithelial cells in Giemsa-stained conjunctival scrapings differentiate trachoma from nonchlamydial conjunctivitis. Inclusion bodies are also found in adult inclusion conjunctivitis (see p. 583), but the setting and developing clinical picture distinguish it from trachoma. Palpebral vernal conjunctivitis appears similar to trachoma in its follicular hypertrophic stage, but symptoms are different, milky flat-topped papillae are present, and eosinophils (not basophilic inclusion bodies) are found in the scrapings.

Treatment

• Oral azithromycin

For individual or sporadic cases, azithromycin 20 mg/kg (maximum 1 g) po as a single dose is 78% effective. Alternatives are doxycycline 100 mg bid or tetracycline 250 mg qid for 4 wk. In hyperendemic areas, tetracycline or erythromycin ophthalmic ointment applied bid for 5 consecutive days each month for 6 mo has been effective as treatment and prophylaxis. Endemic trachoma has been dramatically reduced by using community-wide oral azithromycin in a single dose or in repeated doses. Reinfection due to re-exposure is common among endemic areas. Better personal hygiene and environmental measures (eg, access to potable water) can reduce reinfection.

Eyelid deformities (eg, entropion) should be treated surgically.

Allergic Conjunctivitis

(Atopic Conjunctivitis; Atopic Keratoconjunctivitis; Hay Fever Conjunctivitis; Perennial Allergic Conjunctivitis; Seasonal Allergic Conjunctivitis; Vernal Keratoconjunctivitis)

Allergic conjunctivitis is an acute, intermittent, or chronic conjunctival inflammation usually caused by airborne allergens. Symptoms include itching, lacrimation, discharge, and conjunctival hyperemia. Diagnosis is clinical. Treatment is with topical antihistamines and mast cell stabilizers.

Etiology

Allergic conjunctivitis is due to a type I hypersensitivity reaction to a specific antigen.

Seasonal allergic conjunctivitis (hay fever conjunctivitis) is caused by airborne pollen of trees, grasses, or weeds. It tends to peak during the spring, late summer, or early fall and disappear during the winter months—corresponding to the life cycle of the causative plant.

Perennial allergic conjunctivitis (atopic conjunctivitis, atopic keratoconjunctivitis) is caused by dust mites, animal dander, and other nonseasonal allergens. These allergens, particularly those in the home, tend to cause symptoms year-round.

Vernal keratoconjunctivitis is a more severe type of conjunctivitis most likely allergic in origin. It is most common among males aged 5 to 20 who also have eczema, asthma, or seasonal allergies. Vernal conjunctivitis typically reappears each spring and subsides in the fall and winter. Many children outgrow the condition by early adulthood.

Symptoms and Signs

General: Patients report bilateral mild to intense ocular itching, conjunctival hyperemia, photosensitivity (photophobia in severe cases), eyelid edema, and watery or stringy discharge. Concomitant rhinitis is common. Many patients have other atopic diseases, such as eczema, allergic rhinitis, or asthma.

Findings characteristically include conjunctival edema and hyperemia and a discharge. The bulbar conjunctiva may appear translucent, bluish, and thickened. Chemosis and a characteristic boggy blepharedema of the lower eyelid are common. Chronic itching can lead to chronic eyelid rubbing, periocular hyperpigmentation, and dermatitis.

Seasonal and perennial conjunctivitis: Fine papillae on the upper tarsal conjunctiva give it a velvety appearance. In more severe forms, larger tarsal conjunctival papillae, conjunctival scarring, corneal neovascularization, and corneal scarring with variable loss of visual acuity can occur.

Vernal keratoconjunctivitis: Usually, the palpebral conjunctiva of the upper eyelid is involved, but the bulbar conjunctiva is sometimes affected. In the palpebral form, square, hard, flattened, closely packed, pale pink to grayish cobblestone papillae are present, chiefly in the upper tarsal conjunctiva (see Plate 8). The uninvolved tarsal conjunctiva is milky white. In the bulbar (limbal) form, the circumcorneal conjunctiva becomes hypertrophied and grayish. Discharge may be tenacious and mucoid, containing numerous eosinophils.

Occasionally, a small, circumscribed loss of corneal epithelium occurs, causing pain and increased photophobia. Other corneal changes (eg, central plaques) and white limbal deposits of eosinophils (Trantas' dots) may be seen.

Diagnosis

The diagnosis is usually clinical. Eosinophils are present in conjunctival scrapings, which may be taken from the lower or upper tarsal conjunctiva; however, such testing is rarely indicated.

Treatment

• Symptomatic measures

• Topical antihistamines, vasoconstrictors, NSAIDs, mast cell stabilizers, or a combination

• Topical corticosteroids or cyclosporine for recalcitrant cases

Avoidance of known allergens and use of tear supplements can reduce symptoms; antigen desensitization is occasionally helpful. Topical OTC antihistamine/vasoconstrictors (eg, naphazoline/pheniramine) are useful for mild cases. If these drugs are insufficient, topical prescription antihistamines (eg, olopatadine, ketotifen), NSAIDs (eg, ketorolac), or mast cell stabilizers (eg, pemirolast, nedocromil, azelastine) can be used separately or in combination. Topical corticosteroids (eg, loteprednol, fluorometholone 0.1%, prednisolone acetate 0.12% to 1% drops tid) can be useful in recalcitrant cases. Because topical corticosteroids can exacerbate ocular herpes simplex virus infections, possibly leading to corneal ulceration and perforation and, with long-term use, to glaucoma and possibly cataracts, their use should be initiated and monitored by an ophthalmologist. Topical cyclosporine may be indicated when

corticosteroids are needed but cannot be used.

Seasonal allergic conjunctivitis is less likely to require multiple drugs or intermittent topical corticosteroids.

Other Conjunctival Disorders

Pinguecula and pterygium: These lesions are benign growths of the conjunctiva that can result from chronic actinic irritation. Both typically appear adjacent to the cornea at the 3-o'clock position, the 9-o'clock position, or both (see Fig. 63-1).

A **pinguecula** is a raised yellowish white mass on the bulbar conjunctiva, adjacent to the cornea. It does not tend to grow onto the cornea. However, it may cause irritation or cosmetic blemish and, although rarely necessary, can easily be removed.

A **pterygium** is a fleshy triangular growth of bulbar conjunctiva that may spread across and distort the cornea, induce astigmatism, and change the refractive power of the eye. Symptoms may include decreased vision and foreign body sensation. It is more common in hot, dry climates. Removal is often indicated for cosmesis, to reduce irritation, and to improve or preserve vision.

Subconjunctival hemorrhages: These extravasations of blood beneath the conjunctiva usually result from minor trauma, straining, sneezing, or coughing; rarely, they occur spontaneously. The extent and location of hyperemia can help determine etiology. Diffuse hyperemia of the bulbar and tarsal conjunctivae is typical of conjunctivitis. Subconjunctival hemorrhages alarm the patient but are of no pathologic significance except when associated with blood dyscrasia, which is rare, or other facial or ocular injuries. They are absorbed spontaneously, usually within 2 wk. Topical corticosteroids, antibiotics, vasoconstrictors, and compresses do not speed reabsorption; reassurance is adequate therapy.

Episcleritis

Episcleritis is self-limiting, recurring, idiopathic inflammation of the episcleral tissue that does not threaten vision. Symptoms are a localized area of hyperemia of the globe, irritation, and lacrimation. Diagnosis is clinical. Treatment is symptomatic.

Episcleritis occurs in young adults, more commonly among women. It is usually idiopathic; it can be associated with connective tissue diseases and rarely with serious systemic diseases.

Mild irritation occurs. Additionally, a bright red patch is present just under the bulbar conjunctiva (simple episcleritis). A hyperemic, edematous, raised nodule (nodular episcleritis) may also be present. The palpebral conjunctiva is normal.

Episcleritis is distinguished from conjunctivitis because hyperemia is localized to a limited area of the globe and lacrimation is much less. It is distinguished from scleritis by lack of photophobia and lack of severe pain.

The condition is self-limited, and a diagnostic assessment for systemic disorders is not routinely warranted. A topical corticosteroid (eg, prednisolone acetate, 1% drops qid for 5 days, gradually reduced over 3 wk) or an oral NSAID usually shortens the attack; corticosteroids are usually prescribed by an ophthalmologist. Topical vasoconstrictors (eg, tetrahydrozoline) to improve appearance are optional.

[**Fig. 63-1.** Pinguecula and pterygium.]

Scleritis

Scleritis is a severe, destructive, vision-threatening inflammation involving the deep episclera and sclera. Symptoms are moderate to marked pain, hyperemia of the globe, lacrimation, and photophobia. Diagnosis is clinical. Treatment is with systemic corticosteroids and possibly immunosuppressants.

Scleritis is most common among women aged 30 to 50 yr, and many have connective tissue diseases, such as RA, SLE, polyarteritis nodosa, Wegener's granulomatosis, or relapsing polychondritis. A few cases are infectious in origin. About half of the cases of scleritis have no known cause. Scleritis most commonly involves the anterior segment and occurs in 3 types—diffuse, nodular, and necrotizing (scleromalacia perforans).

Symptoms and Signs

Pain (often characterized as a deep, boring ache) is severe enough to interfere with sleep and appetite. Photophobia and lacrimation may occur. Hyperemic patches develop deep beneath the bulbar conjunctiva and are more violaceous than those of episcleritis or conjunctivitis. The palpebral conjunctiva is normal. The involved area may be focal (usually one quadrant of the globe) or involve the entire globe and may contain a hyperemic, edematous, raised nodule (nodular scleritis) or an avascular area (necrotizing scleritis). Posterior scleritis is less common and is less likely to cause red eye but more likely to cause blurred or decreased vision.

In severe cases of necrotizing scleritis, perforation of the globe and loss of the eye may result. Connective tissue disease occurs in 20% of patients with diffuse or nodular scleritis and in 50% of patients with necrotizing scleritis. Necrotizing scleritis in patients with connective tissue disease signals underlying systemic vasculitis.

Diagnosis

Diagnosis is made clinically and by slit-lamp examination. Smears or rarely biopsies are necessary to confirm infectious scleritis. CT or ultrasonography may be needed for posterior scleritis.

Prognosis

Of patients with scleritis, 14% lose significant visual acuity within 1 yr, and 30% lose significant visual acuity within 3 yr. Patients with necrotizing scleritis and underlying systemic vasculitis have a mortality rate of up to 50% in 10 yr (mostly due to MI).

Treatment

• Systemic corticosteroids

Occasionally, NSAIDs are sufficient for mild cases. However, usually a systemic corticosteroid (eg, prednisone 1 mg/kg po once/day) is the initial therapy. If patients are unresponsive to or intolerant of systemic corticosteroids or have necrotizing scleritis and connective tissue disease, systemic immunosuppression with cyclophosphamide or azathioprine is indicated, but only in consultation with a rheumatologist. Scleral grafts may be indicated for threatened perforation.

Chapter 64. Corneal Disorders

Introduction

The cornea is subject to infection, noninfectious inflammation, ulceration, mechanical damage, and environmental injury. Infection (keratitis), frequently with secondary conjunctivitis, can be due to viruses, bacteria, *Acanthamoeba*, or fungi. Ulceration usually represents progression of keratitis. Symptoms that suggest corneal involvement rather than simple conjunctivitis include pain, particularly with exposure to light, and slight impairment of vision. Evaluation of the cornea requires slit-lamp examination and sometimes microbial studies.

Bullous Keratopathy

Bullous keratopathy is the presence of corneal epithelial bullae, resulting from corneal endothelial disease.

Bullous keratopathy is caused by edema of the cornea, resulting from failure of the corneal endothelium to maintain the normally dehydrated state of the cornea. Most frequently, it is due to Fuchs' corneal endothelial dystrophy or corneal endothelial trauma. Fuchs' dystrophy causes bilateral, progressive corneal endothelial cell loss, sometimes leading to symptomatic bullous keratopathy by age 50 to 60. Corneal endothelial trauma can occur during intraocular surgery (eg, cataract removal) or after placement of a poorly designed or malpositioned intraocular lens implant, leading to bullous keratopathy. Bullous keratopathy after cataract removal is called pseudophakic (if an intraocular lens implant is present) or aphakic (if no intraocular lens implant is present) bullous keratopathy.

Subepithelial fluid-filled bullae form on the corneal surface as the corneal stroma swells, leading to eye discomfort, decreased visual acuity, loss of contrast, glare, and photophobia. Sometimes bullae rupture, causing pain and foreign body sensation. Bacteria can invade a ruptured bulla, leading to a corneal ulcer.

The bullae and swelling of the corneal stroma can be seen on slit-lamp examination.

Treatment requires an ophthalmologist and includes topical dehydrating agents (eg, hypertonic saline), intraocular pressure-lowering agents, soft contact lenses for some mild to moderate cases, and treatment of any secondary microbial infection. Corneal transplantation is usually curative.

Corneal Ulcer

A corneal ulcer is a corneal epithelial defect with underlying inflammation (which soon results in necrosis of corneal tissue) due to invasion by bacteria, fungi, viruses, or *Acanthamoeba*. It can be initiated by mechanical trauma or nutritional deficiencies. Symptoms are progressive redness, foreign body sensation, ache, photophobia, and lacrimation. Diagnosis is by slit-lamp examination, fluorescein staining, and microbial studies. Treatment with topical antimicrobials and often dilating drops is urgent and requires an ophthalmologist.

Etiology

Corneal ulcers have many causes (see Table 64-1). Bacterial ulcers (most commonly due to contact lens wear) may complicate herpes simplex keratitis and be particularly refractory to treatment. Ulcers caused by *Acanthamoeba* (also most commonly due to contact lens wear) and fungi (most commonly due to trauma with vegetable material) are indolent but progressive; those caused by *Pseudomonas aeruginosa* (seen almost exclusively in contact lens wearers) develop rapidly, causing deep and extensive corneal necrosis. Wearing contact lenses while sleeping or wearing inadequately disinfected contact lenses can cause corneal ulcers (see p. 572).

Pathophysiology

Ulcers are characterized by corneal epithelial defects with underlying inflammation, and soon necrosis of

the corneal stroma develops. Corneal ulcers tend to heal with scar tissue, resulting in opacification of the cornea and decreased visual acuity. Uveitis, corneal perforation with iris prolapse, pus in the anterior chamber (hypopyon), panophthalmitis, and destruction of the eye may occur with or without treatment. More severe symptoms and complications tend to occur with deeper ulcers.

Symptoms and Signs

Conjunctival redness, eye ache, foreign body sensation, photophobia, and lacrimation may be minimal initially.

A corneal ulcer begins as a corneal epithelial defect that stains with fluorescein and an underlying dull, grayish, circumscribed superficial opacity. Subsequently, the ulcer suppurates and necroses to form an excavated ulcer. Considerable circumcorneal conjunctival hyperemia is usual (see Plate 9). In long-standing

[**Table 64-1.** Causes of Corneal Ulcers]

cases, blood vessels may grow in from the limbus (corneal neovascularization). The ulcer may spread to involve the width of the cornea, may penetrate deeply, or both. Hypopyon (layered WBCs in the anterior chamber) may occur.

Corneal ulcers due to *Acanthamoeba* are often intensely painful and may show transient corneal epithelial defects, multiple corneal stromal infiltrates, and, later, a large ringshaped infiltrate. Fungal ulcers, which are more chronic than bacterial ulcers, are densely infiltrated and show occasional discrete islands of infiltrate (satellite lesions) at the periphery.

Diagnosis

• Slit-lamp examination

Diagnosis is made by slit-lamp examination; a corneal infiltrate with an epithelial defect that stains with fluorescein is diagnostic. All but small ulcers should be cultured by scraping with a sterile platinum spatula (typically by an ophthalmologist). Microscopic examination of scrapings can identify *Acanthamoeba*.

Treatment

• Empiric topical broad-spectrum antibiotic therapy

• More specific antimicrobial therapy directed at the cause

Treatment for corneal ulcers, regardless of cause, begins with moxifloxacin 0.5% or gatifloxacin 0.3% for small ulcers and fortified (higher than stock concentration) antibiotic drops, such as tobramycin 15 mg/mL and cefazolin 50 mg/mL, for more significant ulcers, particularly those that are near the center of the cornea. Frequent dosing (eg, q 15 min for 4 doses, followed by q 1 h around the clock) is necessary initially. Patching is contraindicated because it creates a stagnant, warm environment that favors bacterial growth and prevents the administration of topical drugs.

Herpes simplex (see below) is treated with trifluridine 1% drops q 2 h while the patient is awake or acyclovir 400 mg po 5 times/day for about 14 days.

Fungal infections are treated with one of many topical antifungal drops (eg, natamycin 5%, amphotericin B 0.15%), initially q 1 h during the day and q 2 h overnight. Deep infections may require addition of oral ketoconazole, fluconazole, or itraconazole.

If *Acanthamoeba* is identified, traditional therapy is propamidine and neomycin supplemented with miconazole, clotrimazole, or oral ketoconazole. Additional treatments include polyhexamethylene biguanide 0.02% or chlorhexidine 0.02% q 1 to 2 h until clinical improvement is evident, then gradually reduced to 4 times/day and continued for a number of months until all inflammation has resolved.

Polyhexamethylene biguanide and chlorhexidine are not commercially available as ocular agents but can be prepared by a compounding pharmacy. Topical propamidine 0.1% q 1 to 2 h is often added for 3 days.

For all ulcers, treatment may also include a cycloplegic, such as atropine 1% or scopolamine 0.25% 1 drop tid, to decrease the ache of a corneal ulcer and to reduce the formation of posterior synechiae. In severe cases, debridement of the infected epithelium or even penetrating keratoplasty may be required. Patients who are poorly compliant or who have large, central, or refractory ulcers may need to be hospitalized.

Herpes Simplex Keratitis

(Herpes Simplex Keratoconjunctivitis)

Herpes simplex keratitis is corneal infection with herpes simplex virus (see also p. 1417). It may involve the iris. Symptoms and signs include foreign body sensation, lacrimation, photophobia, and conjunctival hyperemia. Recurrences are common and may lead to corneal hypoesthesia, ulceration, and permanent scarring. Diagnosis is based on the characteristic dendritic corneal ulcer and sometimes viral culture. Treatment is with topical and occasionally systemic antiviral drugs.

Herpes simplex usually affects the corneal surface but sometimes involves the deeper layers of the cornea (corneal stroma). Stromal involvement is probably an immunologic response to the virus.

As with all herpes simplex virus infections, there is a primary infection, followed by a latent phase, in which the virus goes into the nerve roots. Latent virus may reactivate, causing recurrent symptoms.

Symptoms and Signs

Primary infection: The initial (primary) infection is usually nonspecific self-limiting conjunctivitis, often in early childhood and sometimes without corneal involvement. If the cornea is involved, early symptoms include foreign body sensation, lacrimation, photophobia, and conjunctival hyperemia. Sometimes vesicular blepharitis (blisters on the eyelid) follows, symptoms worsen, vision blurs, and blisters break down and ulcerate, then resolve without scarring in about a week.

Recurrent infection: Recurrences usually take the form of epithelial keratitis (also called dendritic keratitis) with tearing, foreign body sensation, and a characteristic branching (dendritic or serpentine) lesion of the corneal epithelium with knoblike terminals that stain with fluorescein (see Plate 14). Multiple recurrences may result in corneal hypoesthesia or anesthesia, ulceration, and permanent scarring.

Stromal involvement: Most patients with disciform keratitis, which involves the corneal stroma, have a history of epithelial keratitis. Disciform keratitis is a deeper, disk-shaped, localized area of corneal edema and haze accompanied by anterior uveitis. This form may cause pain and vision loss.

Stromal keratitis can cause necrosis of the stroma and severe ache, photophobia, foreign body sensation, and decreased vision.

Diagnosis

Slit-lamp examination is mandatory. Finding a dendrite is enough to confirm the diagnosis in most cases. When the appearance is not conclusive, viral culture of the lesion can confirm the diagnosis.

Treatment

• Topical trifluridine

• Sometimes oral or IV acyclovir

• For stromal involvement or uveitis, topical corticosteroids in addition to antiviral drugs

Most patients are managed by an ophthalmologist. If stromal or uveal involvement occurs, treatment is more involved and referral to an ophthalmologist is mandatory.

Topical therapy (eg, trifluridine 1% drops 9 times/day) is usually effective. Occasionally, acyclovir 400 mg po 5 times/day is indicated. Immunocompromised patients may require IV antivirals (eg, acyclovir 5 mg/kg IV q 8 h for 7 days). If the epithelium surrounding the dendrite is loose and edematous, debridement by gentle swabbing with a cotton-tipped applicator before beginning drug therapy may speed healing.

Topical corticosteroids are contraindicated in epithelial keratitis but may be effective when used with an antiviral drug to manage later-stage stromal involvement (disciform or stromal keratitis) or uveitis. In such cases, patients may be given prednisolone acetate 1% instilled q 2 h initially, lengthening the interval to q 4 to 8 h as symptoms improve. Topical drugs to relieve photophobia include atropine 1% or scopolamine 0.25% tid.

Herpes Zoster Ophthalmicus

(Herpes Zoster Virus Ophthalmicus; Ophthalmic Herpes Zoster; Varicella-Zoster Virus Ophthalmicus)

Herpes zoster ophthalmicus is reactivation of a varicella-zoster virus infection (shingles) (see also p. 1420) involving the eye. Symptoms and signs, which may be intense, include dermatomal forehead rash and painful inflammation of all the tissues of the anterior and, rarely, posterior structures of the eye. Diagnosis is based on the characteristic appearance of the anterior structures of the eye plus zoster dermatitis of the first branch of the trigeminal nerve. Treatment is with oral antiviral drugs, mydriatics, and topical corticosteroids.

Herpes zoster of the forehead involves the globe in three fourths of cases when the nasociliary nerve is affected (as indicated by a lesion on the tip of the nose) and in one third of cases not involving the tip of the nose. Overall, the globe is involved in half of patients.

Symptoms and Signs

A prodrome of tingling of the forehead may occur. During acute disease, in addition to the forehead rash, symptoms and signs may include severe pain; marked eyelid edema; conjunctival, episcleral, and circumcorneal conjunctival hyperemia; corneal edema; and photophobia (see Plate 15).

Complications: Keratitis accompanied by uveitis may be severe and followed by scarring. Late sequelae —glaucoma, cataract, chronic or recurrent uveitis, corneal scarring, corneal neovascularization, and hypesthesia—are common and may threaten vision. Postherpetic neuralgia may develop late.

Diagnosis

• Zoster rash on the forehead or eyelid plus eye findings

Diagnosis is based on a typical acute herpes zoster rash on the forehead, eyelid, or both or on a characteristic history plus signs of previous zoster rash. Vesicular or bullous lesions in this distribution that do not yet involve the eye suggest significant risk and should prompt an ophthalmologic consultation to determine whether the eye is involved. Culture and immunologic or PCR studies of skin at initial evaluation or serial serologic tests are done only when lesions are atypical and the diagnosis uncertain.

Treatment

• Oral antivirals (eg, acyclovir, famciclovir, valacyclovir)

• Sometimes topical corticosteroids

Early treatment with acyclovir 800 mg po 5 times/day or famciclovir 500 mg or valacyclovir 1 g po tid for 7 days reduces ocular complications. Patients with keratitis or uveitis require topical corticosteroids (eg, prednisolone acetate 1% instilled qid initially, lengthening the interval as symptoms lessen). The pupil should be dilated with atropine 1% or scopolamine 0.25% 1 drop tid. Intraocular pressure must be monitored and treated if it rises significantly above normal values.

Use of a brief course of high-dose oral corticosteroids to prevent postherpetic neuralgia in patients > 60 yr who are in good general health remains controversial.

Interstitial Keratitis

(Parenchymatous Keratitis)

Interstitial keratitis is chronic, nonulcerative inflammation of the middle layers of the cornea (ie, mid-stroma) that is sometimes associated with uveitis. The cause is usually infectious. Symptoms are photophobia, pain, lacrimation, and vision blurring. Diagnosis is by slit-lamp examination and serologic tests to determine the cause. Treatment is directed at the cause and may require topical corticosteroids.

Interstitial keratitis, a manifestation of certain corneal infections, is rare in the US. Most cases occur in children or adolescents as a late complication of congenital syphilis (see p. 2821). Ultimately, both eyes may be involved. A similar but less dramatic bilateral keratitis occurs in Cogan's syndrome, Lyme disease, and Epstein-Barr virus infection. Rarely, acquired syphilis, herpes simplex, herpes zoster, or TB may cause a unilateral form in adults.

Symptoms and Signs

Photophobia, pain, lacrimation, and vision blurring are common. The lesion begins as patches of inflammation in the middle corneal layers (ie, mid-stroma) that cause opacification. Typically with syphilis and occasionally with other causes, the entire cornea develops a ground-glass appearance, obscuring the iris. New blood vessels grow in from the limbus (neovascularization) and produce orange-red areas (salmon patches). Anterior uveitis and choroiditis are common in syphilitic interstitial keratitis. Inflammation and neovascularization usually begin to subside after 1 to 2 mo. Some corneal opacity usually remains, causing mild to moderate vision impairment.

Diagnosis

• Corneal opacification and other typical findings on slit-lamp examination

• Serologic testing to determine etiology

The specific etiology must be determined. The stigmas of congenital syphilis, vestibuloauditory symptoms, history of an expanding rash, and tick exposure support a specific etiology. However, all patients should have serologic testing, including all of the following:

• Fluorescent treponemal antibody absorption test or the microhemagglutination assay for *Treponema pallidum*

• Lyme titer

• Epstein-Barr virus panel

Patients with negative serologic test results may have Cogan's syndrome, an idiopathic syndrome consisting of interstitial keratitis and vestibular and auditory deficits. To prevent permanent vestibuloauditory damage, symptoms of hearing loss, tinnitus, or vertigo require referral to an otolaryngologist.

Treatment

• Sometimes topical corticosteroids

Keratitis may resolve with treatment of the underlying condition. Additional topical treatment with a corticosteroid, such as prednisolone 1% qid, is often advisable. An ophthalmologist should be consulted.

Cogan's Syndrome

Cogan's syndrome is a rare autoimmune disease involving the eye and the inner ear.

Cogan's syndrome affects young adults, with 80% of patients between 14 and 47 yr. The disease appears to result from an autoimmune reaction directed against an unknown common autoantigen in the cornea and inner ear. About 10 to 30% of patients also have severe systemic vasculitis, which may include life-threatening aortitis.

Symptoms and Signs

The presenting symptoms involve the ocular system in 38% of patients, the vestibuloauditory system in 46%, and both in 15%. By 5 mo, 75% of patients have both ocular and vestibuloauditory symptoms. Nonspecific systemic complaints include fever, headache, joint pain, and myalgia.

Ocular: Ocular involvement includes any combination of the following:

• Bilateral interstitial keratitis or other corneal stromal keratitis

• Episcleritis or scleritis

• Uveitis

• Papillitis

• Other orbital inflammation (eg, vitritis, choroiditis)

Ocular symptoms include irritation, pain, photophobia, and decreased vision. Ocular examination shows a patchy corneal stromal infiltrate typical of interstitial keratitis (see p. 591), ocular redness, optic nerve edema, proptosis, or a combination of these symptoms.

Vestibuloauditory: Vestibuloauditory symptoms include sensorineural hearing loss, tinnitus, and vertigo.

Vascular: A diastolic heart murmur may be present when aortitis is significant. Claudication may be present if limb vessels are affected.

Diagnosis

Diagnosis is based on clinical findings and exclusion of other causes (eg, syphilis, Lyme disease, Epstein-Barr virus infection) by appropriate serologic tests. Evaluation by an ophthalmologist and otolaryngologist is important.

Treatment

• Initially topical and sometimes systemic corticosteroids

Untreated disease may lead to corneal scarring and visual loss and, in 60 to 80% of patients, permanent hearing loss. Keratitis, episcleritis, and anterior uveitis can usually be treated with topical prednisolone acetate 1% q 1 h to qid. To treat deeper ocular inflammation and especially to treat vestibuloauditory symptoms before they become permanent, prednisone 1 mg/kg po once/day is begun as soon as possible and continued for 2 to 6 mo. Some clinicians add cyclophosphamide, methotrexate, or cyclosporine for recalcitrant cases.

Keratoconjunctivitis Sicca

(Dry Eyes; Keratitis Sicca)

Keratoconjunctivitis sicca is chronic, bilateral desiccation of the conjunctiva and cornea due to an inadequate tear film. Symptoms include itching, burning, irritation, and photophobia. Diagnosis is clinical; the Schirmer test may be helpful. Treatment is with topical tear supplements and sometimes blockage of the nasolacrimal openings.

Etiology

There are 2 main types:

- Aqueous tear-deficient keratoconjunctivitis sicca is caused by inadequate tear volume.

- Evaporative keratoconjunctivitis sicca (more common) is caused by accelerated tear evaporation due to poor tear quality.

Aqueous tear-deficient keratoconjunctivitis sicca is most commonly an isolated idiopathic condition in postmenopausal women. It is also commonly part of Sjogren's syndrome (see p. 303), RA, or SLE. Less commonly, it is secondary to other conditions that scar the lacrimal ducts (eg, cicatricial pemphigoid, Stevens-Johnson syndrome, trachoma). It may result from a damaged or malfunctioning lacrimal gland due to graft-vs-host disease, HIV (diffuse infiltrative lymphocytosis syndrome), local radiation therapy, or familial dysautonomia.

Evaporative keratoconjunctivitis sicca is caused by loss of the tear film due to abnormally rapid evaporation caused by an inadequate oil layer on the surface of the aqueous layer of tears. Symptoms may result from abnormal oil quality (ie, meibomian gland dysfunction) or a degraded normal oil layer (ie, seborrheic blepharitis). Patients frequently have acne rosacea.

Drying can also result from exposure due to inadequate eye closure at night (nocturnal lagophthalmos) or, rarely, from inadequate tear volume due to an insufficient blink rate.

Symptoms and Signs

Patients report itching; burning; a gritty, pulling, or foreign body sensation; or photophobia. A sharp stabbing pain, eye strain or fatigue, and blurred vision may also occur. Some patients note a flood of tears after severe irritation. Typically, symptoms fluctuate in intensity and may be intermittent. Certain factors can worsen symptoms:

- Prolonged visual efforts (eg, reading, working on the computer, driving, watching television)

- Local environments that are dry, windy, dusty, or smoky

- Certain systemic drugs, including isotretinoin, sedatives, diuretics, antihypertensives, oral contraceptives, and all anticholinergics (including antihistamines and many GI drugs)

Symptoms lessen on cool, rainy, or foggy days or in other high-humidity environments, such as in the shower. Recurrent and prolonged blurring and frequent intense irritation can impair daily function. However, permanent impairment of vision is rare.

With both forms, the conjunctiva is hyperemic, and there is often scattered, fine, punctate loss of corneal epithelium (superficial punctate keratitis), conjunctival epithelium, or both. When the condition is severe, the involved areas, mainly between the eyelids (the intrapalpebral or exposure zone), stain with fluorescein. Patients often blink at an accelerated rate because of irritation.

With the aqueous tear-deficient form, the conjunctiva can appear dry and lusterless with redundant folds.

With the evaporative form, abundant tears may be present as well as foam at the eyelid margin. Very rarely, severe, advanced, chronic drying leads to significant vision loss due to keratinization of the ocular surface or loss of corneal epithelium, leading to sequelae such as scarring, neovascularization, infections, ulceration, and perforation.

Diagnosis

• Schirmer test and tear breakup tests

Diagnosis is based on characteristic symptoms and clinical appearance. The Schirmer test and tear breakup test may differentiate type.

The Schirmer test determines whether tear production is normal. After blotting the closed eye to remove excess tears, a strip of filter paper is placed, without topical anesthesia, at the junction of the middle and lateral third of the lower eyelid. If < 5.5 mm of wetting occurs after 5 min on 2 successive occasions, the patient has aqueous tear-deficient keratoconjunctivitis sicca.

With evaporative keratoconjunctivitis sicca, the Schirmer test is usually normal. The tear film can be made visible under cobalt blue light at the slit lamp by instillation of a small volume of highly concentrated fluorescein (made by wetting a fluorescein strip with saline and shaking the strip to remove any excess moisture). Blinking several times reapplies a complete tear film. The patient then stares, and the length of time until the first dry spot develops is determined (tear breakup test, or TBUT). An accelerated rate of intact tear film breakup (< 10 sec) is characteristic of evaporative keratoconjunctivitis sicca.

If aqueous tear-deficient keratoconjunctivitis sicca is diagnosed, Sjogren's syndrome (see p. 303) should be suspected, especially if xerostomia is also present. Serologic tests and labial salivary gland biopsy are used for diagnosis. Patients with primary or secondary Sjogren's syndrome are at increased risk of several serious diseases (eg, primary biliary cirrhosis, non-Hodgkin lymphoma). Therefore, proper evaluation and monitoring are essential.

Treatment

• Artificial tears

• Sometimes occlusion of nasolacrimal punctum or tarsorrhaphy

Frequent use of artificial tears can be effective for both forms. More viscous artificial tears coat the ocular surface longer, and artificial tears that contain polar lipids such as glycerin reduce evaporation; both types are particularly useful in evaporative keratoconjunctivitis sicca. Artificial tear ointments applied before sleep are particularly useful when patients have nocturnal lagophthalmos or irritation on waking. Most cases are treated adequately throughout the patient's life with such supplementation. Staying hydrated, using humidifiers, and avoiding dry, drafty environments can often help. Not smoking and avoiding secondary smoke are important. In recalcitrant cases, occlusion of the nasolacrimal punctum may be indicated. In severe cases, a partial tarsorrhaphy can reduce tear loss through evaporation. Topical cyclosporine and ω-3 fatty acid dietary supplements may be a useful adjunct in some patients.

Patients with evaporative keratoconjunctivitis sicca often benefit from treatment of concomitant blepharitis and associated rosacea with measures such as warm compresses, eyelid margin scrubs, and intermittent topical eyelid antibiotic ointments (eg, bacitracin at bedtime), systemic doxycycline 50 to 100 mg po once or twice/day (contraindicated in pregnant or nursing patients), or both.

Cyclosporine drops that decrease the inflammation associated with dryness of the eye are available. They lead to meaningful improvement but only in a fraction of patients. These drops sting and take months before an effect is noticed.

Keratoconus

Keratoconus is a bulging distortion of the cornea, leading to loss of visual acuity.

Keratoconus is a slowly progressive thinning and bulging of the cornea, usually bilateral, beginning between ages 10 and 25. Its cause is unknown.

The distorted cone shape of the cornea causes major changes in the refractive characteristics of the cornea (irregular astigmatism) that cannot be fully corrected with glasses. Progressing keratoconus necessitates frequent change of eyeglasses. Contact lenses may provide better vision correction and should be tried when eyeglasses are not satisfactory. Corneal transplant surgery may be necessary if visual acuity with contact lenses is inadequate, contact lenses are not tolerated, or a visually significant corneal scar (caused by tearing of stromal fibers) is present.

Newer treatments seem promising. Implantation of corneal ring segments appears to have the potential to save selected patients from transplantation. Corneal cross-linking, an ultraviolet light treatment that strengthens the cornea, has had positive results in European studies and may become more common.

Keratomalacia

(Xerotic Keratitis; Xerophthalmia)

Keratomalacia is degeneration of the cornea caused by nutritional deficiency.

Keratomalacia is caused by vitamin A deficiency typically in patients with protein-calorie undernutrition. It is characterized by a hazy, dry cornea. Corneal ulceration with secondary infection is common. The lacrimal glands and conjunctiva are also affected. Lack of tears causes extreme dryness of the eyes, and foamy spots appear on the temporal and often nasal bulbar conjunctiva (Bitot's spots). Night blindness may occur. For further details, including specific therapy, see Vitamin A Deficiency on p. 34.

Peripheral Ulcerative Keratitis

(Marginal Keratolysis; Peripheral Rheumatoid Ulceration)

Peripheral ulcerative keratitis is inflammation and ulceration of the cornea that often occurs with chronic connective tissue diseases. Irritation and decreased vision result.

Peripheral ulcerative keratitis is a serious corneal ulceration; it often occurs with autoimmune diseases that are active, long-standing, or both, such as RA, Wegener's granulomatosis, and relapsing polychondritis.

Patients often have decreased visual acuity, photophobia, and foreign body sensation. A crescentic area of opacification in the periphery of the cornea, due to infiltration by WBCs and ulceration, stains with fluorescein. Infectious causes, such as bacteria, fungi, and herpes simplex virus, must be ruled out by culturing the ulcer and eyelid margins.

Among patients with rheumatic disease and peripheral ulcerative keratitis, the 10-yr mortality rate is about 40% (usually due to MI) without treatment and about 8% with systemic cytotoxic therapy.

Any patient with peripheral ulcerative keratitis should be promptly referred to an ophthalmologist. Systemic cyclophosphamide or other immunosuppressants treat the keratitis, life-threatening vasculitis, and underlying autoimmune disease. Treatment also includes local approaches to control inflammation (eg, tissue adhesive and bandage contact lenses) and repair damage (eg, patch grafts). Other possibly helpful drugs include collagenase inhibitors, such as systemic tetracycline or topical 20% *N*-acetylcysteine.

Phlyctenular Keratoconjunctivitis

(Phlyctenular Conjunctivitis; Phlyctenulosis)

Phlyctenular keratoconjunctivitis, a hypersensitivity reaction of the cornea and conjunctiva to

bacterial antigens, is characterized by discrete nodular areas of corneal or conjunctival inflammation.

Phlyctenular keratoconjunctivitis results from a hypersensitivity reaction to bacterial antigens, primarily staphylococcal, but TB, *Chlamydia*, and other agents have been implicated. It is more common in children. Many patients also have blepharitis.

Patients have multiple lesions, consisting of small yellow-gray nodules (phlyctenules) that appear at the limbus, on the cornea, or on the bulbar conjunctiva and persist from several days to 2 wk. On the conjunctiva, these nodules ulcerate but heal without a scar. When the cornea is affected, severe lacrimation, photophobia, blurred vision, aching, and foreign body sensation may be prominent. Frequent recurrence, especially with secondary infection, may lead to corneal opacity and neovascularization with loss of visual acuity.

Diagnosis is by characteristic clinical appearance. Testing for TB may be indicated (eg, for patients at risk).

Treatment for nontuberculous cases is with a topical corticosteroid-antibiotic combination. If patients have seborrheic blepharitis, eyelid scrubs may help prevent recurrence.

Superficial Punctate Keratitis

Superficial punctate keratitis is corneal inflammation of diverse causes characterized by scattered, fine, punctate corneal epithelial loss or damage. Symptoms are redness, lacrimation, photophobia, and slightly decreased vision. Diagnosis is by slit-lamp examination. Treatment depends on the cause.

Superficial punctate keratitis is a nonspecific finding. Causes may include any of the following:

• Viral conjunctivitis (most commonly adenovirus)

• Blepharitis

• Keratoconjunctivitis sicca

• Trachoma

• Chemical burns

• Ultraviolet (UV) light exposure (eg, welding arcs, sunlamps, snow glare)

• Contact lens overwear

• Systemic drugs (eg, adenine arabinoside)

• Topical drug or preservative toxicity.

Symptoms include photophobia, foreign body sensation, lacrimation, redness, and slightly decreased vision. Slit-lamp or ophthalmoscope examination of the cornea reveals a characteristic hazy appearance with multiple punctate speckles that stain with fluorescein. With viral conjunctivitis, preauricular adenopathy is common and chemosis may occur.

Keratitis that accompanies adenovirus conjunctivitis resolves spontaneously in about 3 wk. Blepharitis (see p. 575), keratoconjunctivitis sicca (see p. 592), and trachoma (see p. 583) require specific therapy. When caused by overwearing contact lenses, keratitis is treated with discontinuation of the contact lens and an antibiotic ointment (eg, ciprofloxacin 0.3% qid), but the eye is not patched because serious infection may result. Contact lens wearers with superficial punctate keratitis should be examined the next day. Suspected causative topical drugs (active ingredient or preservative) should be stopped.

Ultraviolet keratitis: UVB light (wavelength < 300 nm) can burn the cornea, causing keratitis or keratoconjunctivitis. Arc welding is a common cause; even a brief, unprotected glance at a welding arc may result in a burn. Other causes include high-voltage electric sparks, artificial sun lamps, and sunlight reflected off snow at high altitudes. UV radiation increases 4 to 6% for every 1000-ft (305-m) increase in altitude above sea level, and snow reflects 85% of UVB.

Symptoms are usually not apparent for 8 to 12 h after exposure and last 24 to 48 h. Patients have lacrimation, pain, redness, swollen eyelids, photophobia, headache, foreign body sensation, and decreased vision. Permanent vision loss is rare.

Diagnosis is by history, presence of superficial punctate keratitis, and absence of a foreign body or infection.

Treatment consists of an antibiotic ointment (eg, bacitracin or gentamicin 0.3% ointment q 8 h) and occasionally a short-acting cycloplegic drug (eg, cyclopentolate 1% drop q 4 h). Severe pain may require systemic analgesics. The corneal surface regenerates spontaneously in 24 to 48 h. The eye must be rechecked in 24 h. Dark glasses or welder's helmets that block UV light are preventive.

Corneal Transplantation

(Corneal Graft; Penetrating Keratoplasty)

Indications: Corneal transplantations are done for several reasons:

- To reconstruct the cornea (eg, replacing a perforated cornea)
- To relieve intractable pain (eg, severe foreign body sensation due to recurrent ruptured bullae in bullous keratopathy)
- To treat a disorder unresponsive to medical management (eg, severe, uncontrolled fungal corneal ulcer)
- To improve the optical qualities of the cornea and thus improve vision (eg, replacing a cornea that is scarred after a corneal ulcer, is clouded because of edema as occurs in Fuchs' dystrophy or after cataract surgery, is opaque because of deposits of nontransparent abnormal corneal stromal proteins as occurs in hereditary corneal stromal dystrophy, or has irregular astigmatism as occurs with keratoconus)

The most common indications are the following:

- Bullous keratopathy (pseudophakic or aphakic, Fuchs' endothelial dystrophy)
- Keratoconus
- Repeat graft
- Keratitis or postkeratitis (caused by viral, bacterial, fungal, or *Acanthamoeba* infection or perforation)
- Corneal stromal dystrophies

Procedure: Tissue matching is not routinely done. Cadaveric donor tissue cannot be used from anyone suspected of having a communicable disease.

Corneal transplantation can be done using general anesthesia or local anesthesia plus IV sedation.

Topical antibiotics are used for several weeks postoperatively and topical corticosteroids for several months. To protect the eye from inadvertent trauma after transplantation, the patient wears shields, glasses, or sunglasses. If transplantation involves the full thickness of the cornea (as in penetrating

keratoplasty, or PKP), achievement of full visual potential may take up to 18 mo because of changing refraction with wound healing and after suture removal. If only the endothelium is replaced (as in Descemet's stripping endothelial keratoplasty), achievement of full visual potential usually occurs by 6 mo. In many patients, earlier and better vision is attained by wearing a rigid contact lens over the corneal transplant.

Complications: Complications include the following:

• Graft rejection

• Infection (intraocular and corneal)

• Wound leak

• Glaucoma

• Graft failure

• High refractive error (especially astigmatism, myopia, or both)

• Recurrence of disease (with herpes simplex or hereditary corneal stromal dystrophy)

Graft rejection rates are usually < 10% but may be up to 68% in higher-risk patients. Rejection symptoms include decreased vision, photosensitivity, ocular ache, and ocular redness. Graft rejection is treated with topical corticosteroids (eg, prednisolone 1% hourly), sometimes with a supplemental periocular injection (eg, triamcinolone acetonide 40 mg). If graft rejection is severe or if graft function is marginal, additional corticosteroids are given orally (eg, prednisone 1 mg/kg once/day) and occasionally IV (eg, methylprednisolone 3 to 5 mg/kg once). Typically, the rejection episode reverses, and graft function returns fully. The graft may fail if the rejection episode is unusually severe or long-standing or if multiple episodes of graft rejection occur. Regraft is possible, but the long-term prognosis is worse than for the original graft.

Prognosis

The chance of long-term transplant success is

• > 90% for keratoconus, corneal scars, early bullous keratopathy, or hereditary corneal stromal dystrophies

• 80 to 90% for more advanced bullous keratopathy or inactive viral keratitis

• 50% for active corneal infection

• 0 to 50% for chemical or radiation injury

The generally high rate of success of corneal transplantation is attributable to many factors, including the avascularity of the cornea and the fact that the anterior chamber has venous drainage but no lymphatic drainage. These conditions promote low-zone tolerance (an immunologic tolerance that results from constant exposure to low doses of an antigen) and a process termed anterior chamber-associated immune deviation, in which there is active suppression of intraocular lymphocytes and delayed-type hypersensitivity to transplanted intraocular antigens. Another important factor is the effectiveness of the corticosteroids used topically, locally, and systemically to treat graft rejection.

Corneal Limbal Stem Cell Transplantation

Corneal limbal stem cell transplantation surgically replaces critical stem cells at the limbus (the area where the conjunctiva meets the cornea). Host stem cells normally reside in this area. Transplantation is done when the host stem cells have been too severely damaged to recover from disease or injury.

Conditions such as severe chemical burns, Stevens-Johnson syndrome, and severe contact lens overwear may cause persistent nonhealing corneal epithelial defects. These defects result from failure of corneal epithelial stem cells to produce sufficient epithelial cells to repopulate the cornea. If untreated, persistent nonhealing corneal epithelial defects are vulnerable to infection, which can lead to scarring, perforation, or both. Under these circumstances, a corneal transplant, which replaces only the central cornea and not the limbus, is insufficient; stem cells are needed to produce new cells that repopulate the cornea, restoring the regenerative capacity of the ocular surface.

Corneal limbal stem cells can be transplanted from the patient's healthy eye or from a cadaveric donor eye. The patient's damaged corneal epithelial stem cells are removed by a partial-thickness dissection of the limbus (ie, all the epithelium and the superficial stroma of the limbus). Donor limbal tissue, which is prepared by a similar dissection, is sutured into the prepared bed.

Chapter 65. Glaucoma

Introduction

Glaucomas are a group of eye disorders characterized by progressive optic nerve damage at least partly due to increased intraocular pressure (IOP). Glaucoma is the 3rd most common cause of blindness worldwide and the 2nd most common cause of blindness in the US, where it is the leading cause of blindness for blacks and Hispanics. About 3 million Americans and 14 million people worldwide have glaucoma, but only half are aware of it. Glaucoma can occur at any age but is 6 times more common among people > 60 yr.

Glaucomas are categorized as open-angle or closed-angle (angle-closure)—see Tables 65-1, 65-2, and 65-3. The "angle" refers to the angle formed by the junction of the iris and cornea at the periphery of the anterior chamber (see Fig. 65-1). The angle is where > 98% of the aqueous humor exits the eye via either the trabecular meshwork and Schlemm's canal (the major pathway, particularly in the elderly) or the ciliary body face and choroidal vasculature. These outflow pathways are not simply a mechanical filter and drain but instead involve active physiologic processes.

Glaucomas are further subdivided into primary (cause of outflow resistance or angle closure is unknown) and secondary (outflow resistance results from another disorder), accounting for > 20 adult types.

Pathophysiology

Axons of retinal ganglion cells travel through the optic nerve carrying images from the eye to the brain. Damage to these axons causes ganglion cell death with resultant optic nerve atrophy and patchy vision loss. Elevated IOP (in unaffected eyes, the average range is 11 to 21 mm Hg) plays a role in axonal damage, either by direct nerve compression or diminution of blood flow. However, the relationship between pressure and nerve damage is variable. Of people with IOP > 21 mm Hg (ie, ocular hypertension), only about 1 to 2%/yr (about 10% over 5 yr) develop glaucoma. Additionally, about one third of patients with glaucoma do not have IOPs > 21 mm Hg (known as lowtension glaucoma or normal-tension glaucoma).

IOP is determined by the balance of aqueous secretion and drainage. Elevated IOP is caused by inhibited or obstructed outflow, not oversecretion. In open-angle glaucoma, IOP is elevated because outflow is inadequate despite an angle that appears unobstructed. In angle-closure glaucoma, IOP is elevated when a physical distortion of the peripheral iris mechanically blocks outflow.

Symptoms and Signs

Symptoms and signs vary with the type of glaucoma, but the defining characteristic is optic nerve damage as evidenced by an abnormal optic disk (see p. 601 and Plate 13) and certain types of visual field deficits (see p. 601).

IOP may be elevated or within the average range. (For techniques of measurement, see p. 540)

Diagnosis

• Characteristic visual field defects

• Exclusion of other causes

• IOP usually > 21 mm Hg (but not required for the diagnosis)

Glaucoma should be suspected in a patient with any of the following:

• Typical visual field defects

• Abnormal optic nerve on ophthalmoscopy

• Elevated IOP

Such patients (and those with any risk factors) should be referred to an ophthalmologist for a comprehensive examination that includes a thorough history, family history, examination of the optic disks (preferably using a binocular examination technique), formal visual field examination, IOP measurement, and gonioscopy (visualization of the anterior chamber angle with a special mirrored contact lens prism). Glaucoma is diagnosed when characteristic findings of optic nerve damage are present and other causes (eg, multiple sclerosis)

[Table 65-1. Open-Angle Glaucoma: Classification Based on Mechanisms of Outflow Obstruction*]

have been excluded. Elevated IOP makes the diagnosis more likely but is not essential.

Screening: Screening can be done by primary physicians by checking visual fields with frequency-doubling technology (FDT) perimetry and ophthalmoscopic evaluation of the optic nerve. FDT perimetry involves use of a desktop device that can screen for visual field abnormalities suggestive of glaucoma in 2 to 3 min per eye. Although IOP should be measured, screening based only on IOP has low sensitivity, low specificity, and low positive

[Table 65-2. Angle-Closure Glaucoma: Classification Based on Mechanisms of Outflow Obstruction*]

predictive value. Patients > 40 yr and those who have risk factors for open-angle or angle-closure glaucoma should receive a comprehensive eye examination every 1 to 2 yr.

Treatment

• Decreasing IOP by using drugs or laser or incisional surgery

[Table 65-3. Developmental Abnormalities of the Anterior Chamber Angle Causing Glaucoma: Classification Based on Mechanisms of Outflow Obstruction*]

Patients with characteristic optic nerve and corresponding visual field changes are treated regardless of IOP. Lowering the IOP is the only clinically proven treatment. For chronic adult and juvenile glaucomas, the initial target IOP is at least 20% below pretreatment readings.

Three methods are available: drugs, laser surgery, and incisional surgery. The type of glaucoma determines the appropriate method. Drugs and most laser surgeries (trabeculoplasty) modify the existing aqueous secretion and drainage system. Most incisional surgeries (eg, guarded filtration procedures [trabeculectomy], glaucoma drainage implant devices [tube shunts]) create a new drainage system.

Prophylactic IOP lowering in patients with ocular hypertension delays the onset of glaucoma. However, because the rate of conversion from ocular hypertension to glaucoma in untreated people is low, the decision to treat prophylactically should be individualized based on the presence of risk factors, magnitude of IOP elevation, and patient factors (ie, preference for drugs vs surgery, drug adverse effects). Generally, treatment is recommended for patients with IOP > 30 mm Hg even if the visual field is full and the optic nerve disk appears healthy because the likelihood of damage is significant at that IOP level.

[Fig. 65-1. Aqueous humor production and flow.]

Primary Open-Angle Glaucoma

Primary open-angle glaucoma is a syndrome of optic nerve damage associated with an open

anterior chamber angle and an elevated or sometimes average intraocular pressure (IOP). Symptoms occur late and involve visual field loss. Diagnosis is by ophthalmoscopy, gonioscopy, visual field examination, and measurement of IOP. Treatment includes topical drugs (eg, prostaglandin analogs, β-blockers) and often requires laser or incisional surgery to increase aqueous drainage.

Etiology

Although open-angle glaucomas can have numerous causes (see Table 65-1), 60 to 70% of cases have no identifiable cause and are termed primary open-angle glaucoma. Both eyes usually are affected, but typically not equally.

Risk factors include older age, positive family history, black race, thinner central corneal thickness, systemic hypertension, diabetes, and myopia. In blacks, glaucoma is more severe and develops at an earlier age, and blindness is 6 to 8 times more likely.

Pathophysiology

IOP can be elevated or within the average range.

Elevated-pressure glaucoma: Two thirds of patients with glaucoma have elevated (> 21 mm Hg) IOP. Aqueous humor drainage is inadequate, whereas production by the ciliary body is normal. Identifiable mechanisms (ie, secondary open-angle glaucomas) are not present. These mechanisms include developmental anomalies, scarring caused by trauma or infection, and plugging of channels by detached iris pigment (ie, pigment dispersion syndrome) or abnormal protein deposits (eg, pseudoexfoliation syndrome).

Normal- or low-pressure glaucoma: In at least one third of patients with glaucoma, IOP is within the average range, but optic nerve damage and visual field loss typical of glaucoma are present. These patients have a higher incidence of vasospastic diseases (eg, migraines, Raynaud's syndrome) than the general population, suggesting that a vascular disorder compromising blood flow to the optic nerve may play a role.

Symptoms and Signs

Early symptoms are uncommon. Usually, the patient becomes aware of visual field loss only when optic nerve atrophy is marked; the typically asymmetric deficits contribute to delay in recognition. However, some patients have complaints, such as missing stairs if their inferior visual field has been lost, noticing portions of words missing when reading, or having difficulty with driving.

Examination findings include an unobstructed open angle on gonioscopy and characteristic optic nerve appearance and visual field defects. IOP may be normal or high but is almost always higher in the eye with more optic nerve damage.

Optic nerve appearance: The optic nerve head (ie, disk) is normally a slightly vertically elongated circle with a centrally located depression called the cup. The neurosensory rim is the tissue between the margin of the cup and the edge of the disk and is composed of the ganglion cell axons from the retina.

Characteristic optic nerve changes include

- Increased cup:disk ratio
- Thinning of the neurosensory rim
- Pitting or notching of the rim
- Nerve fiber layer hemorrhage that crosses the disk margin (ie, Drance hemorrhage or splinter hemorrhages)

• Vertical elongation of the cup

• Quick angulations in the course of the exiting blood vessels

Thinning of the neurosensory rim over time alone can be diagnostic of glaucoma regardless of the IOP or visual field. However, most initial diagnoses of glaucoma involve some visual field change.

Visual field defects: Visual field changes caused by lesions of the optic nerve include

• Nasal step defects (which do not cross the horizontal meridian—an imaginary horizontal line between the upper and lower parts of the visual field)

• Arcuate (arc-shaped) scotomata extending nasally from the blind spot

• Temporal wedge defects

• Paracentral scotomata

In contrast, deficits of the more proximal visual pathways (ie, from the lateral geniculate nucleus to the occipital lobe) involve quadrants or hemispheres of the visual field; thus, deficits do not cross the vertical meridian.

Diagnosis

• Visual field testing

• Ophthalmoscopy

• Measurement of IOP

• Exclusion of other optic neuropathies

Diagnosis is suggested by the examination, but similar findings can result from other optic neuropathies (eg, caused by ischemia, cytomegalovirus infection, or vitamin B_{12} deficiency).

Before a diagnosis of normal-pressure glaucoma can be established, the following factors may need to be ruled out: inaccurate IOP readings, large diurnal fluctuations (causing intermittent normal readings), optic nerve damage caused by previously resolved glaucoma (eg, a previously elevated IOP due to corticosteroid use or uveitis), intermittent angle-closure glaucoma, and other ocular or neurologic disorders that cause similar visual field defects.

Optic disk photography or a detailed optic disk drawing is helpful for future comparison. The frequency of follow-up examinations varies from weeks to years, depending on the patient's reliability, severity of the glaucoma, and response to treatment.

Treatment

• Decreasing IOP 20 to 40%

• Initially, drugs (eg, prostaglandin analogs, β-blockers such as timolol)

• Sometimes surgery, such as laser trabeculoplasty or guarded filtration procedure

Vision lost by glaucoma cannot be recovered. The goal is to prevent further optic nerve and visual field damage by lowering IOP. The target level is 20 to 40% below pretreatment readings. In general, the greater the damage caused by glaucoma, the lower the IOP must be to prevent further damage. If damage progresses, the IOP goal is lowered further and additional therapy is initiated.

Initial treatment is usually drug therapy, proceeding to laser therapy and then incisional surgery if the target IOP is not met. Surgery may be the initial treatment if IOP is extremely high.

Drug therapy: Multiple drugs are available (see Table 65-4). Topical agents are preferred. The most popular are prostaglandin analogs, followed by β-blockers (particularly timolol). Other drugs include α_2-selective adrenergic agonists, cholinergic agonists, and carbonic anhydrase inhibitors. Oral carbonic anhydrase inhibitors are effective, but adverse effects limit their use.

Patients taking topical glaucoma drugs should be taught passive lid closure with punctal occlusion to help reduce systemic absorption and associated adverse effects, although the effectiveness of these maneuvers is controversial. Patients who have difficulty instilling drops directly onto the conjunctiva may place the drop on the nose just medial to the medial canthus, then roll the head slightly toward the eye so that the liquid flows into the eye.

Typically, to gauge effectiveness, clinicians start drugs in only one eye (one-eye trial); once improvement in the treated eye has been confirmed at a subsequent visit (typically 1 to 4 wk later), both eyes are treated.

Surgery: Surgery for primary open-angle and normal-pressure glaucoma includes laser trabeculoplasty, a guarded filtration procedure, and possibly tube shunts or ciliodestructive procedures.

Argon laser trabeculoplasty (ALT) may be the initial treatment for patients who do not respond to or who cannot tolerate drug therapy. Laser energy is applied to either 180° or 360° of the trabecular meshwork to improve the drainage of aqueous humor. Within 2 to 5 yr, about 50% of patients require additional drug therapy or surgery because of insufficient IOP control.

Selective laser trabeculoplasty (SLT) uses a pulsed double-frequency neodymium:yttrium-aluminum-garnet laser. SLT and ALT are equally effective initially, but SLT may have greater effectiveness in subsequent treatments.

A **guarded filtration procedure** is the most commonly used filtration procedure. A hole is made in the limbal sclera (trabeculectomy), which is covered by a partial-thickness scleral flap that controls egress of aqueous from the eye to the subconjunctival space, forming a filtration bleb. Adverse effects of glaucoma filtration surgery include acceleration of cataract growth, pressures that are too low, and transient swelling during the perioperative period. Patients with trabeculectomies are at increased risk of bacterial endophthalmitis and should be instructed to report any symptoms or signs of bleb infection (blebitis) or endophthalmitis immediately.

Viscocanalostomy, canaloplasty, and Trabectome® surgery are newer filtration procedures that do not involve creating a fistula between the anterior chamber and subconjunctival space. Viscocanalostomy and canaloplasty involve dilating Schlemm's canal. Trabectome® surgery uses a proprietary device to remove a portion of the inner aspect of one of the drains of the eye (trabecular meshwork). More long-term studies with these procedures are needed and are on-going. Currently, these new procedures do not appear as effective as trabeculectomy but seem to offer greater safety.

Angle-Closure Glaucoma

Angle-closure glaucoma is glaucoma associated with a physically obstructed anterior chamber angle, which may be chronic or, rarely, acute. Symptoms of acute angle closure are severe ocular pain and redness, decreased vision, colored halos around lights, headache, nausea, and vomiting. Intraocular pressure (IOP) is elevated. Immediate treatment of the acute condition with multiple topical and systemic drugs is required to prevent permanent vision loss, followed by the definitive treatment, iridotomy.

Angle-closure glaucoma accounts for about 10% of all glaucomas in the US.

Etiology

Angle-closure glaucoma is caused by factors that either pull or push the iris up into the angle (ie, junction of the iris and cornea at the periphery of the anterior chamber), physically blocking drainage of aqueous and raising IOP (see Table 65-2). Elevated IOP damages the optic nerve.

Pathophysiology

Angle closure may be primary (cause is unknown) or secondary to another condition (see Table 65-2) and can be acute, subacute (intermittent), or chronic.

[**Table 65-4.** Drugs Used to Treat Glaucoma]

Primary angle-closure glaucoma: Narrow angles are not present in young people. As people age, the lens of the eye continues to grow. In some but not all people, this growth pushes the iris forward, narrowing the angle. Risk factors for developing narrow angles include Asian ethnicity, hyperopia, family history, and advanced age.

In people with narrow angles, the distance between the pupillary iris and the lens is also very narrow. When the iris dilates, forces pull it centripetally and posteriorly causing iris-lens contact, which prevents aqueous from passing between the lens and iris into the anterior chamber (this mechanism is termed pupillary block). Pressure from the continued secretion of aqueous into the posterior chamber by the ciliary body pushes the peripheral iris anteriorly (causing a forward-bowing iris called iris bombe), closing the angle. This closure blocks aqueous outflow, resulting in rapid (within hours) and severe (> 40 mm Hg) elevation of IOP. Because of the rapid onset, this condition is called primary acute angle-closure glaucoma and is an ophthalmic emergency requiring immediate treatment.

Intermittent angle-closure glaucoma occurs if the episode of pupillary block resolves spontaneously after several hours, usually after sleeping supine.

Chronic angle-closure glaucoma occurs if the angle narrows slowly, allowing scarring between the peripheral iris and trabecular meshwork; IOP elevation is slow.

Pupillary dilation (mydriasis) can push the iris into the angle and precipitate acute angle-closure glaucoma in any person with narrow angles. This development is of particular concern when applying topical agents to dilate the eye for examination (eg, cyclopentolate, phenylephrine) or for treatment (eg, homatropine) or when giving systemic drugs that have the potential to dilate the pupils (eg, scopolamine, α-adrenergic agonists commonly used to treat urinary incontinence, drugs with anticholinergic effects).

Secondary angle-closure glaucomas: The mechanical obstruction of the angle is due to a coexisting condition, such as proliferative diabetic retinopathy (PDR), ischemic central vein occlusion, uveitis, or epithelial down-growth. Contraction of a neovascular membrane (eg, in PDR) or inflammatory scarring associated with uveitis can pull the iris into the angle.

Symptoms and Signs

Acute angle-closure glaucoma: Patients have severe ocular pain and redness, decreased vision, colored halos around lights, headache, nausea, and vomiting. The systemic complaints may be so severe that patients are misdiagnosed as having a neurologic or GI problem. Examination typically reveals conjunctival hyperemia, a hazy cornea, a fixed mid-dilated pupil, and anterior chamber inflammation. Vision is decreased. IOP is usually 40 to 80 mm Hg. The optic nerve is difficult to visualize because of corneal edema, and visual field testing is not done because of discomfort.

Chronic angle-closure glaucoma: This type of glaucoma manifests similarly to open-angle glaucoma (see p. 600). Some patients have ocular redness, discomfort, blurred vision, or headache that lessens with sleep (perhaps because of sleep-induced miosis and posterior displacement of the lens by gravity). On gonioscopy, the angle is narrow, and peripheral anterior synechiae (PAS) may be seen. IOP may be normal but is usually higher in the affected eye.

Diagnosis

- **Acute:** Measurement of IOP and clinical findings

- **Chronic:** Gonioscopy showing peripheral anterior synechiae and characteristic optic nerve and visual field abnormalities

Diagnosis of acute angle-closure glaucoma is clinical and by measurement of IOP. Gonioscopy may be difficult to perform in the involved eye because of a clouded cornea with friable corneal epithelium. However, examination of the other eye reveals a narrow or occludable angle. If the other eye has a wide angle, a diagnosis other than primary angle-closure glaucoma should be considered.

Diagnosis of chronic angle-closure glaucoma is based on the presence of PAS on gonioscopy and characteristic optic nerve and visual field changes (see p. 601).

Treatment

- **Acute:** Timolol, pilocarpine, and apraclonidine drops and a systemic osmotic drug followed promptly by laser peripheral iridotomy

- **Chronic:** Similar to primary open-angle glaucoma except that laser peripheral iridotomy may be done if the clinician feels that the procedure may slow the mechanical closing of the angle

Acute angle-closure glaucoma: Treatment must be initiated immediately because vision can be lost quickly and permanently. The patient should receive several drugs at once. A suggested regimen is timolol 0.5% one drop q 30 min for 2 doses; pilocarpine 2 to 4% one drop q 15 min for the first 1 to 2 h; apraclonidine 0.5 to 1% one drop q 30 min for 2 doses; acetazolamide 500 mg po initially followed by 250 mg q 6 h; and an osmotic agent, such as oral glycerol 1 mL/kg diluted with an equal amount of cold water, mannitol 1.0 to 1.5 mg/kg IV, or isosorbide 100 g po (220 mL of a 45% solution [NOTE: This form of isosorbide is not isosorbide dinitrate.]). Response is evaluated by measuring IOP. Miotics are generally not effective when IOP is > 40 or 50 mm Hg because of an anoxic pupillary sphincter.

Definitive treatment is with laser peripheral iridotomy (LPI), which opens another pathway for fluid to pass from the posterior to the anterior chamber, breaking the pupillary block. It is done as soon as the cornea is clear and inflammation has subsided. In some cases the cornea clears within hours of lowering the IOP; in other cases, it can take 1 to 2 days. Because the chance of having an acute attack in the other eye is 80%, LPI is done on both eyes.

The risk of complications with LPI is extremely low compared with its benefits. Glare, which can be bothersome, may occur if the iridotomy is not placed superiorly enough for the upper lid to cover it.

Chronic angle-closure glaucoma: Patients with chronic, subacute, or intermittent angle-closure glaucoma should also have LPI. Additionally, patients with a narrow angle, even in the absence of symptoms, should undergo prompt LPI to prevent angle-closure glaucoma.

The drug and surgical treatments are the same as with open-angle glaucoma. Laser trabeculoplasty is relatively contraindicated if the angle is so narrow that additional PAS may form after the laser procedure.

Chapter 66. Cataract

(For developmental or congenital cataracts, see p. 2920.)

A cataract is a congenital or degenerative opacity of the lens. The main symptom is gradual, painless vision blurring. Diagnosis is by ophthalmoscopy and slit-lamp examination. Treatment is surgical removal and placement of an intraocular lens.

Lens opacity can develop in several locations:

• Central lens nucleus (nuclear cataract)

• Beneath the posterior lens capsule (posterior subcapsular cataract)

Etiology

Cataracts occur with aging. Other risk factors may include the following:

• Trauma (sometimes causing cataracts years later)

• Smoking

• Alcohol use

• Exposure to x-rays

• Heat from infrared exposure

• Systemic disease (eg, diabetes)

• Uveitis

• Systemic drugs (eg, corticosteroids)

• Undernutrition

• Dark eyes

• Possibly chronic ultraviolet exposure

Many people have no risk factors other than age. Some cataracts are congenital, associated with numerous syndromes and diseases.

Symptoms and Signs

Cataracts generally develop slowly over years. Early symptoms may be loss of contrast, glare (halos and starbursts around lights), needing more light to see well, and problems distinguishing dark blue from black. Painless blurring eventually occurs. The degree of blurring depends on the location and extent of the opacity. Double vision occurs rarely.

With a nuclear cataract (see Plate 4), distance vision worsens. Near vision may improve in the early stages because of changes in the refractive index of the lens; presbyopic patients may be temporarily able to read without glasses (second sight).

A posterior subcapsular cataract disproportionately affects vision because the opacity is located at the crossing point of incoming light rays. Such cataracts reduce visual acuity more when the pupil constricts (eg, in bright light, during reading). They are also the type most likely to cause loss of contrast as well as

glare, especially from bright lights or from car headlights while driving at night.

Rarely, the cataract swells, occluding the trabecular drainage meshwork and causing secondary closed-angle glaucoma and pain.

Diagnosis

• Ophthalmoscopy followed by slit-lamp examination

Diagnosis is best made with the pupil dilated. Well-developed cataracts appear as gray, white, or yellow-brown opacities in the lens. Examination of the red reflex through the dilated pupil with the ophthalmoscope held about 30 cm away usually discloses subtle opacities. Small cataracts stand out as dark defects in the red reflex. A large cataract may obliterate the red reflex. Slit-lamp examination provides more details about the character, location, and extent of the opacity.

Treatment

• Surgical removal of the cataract

• Placement of an intraocular lens

Frequent refractions and corrective lens prescription changes may help maintain useful vision during cataract development. Occasionally, long-term pupillary dilation (with phenylephrine 2.5% q 4 to 8 h) is helpful for small centrally located cataracts. Indirect lighting while reading minimizes pupillary constriction and may optimize vision for close tasks. Polarized lenses reduce glare.

Usual indications for surgery include the following:

• Best vision obtained with glasses is worse than 20/40 (< 6/12), or vision is significantly decreased under glare conditions (eg, oblique lighting while trying to read a chart) in a patient with bothersome halos or starbursts.

• Patients sense that vision is limiting (eg, by preventing activities of daily living such as driving, reading, hobbies, and occupational activities).

• Vision could potentially be meaningfully improved if the cataract is removed (ie, a significant portion of the vision loss must be caused by the cataract).

Far less common indications include cataracts that cause glaucoma or that obscure the fundus in patients who need periodic fundus examinations for management of diseases such as diabetic retinopathy and glaucoma. There is no advantage to removing a cataract early.

Cataract extraction is usually done using a topical or local anesthetic and IV sedation. There are 3 extraction techniques. In **intracapsular cataract extraction**, the cataract and lens capsule are removed in one piece; this technique is rarely used. In **extracapsular cataract extraction**, the hard central nucleus is removed in one piece and then the soft cortex is removed in multiple small pieces. In **phacoemulsification**, the hard central nucleus is dissolved by ultrasound and then the soft cortex is removed in multiple small pieces. Phacoemulsification requires the smallest incision, thus enabling the fastest healing, and is usually the preferred procedure. In extracapsular extraction and phacoemulsification, the lens capsule is not removed.

A plastic or silicone lens is almost always implanted intraocularly to replace the optical focusing power lost by removal of the crystalline lens. The lens implant is usually placed on or within the lens capsule (posterior chamber lens). The lens can also be placed in front of the iris (anterior chamber lens) or attached to the iris and within the pupil (iris plane lens). Iris plane lenses are rarely used in the US because many designs led to a high frequency of postoperative complications. Multifocal intraocular lenses are newer and have different focusing zones that may reduce dependence on glasses after surgery. Patients occasionally experience glare or halos with these lenses, especially under low-light

conditions.

In most cases, a tapering schedule of topical antibiotics (eg, moxifloxacin 0.5% 1 drop qid) and topical corticosteroids (eg, prednisolone acetate 1% 1 drop qid) is used for up to 4 wk postsurgery. Patients often wear an eye shield while sleeping and should avoid the Valsalva maneuver, heavy lifting, excessive forward bending, and eye rubbing for several weeks.

Major complications of cataract surgery are rare. Complications include the following:

- Intraoperative: Bleeding beneath the retina, causing the intraocular contents to extrude through the incision (choroidal hemorrhage), vitreous prolapsing out of the incision (vitreous loss), fragments of the cataract dislocating into the vitreous, incisional burn, and detachment of corneal endothelium and its basement membrane (Descemet's membrane)

- Within the first week: Endophthalmitis (infection within the eye) and glaucoma

- Within the first month: Cystoid macular edema

- Months later: Bullous keratopathy (ie, swelling of the cornea due to damage to the corneal pump cells during cataract surgery), retinal detachment, and posterior capsular opacification (common, but treatable with laser)

After surgery, vision returns to 20/40 (6/12) or better in 95% of eyes if there are no preexisting disorders such as amblyopia, retinopathy, macular degeneration, and glaucoma. If an intraocular lens is not implanted, contact lenses or thick glasses are needed to correct the resulting hyperopia.

Prevention

Many ophthalmologists recommend ultraviolet-coated eyeglasses or sunglasses as a preventive measure. Reducing risk factors such as alcohol, tobacco, and corticosteroids and controlling blood glucose in diabetes delay onset. A diet high in vitamin C, vitamin A, and carotenoids (contained in vegetables such as spinach and kale) may protect against cataracts.

Chapter 67. Uveitis

Introduction

Uveitis is inflammation of the uveal tract—the iris, ciliary body, and choroid. Most cases are idiopathic, but identifiable causes include various infections and systemic diseases, many of which are autoimmune. Symptoms include decreased vision, ocular ache, redness, photophobia, and floaters. Although intraocular inflammation is identified clinically, identifying the cause of the inflammation typically requires testing. Treatment depends on cause but typically includes topical, locally injected, or systemic corticosteroids with a topical cycloplegic-mydriatic drug. Noncorticosteroid immunosuppressive drugs may be used in severe and refractory cases. Infectious causes require antimicrobial therapy.

Inflammation of the uvea (uveitis) may occur with or without vitreitis, retinitis, papillitis, or optic neuritis. Uveitis is classified anatomically as anterior, intermediate, or posterior uveitis or panuveitis.

Anterior uveitis is localized primarily to the anterior segment of the eye and includes iritis (inflammation in the anterior chamber alone) and iridocyclitis (inflammation in the anterior chamber and anterior vitreous).

Intermediate uveitis (peripheral uveitis or chronic cyclitis) occurs in the vitreous.

Posterior uveitis refers to any form of retinitis, choroiditis, or inflammation of the optic disk.

Panuveitis (also called diffuse uveitis) implies inflammation in both the anterior and posterior chambers.

Etiology

Most cases are idiopathic and presumed to be autoimmune in origin. Identifiable causes include

• Trauma

• Ocular and systemic infections

• Systemic autoimmune disorders

The most common cause of anterior uveitis is trauma (traumatic iridocyclitis). Other causes are spondyloarthropathies (20 to 25%), juvenile idiopathic arthritis, and herpesvirus (herpes simplex and varicella-zoster) infection. Half of all cases of anterior uveitis are idiopathic.

Most intermediate uveitis is idiopathic. Uncommon identifiable causes include multiple sclerosis, sarcoidosis, TB, syphilis, and, in endemic regions, Lyme disease.

Most posterior uveitis (retinitis) is idiopathic. The most commonly recognized cause of posterior uveitis in immunocompetent patients is toxoplasmosis; the most commonly recognized cause in patients with HIV/AIDS is cytomegalovirus (CMV).

The most commonly identified cause of panuveitis is sarcoidosis, but most cases remain idiopathic despite appropriate testing.

Infrequently, systemic drugs cause uveitis (usually anterior). Examples are sulfonamides, pamidronate (an inhibitor of bone resorption), rifabutin, and cidofovir.

Systemic diseases causing uveitis and their treatment are discussed elsewhere in THE MANUAL.

Symptoms and Signs

Symptoms and signs may be subtle and vary depending on the site and severity of inflammation.

Anterior uveitis tends to be the most symptomatic, usually manifesting with pain (ocular ache), redness, photophobia, and, to a variable degree, decreased vision. Signs include hyperemia of the conjunctiva adjacent to the cornea (ciliary flush or limbal injection). Slit-lamp findings include cells and flare (a haze) in the anterior chamber (aqueous humor), keratic precipitates (WBC clumps on the inner corneal surface), and posterior synechiae. With severe anterior uveitis, WBCs may layer in the anterior chamber (hypopyon).

Intermediate uveitis is typically painless and manifests with floaters and decreased vision. The primary sign is cells in the vitreous humor. Aggregates and condensations of inflammatory cells often occur over the pars plana (near the junction of the iris and sclera), forming snowballs. Vision may be decreased because of floaters or cystoid macular edema, which results from fluid leakage from blood vessels in the macula. Confluent and condensed vitreous cells and snowballs over the pars plana may cause a classic snowbank appearance, which can be associated with neovascularization of the retinal periphery.

Posterior uveitis may give rise to diverse symptoms but most commonly causes floaters and decreased vision as occurs in intermediate uveitis. Signs include cells in the vitreous humor; white or yellow-white lesions in the retina (retinitis), underlying choroid (choroiditis), or both; exudative retinal detachments; retinal vasculitis; and optic disk edema.

Panuveitis may cause any combination of the previously mentioned symptoms and signs.

Consequences: Consequences of uveitis include profound and irreversible vision loss, especially when uveitis is unrecognized, inadequately treated, or both. The most frequent complications include cataract; glaucoma; retinal detachment; neovascularization of the retina, optic nerve, or iris; and cystoid macular edema (the most common cause of decreased vision in patients with uveitis).

Diagnosis

• Slit-lamp examination

• Ophthalmoscopy after pupil dilation

Uveitis should be suspected in any patient who has ocular ache, redness, photophobia, floaters, or decreased vision. Patients with anterior uveitis have ocular ache in the affected eye if light is shined in the unaffected eye (true photophobia), which is uncommon in conjunctivitis. Diagnosis of anterior uveitis is by recognizing cells and flare in the anterior chamber. Cells and flare are seen with a slit lamp and are most evident when using a narrow, intensely bright light focused on the anterior chamber in a dark room. Findings of intermediate and posterior uveitis are most easily seen after dilating the pupil (see p. 538). Indirect ophthalmoscopy (usually done by an ophthalmologist) is more sensitive than direct ophthalmoscopy. (NOTE: If uveitis is suspected, patients should be referred immediately for complete ophthalmologic evaluation.)

Many conditions that cause intraocular inflammation can mimic uveitis and should be considered in the appropriate clinical settings. Such conditions include intraocular cancers in the very young (typically retinoblastoma and leukemia) and in the elderly (intraocular lymphoma). Less commonly, retinitis pigmentosa (see p. 618) can manifest with mild inflammation, which may be confused with uveitis.

Treatment

• Corticosteroids (usually topical)

• Cycloplegic-mydriatic drugs

Treatment of active inflammation usually involves corticosteroids given topically or by periocular or intraocular injection along with a cycloplegic-mydriatic drug (eg, homatropine 2% or 5% drops bid to qid depending on severity). Antimicrobial drugs are used to treat infectious uveitis. Particularly severe or chronic cases may require systemic corticosteroids, systemic noncorticosteroid immunosuppressive

drugs, laser phototherapy, cryotherapy applied transsclerally to the retinal periphery, or surgical removal of the vitreous (vitrectomy).

Uveitis Caused by Connective Tissue Disease

A number of connective tissue diseases cause inflammation of the uveal tract.

Spondyloarthropathies: The seronegative spondyloarthropathies (see p. 341) are a common cause of anterior uveitis. RA, in contrast, is not associated with uveitis. Ocular inflammation is most common with ankylosing spondylitis but also occurs with reactive arthritis, inflammatory bowel disease (ulcerative colitis and Crohn's disease), and psoriatic arthritis. Uveitis is classically unilateral, but recurrences are common and active inflammation may alternate between eyes. Men are affected more commonly than women. Most patients, regardless of sex, are HLA-B27 positive.

Treatment requires a topical corticosteroid and a cycloplegic-mydriatic drug. Occasionally, periocular corticosteroids are required.

Juvenile idiopathic arthritis (JIA, also known as juvenile RA): JIA characteristically causes chronic bilateral iridocyclitis in children, particularly those with the pauciarticular variety (see p. 339). Unlike most forms of anterior uveitis, however, JIA tends not to cause pain, photophobia, and conjunctival injection but only blurring and meiosis and is, therefore, often referred to as white iritis. JIA-associated uveitis is more common among girls.

Recurrent bouts of inflammation are best treated with a topical corticosteroid and a cycloplegic-mydriatic drug. Long-term control often requires use of a noncorticosteroid immunosuppressive drug (eg, methotrexate, mycophenolate mofetil).

Sarcoidosis: Sarcoidosis (see also p. 1965) accounts for 10 to 20% of cases of uveitis, and about 25% of patients with sarcoidosis develop uveitis. Sarcoid uveitis is more common among blacks and the elderly.

Virtually any symptoms and signs of anterior, intermediate, posterior, or panuveitis can occur. Suggestive findings include conjunctival granulomas, large keratic precipitates on the corneal endothelium (so-called granulomatous or mutton fat precipitates), iris granulomas, and retinal vasculitis. Biopsy of suggestive lesions, which provides the most secure diagnosis, is usually done on the conjunctiva; it is rarely done on intraocular tissues because of the risk associated with the procedure.

Treatment usually involves topical, periocular, intraocular, or systemic corticosteroids, or a combination, along with a topical cycloplegic-mydriatic drug. Patients with moderate to severe inflammation may require a noncorticosteroid immunosuppressive drug (eg, methotrexate, mycophenolate mofetil, azathioprine).

Behcet's syndrome: This condition is rare in North America but is a fairly common cause of uveitis in the Middle East and Far East (see also p. 315).

Typical findings include severe anterior uveitis with hypopyon, retinal vasculitis, and optic disk inflammation. The clinical course is usually severe with multiple recurrences.

Diagnosis requires the presence of associated systemic manifestations, such as oral aphthous or genital ulcers; dermatitis, including erythema nodosum; thrombophlebitis; or epididymitis. Oral aphthae may be biopsied to show an occlusive vasculitis. There are no laboratory tests for Behcet's syndrome.

Treatment with local and systemic corticosteroids and a cycloplegic-mydriatic drug may alleviate acute exacerbations, but most patients eventually require systemic corticosteroids and a noncorticosteroid immunosuppressive drug (eg, cyclosporine, chlorambucil) to control the inflammation and avoid the serious complications of long-term corticosteroid treatment. Biologic agents such as interferons and tumor necrosis factor inhibitors have been effective in selected patients unresponsive to other therapies.

Vogt-Koyanagi-Harada (VKH) syndrome: VKH syndrome is an uncommon systemic disorder

characterized by uveitis accompanied by cutaneous and neurologic abnormalities. VKH syndrome is particularly common among people of Asian, Asian Indian, and American Indian descent. Women in their 20s and 30s are affected more often than men. The etiology is unknown, although an autoimmune reaction directed against melanin-containing cells in the uveal tract, skin, inner ear, and meninges is strongly suspected.

Neurologic symptoms tend to occur early and include tinnitus, dysacusis (auditory agnosia), vertigo, headache, and meningismus. Cutaneous findings frequently occur later and include patchy vitiligo (especially common on the eyelids, low back, and buttocks), poliosis (a localized patch of white hair), and alopecia, often involving the head and neck. Common findings include serous retinal detachment, optic disk edema, and choroiditis. Long-term complications include cataracts, glaucoma, subretinal fibrosis, and choroidal neovascularization.

Early treatment includes local and systemic corticosteroids and a cycloplegic-mydriatic drug. Many patients also require a noncorticosteroid immunosuppressive drug (eg, methotrexate, azathioprine, mycophenolate mofetil).

Endophthalmitis

Endophthalmitis is an acute panuveitis resulting most often from bacterial infection.

Most cases of endophthalmitis are caused by gram-positive bacteria, such as *Staphylococcus epidermidis* or *S. aureus*. Gram-negative organisms can also cause endophthalmitis, tend to be more virulent, and predict a poorer prognosis. Fungal and protozoan causes of endophthalmitis are rare. Most cases occur after penetrating ocular trauma or intraocular surgery (exogenous). Less commonly, infection reaches the eye via the bloodstream after systemic surgery or dental procedures or when IV lines or IV drugs are used (endogenous).

Endophthalmitis is a medical emergency because vision prognosis is directly related to the time from onset to treatment. Rarely, untreated intraocular infections extend beyond the confines of the eye to involve the orbit and CNS.

Exogenous endophthalmitis typically causes severe ocular ache and decreased vision. Signs include intense conjunctival hyperemia and intraocular inflammation within the anterior chamber and vitreous, occasionally with eyelid edema.

Diagnosis requires a high index of suspicion in at-risk patients, especially those with recent eye surgery or trauma. Gram stain and culture of aspirates from the anterior chamber and vitreous are standard. Patients with suspected endogenous endophthalmitis should also have blood and urine cultures.

Initial treatment includes broad-spectrum intravitreal antibiotics, most commonly vancomycin and ceftazidime. Patients with endogenous endophthalmitis should receive both intravitreal and IV antibiotics. Therapy is modified based on culture and sensitivity results.

Vision prognosis is often poor, even with early and appropriate treatment. Patients with count-fingers or worse vision at presentation should be considered for vitrectomy and use of intraocular corticosteroids. Corticosteroids are, however, contraindicated in fungal endophthalmitis.

Infectious Uveitis

A number of infectious diseases cause uveitis (see Table 67-1). The most common are

[**Table 67-1.** Infectious Causes of Uveitis]

herpes simplex virus, varicella-zoster virus, and CMV infection and toxoplasmosis. Different organisms affect different parts of the uveal tract.

Herpesvirus: Herpes simplex virus (see also p. 1417) causes anterior uveitis. Varicellazoster virus does so less commonly, although the prevalence of zoster-associated anterior uveitis increases with age. Symptoms include ocular ache, photophobia, and decreased vision. Signs include redness; conjunctival injection and anterior chamber inflammation (cells and flare), often accompanied by corneal inflammation (keratitis); decreased corneal sensation; and patchy or sectorial iris atrophy. Intraocular pressure may be elevated as well; elevation can be detected by using applination tonometry with a Schiotz tonometer, a Goldmann tonometer, or a pneumotonometer.

Treatment should generally be initiated by an ophthalmologist and should include a topical corticosteroid and a cycloplegic-mydriatic drug. Acyclovir (400 mg po 5 times/day for herpes simplex virus and 800 mg po 5 times/day for herpes zoster virus) may also be given. Drops to lower intraocular pressure may be required in patients with ocular hypertension.

Much less commonly, varicella-zoster and herpes simplex viruses cause a rapidly progressing form of retinitis called acute retinal necrosis (ARN), which typically manifests as confluent retinitis, occlusive retinal vasculitis, and moderate to severe vitreous inflammation. One third of ARN cases become bilateral, and in three fourths of eyes, retinal detachment occurs. ARN may also occur in patients with HIV/AIDS, but severely immunocompromised patients can have less prominent vitreous inflammation. Vitreous biopsy for culture and PCR analysis may be useful in diagnosing ARN. Treatment options include IV acyclovir, IV ganciclovir or foscarnet, intravitreal ganciclovir or foscarnet, and oral valacyclovir or valganciclovir.

Toxoplasmosis: Toxoplasmosis (see also p. 1390) is the most common cause of retinitis in immunocompetent patients. Most cases are transmitted congenitally, although acquired cases occur. Symptoms of floaters and decreased vision may be due to cells in the vitreous humor or to retinal lesions or scars. Concurrent anterior segment involvement can occur and may cause ocular ache, redness, and photophobia. Laboratory testing should include serum anti-*Toxoplasma* antibody titers.

Treatment is recommended for patients with posterior lesions that threaten vital visual structures, such as the optic disk or macula, and for immunocompromised patients. Multidrug therapy is commonly prescribed; it includes pyrimethamine, sulfonamides, clindamycin, and, in select cases, systemic corticosteroids. Corticosteroids should not, however, be used without concurrent antimicrobial coverage. Long-acting periocular and intraocular corticosteroids (eg, triamcinolone acetonide) should be avoided. Patients with small peripheral lesions that do not directly threaten vital visual structures may be observed without treatment and should begin to show slow improvement in 1 to 2 mo.

Cytomegalovirus: CMV (see also p. 1416) is the most common cause of retinitis in immunocompromised patients, affecting ≤ 5% of patients with HIV/AIDS receiving highly active antiretroviral therapy (HAART). Most affected patients have a CD4+ count < 100 cells/µL. CMV retinitis may also occur in neonates and in pharmacologically immunosuppressed patients but is uncommon.

The diagnosis is largely clinical based on direct or indirect ophthalmoscopic examination; serologic tests are of limited use. Treatment in patients with HIV/AIDS is with systemic or local (implant) ganciclovir, systemic foscarnet, or valganciclovir. Therapy is typically continued indefinitely, unless immune reconstitution is achieved with combination antiretroviral therapy (typically a CD4+ count > 100 cells/µL for at least 3 mo).

Sympathetic Ophthalmia

Sympathetic ophthalmia is inflammation of the uveal tract after trauma or surgery to the other eye.

Sympathetic ophthalmia is a rare granulomatous uveitis that occurs after penetrating trauma or surgery to the other eye. Sympathetic ophthalmia has been estimated to occur in up to 0.5% of nonsurgical and in < 0.1% of surgical penetrating eye wounds. The underlying mechanism is thought to be an autoimmune reaction directed against melanin-containing cells in the uvea. Uveitis appears within 2 to 12 wk after injury in about 80% of cases. Isolated cases of sympathetic ophthalmia have occurred as early as 1 wk or as late as 30 yr after the initial injury or surgery.

Symptoms typically include floaters and decreased vision. Choroiditis, often with overlying exudative retinal detachment, is common.

Treatment typically requires oral corticosteroids plus a long-term noncorticosteroid immunosuppressive drug. Prophylactic enucleation of a severely injured eye should be considered within 2 wk of vision loss to minimize the risk of sympathetic ophthalmia developing in the other eye, but only when the injured eye has no vision potential.

Chapter 68. Retinal Disorders

Introduction

(For Retinopathy of Prematurity, see p. 2781.)

The retina is the light-sensing layer of tissue at the back of the eye; it contains the rods, cones, and nerve endings that transform light into neural impulses. Retinal disorders may be inherited or caused by vascular disease, inflammation, infection, cancer, or trauma. Visual rehabilitation is indicated for all patients who have severe vision loss.

Age-Related Macular Degeneration

(Senile Macular Degeneration)

Age-related macular degeneration (AMD) is the most common cause of irreversible central vision loss in elderly patients. Funduscopic findings are diagnostic; fluorescein angiography and optical coherence tomography assist in directing treatment. Treatment is with dietary supplements, intravitreal injection of anti-vascular endothelial growth factor, laser photocoagulation, photodynamic therapy, and low-vision devices.

AMD is a leading cause of permanent, irreversible vision loss in the elderly. It is more common among whites.

Etiology

Risk factors include the following:

• Genetic variants (eg, abnormal complement factor H)

• Smoking

• Cardiovascular disease

• Hypertension

• A diet low in ω-3 fatty acids and dark green leafy vegetables

• Age

Pathophysiology

Two different forms occur:

• Dry (atrophic), in about 90% of cases

• Wet (exudative or neovascular), in about 10% of cases

Ninety percent of the blindness caused by AMD occurs in patients who have the wet form.

Dry AMD causes retinal pigmentation changes, yellow spots (drusen—see Plate 3), and areas of chorioretinal atrophy (referred to as geographic atrophy). There is no elevated macular scar, edema, hemorrhage, or exudation.

Wet AMD begins as dry AMD. Choroidal neovascularization (abnormal new vessel formation) occurs under the retina. Localized macular edema or hemorrhage may elevate an area of the macula or cause a localized retinal pigment epithelial detachment. Eventually, neovascularization causes an elevated scar under the macula.

Symptoms and Signs

Dry AMD: The loss of central vision is slow, painless, and usually mild. Central blind spots (scotomas) usually occur late and can sometimes become severe. Symptoms are usually bilateral.

Funduscopic changes include the following:

• Pigment changes

• Drusen

• Areas of chorioretinal atrophy

Wet AMD: Rapid vision loss is more typical of wet AMD. The first symptom is usually visual distortion, such as a central blind spot (scotoma) or curving of straight lines (metamorphopsia). Peripheral vision and color vision are generally unaffected; however, the patient may become legally blind (< 20/200 vision) in the affected eye or eyes, particularly if AMD is not treated. Wet macular degeneration usually affects one eye at a time; thus, symptoms of wet AMD are often unilateral.

Funduscopic changes include the following:

• Subretinal hemorrhage in or around the macula

• Localized retinal elevation

• Retinal edema

• Gray discoloration of the subretinal space

• Exudates in or around the macula

• Detachment of retinal pigment epithelium

Diagnosis

• Funduscopic examination

• Fluorescein angiography

• Optical coherence tomography

Both forms of AMD are diagnosed by funduscopic examination. Visual changes can often be detected with an Amsler grid (see p. 539). Fluorescein angiography is done when findings suggest wet AMD. Angiography demonstrates and characterizes subretinal choroidal neovascular membranes and can delineate areas of geographic atrophy. Optical coherence tomography (OCT) aids in identifying intraretinal and subretinal fluid and can help assess response to treatment.

Treatment

• Dietary supplements for dry or unilateral wet AMD

• Intravitreal anti-vascular endothelial growth factor drugs or laser treatments for wet AMD

• Supportive measures

Dry AMD: There is no way to reverse damage caused by dry AMD, but patients with extensive drusen, pigment changes, or geographic atrophy benefit from daily supplements of the following:

• Zinc oxide 80 mg

• Copper 2 mg

• Vitamin C 500 mg

• Vitamin E 400 IU

• β-Carotene 15 mg (or vitamin A 28,000 IU)

Vitamin A is sometimes substituted for β-carotene. In smokers, β-carotene and vitamin A can increase the risk of lung cancer. For this reason, they are contraindicated in patients who have smoked in the previous 7 yr. Reducing cardiovascular risk factors, including eating foods high in ω-3 fatty acids and dark green leafy vegetables may help.

Wet AMD: Patients with wet AMD in one eye may benefit from daily supplements that are recommended for dry AMD. The choice of other treatment depends on the size, location, and type of neovascularization. Intravitreal injection of anti-vascular endothelial growth factor (VEGF) drugs (usually ranibizumab or bevacizumab or, occasionally, pegaptanib) can substantially reduce the risk of vision loss and can help restore reading vision in up to one third of patients. Thermal laser photocoagulation of neovascularization outside the fovea may prevent severe vision loss. Photodynamic therapy, a type of laser treatment, helps under specific circumstances. Corticosteroids (eg, triamcinolone) are sometimes injected intraocularly along with an anti-VEGF drug. Other treatments, including transpupillary thermotherapy, subretinal surgery, and macular translocation surgery, are seldom used.

Supportive measures: For patients who have lost central vision, low-vision devices such as magnifiers, high-power reading glasses, computer monitors, and telescopic lenses, are available. Also, certain types of software can display computer data in large print or read information aloud in a synthetic voice. Low-vision counseling is advised.

Central Retinal Artery Occlusion

(Retinal Artery Occlusion)

Central retinal artery occlusion is blockage of the central retinal artery, usually due to an embolism. Its symptom is sudden, painless, unilateral blindness. Diagnosis is by history and characteristic retinal findings on funduscopy. Decreasing intraocular pressure can be attempted within the first 24 h of occlusion. If patients present within the first few hours of occlusion, some centers catheterize the carotid artery and selectively inject thrombolytic drugs.

Etiology

Retinal artery occlusion may be due to embolism or thrombosis.

Emboli may come from any of the following:

• Atherosclerotic plaques

• Endocarditis

• Fat

• Atrial myxoma

Giant cell arteritis (see p. 319) is another important cause of arterial occlusion.

Occlusion can affect a branch of the retinal artery as well as the central retinal artery.

Neovascularization (abnormal new vessel formation) of the retina or iris (rubeosis iridis) with secondary (neovascular) glaucoma can occur weeks to months after occlusion. Vitreous hemorrhage may result from retinal neovascularization.

Symptoms and Signs

Retinal artery occlusion causes sudden, painless blindness or visual field defect, usually unilaterally.

The pupil may respond poorly to direct light but constricts briskly when the other eye is illuminated (relative afferent pupillary defect). In acute cases, funduscopy discloses a pale, opaque fundus with a red fovea (cherry-red spot—see Plate 5). Typically, the arteries are attenuated and may even appear bloodless. An embolic obstruction is sometimes visible. If a major branch is occluded rather than the entire artery, fundus abnormalities and vision loss are limited to that sector of the retina.

Patients who have giant cell arteritis often have headache, a tender and palpable temporal artery, jaw claudication, fatigue, or a combination.

Diagnosis

• Clinical evaluation

• Sometimes fluorescein angiography

The diagnosis is suspected when a patient has acute, painless vision loss. Funduscopy is usually confirmatory. Fluorescein angiography is often done and shows obstruction clearly.

Once the diagnosis is made, carotid Doppler ultrasonography and echocardiography should be done to locate any embolic source so that further embolization can be prevented.

If giant cell arteritis is suspected, ESR, C-reactive protein, and platelet count are done.

Prognosis

Patients with a branch artery occlusion often maintain good to fair vision, but vision loss is often profound with central artery occlusion, even with treatment. Once retinal infarction occurs (possibly in < 2 h, almost always by 24 h), vision loss is permanent.

Treatment

• Sometimes reduction of intraocular pressure

Immediate treatment is indicated if occlusion occurred within 24 h of presentation. Reduction of intraocular pressure by ocular hypotensive drugs (eg, topical timolol 0.5%, acetazolamide 500 mg IV or po), intermittent digital massage over the closed eyelid, or anterior chamber paracentesis may dislodge an embolus and allow it to enter a smaller branch of the artery, thus reducing the area of retinal ischemia. Some centers have tried infusing thrombolytics into the carotid artery to dissolve the obstructing clot. Nonetheless, treatments for retinal artery occlusions rarely improve visual acuity. Surgical or laser-mediated embolectomy is available but not commonly done.

Patients with occlusion secondary to temporal arteritis should receive high-dose systemic corticosteroids.

Central Retinal Vein Occlusion

(Retinal Vein Occlusion)

Central retinal vein occlusion is a blockage of the central retinal vein by a thrombus. It causes

painless vision loss, usually suddenly. Diagnosis is by funduscopy. Most treatments are ineffective.

Etiology

Major risk factors include

• Hypertension

• Age

Other risk factors include

• Glaucoma

• Diabetes

• Increased blood viscosity

Occlusion may also be idiopathic. The condition is uncommon among young people. Occlusion may affect a branch of the retinal vein or the central retinal vein.

Neovascularization of the retina or iris (rubeosis iridis) with secondary (neovascular) glaucoma can occur weeks to months after occlusion. Vitreous hemorrhage may result from retinal neovascularization.

Symptoms and Signs

Painless visual loss is usually sudden, but it can also occur gradually over a period of days to weeks. Funduscopy reveals hemorrhages throughout the retina, engorgement and tortuousness of the retinal veins, and, usually, significant retinal edema (see
Plate 6). These changes are limited to one quadrant if obstruction involves only a branch of the central retinal vein.

Diagnosis

• Funduscopy

The diagnosis is suspected in patients with painless visual loss, particularly those at risk. Funduscopy confirms the diagnosis. Patients with a central retinal vein occlusion are evaluated for hypertension and glaucoma and tested for diabetes. Young patients are tested for increased blood viscosity (with a CBC and other coagulable factors as deemed necessary).

Prognosis

Most patients have some visual deficit. In mild cases, there can be spontaneous improvement to near-normal vision over a variable period of time. Visual acuity at presentation is a good indicator of final vision. If visual acuity is at least 20/40, visual acuity will likely remain good, occasionally near normal. If visual acuity is worse than 20/200, it will remain at that level or worsen in 80% of patients.

Treatment

• Panretinal photocoagulation if neovascularization develops

There is no generally accepted medical therapy for occlusion itself. However, if neovascularization develops, panretinal photocoagulation should be initiated because it may decrease vitreous hemorrhages and prevent neovascular glaucoma.

Clinical trials are investigating intravitreal injection of corticosteroids and anti-vascular endothelial growth

factor drugs.

Diabetic Retinopathy

Diabetic retinopathy includes microaneurysms, intraretinal hemorrhage, exudates, macular edema, macular ischemia, neovascularization, vitreous hemorrhage, and traction retinal detachment. Symptoms may not develop until late in the disease. Diagnosis is by funduscopy; further details are elucidated by fluorescein angiography and optical coherence tomography. Treatment includes control of diabetes and BP and ocular laser photocoagulation, intravitreal injection of drugs, vitrectomy, or a combination.

Pathophysiology

Diabetic retinopathy is a major cause of blindness. The degree of retinopathy is highly correlated with

• Duration of diabetes

• Blood glucose levels

• BP levels

Pregnancy can impair blood glucose control and thus worsen retinopathy.

Nonproliferative retinopathy: (also called background retinopathy) develops first and causes increased capillary permeability, microaneurysms, hemorrhages, exudates, macular ischemia, and macular edema (thickening of the retina caused by fluid leakage from capillaries).

Proliferative retinopathy: develops after nonproliferative retinopathy and is more severe; it may lead to vitreous hemorrhage and traction retinal detachment. Proliferative retinopathy is characterized by abnormal new vessel formation (neovascularization), which occurs on the inner (vitreous) surface of the retina and may extend into the vitreous cavity and cause vitreous hemorrhage. The neovascularization is often accompanied by preretinal fibrous tissue, which, along with the vitreous humor, can contract, resulting in traction retinal detachment. Neovascularization may also occur in the anterior segment of the eye on the iris; neovascular membrane growth in the angle of the eye at the peripheral margin of the iris can result, leading to neovascular glaucoma. Vision loss with proliferative retinopathy may be severe.

Clinically significant macular edema can occur with nonproliferative or proliferative retinopathy and is the most common cause of vision loss due to diabetic retinopathy.

Symptoms and Signs

Nonproliferative retinopathy: Vision symptoms accompany macular edema or macular ischemia. However, patients may be unaware of vision loss. The first signs of nonproliferative retinopathy are

• Capillary microaneurysms

• Dot and blot retinal hemorrhages

• Hard exudates

• Cotton-wool spots (soft exudates)

Hard exudates are discrete, yellow, and generally deeper than retinal vessels and suggest retinal edema. Cotton-wool spots are areas of microinfarction that lead to retinal opacification; they are fuzzy-edged and white and obscure underlying vessels (see
Plate 10).

Signs in later stages are

• Macular edema (seen on slit-lamp biomicroscopy as elevation and blurring of retinal layers)

• Venous dilation and intraretinal microvascular abnormalities

Proliferative retinopathy: Symptoms may include blurred vision, black spots or flashing lights in the field of vision, and sudden, severe painless vision loss. Some of these symptoms may be caused by vitreous hemorrhage or traction retinal detachment.

Proliferative retinopathy, unlike nonproliferative retinopathy, causes fine preretinal capillaries (newly developed capillaries) to appear on the optic nerve or retinal surface (see Plates 11 and 23). Macular edema or retinal hemorrhage may be visible on funduscopy.

Diagnosis

• Funduscopy

• Fluorescein angiography

• Sometimes optical coherence tomography

Diagnosis is by funduscopy. Fluorescein angiography is used to determine the extent of damage, to develop a treatment plan, and to monitor the results of treatment. Optical coherence tomography is also useful to assess severity of macular edema and treatment response.

Screening: Because early detection is important, all patients with diabetes should have an annual dilated ophthalmologic examination. Pregnant patients with diabetes should be examined every trimester. Vision symptoms are indications for ophthalmologic referral.

Treatment

• Control of blood glucose and BP

• For macular edema, focal laser and possibly vitrectomy or intravitreal drugs

• For high-risk or complicated proliferative retinopathy, panretinal laser photocoagulation and sometimes vitrectomy

Control of blood glucose and BP are critical; intensive control of blood glucose slows progression of retinopathy. Clinically significant diabetic macular edema is treated with focal laser. Intravitreal injection of triamcinolone, as well as anti-vascular endothelial growth factor (VEGF) drugs, may help in more severe cases. Vitrectomy can help in recalcitrant diabetic macular edema. In select cases of severe nonproliferative retinopathy, panretinal laser photocoagulation may be used; however, most patients can be followed closely until proliferative retinopathy develops.

Proliferative diabetic retinopathy with high-risk characteristics of vitreous hemorrhage, extensive preretinal neovascularization, or anterior segment neovascularization/neovascular glaucoma, should be treated with panretinal laser photocoagulation. This treatment reduces the risk of severe vision loss significantly.

Vitrectomy can help preserve and often restore lost vision in patients with any of the following:

• Vitreous hemorrhage that persists for 3 mo

• Extensive preretinal membrane formation

• Traction retinal detachment

Prevention

Control of blood glucose and BP is critical; intensive control of blood glucose delays onset of retinopathy.

Hypertensive Retinopathy

Hypertensive retinopathy is retinal vascular damage caused by hypertension. Symptoms develop late. Funduscopic examination shows arteriolar constriction, arteriovenous nicking, vascular wall changes, flame-shaped hemorrhages, cotton-wool spots, yellow hard exudates, and papilledema. Treatment is directed at controlling BP and, when vision loss occurs, treating the retina.

Pathophysiology

Acute BP elevation typically causes reversible vasoconstriction in retinal blood vessels, and hypertensive crisis may cause papilledema. More prolonged or severe hypertension leads to exudative vascular changes, a consequence of endothelial damage and necrosis. Other changes (eg, arteriole wall thickening) typically require years of elevated BP to develop. Smoking compounds the adverse effects of hypertension on the retina.

Hypertension is a major risk factor for other retinal disorders (eg, retinal artery or vein occlusion, diabetic retinopathy). Also, hypertension combined with diabetes greatly increases risk of vision loss. Patients with hypertensive retinopathy are at high risk of hypertensive damage to other end organs.

Symptoms and Signs

Symptoms usually do not develop until late in the disease.

In the early stages, funduscopy identifies arteriolar constriction, with a decrease in the ratio of the width of the retinal arterioles to the retinal venules.

Chronic, poorly controlled hypertension causes the following:

• Permanent arterial narrowing

• Arteriovenous crossing abnormalities (arteriovenous nicking)

• Arteriosclerosis with moderate vascular wall changes (copper wiring) to more severe vascular wall hyperplasia and thickening (silver wiring)

Sometimes total vascular occlusion occurs. Arteriovenous nicking is a major predisposing factor to the development of a branch retinal vein occlusion.

If acute disease is severe, the following can develop:

• Superficial flame-shaped hemorrhages

• Small white superficial foci of retinal ischemia (cotton-wool spots—see Plate 18)

• Yellow hard exudates

• Optic disk edema (papilledema)

Yellow hard exudates represent intraretinal lipid deposition from leaking retinal vessels. These exudates can form a star-shaped lesion in the macula, particularly when hypertension is severe (see Plate 17). In severe hypertension, the optic disk becomes congested and edematous (papilledema

indicating hypertensive crisis).

Diagnosis

Diagnosis is by history (duration and severity of hypertension) and funduscopy.

Treatment

Hypertensive retinopathy is managed primarily by controlling hypertension. Other vision-threatening conditions should also be aggressively controlled. If vision loss occurs, treatment of the retinal edema with laser or with intravitreal injection of corticosteroids or anti-vascular endothelial growth factor (VEGF) drugs may be useful.

Retinal Detachment

Retinal detachment is separation of the neural retina from the underlying retinal pigment epithelium. The most common cause is a retinal tear. Symptoms are decreased peripheral or central vision, often described as a curtain or dark cloud coming across the field of vision. Associated symptoms can include painless vision disturbances, including flashing lights and excessive floaters. Traction and serous retinal detachments cause either central or peripheral vision loss. Diagnosis is by funduscopy; ultrasonography may help determine the presence and type of retinal detachment if it cannot be seen with funduscopy. Immediate treatment is imperative if rhegmatogenous retinal detachment is acute and threatens central vision. Treatment of rhegmatogenous detachment may include sealing retinal holes (by laser, diathermy, or cryotherapy), supporting the holes with scleral buckling, pneumatic retinopexy, and vitrectomy.

Etiology

There are 3 types of detachment: rhegmatogenous, which involves a retinal tear, and traction and serous (exudative) detachment, which do not involve a tear (nonrhegmatogenous).

Rhegmatogenous detachment is the most common. Risk factors include the following:

• Myopia

• Previous cataract surgery

• Ocular trauma

Traction retinal detachment can be caused by vitreoretinal traction due to preretinal fibrous membranes as may occur in proliferative diabetic or sickle cell retinopathy.

Serous detachment results from transudation of fluid into the subretinal space. Causes include severe uveitis, especially in Vogt-Koyanagi-Harada syndrome, choroidal hemangiomas, and primary or metastatic choroidal cancers (see p. 619).

Symptoms and Signs

Retinal detachment is painless. Early symptoms of rhegmatogenous detachment may include dark or irregular vitreous floaters (particularly in large numbers), flashes of light (photopsias), and blurred vision. As detachment progresses, the patient notices a curtain, veil, or grayness in the field of vision. If the macula is involved, central vision becomes poor. Patients may have simultaneous vitreous hemorrhage. Traction and exudative (serous) retinal detachments can cause blurriness of vision, but they may not cause any symptoms in the early stages.

Diagnosis

• Indirect funduscopy with pupillary dilation

Retinal detachment should be suspected in patients, particularly those at risk, who have any of the following:

• Sudden increase or change in floaters

• Photopsias

• Curtain or veil across the visual field

• Any sudden, unexplained loss of vision

• Vitreous hemorrhage that obscures the retina

Funduscopy shows the retinal detachment and can differentiate the subtypes of retinal detachment in nearly all cases. Direct funduscopy using a handheld ophthalmoscope can miss some retinal detachments, which may be peripheral. Peripheral fundus examination, using either indirect ophthalmoscopy with scleral depression or using a 3-mirror lens, should be done.

If vitreous hemorrhage (which may be due to a retinal tear), cataract, corneal opacification, or traumatic injury obscures the retina, retinal detachment should be suspected and B-scan ultrasonography should be done.

Treatment

• Sealing retinal holes

• Scleral buckling

• Pneumatic retinopexy

• Vitrectomy

Although often localized, retinal detachments due to retinal tears can expand to involve the entire retina if they are not treated promptly. *Any patient with a suspected or established retinal detachment should be examined urgently by an ophthalmologist*.

Rhegmatogenous detachment is treated with one or more methods, depending on the cause and location of the lesion. One method involves sealing the retinal holes by laser, diathermy, or cryotherapy. The eye may be treated by scleral buckling (which indents the sclera, pushing the retina inward and thereby relieving vitreous traction on the retina); during this procedure, fluid may be drained from the subretinal space. Pneumatic retinopexy (intravitreal injection of gas) and vitrectomy are other treatments. Retinal tears without detachment can be sealed by laser photocoagulation or transconjunctival cryopexy. Nearly all rhegmatogenous detachments can be reattached surgically.

Nonrhegmatogenous detachments due to vitreoretinal traction may be treated by surgical vitrectomy; transudative detachments due to uveitis may respond to systemic corticosteroids, systemic corticosteroid-sparing drugs (eg, methotrexate, azathioprine, anti-tumor necrosis factor drugs), or a slow-release corticosteroid implant, which is surgically implanted into the eye. Primary and metastatic choroidal cancers also require treatment. Choroidal hemangiomas may respond to localized photocoagulation.

Retinitis Pigmentosa

Retinitis pigmentosa is a slowly progressive, bilateral degeneration of the retina and retinal pigment epithelium caused by various genetic mutations. Symptoms include night blindness and loss of peripheral vision. Diagnosis is by funduscopy, which demonstrates pigmentation in a bone-spicule configuration in the equatorial retina, narrowing of the retinal arterioles, a waxy

pallor of the optic disk, posterior subcapsular cataracts, and cells in the vitreous. Electroretinography helps confirm the diagnosis.

Abnormal gene coding for retinal proteins appears to be the cause of retinitis pigmentosa; several genes have been identified. Transmission may be autosomal recessive, autosomal dominant, or, infrequently, X-linked. It may occur as part of a syndrome (eg, Bassen-Kornzweig, Laurence-Moon). Some of these syndromes include congenital hearing loss as well.

Symptoms and Signs

Retinal rods are affected, causing defective night vision that becomes symptomatic at varying ages, sometimes in early childhood. Night vision may eventually be lost. A peripheral ring scotoma (detectable by visual field testing) widens gradually, so that central vision may also be affected in advanced cases.

The most conspicuous funduscopic finding is hyperpigmentation in a bone-spicule configuration in the midperipheral retina. Other findings include the following:

• Narrowing of the retinal arterioles

• Cystoid macular edema

• Waxy yellow appearance of the disk

• Posterior subcapsular cataracts

• Cells in the vitreous (less commonly)

• Myopia

Diagnosis

• Funduscopy

• Electroretinography

The diagnosis is suspected in patients with poor night vision or a family history. Diagnosis is by funduscopy, usually supplemented with electroretinography. Other retinopathies that can simulate retinitis pigmentosa should be excluded; they include retinopathies associated with syphilis, rubella, phenothiazine or chloroquine toxicity, and nonocular cancer. Family members should be examined and tested as necessary or desired to establish the hereditary pattern. Patients with a hereditary syndrome may wish to seek genetic counseling before having children.

Treatment

• Vitamin A

There is no way to reverse damage caused by retinitis pigmentosa, but vitamin A palmitate 20,000 units po once/day may help slow disease progression in some patients. Patients taking vitamin A palmitate should have regular liver function tests. Vision decreases as the macula becomes increasingly involved and can evolve to legal blindness.

Epiretinal Membrane

(Macular Pucker; Cellophane Maculopathy; Premacular Fibrosis)

Epiretinal membrane is formation of a thin membrane over the retina, which interferes with vision.

Epiretinal membrane typically occurs after age 50 and is most common among people > 75. An epiretinal membrane is a thin fibrotic membrane that forms over the retina and contracts, wrinkling the retina underneath.

Risk factors for epiretinal membrane are the following:

• Diabetic retinopathy

• Uveitis

• Retinal detachment

• Ocular injury

Most cases are idiopathic.

Symptoms may include blurred vision or distorted vision (eg, straight lines may appear wavy). Many patients say that it seems like they are looking through plastic wrap or cellophane. Diagnosis is by funduscopy. Fluorescein angiography and optical coherence tomography may also be helpful.

Most people need no treatment. If problems with vision are significant, the membrane can be removed surgically (membrane peel).

Cancers Affecting the Retina

Cancers affecting the retina usually begin in the choroid. Because the retina depends on the choroid for its support and half of its blood supply, damage to the choroid by a cancer is likely to affect vision.

Choroidal melanoma: Choroidal melanoma originates in the choroidal melanocytes. Choroidal melanoma is the most common cancer originating in the eye, with an incidence of about 1 in 2500 whites. It is less common among darker-skinned people. It occurs most frequently at age 55 to 60. It may spread locally or metastasize and be fatal.

Symptoms tend to develop late and include loss of vision and symptoms of retinal detachment (see p. 617).

Diagnosis is by funduscopy, supplemented, when indicated, by other tests, such as ultrasonography, CT, fluorescein angiography, and serial photographs.

Small cancers are treated with laser, radiation, or radioactive implants, which may preserve vision and save the eye. Rarely, local resection is used. Large cancers require enucleation.

Choroidal metastases: Choroidal metastases are common because the choroid is highly vascular. The most common primary cancers are those of the breast in women and of the lung and prostate in men.

Symptoms tend to develop late and include loss of vision and symptoms of retinal detachment.

Diagnosis is often incidental during routine ophthalmoscopy. Ultrasonography is usually done, and the diagnosis is confirmed using fine-needle biopsy.

Treatment is usually with chemotherapy, radiation therapy, or both.

Chapter 69. Optic Nerve Disorders

Introduction

The optic pathway includes the retina, optic nerve, optic chiasm, optic radiations, and occipital cortex (see Fig. 69-1). Damage along the optic pathway causes a variety of visual field changes (see Table 60-1 on p. 540).

Hereditary Optic Neuropathies

Hereditary optic neuropathies are genetic defects that cause vision loss, occasionally with cardiac or neurologic abnormalities. There is no effective treatment.

Hereditary optic neuropathies typically manifest in childhood or adolescence with

[**Fig. 69-1.** Higher visual pathways—lesion sites and corresponding visual field defects.]

bilateral, symmetric central vision loss. Optic nerve damage is usually permanent and in some cases progressive. By the time optic atrophy is detected, substantial optic nerve injury has already occurred.

Dominant optic atrophy: This disorder is inherited in an autosomal dominant fashion. It is believed to be the most common of the hereditary optic neuropathies, with prevalence in the range of 1:10,000 to 1:50,000. It is thought to be optic abiotrophy, premature degeneration of the optic nerve leading to progressive vision loss. Onset is in the 1st decade of life.

Leber's hereditary optic neuropathy: This disorder involves a mitochondrial DNA abnormality that affects cellular respiration. Although mitochondrial DNA throughout the body is affected, vision loss is the primary manifestation. Most cases (80 to 90%) occur in males. The disease is inherited with a maternal inheritance pattern, meaning that all offspring of a woman with the abnormality inherit the abnormality, but only females can pass on the abnormality because the zygote receives mitochondria only from the mother.

Symptoms and Signs

Dominant optic atrophy: Most patients have no associated neurologic abnormalities, although nystagmus and hearing loss have been reported. The only symptom is slowly progressive bilateral vision loss, usually mild until late in life. The entire optic disk or, at times, only the temporal part is pale without visible vessels. A blue-yellow color vision deficit is characteristic.

Leber's hereditary optic neuropathy: Vision loss typically begins between 15 and 35 yr (range, 1 to 80 yr). Painless central vision loss in one eye is usually followed weeks to months later by loss in the other eye. Simultaneous vision loss has been reported. Most patients lose vision to worse than 20/200 acuity. Ophthalmoscopic examination may show telangiectatic microangiopathy, swelling of the nerve fiber layer around the optic disk, and an absence of leakage on fluorescein angiography. Eventually, optic atrophy supervenes.

Some patients with Leber's hereditary optic neuropathy have cardiac conduction defects. Other patients have minor neurologic abnormalities, such as a postural tremor, loss of ankle reflexes, dystonia, spasticity, or a multiple sclerosis-like illness.

Diagnosis

Molecular genetic testing is available to confirm the diagnosis of dominant optic atrophy.

Diagnosis of Leber's hereditary optic atrophy is mainly clinical. ECG should be done to diagnose occult cardiac conduction defects.

Treatment

• Symptomatic treatment

There is no effective treatment for the hereditary optic neuropathies. Low-vision aids (eg, magnifiers, large-print devices, talking watches) may be helpful. Genetic counseling is suggested.

Leber's hereditary optic neuropathy: Corticosteroids, vitamin supplements, and antioxidants have been tried without success. A small study found benefits from quinone analogs (ubiquinone and idebenone) during the early phase. Suggestions to avoid agents that might stress mitochondrial energy production (eg, alcohol) have no proven benefit but are theoretically reasonable. Patients should avoid tobacco products and excessive alcohol intake. Cardiac and neurologic abnormalities should be referred to a specialist.

Ischemic Optic Neuropathy

Ischemic optic neuropathy is infarction of the optic disk. The only constant symptom is painless vision loss. Diagnosis is clinical. Treatment is ineffective.

Two varieties of optic nerve infarction exist: nonarteritic and arteritic. The nonarteritic variant occurs more frequently, typically affecting people about 50 yr and older. Vision loss tends not to be as severe as in the arteritic variant, which typically affects an older group, typically about 70 yr and older.

Most ischemic optic neuropathy is unilateral. Bilateral, sequential cases occur in about 20%, but bilateral simultaneous involvement is uncommon. Atherosclerotic narrowing of the posterior ciliary arteries may predispose to nonarteritic optic nerve infarction, particularly after a hypotensive episode. Any of the inflammatory arteritides, especially giant cell arteritis (see p. 319), can precipitate the arteritic form.

Acute ischemia causes nerve edema, which further worsens ischemia. A small optic cup to optic disk ratio is a risk factor for nonarteritic ischemic optic neuropathy but not for the arteritic variety. Usually, no medical condition is apparent to cause the nonarteritic variety, although diabetes and hypertension are present in some patients and are thought to be risk factors. Vision loss on awakening leads investigators to suspect nocturnal hypotension as a potential cause of the nonarteritic variety.

Symptoms and Signs

Vision loss with both varieties is typically rapid (over minutes, hours, or days) and painless. Some patients notice the loss on awakening. Symptoms such as general malaise, muscle aches and pains, headaches over the temple, pain when combing hair, jaw claudication, and tenderness over the temporal artery may be present with temporal arteritis; however, such symptoms may not occur until after vision is lost. Visual acuity is reduced, and an afferent pupillary defect is present. The optic disk is swollen with surrounding hemorrhages. Visual field examination often shows a defect in the inferior and central visual fields.

Diagnosis

• ESR

• CT or MRI if vision loss is progressive

Diagnosis is based mainly on a clinical evaluation, but ancillary testing may be needed. Most important is to exclude the arteritic variety because the other eye is at risk if treatment is not started quickly. ESR is usually dramatically elevated in the arteritic variety and is normal in the nonarteritic variety. C-reactive protein is also a useful monitoring test. If temporal arteritis is suspected, temporal artery biopsy should be done. For isolated cases of progressive vision loss, CT or MRI should be done to rule out compressive lesions.

Prognosis

There is no effective treatment, and most lost vision is not recovered; however, in the nonarteritic variety,

up to 40% of patients spontaneously recover some useful vision.

Treatment

• Corticosteroids for the arteritic variety

The arteritic variety is treated with oral corticosteroids (prednisone 80 mg po once/day and tapered based on ESR) to protect the other eye. Treatment should not be delayed while awaiting biopsy results. Treatment of the nonarteritic variety with aspirin or corticosteroids has not been helpful. Risk factors are controlled. Low-vision aids (eg, magnifiers, large-print devices, talking watches) may be helpful in both types.

Optic Neuritis

Optic neuritis is inflammation of the optic nerve. Symptoms are usually unilateral, with eye pain and partial or complete vision loss. Diagnosis is primarily clinical. Treatment is directed at the underlying condition; most cases resolve spontaneously.

Etiology

Optic neuritis is most common among adults 20 to 40 yr. Most cases result from demyelinating disease, particularly multiple sclerosis (see p. 1779), in which case there may be recurrences. Optic neuritis is often the presenting manifestation of multiple sclerosis. Other causes include the following:

• Infectious diseases (eg, viral encephalitis [particularly in children], sinusitis, meningitis, TB, syphilis, HIV)

• Tumor metastasis to the optic nerve

• Chemicals and drugs (eg, lead, methanol, quinine, arsenic, antibiotics)

Rare causes include diabetes, pernicious anemia, Graves' disease, bee stings, and trauma. Often, the cause remains obscure despite thorough evaluation.

Symptoms and Signs

The main symptom is vision loss, frequently maximal within 1 or 2 days and varying from a small central or paracentral scotoma to complete blindness. Most patients have mild eye pain, which often feels worse with eye movement.

If the optic disk is swollen, the condition is called papillitis. Otherwise, it is called retrobulbar neuritis. The most characteristic findings include reduced visual acuity, a visual field deficit, and disturbed color vision (often out of proportion to loss of visual acuity). An afferent pupillary defect is usually detectable if the contralateral eye is unaffected or involved to a lesser degree. Testing of color vision is a useful adjunct. In about two thirds of patients, inflammation is entirely retrobulbar, causing no visible changes in the optic fundus. In the rest, disk hyperemia, edema in or around the disk, vessel engorgement, or a combination is present. A few exudates and hemorrhages may be present near or on the optic disk.

Diagnosis

• Clinical evaluation

• MRI

Optic neuritis is suspected in patients with characteristic pain and vision loss. Neuroimaging, preferably with gadolinium-enhanced MRI, is usually done and may show an enlarged, enhancing optic nerve. MRI may also help diagnose multiple sclerosis. Fluid attenuating inversion recovery (FLAIR) MRI sequences may show typical demyelinating lesions in a periventricular location if optic neuritis is related to demyelination.

Prognosis

Prognosis depends on the underlying condition. Most episodes resolve spontaneously, with return of vision in 2 to 3 mo. Most patients with a typical history of optic neuritis and no underlying systemic disease, such as a connective tissue disease, recover vision, but > 25% have a recurrence in the same eye or in the other eye. MRI is used to determine future risk of demyelinating disease.

Treatment

• Corticosteroids

Corticosteroids are an option, especially if multiple sclerosis is suspected. Treatment with methylprednisolone (500 mg to 1000 mg IV once/day) for 3 days followed by prednisone (1 mg/kg po once/day) for 11 days may speed recovery, but ultimate vision results are no different from those with observation alone. IV corticosteroids have been reported to delay onset of multiple sclerosis for at least 2 yr. Treatment with oral prednisone alone does not improve vision outcome and may increase the rate of recurrent episodes. Low-vision aids (eg, magnifiers, large-print devices, talking watches) may be helpful.

Papilledema

Papilledema is swelling of the optic disk due to increased intracranial pressure. All other causes of optic disk swelling, such as that caused by malignant hypertension or thrombosis of the central retinal vein, do not involve increased intracranial pressure and therefore are not causes of papilledema. There are no early symptoms, although vision may be disturbed for a few seconds. Papilledema requires an immediate search for the cause. Diagnosis is by ophthalmoscopy with further tests, usually brain imaging, to determine cause. Treatment is directed at the underlying condition.

Papilledema is a sign of elevated intracranial pressure and is almost always bilateral. Causes include the following:

• Brain tumor or abscess

• Cerebral trauma or hemorrhage

• Meningitis

• Arachnoidal adhesions

• Cavernous or dural sinus thrombosis

• Encephalitis

• Idiopathic intracranial hypertension (pseudotumor cerebri), a condition with elevated CSF pressure and no mass lesion

Symptoms and Signs

Vision is usually not affected initially, but seconds-long graying out of vision, flickering, or blurred or double vision may occur. Patients may have symptoms of increased intracranial pressure, such as headache or nausea and vomiting.

Ophthalmoscopic examination reveals engorged and tortuous retinal veins, a hyperemic and swollen optic disk (optic nerve head), and retinal hemorrhages around the disk but not into the retinal periphery (see Plate 19). Isolated disk edema (eg, caused by optic neuritis or ischemic optic neuropathy) without elevated CSF pressure is not considered papilledema.

In the early stages, visual acuity and pupillary response to light are usually normal and become abnormal only after the condition is well advanced. Visual field testing may detect an enlarged blind spot. Later, nerve fiber bundle defects may be apparent.

Diagnosis

• Clinical evaluation

• Immediate neuroimaging

The degree of disk swelling can be quantified by comparing the plus lens numbers needed to focus an ophthalmoscope on the most elevated portion of the disk and on the unaffected portion of the retina.

Differentiating papilledema from other causes of a swollen optic disk, such as optic neuritis, ischemic optic neuropathy, hypotony, central retinal vein occlusion, uveitis, or pseudo swollen disks (eg, optic nerve drusen), requires a thorough ophthalmologic evaluation. If papilledema is suspected clinically, MRI with gadolinium contrast or CT with contrast is done immediately to exclude causes such as an intracranial mass. Lumbar puncture and measurement of CSF pressure should be done if a mass lesion has been ruled out. Lumbar puncture in patients with intracranial mass lesions can result in brain stem herniation. B-scan ultrasonography is the best diagnostic tool for the pseudo disk edema of optic nerve drusen.

Treatment

• Treatment of underlying disorder

Urgent treatment of the underlying disorder is indicated to decrease intracranial pressure. If intracranial pressure is not reduced, secondary optic nerve atrophy and vision loss eventually occur, along with other serious neurologic sequelae.

Toxic Amblyopia

(Nutritional Amblyopia)

Toxic amblyopia is reduction in visual acuity believed to be the result of a toxic reaction in the orbital portion (papillomacular bundle) of the optic nerve. It can be caused by various toxic and nutritional factors and probably unknown factors. The main symptom is painless vision loss. Diagnosis is by history and visual field examination. Treatment is avoiding suspected toxic agents and improving nutrition.

Etiology

Toxic amblyopia is usually bilateral and symmetric. In alcoholics, undernutrition may be the cause. True tobacco-induced amblyopia is rare. Lead, methanol, chloramphenicol, digoxin, ethambutol, and many other chemicals can damage the optic nerve. Deficiencies of protein and antioxidants are likely risk factors. Toxic amblyopia may occur with other nutritional disorders, such as Strachan's syndrome (polyneuropathy and orogenital dermatitis).

Symptoms and Signs

Vision blurring and dimness typically develop over days to weeks. An initially small central or pericentral scotoma slowly enlarges, typically involving both the fixation and the blind spot (centrocecal scotoma), and progressively interferes with vision. Total blindness may occur in methanol ingestion, but other nutritional causes typically do not cause profound vision loss. Retinal abnormalities do not usually occur, but temporal disk pallor may develop late.

Diagnosis

• Mainly clinical evaluation

A history of undernutrition or toxic or chemical exposure combined with typical bilateral scotomata on visual field testing justifies treatment. Laboratory testing for lead, methanol, and other suspected toxins is done.

Prognosis

Vision may improve if the cause is treated or removed quickly. Once the optic nerve has atrophied, vision usually does not recover.

Treatment

The cause is treated. Exposure to toxic substances should stop immediately. Chelation therapy is indicated in lead poisoning. Dialysis, fomepizole, ethanol, or a combination is used for methanol poisoning. Treatment with oral or parenteral B vitamins before vision loss becomes severe may reverse the condition when undernutrition is the presumed cause.

Low-vision aids (eg, magnifiers, large-print devices, talking watches) may be helpful.

The role of antioxidants has not been fully characterized. Their use could be justified on a theoretic basis; however, there is no proof of efficacy, and the at-risk population that should receive such supplements has not been defined.

Chapter 70. Orbital Diseases

Introduction

Orbital diseases may be vascular, thyroid-related (Graves' disease), infectious, inflammatory, or neoplastic. Cavernous sinus thrombosis causes many of the same symptoms and signs as orbital diseases. Infiltrative ophthalmopathy due to Graves' disease, the most frequent cause of orbital disease, is discussed on p. 780. Orbital fractures are discussed on p. 3232. (See Fig. 60-1 on p. 537 for anatomy of the orbit.)

Cavernous Sinus Thrombosis

Cavernous sinus thrombosis (CST) is a very rare, typically septic thrombosis of the cavernous sinus, usually caused by bacterial sinusitis. Symptoms and signs include pain, proptosis, ophthalmoplegia, vision loss, papilledema, and fever. Diagnosis is confirmed by CT or MRI. Treatment is with IV antibiotics. Complications are common, and prognosis is poor.

Etiology

The cavernous sinuses are trabeculated sinuses located at the base of the skull that drain venous blood from facial veins. CST is an extremely rare complication of common facial infections, most notably nasal furuncles (50%), sphenoidal or ethmoidal sinusitis (30%), and dental infections (10%). Most common pathogens are *Staphylococcus aureus* (70%), followed by *Streptococcus* sp; anaerobes are more common when the underlying condition is dental or sinus infection.

Thrombosis of the lateral sinus (related to mastoiditis) and thrombosis of the superior sagittal sinus (related to bacterial meningitis) occur but are rarer than CST.

Pathophysiology

The 3rd, 4th, and 6th cranial nerves and the ophthalmic and maxillary branches of the 5th cranial nerve are adjacent to the cavernous sinus and are commonly affected. Complications include meningoencephalitis, brain abscess, stroke, blindness, and pituitary insufficiency.

Symptoms and Signs

Initial symptoms are progressively severe headache or facial pain, usually unilateral and localized to retro-orbital and frontal regions. High fever is common. Later, ophthalmoplegia (initially the 6th cranial nerve, lateral gaze), proptosis, and lid edema develop and often become bilateral. Facial sensation may be diminished or absent. Decreased level of consciousness, confusion, seizures, and focal neurologic deficits are signs of CNS spread. Patients may also have anisocoria or mydriasis (3rd cranial nerve dysfunction), papilledema, and vision loss.

Diagnosis

• MRI or CT

CST is often misdiagnosed because it is rare. It should be considered in patients who have signs consistent with orbital cellulitis. Features that distinguish CST from orbital cellulitis include cranial nerve dysfunction, bilateral eye involvement, and mental status changes.

Diagnosis is based on neuroimaging. MRI is the better study, but CT is also helpful. Useful adjunct testing may include blood cultures and lumbar puncture. Lumbar puncture may show inflammatory cells (PMNs, lymphocytes, monocytes); other possible abnormalities include low glucose, high protein, and positive CSF cultures. Cultures of any suspected source infections are also done.

Prognosis

Mortality is 30% in all patients and 50% in those with underlying sphenoid sinusitis. An additional 30% develop serious sequelae (eg, ophthalmoplegia, blindness, disability due to stroke, pituitary insufficiency), which may be permanent.

Treatment

• IV high-dose antibiotics

• Sometimes corticosteroids

Initial antibiotics can include nafcillin or oxacillin 1 to 2 g q 4 to 6 h combined with a 3rd-generation cephalosporin (eg, ceftriaxone 1 g q 12 h). In areas where methicillin-resistant *S. aureus* is prevalent, vancomycin 1 g IV q 12 h should be substituted for nafcillin or oxacillin. A drug for anaerobes (eg, metronidazole 500 mg q 8 h) should be added if an underlying sinusitis or dental infection is present.

In cases with underlying sphenoid sinusitis, surgical sinus drainage is indicated, especially if there is no clinical response to antibiotics within 24 h.

Secondary treatment may include corticosteroids (eg, dexamethasone 10 mg po q 6 h) for cranial nerve dysfunction; anticoagulation is controversial because most patients respond to antibiotics, and adverse effects may exceed benefits.

Inflammatory Orbital Disease

Orbital inflammation (inflammatory orbital pseudotumor) can affect any or all structures within the orbit. The inflammatory response can be nonspecific, granulomatous, or vasculitic. The inflammation can be part of an underlying medical disorder or can exist in isolation. Patients of all ages can be affected. The process can be acute or chronic and can recur.

Symptoms and Signs

Symptoms and signs typically include a sudden onset of pain along with swelling and erythema of the eyelids. Proptosis, diplopia, and vision loss are also possible.

Diagnosis

• CT or MRI

Similar findings occur with orbital infection, but there is no history of trauma or adjacent focus of infection (eg, sinusitis). Neuroimaging with CT or MRI is required. For chronic or recurrent disease, biopsy may be used to find evidence of an underlying medical condition.

Treatment

Treatment depends on the type of inflammatory response and may include oral corticosteroids, radiation therapy, and one of several immunomodulating drugs. In difficult cases, some initial success has occurred with monoclonal antibodies against tumor necrosis factor α or with another monoclonal antibody that causes lymphocyte depletion.

Preseptal and Orbital Cellulitis

Preseptal cellulitis (periorbital cellulitis) is infection of the eyelid and surrounding skin anterior to the orbital septum. Orbital cellulitis (postseptal cellulitis) is infection of the orbital tissues posterior to the orbital septum. Either can be caused by an external focus of infection (eg, a wound), infection that extends from the nasal sinuses or teeth, or metastatic spread from infection elsewhere. Symptoms include eyelid pain, discoloration, and swelling; orbital cellulitis also causes fever, malaise, proptosis, impaired ocular movement, and impaired vision. Diagnosis is based on history, examination, and CT or MRI. Treatment is with antibiotics and

sometimes surgical drainage.

Preseptal cellulitis and orbital cellulitis are 2 distinct diseases that share a few clinical symptoms and signs. Preseptal cellulitis usually begins superficial to the orbital septum. Orbital cellulitis usually begins deep to the orbital septum. Both are more common among children; preseptal cellulitis is far more common than orbital cellulitis.

Etiology

Preseptal cellulitis is caused by contiguous spread of infection from local facial or eyelid injuries, insect or animal bites, conjunctivitis, chalazion, or sinusitis.

Orbital cellulitis is most often caused by extension of infection from adjacent sinuses, especially the ethmoid sinus (75 to 90%); it is less commonly caused by direct infection accompanying local trauma (eg, insect or animal bite, penetrating eyelid injuries) or contiguous spread of infection from the face or teeth or by hematogenous spread.

Pathogens vary by etiology and patient age. *Streptococcus pneumoniae* is the most frequent pathogen associated with sinus infection, whereas *Staphylococcus aureus* and *Streptococcus pyogenes* predominate when infection arises from local trauma. *Haemophilus influenzae* type b, once a common cause, is now less common because of widespread vaccination. Fungi are uncommon pathogens, causing orbital cellulitis in diabetic or immunosuppressed patients. Infection in children < 9 yr is typically with a single aerobic organism; patients > 15 yr typically have polymicrobial mixed aerobic and anaerobic (*Bacteroides*, *Peptostreptococcus*) infections.

Pathophysiology

Because orbital cellulitis originates from large adjacent foci of fulminant infection (eg, sinusitis) separated by only a thin bone barrier, orbital infection can be extensive and severe. Subperiosteal fluid collections, some quite large, can accumulate; they are called subperiosteal abscesses, but many are sterile initially.

Complications include vision loss (3 to 11%) due to ischemic retinopathy and optic neuropathy caused by increased intraorbital pressure; restricted ocular movements (ophthalmoplegia) caused by soft-tissue inflammation; and intracranial sequelae from central spread of infection, including cavernous sinus thrombosis, meningitis, and cerebral abscess.

Symptoms and Signs

Symptoms and signs of preseptal cellulitis include tenderness, swelling, warmth, and redness or discoloration (violaceous in the case of *H. influenzae*) of the eyelid. Patients may be unable to open their eyes because of swelling, but visual acuity is not affected.

Symptoms and signs of orbital cellulitis include swelling and redness of the eyelid and surrounding soft tissues, conjunctival hyperemia and chemosis, decreased ocular motility, pain with eye movements, decreased visual acuity, and proptosis caused by orbital swelling. Signs of the primary infection are also often present (eg, nasal discharge and bleeding with sinusitis, periodontal pain and swelling with abscess). Fever, malaise, and headache should raise suspicion of associated meningitis. Some or all of these findings may be absent early in the course of the infection.

Subperiosteal abscesses, if large enough, can contribute to symptoms of orbital cellulitis such as swelling and redness of the eyelid, decreased ocular motility, proptosis, and decreased visual acuity.

Diagnosis

• Mainly clinical evaluation

• CT or MRI if orbital cellulitis is possible

Diagnosis is suspected clinically. Other disorders to consider include trauma, insect or animal bites without cellulitis, retained foreign bodies, allergic reactions, tumors, and inflammatory orbital pseudotumor.

Eyelid swelling may require the use of lid retractors for evaluation of the globe, and initial signs of complicated infection may be subtle. An ophthalmologist should be consulted when orbital cellulitis is suspected.

Preseptal cellulitis and orbital cellulitis are often distinguishable clinically. Preseptal cellulitis is likely if eye findings are normal except for eyelid swelling. The presence of a local nidus of infection on the skin makes preseptal cellulitis even more likely.

If findings are equivocal, if the examination is difficult (as in young children), or if nasal discharge is present (suggesting sinusitis), CT or MRI should be done to confirm orbital cellulitis, to exclude tumor and pseudotumor, and to diagnose sinusitis if present. MRI is better than CT if cavernous sinus thrombosis is being considered.

The direction of proptosis may be a clue to the site of infection; eg, extension from the frontal sinus pushes the globe down and out, and extension from the ethmoid sinus pushes the globe laterally and out.

Blood cultures are often done (ideally before beginning antibiotics) in patients with orbital cellulitis but are positive in less than one third. Lumbar puncture is done if meningitis is suspected. Cultures of the paranasal sinus fluid are done if sinusitis is the suspected source. Other laboratory tests are not particularly helpful.

Treatment

• Antibiotics

Preseptal cellulitis: Initial therapy should be directed against sinusitis pathogens (*S. pneumoniae*, nontypable *H. influenzae*, *S. aureus*, *Moraxella catarrhalis*); however, in areas where methicillin-resistant *S. aureus* is prevalent, clinicians should add appropriate antibiotics (eg, clindamycin, trimethoprim/sulfamethoxazole, or doxycycline for oral treatment and vancomycin for inpatient treatment). In patients with dirty wounds, gram-negative infection must be considered.

Outpatient treatment is an option if orbital cellulitis has been definitively excluded; children should have no signs of systemic infection and should be in the care of responsible parents or guardians. Patients should be closely followed by an ophthalmologist. Outpatient treatment options include amoxicillin/clavulanate 30 mg/kg po q 8 h (for children < 12 yr) or 500 mg po tid or 875 mg po bid (for adults) for 10 days.

For inpatients, ampicillin/sulbactam 50 mg/kg IV q 6 h (for children) or 1.5 to 3 g (for adults) IV q 6 h (maximum 8 g ampicillin/day) for 7 days is an option.

Orbital cellulitis: Patients with orbital cellulitis should be hospitalized and treated with meningitis-dose antibiotics. A 2nd- or 3rd-generation cephalosporin, such as cefotaxime 50 mg/kg IV q 6 h (for children < 12 yr) or 1 to 2 g IV q 6 h (for adults) for 14 days, is an option when sinusitis is present; imipenem, ceftriaxone, and piperacillin/tazobactam are other options. If cellulitis is related to trauma or foreign body, treatment should cover gram-positive (vancomycin 1 g IV q 12 h) and gram-negative (eg, ertapenem 100 mg IV once/day) pathogens and be taken for 7 to 10 days or until clinical improvement.

Surgery to decompress the orbit, drain an abscess, open infected sinuses, or a combination is indicated in any of the following circumstances:

• Vision is compromised.

• Suppuration or foreign body is suspected.

• Imaging shows orbital or large subperiosteal abscess.

• The infection does not resolve with antibiotics.

Tumors of the Orbit

Orbital tumors can be benign or malignant and arise primarily within the orbit or secondarily from an adjacent source, such as the eyelid, paranasal sinus, or intracranial compartment.

Causes differ by age group. The more common benign pediatric tumors include dermoid tumors and vascular lesions such as capillary hemangioma and lymphangioma. In adults, cavernous hemangiomas predominate.

Some orbital tumors usually cause proptosis and displacement of the globe in a direction opposite the tumor. Pain, diplopia, and vision loss may also be present. Diagnosis, in most cases, is based on the history, examination, and neuroimaging (CT, MRI, or both).

Treatment

Treatment varies by tumor type. Treatment of dermoid tumors is excision. Capillary hemangiomas tend to spontaneously involute and therefore do not need any treatment; however, especially when located on the upper eyelid, they may affect vision and require treatment with interlesional injection of corticosteroids or surgical debulking.

Children: The common pediatric malignant tumors include rhabdomyosarcoma and metastatic lesions related to leukemia or neuroblastoma. If rhabdomyosarcoma is resectable, surgery is done, followed by chemotherapy and orbital radiation therapy. Leukemic disease is usually managed by orbital radiation therapy, chemotherapy, or both.

Adults: The most common benign tumors are meningiomas, mucoceles, and cavernous hemangiomas. When symptomatic, sphenoid wing meningiomas are treated with debulking via craniotomy, sometimes followed by a course of radiation therapy. Because meningioma cells infiltrate bone of the skull base, complete resection usually is not possible. Mucoceles are treated by draining them into the nose because they most commonly arise from the ethmoid or frontal sinus. Cavernous hemangiomas are excised.

Common malignant tumors include lymphoma, squamous cell carcinoma, and metastatic disease. Lymphomas involving the orbit are typically B-cell and characteristically low grade. Lymphomas can be bilateral and simultaneous and can be part of a systemic process or exist in the orbit in isolation. Radiation therapy effectively treats orbital lymphomas with few adverse effects, although the addition of monoclonal antibodies against a surface receptor (CD20) on the lymphocyte is also effective. Most squamous cell carcinomas arise from the adjacent paranasal sinuses. Surgery, radiation therapy, or both form the backbone of therapy. Metastatic disease is usually treated with radiation therapy. Metastatic disease involving the orbit is usually an unfavorable prognostic sign; carcinoid tumors are a notable exception.

7 - Dermatologic Disorders

Chapter 71. Approach to the Dermatologic Patient

Introduction

History and physical examination are adequate for diagnosing many skin lesions. Some require biopsy or other testing.

Important information to obtain from history includes

• Personal or family history of atopy (suggesting atopic dermatitis)

• Occupational exposures (contact dermatitis)

• Long-term exposure to sunlight or other forms of radiation (benign and malignant skin tumors)

• Systemic disease (diabetes and *Candida* or tinea, hepatitis C and cryoglobulinemia)

• Sexual history (syphilis and gonorrhea)

• Use of drugs (Stevens-Johnson syndrome, toxic epidermal necrolysis)

• Travel history (Lyme disease, skin infections)

A negative history is as important as a positive history. The history of the particular skin lesions is also important, including time and site of initial appearance, spread, change in appearance, and triggering factors.

Visual inspection is the central evaluation tool; many skin disorders are diagnosed by the characteristic appearance or morphology of the lesions.

Description of Skin Lesions

An extensive language has been developed to standardize the description of skin lesions, including

• Primary morphology (lesion type)

• Secondary morphology (configuration)

• Texture

• Distribution

• Color

Rash is a general term for a temporary skin eruption.

Primary Morphology

Macules are flat, nonpalpable lesions usually < 10 mm in diameter. Macules represent a change in color and are not raised or depressed compared to the skin surface. A patch is a large macule. Examples include freckles, flat moles, tattoos, port-wine stains, and the rashes of rickettsial infections, rubella, measles, and some allergic drug eruptions.

Papules are elevated lesions usually < 10 mm in diameter that can be felt or palpated. Examples include nevi, warts, lichen planus, insect bites, seborrheic and actinic keratoses, some lesions of acne, and skin cancers. The term maculopapular is often loosely and improperly used to describe many red skin rashes;

because this term is nonspecific and easily misused, it should be avoided.

Plaques are palpable lesions > 10 mm in diameter that are elevated or depressed compared to the skin surface. Plaques may be flat topped or rounded. Lesions of psoriasis and granuloma annulare commonly form plaques.

Nodules are firm papules or lesions that extend into the dermis or subcutaneous tissue. Examples include cysts, lipomas, and fibromas.

Vesicles are small, clear, fluid-filled blisters < 10 mm in diameter. Vesicles are characteristic of herpes infections, acute allergic contact dermatitis, and some autoimmune blistering disorders (eg, dermatitis herpetiformis).

Bullae are clear fluid-filled blisters > 10 mm in diameter. These may be caused by burns, bites, irritant or allergic contact dermatitis, and drug reactions. Classic autoimmune bullous diseases include pemphigus vulgaris and bullous pemphigoid. Bullae also may occur in inherited disorders of skin fragility.

Pustules are vesicles that contain pus. Pustules are common in bacterial infections and folliculitis and may arise in some inflammatory disorders including pustular psoriasis.

Urticaria (wheals or hives—see Plate 53) is characterized by elevated lesions caused by localized edema. Wheals are a common manifestation of hypersensitivity to drugs, stings or bites, autoimmunity, and, less commonly, physical stimuli including temperature, pressure, and sunlight. The typical wheal lasts < 24 h.

Scales are heaped-up accumulations of horny epithelium that occur in disorders such as psoriasis, seborrheic dermatitis, and fungal infections. Pityriasis rosea and chronic dermatitis of any type may be scaly.

Crusts (scabs) consist of dried serum, blood, or pus. Crusting can occur in inflammatory or infectious skin diseases (eg, impetigo).

Erosions are open areas of skin that result from loss of part or all of the epidermis. Erosions can be traumatic or can occur with various inflammatory or infectious skin diseases. An excoriation is a linear erosion caused by scratching, rubbing, or picking.

Ulcers result from loss of the epidermis and at least part of the dermis. Causes include venous stasis dermatitis, physical trauma with or without vascular compromise (eg, from decubitus ulcers, peripheral arterial disease), infections, and vasculitis.

Petechiae are nonblanchable punctate foci of hemorrhage. Causes include platelet abnormalities (eg, thrombocytopenia, platelet dysfunction), vasculitis, and infections (eg, meningococcemia, Rocky Mountain spotted fever, other rickettsioses).

Purpura is a larger area of hemorrhage that may be palpable. Palpable purpura is considered the hallmark of leukocytoclastic vasculitis. Purpura may indicate a coagulopathy. Large areas of purpura may be called ecchymoses or, colloquially, bruises.

Atrophy is thinning of the skin, which may appear dry and wrinkled, resembling cigarette paper. Atrophy may be caused by chronic sun exposure, aging, and some inflammatory and neoplastic skin diseases, including cutaneous T-cell lymphoma and lupus erythematosus. Atrophy also may result from long-term use of potent topical corticosteroids.

Scars are areas of fibrosis that replace normal skin after injury. Some scars become hypertrophic or thickened and raised. Keloids are hypertrophic scars that extend beyond the original wound margin.

Telangiectases are foci of small, permanently dilated blood vessels that are most often idiopathic but may occur in rosacea, systemic diseases (especially systemic sclerosis), or inherited diseases (eg,

ataxia-telangiectasia, hereditary hemorrhagic telangiectasia) or after long-term therapy with topical fluorinated corticosteroids.

Secondary Morphology (Configuration)

Configuration is the shape of single lesions and the arrangement of clusters of lesions.

Linear lesions take on the shape of a straight line and are suggestive of some forms of contact dermatitis, linear epidermal nevi, and lichen striatus.

Annular lesions are rings with central clearing. Examples include granuloma annulare, some drug eruptions, some dermatophyte infections (eg, ringworm), and secondary syphilis.

Nummular lesions are circular or coin-shaped; an example is nummular eczema.

Target (bull's-eye or iris) lesions appear as rings with central duskiness and are classic for erythema multiforme.

Serpiginous lesions have linear, branched, and curving elements. Examples include some fungal and parasitic infections (eg, cutaneous larva migrans).

Reticulated lesions have a lacy or networked pattern. Examples include cutis marmorata and livedo reticularis.

Herpetiform describes grouped papules or vesicles arranged like those of a herpes simplex infection.

Zosteriform describes lesions clustered in a dermatomal distribution similar to herpes zoster.

Texture

Some skin lesions have visible or palpable texture that suggests a diagnosis.

Verrucous lesions have an irregular, pebbly, or rough surface. Examples include warts and seborrheic keratoses.

Lichenification is thickening of the skin with accentuation of normal skin markings; it results from repeated rubbing.

Induration, or deep thickening of the skin, can result from edema, inflammation, or infiltration, including by cancer. Indurated skin has a hard, resistant feeling. Induration is characteristic of panniculitis, some skin infections, and cutaneous metastatic cancers.

Umbilicated lesions have a central indentation and are usually viral. Examples include molluscum contagiosum and herpes simplex.

Xanthomas, which are yellowish, waxy lesions, may occur in lipid disorders.

Location and Distribution

It is important to note whether

• Lesions are single or multiple

• Particular body parts are affected (eg, palms or soles, scalp, mucosal membranes)

• Distribution is random or patterned, symmetric or asymmetric

• Lesions are on sun-exposed or protected skin

Although few patterns are pathognomonic, some are consistent with certain diseases.

Psoriasis frequently affects the scalp, extensor surfaces of the elbows and knees, umbilicus, and the gluteal cleft.

Lichen planus frequently arises on the wrists, forearms, genitals, and lower legs.

Vitiligo may be patchy and isolated or may group around the distal extremities and face.

Chronic cutaneous lupus erythematosus has characteristic lesions on sun-exposed skin of the face, especially the forehead, nose, and the conchal bowl of the ear.

Hidradenitis suppurativa involves skin containing a high density of apocrine glands, including the axillae, groin, and under the breasts.

Color

Red skin (erythema) can result from many different inflammatory or infectious diseases. Cutaneous tumors are often pink or red. Superficial vascular lesions such as port-wine stains may appear red.

Orange skin is most often seen in hypercarotenemia, a usually benign condition of carotene deposition after excess dietary ingestion of β-carotene.

Yellow skin is typical of jaundice, xanthelasmas and xanthomas, and pseudoxanthoma elasticum.

Green fingernails suggest *Pseudomonas aeruginosa* infection.

Violet skin may result from cutaneous hemorrhage or vasculitis. Vascular lesions or tumors, such as Kaposi's sarcoma and hemangiomas, can appear purple. A lilac color of the eyelids or heliotrope eruption is characteristic of dermatomyositis.

Shades of blue, silver, and gray can result from deposition of drugs or metals in the skin, including minocycline, amiodarone, and silver (argyria). Ischemic skin appears purple to gray in color. Deep dermal nevi appear blue.

Black skin lesions may be melanocytic, including nevi and melanoma. Black eschars are collections of dead skin that can arise from vascular infarction, which may be caused by infection (eg, anthrax, angioinvasive fungi including *Rhizopus*, meningococcemia), calciphylaxis, arterial insufficiency, or vasculitis.

Other Clinical Signs

Dermatographism is the appearance of an urticarial wheal after focal pressure (eg, stroking or scratching the skin) in the distribution of the pressure. Up to 5% of normal patients may exhibit this sign, which is a form of physical urticaria.

Darier's sign refers to rapid swelling of a lesion when stroked. It occurs in patients with urticaria pigmentosa or mastocytosis.

Nikolsky's sign is epidermal shearing that occurs with gentle lateral pressure on seemingly uninvolved skin in patients with toxic epidermal necrolysis and some autoimmune bullous diseases.

Auspitz sign is the appearance of pinpoint bleeding after scale is removed from plaques in psoriasis.

Koebner phenomenon describes the development of lesions within areas of trauma (eg, caused by scratching, rubbing, injury). Psoriasis frequently exhibits this phenomenon, as may lichen planus.

Diagnostic Tests

Diagnostic tests are indicated when the cause of a skin lesion or disease is not obvious from history and physical examination alone (for patch testing, see p. 667).

Biopsy: A skin biopsy can be done by a primary care physician. One procedure is a punch biopsy, in which a tubular punch (diameter usually 4 mm) is inserted into deep dermal or subcutaneous tissue to obtain a specimen, which is snipped off at its base. More superficial lesions may be biopsied by shaving with a scalpel or razor blade. Bleeding is controlled by aluminum chloride solution or electrodesiccation; large incisions are closed by sutures. Larger or deeper biopsies can be done by excising a wedge of skin with a scalpel. All pigmented lesions should be excised deeply for histologic evaluation of depth; superficial biopsies are often inadequate. Diagnosis and cure are achieved simultaneously for most small tumors by complete excision that includes a small border of normal skin.

Scrapings: Skin scrapings help diagnose fungal infections and scabies. For fungal infection, scales are taken from the border of the lesion and placed onto a microscope slide. Then a drop of 10 to 20% potassium hydroxide (KOH) is added. Hyphae, budding yeast, or both confirm the diagnosis of tinea or candidiasis. For scabies, scrapings are taken from suspected burrows and placed directly under a coverslip with mineral oil; findings of mites, feces, or eggs confirm the diagnosis.

Wood's light: Wood's light (black light) can help distinguish hypopigmentation from depigmentation (depigmentation of vitiligo fluoresces ivory-white and hypopigmented lesions do not). Erythrasma fluoresces bright orangered. Tinea capitis caused by *Microsporum canis* and *Microsporum audouinii* fluoresces a light, bright green. (NOTE: Most tinea capitis in the US is caused by *Trichophyton* species, which do not fluoresce.) The earliest clue to cutaneous *Pseudomonas* infection (eg, in burns) may be green fluorescence.

Tzanck testing: Tzanck testing can be used to diagnose viral disease, such as herpes simplex and herpes zoster, and is done when active intact vesicles are present. Tzanck testing cannot distinguish between herpes simplex and herpes zoster infections. An intact blister is the preferred lesion for examination. The blister roof is removed with a sharp blade, and the base of the unroofed vesicle is scraped with a #15 scalpel blade. The scrapings are transferred to a slide and stained with Wright's stain or Giemsa stain. Multinucleated giant cells are a sign of herpes infection.

Diascopy: Diascopy is used to determine whether a lesion is vascular (inflammatory) or nonvascular (nevus) or hemorrhagic (petechia or purpura). A microscope slide is pressed against a lesion to see whether it blanches. Hemorrhagic lesions and nonvascular lesions do not blanch; inflammatory lesions do. Diascopy is sometimes used to identify sarcoid skin lesions, which, when tested, turn an apple jelly color.

Itching

(Pruritus)

Itching is a symptom that can cause significant discomfort and is one of the most common reasons for consultation with a dermatologist. Itching leads to scratching, which can cause inflammation, skin degradation, and possible secondary infection. The skin can become lichenified, scaly, and excoriated.

Pathophysiology

Itch can be prompted by diverse stimuli, including light touch, vibration, and wool fibers. There are a number of chemical mediators as well as different mechanisms by which the sensation of itch occurs.

Mediators: Histamine is one of the most significant mediators. It is synthesized and stored in mast cells in the skin and is released in response to various stimuli. Other mediators (eg, neuropeptides) can either cause the release of histamine or act as pruritogens themselves, thus explaining why antihistamines ameliorate some cases of itching and not others. Opioids have a central pruritic action as well as

stimulating the peripherally mediated histamine itch.

Mechanisms: There are 4 mechanisms of itch:

• Dermatologic—typically caused by inflammatory or pathologic processes (eg, urticaria, eczema)

• Systemic—related to diseases of organs other than skin (eg, cholestasis)

• Neuropathic—related to disorders of the CNS or peripheral nervous system (eg, multiple sclerosis)

• Psychogenic—related to psychiatric conditions

Intense itching stimulates vigorous scratching, which in turn can cause secondary skin conditions (eg, inflammation, excoriation, infection), which can lead to more itching. However, scratch can temporarily reduce the sensation of itch by activating inhibitory neuronal circuits.

Etiology

Itching can be a symptom of a primary skin disease or, less commonly, a systemic disease (see Table 71-1).

[**Table 71-1.** Some Causes of Itching]

Skin disorders: Many skin disorders cause itching. The most common include

• Dry skin

• Atopic dermatitis (eczema)

• Contact dermatitis

• Fungal skin infections

Systemic disorders: In systemic disorders, itching may occur with or without skin lesions. However, when itching is prominent without any identifiable skin lesions, systemic disorders and drugs should be considered more strongly. Systemic disorders are less often a cause of itching than skin disorders, but some of the more common causes include

• Allergic reaction (eg, to foods, drugs, bites and stings)

• Cholestasis

• Chronic renal failure

Less common systemic causes of itching include hyperthyroidism, hypothyroidism, diabetes, iron deficiency, dermatitis herpetiformis, and polycythemia vera.

Drugs: Drugs can cause itching as an allergic reaction or by directly triggering histamine release (most commonly morphine, some IV contrast agents).

Evaluation

History: History of present illness should determine onset of itching, initial location, course, duration, patterns of itching (eg, nocturnal or diurnal, intermittent or persistent, seasonal variation), and whether any rash is present. A careful drug history should be obtained; both oral (eg, opioids, cocaine, aspirin, prescription and OTC) and topical (eg, hydrocortisone, benadryl, moisturizers) drugs are included. History also should include any factors that make the itching better or worse.

Review of systems should seek symptoms of causative disorders, including steatorrhea and right upper quadrant pain (cholestasis); constitutional symptoms of fever, weight loss, and night sweats (cancer); intermittent weakness, numbness, tingling, and visual disturbances or loss (multiple sclerosis); irritability, sweating, weight loss, and palpitations (hyperthyroidism) or depression, dry skin, and weight gain (hypothyroidism); urinary frequency, excessive thirst, and weight loss (diabetes); and headache, pica, hair thinning, and exercise intolerance (iron deficiency anemia).

Past medical history should identify known causative disorders (eg, renal disease, cholestatic disorder, cancer being treated with chemotherapy) and the patient's emotional state. Social history should focus on family members with similar itching and skin symptoms (eg, scabies, pediculosis); relationship of itching to occupation or exposures to plants, animals, or chemicals; and history of recent travel.

Physical examination: Physical examination begins with a review of clinical appearance for signs of jaundice, weight loss or gain, and fatigue. Close examination of the skin should be done, taking note of presence, morphology, extent, and distribution of lesions. Cutaneous examination also should make note of signs of secondary infection (eg, erythema, swelling, warmth, yellow or honey-colored crusting).

The examination should make note of significant adenopathy suggestive of cancer. Abdominal examination should focus on organomegaly, masses, and tenderness (cholestatic disorder or cancer). Neurologic examination focuses on weakness, spasticity, or numbness (multiple sclerosis).

Red flags: The following findings are of particular concern:

• Constitutional symptoms of weight loss, fatigue, and night sweats

• Extremity weakness, numbness, or tingling

• Abdominal pain and jaundice

• Urinary frequency, excessive thirst, and weight loss

Interpretation of findings: Generalized itching that begins shortly after use of a drug is likely caused by that drug. Localized itching (often with rash) that occurs in the area of contact with a substance is likely caused by that substance. However, many systemic allergies can be difficult to identify because patients typically have consumed multiple different foods and have been in contact with many substances before developing itching. Similarly, identifying a drug cause in a patient taking several drugs may be difficult. Sometimes the patient has been taking the offending drug for months or even years before developing a reaction.

If an etiology is not immediately obvious, the appearance and location of skin lesions can suggest a diagnosis (see Table 71-1).

In the minority of patients in whom no skin lesions are evident, a systemic disorder should be considered. Some disorders that cause itching are readily apparent on evaluation (eg, chronic renal failure, cholestatic jaundice). Other systemic disorders that cause itching are suggested by findings (see Table 71-1). Rarely, itching is the first manifestation of significant systemic disorders (eg, polycythemia vera, certain cancers, hyperthyroidism).

Testing: Many dermatologic disorders are diagnosed clinically. However, when itching is accompanied by discrete skin lesions of uncertain etiology, biopsy can be appropriate. When an allergic reaction is suspected but the substance is unknown, skin testing (either prick or patch testing depending on suspected etiology) is often done. When a systemic disorder is suspected, testing is directed by the suspected cause and usually involves CBC; liver, renal, and thyroid function measurements; and appropriate evaluation for underlying cancer.

Treatment

Any underlying disorder is treated. Supportive treatment involves the following (see also

Table 71-2):

• Local skin care

• Topical treatment

• Systemic treatment

Skin care: Itching due to any cause benefits from use of cool or lukewarm (but not hot) water when bathing, mild or moisturizing soap, limited bathing duration and frequency, frequent lubrication, humidification of dry air, and avoidance of irritating or tight clothing. Avoidance of contact irritants (eg, wool clothing) also may be helpful.

Topical drugs: Topical drugs may help localized itching. Options include lotions or creams that contain camphor and/or menthol, pramoxine, or corticosteroids. Corticosteroids are effective in relieving itch caused by inflammation but should be avoided for conditions that have no evidence of inflammation. Topical diphenhydramine and doxepin should be avoided because they may sensitize the skin.

Systemic drugs: Systemic drugs are indicated for generalized itching or local itching resistant to topical agents. Antihistamines, most notably hydroxyzine, are effective, especially for nocturnal itch, and are most commonly used. Sedating antihistamines must be used cautiously in elderly patients during the day because they can lead to falls; newer nonsedating antihistamines such as loratadine, fexofenadine, and cetirizine can be useful for daytime itching. Other drugs include doxepin (typically taken at night due to high level of sedation), cholestyramine (for renal failure, cholestasis, polycythemia vera), opioid antagonists such as naltrexone (for biliary pruritus), and possibly gabapentin (for uremic pruritus).

Physical agents that may be effective for itching include ultraviolet phototherapy.

Geriatrics Essentials

Xerotic eczema is very common among elderly patients. It is especially likely if itching is primarily on the lower extremities.

Severe, diffuse itching in the elderly should raise concern for cancer, especially if another etiology is not immediately apparent.

When treating the elderly, sedation can be a significant problem with antihistamines. Use of nonsedating antihistamines during the day and sedating antihistamines at night, liberal use of topical ointments and corticosteroids (when appropriate), and consideration of ultraviolet phototherapy can help avoid the complications of sedation.

Key Points

• Itching is usually a symptom of a skin disorder or systemic allergic reaction but can result from a systemic disorder.

• If skin lesions are not evident, systemic causes should be investigated.

• Skin care (eg, limiting bathing, avoiding irritants, moisturizing regularly, humidifying environment) should be observed.

• Symptoms can be relieved by topical or systemic drugs.

Urticaria

(Hives; Wheals)

Urticaria is migratory, well-circumscribed, erythematous, pruritic plaques on the skin (see Plate 53).

Urticaria also may be accompanied by angioedema, which results from mast cell and basophil activation in the deeper dermis and subcutaneous tissues and manifests as edema of the face and lips, extremities, or genitals. Angioedema can be life-threatening if airway obstruction occurs because of laryngeal edema or tongue swelling.

Pathophysiology

Urticaria results from the release of histamine, bradykinin, kallikrein, and other vasoactive substances from mast cells and basophils in the superficial dermis, resulting in intradermal edema caused by capillary and venous vasodilation and occasionally caused by leukocyte infiltration.

The process can be immune mediated or nonimmune mediated.

Immune-mediated mast cell activation includes

- Type I hypersensitivity reactions, in which allergen-bound IgE antibodies bind to high-affinity cell surface receptors on mast cells and basophils

- Autoimmune disorders, in which antibodies to an IgE receptor functionally cross-link IgE receptors and cause mast cell degranulation

Nonimmune-mediated mast cell activation includes

- Direct nonallergic activation of mast cells by certain drugs

- Drug-induced cyclooxygenase inhibition that activates mast cells by poorly understood mechanisms

[**Table 71-2.** Some Therapeutic Approaches to Itching]

- Activation by physical or emotional stimuli; mechanism is poorly understood but possibly involves the release of neuropeptides that interact with mast cells

Etiology

Urticaria is classified as acute (< 6 wk) or chronic (> 6 wk); acute cases (70%) are more common than chronic (30%).

Acute urticaria (see Table 71-3) most often results from

- Type I hypersensitivity reactions

A presumptive trigger (eg, drug, food ingestion, insect sting, infection) occasionally can be identified.

Chronic urticaria most often results from

- Idiopathic causes

- Autoimmune disorders

Chronic urticaria often lasts months to years, eventually resolving without a cause being found.

Evaluation

Because there are no definitive diagnostic tests for urticaria, evaluation largely relies on history and physical examination.

History: History of present illness should include a detailed account of the individual episodes of urticaria, including distribution, size, and appearance of lesions; frequency of occurrence; duration of individual lesions; and any prior episodes. Activities and exposures during, immediately before, and within the past 24 h of the appearance of urticaria should be noted. Clinicians specifically should ask about recent exercise; exposure to potential allergens (see Table 71-3), insects, or animals; new laundry detergent or soaps; new foods; recent infections; or recent stressful life events. The patient should be asked about the duration between any suspected trigger and the appearance of urticaria and which particular triggers are suspected. Important associated symptoms include pruritus, rhinorrhea, swelling of the face and tongue, and dyspnea.

Review of systems should seek symptoms of causative disorders, including fever, fatigue, abdominal pain, and diarrhea (infection); heat or cold intolerance, tremor, or weight change (autoimmune thyroiditis); joint pain (cryoglobulinemia, SLE); malar rash (SLE); dry eyes and dry mouth (Sjogren's syndrome); cutaneous ulcers and hyperpigmented lesions after resolution of urticaria (urticarial vasculitis); small pigmented papules (mastocytosis); lymphadenopathy (viral illness, cancer, serum sickness); acute or chronic diarrhea (viral or parasitic enterocolitis); and fevers, night sweats, or weight loss (cancer).

Past medical history should include a detailed allergy history, including known atopic conditions (eg, allergies, asthma, eczema) and known possible causes (eg, autoimmune disorders, cancer). All drug use should be reviewed, including OTC drugs and herbal products, specifically any agents particularly associated with urticaria (see Table 71-3). Family history should elicit any history of rheumatoid disease, autoimmune disorders, or cancer. Social history should cover any recent travel and any risk factors for transmission of infectious disease (eg, hepatitis, HIV).

Physical examination: Vital signs should note the presence of bradycardia or tachycardia and tachypnea. General examination should immediately seek any signs of respiratory distress and also note cachexia, jaundice, or agitation.

Examination of the head should note any swelling of the face, lips, or tongue; scleral icterus; malar rash; tender and enlarged thyroid; lymphadenopathy; or dry eyes and dry mouth. The oropharynx should be inspected and the sinuses should be palpated and transilluminated for signs of occult infection (eg, sinus infection, tooth abscess).

Abdominal examination should note any masses, hepatomegaly, splenomegaly, or tenderness. Neurologic examination should note any tremor or hyperreflexia or hyporeflexia. Musculoskeletal examination should note the presence of any inflamed or deformed joints.

Skin examination should note the presence and distribution of urticarial lesions as well as any cutaneous ulceration, hyperpigmentation, small papules, or jaundice. Urticarial lesions usually appear as well-demarcated transient swellings involving the dermis. These swellings are typically red and vary in size from pinprick to covering wide areas. Some lesions can be very large. In other cases, smaller urticarial lesions may become confluent. However, skin lesions also may be absent at the time of the visit. Maneuvers to evoke physical urticaria can be done during the examination, including exposure to vibration (tuning fork), warmth (tuning fork held under warm water), cold (stethoscope or chilled tuning fork), water, or pressure (lightly scratching an unaffected area with a fingernail).

Red flags: The following findings are of particular concern:

• Angioedema (swelling of the face, lips, or tongue)

[**Table 71-3.** Some Causes of Urticaria]

• Stridor, wheezing, or other respiratory distress

• Hyperpigmented lesions, ulcers, or urticaria that persist > 48 h

• Signs of systemic illness (eg, fever, lymphadenopathy, jaundice, cachexia)

Interpretation of findings: Acute urticaria is nearly always due to some defined exposure to a drug or physical stimulus or an acute infectious illness. However, the trigger is not always clear from the history, particularly because allergy may develop without warning to a previously tolerated substance.

Most **chronic urticaria** is idiopathic. The next most common cause is an autoimmune disorder. The causative autoimmune disorder is sometimes clinically apparent. Urticarial vasculitis sometimes is associated with connective tissue disorders (particularly SLE or Sjogren's syndrome). In urticarial vasculitis, urticaria is accompanied by findings of cutaneous vasculitis; it should be considered when the urticaria are painful rather than pruritic, last > 48 h, do not blanch, or are accompanied by vesicles or purpura.

Testing: Usually, no testing is needed for an isolated episode of urticaria unless symptoms and signs suggest a specific disorder (eg, infection).

Unusual, recurrent, or persistent cases warrant further evaluation. Referral for allergy skin testing should be done, and routine laboratory tests should consist of CBC, blood chemistries, liver function tests, and thyroid-stimulating hormone (TSH). Further testing should be guided by symptoms and signs (eg, of autoimmune disorders) and any abnormalities on the screening tests (eg, hepatitis serologies and ultrasonography for abnormal liver function tests; ova and parasites for eosinophilia; cryoglobulin titer for elevated liver function tests or elevated creatinine; thyroid autoantibodies for abnormal TSH).

Skin biopsy should be done if there is any uncertainty as to the diagnosis or if wheals persist > 48 h (to rule out urticarial vasculitis).

Clinicians should not recommend the patient do an empiric challenge (eg, "Try such and such again and see whether you get a reaction") because subsequent reactions may be more severe.

Treatment

Any identified causes are treated or remedied. Implicated drugs or foods should be stopped.

Nonspecific symptomatic treatment (eg, taking cool baths, avoiding hot water and scratching, and wearing loose clothing) may be helpful.

Drugs: Antihistamines remain the mainstay of treatment. They must be taken on a regular basis, rather than as needed. Newer oral antihistamines often are preferred because of once-daily dosing and because some are less sedating. Appropriate choices include

• Cetirizine 10 mg once/day

• Fexofenadine 180 mg once/day

• Desloratadine 5 mg once/day

• Levocetirizine 5 mg once/day

Older oral antihistamines (eg, hydroxyzine 10 to 25 mg q 4 to 6 h; diphenhydramine 25 to 50 mg q 6 h) are sedating but inexpensive and also quite effective.

Systemic corticosteroids (eg, prednisone 30 to 40 mg po once/day) are given for severe symptoms but should not be used long term. Topical corticosteroids or antihistamines are not beneficial.

Angioedema: Patients who have angioedema involving the oropharynx or any involvement of the airway should receive epinephrine 0.3 mL of 1:1000 solution sc and be admitted to the hospital. On discharge, patients should be supplied with and trained in the use of an auto-injectable epinephrine pen.

Geriatrics Essentials

The older oral antihistamines (eg, hydroxyzine, diphenhydramine) are sedating and can cause confusion, urinary retention, and delirium. They should be used cautiously to treat urticaria in elderly patients.

Key Points

• Urticaria can be caused by allergic or nonallergic mechanisms.

• Most acute cases are caused by an allergic reaction to a specific substance.

• Most chronic cases are idiopathic or result from autoimmune disease.

• Treatment is based on severity; nonsedating antihistamines and avoidance of triggers are first-line options.

• Topical corticosteroids and antihistamines are not beneficial.

• Concomitant systemic symptoms require a thorough evaluation for the etiology.

Skin Manifestations of Internal Disease

The skin frequently serves as a marker for underlying internal disease. The type of lesion typically relates to a specific disease or type of disease.

Internal cancer: Of patients with dermatomyositis, about 50% have associated breast, lung, ovarian, and GI cancers.

Acute onset of multiple seborrheic keratoses (Leser-Trelat sign) may indicate underlying internal cancer, particularly adenocarcinoma. However, because of the high prevalence of seborrheic keratoses in healthy adults, this sign may be overdiagnosed.

Acute febrile neutrophilic dermatosis is associated with hematologic cancer.

Acanthosis nigricans (see Plate 24) that is associated with cancer can be of rapid onset and particularly widespread. Pruritus without a clearly associated dermatitis may indicate occult cancer, often lymphoma.

Paraneoplastic pemphigus is a relatively rare autoimmune blistering disease that has been associated with various cancers, including leukemias.

The carcinoid syndrome (flushing and erythema of the neck) is associated with carcinoid tumor.

Erythema gyratum repens is a rare eruption consisting of concentric erythematous lesions, resembling wood grain, which has been associated with various cancers.

Endocrinopathies: Many skin findings are associated with endocrinopathies but are not specific.

Patients with diabetes mellitus may have acanthosis nigricans, necrobiosis lipoidica, perforating disorders, and scleredema adultorum.

Thyroid disease, both hypothyroidism and hyperthyroidism, can affect hair, nails, and skin.

Cushing's disease causes striae distensae, moon facies, and skin fragility.

Addison's disease is characterized by hyperpigmentation that is accentuated in skin creases and areas of trauma.

GI disorders: Skin conditions commonly associated with GI disorders include

- Pyoderma gangrenosum: Inflammatory bowel disease
- Lichen planus and porphyria cutanea tarda: Hepatitis C infection
- Diffuse hyperpigmentation, or bronze diabetes: Hemochromatosis
- Erythema nodosum: Inflammatory bowel disease, sarcoidosis, and various infections
- Eruptive xanthomas: Elevated serum triglycerides

Chapter 72. Principles of Topical Dermatologic Therapy

Introduction

Topical dermatologic treatments include

• Cleansing agents

• Absorbents

• Anti-infective agents

• Anti-inflammatory agents

• Astringents (drying agents that precipitate protein and shrink and contract the skin)

• Emollients (skin hydrators and softeners)

• Keratolytics (agents that soften, loosen, and facilitate exfoliation of the squamous cells of the epidermis)

Vehicles

Topical therapies can be delivered in various vehicles, which include

• Powders

• Liquids

• Combinations of liquid and oil

The vehicle influences a therapy's effectiveness and may itself cause adverse effects (eg, contact or irritant dermatitis). Generally, aqueous preparations are drying (because the liquid evaporates) and are used in acute inflammatory conditions. Oil-based preparations are moisturizing and are preferred for chronic inflammation.

Powders: Inert powders may be mixed with active agents (eg, antifungals) to deliver therapy. They are prescribed for lesions in moist or intertriginous areas.

Liquids: Liquid vehicles include

• Baths and soaks

• Solutions

• Lotions

• Gels

Baths and soaks are used when therapy must be applied to large areas, such as with extensive contact dermatitis or atopic dermatitis.

Solutions are ingredients dissolved in a solvent, usually ethyl alcohol, propylene glycol, polyethylene glycol, or water. Solutions are convenient to apply (especially to the scalp for disorders such as psoriasis or seborrhea) but tend to be drying. Two common solutions are Burow's solution and Domeboro's solution.

Lotions are water-based emulsions. They are easily applied to hairy skin. Lotions cool and dry acute inflammatory and exudative lesions, such as contact dermatitis, tinea pedis, and tinea cruris.

Gels are ingredients suspended in a solvent thickened with polymers. Gels are often more effective for controlled release of topical agents. They are often used in acne, rosacea, and psoriasis of the scalp.

Combination vehicles: Combinations include

• Creams

• Ointments

Combination vehicles usually contain oil and water but may also contain propylene or polyethylene glycol.

Creams are semi-solid emulsions of oil and water. They are used for moisturizing and cooling and when exudation is present. They vanish when rubbed into skin.

Ointments are oil based (eg, petrolatum) with little if any water. Ointments are optimal lubricants and increase drug penetration because of their occlusive nature; a given concentration of drug is generally more potent in an ointment. They are preferred for lichenified lesions and lesions with thick crusts or heaped-up scales, including psoriasis and lichen simplex chronicus. Ointments are less irritating than creams for erosions or ulcers.

Dressings

Dressings protect open lesions, facilitate healing, increase drug absorption, and protect the patient's clothing.

Nonocclusive dressings: The most common are gauze dressings. They maximally allow air to reach the wound, which is often preferred in healing, and allow the lesion to dry. Nonocclusive dressings wetted with solution, usually saline, are used to help cleanse and debride thickened or crusted lesions. The dressings are applied wet and removed after the solution has evaporated (wet-to-dry dressings); materials from the skin then adhere to the dressing.

Occlusive dressings: Occlusive dressings increase the absorption and effectiveness of topical therapy. Most common are transparent films such as polyethylene (plastic household wrap) or flexible, transparent, semi-permeable dressings. Hydrocolloid dressings can be applied with a gauze cover in patients with cutaneous ulceration. Zinc oxide gelatin (Unna's paste boot) is an effective occlusive dressing for patients with stasis dermatitis and ulcers. Plastic tape impregnated with flurandrenolide, a corticosteroid, can be used for isolated or recalcitrant lesions.

Occlusive dressings applied over topical corticosteroids to increase absorption are sometimes used to treat psoriasis, atopic dermatitis, skin lesions of lupus erythematosus, and chronic hand dermatitis, among other conditions. Systemic absorption of topical corticosteroids may occur and cause

• Development of miliaria

• Skin atrophy

• Striae

• Bacterial or fungal infections

• Adrenal suppression

• Acneiform eruptions

Other occlusive dressings are used to protect and help heal open wounds, such as burns (see p. 3242).

Categories and Indications

Major categories of topical agents include

• Cleansing

• Moisturizing

• Drying

• Anti-inflammatory

• Antimicrobial

• Keratolytic

• Astringent

• Antipruritic

Cleansing agents: The principal cleansing agents are soaps, detergents, and solvents. Soap is the most popular cleanser, but synthetic detergents are also used. Baby shampoos are usually well tolerated around the eyes and for cleansing wounds and abrasions; they are useful for removing crusts and scales in psoriasis, eczema, and other forms of dermatitis. However, acutely irritated, weeping, or oozing lesions are most comfortably cleansed with water or isotonic saline.

Water is the principal solvent for cleansing. Organic solvents (eg, acetone, petroleum products, propylene glycol) are very drying, can be irritating, and cause irritant or, less commonly, allergic contact dermatitis. Removal of hardened tar and dried paint from the skin may require a petrolatum-based ointment or commercial waterless cleanser.

Moisturizing agents: Moisturizers (emollients) restore water and oils to the skin and help to maintain skin hydration. They typically contain glycerin, mineral oil, or petrolatum and are available as lotions, creams, ointments, and bath oils. Stronger moisturizers contain urea 2%, lactic acid 5 to 12%, and glycolic acid 10% (higher concentrations are used as keratinolytics, eg, for ichthyosis). They are most effective when applied to already moistened skin (ie, after a bath or shower).

Drying agents: Excessive moisture in intertriginous areas (eg, between the toes; in the intergluteal cleft, axillae, groin, and inframammary areas) can cause irritation and maceration. Powders dry macerated skin and reduce friction by absorbing moisture. However, some powders tend to clump and can be irritating if they become moist. Cornstarch and talc are most often used. Although talc is more effective, talc may cause granulomas if inhaled and is no longer used in baby powders. Cornstarch may promote fungal growth. Aluminum chloride solutions are another type of drying agent (often useful in hyperhidrosis).

Anti-inflammatory agents: Topical anti-inflammatory agents are either corticosteroids or noncorticosteroids.

Corticosteroids are the mainstay of treatment for most noninfectious inflammatory dermatoses. Lotions are useful on intertriginous areas and the face. Gels are useful on the scalp and in management of contact dermatitis. Creams are useful on the face and in intertriginous areas and for management of inflammatory dermatoses. Ointments are useful for dry scaly areas and when increased potency is required. Corticosteroid-impregnated tape is useful to protect an area from excoriation. It also increases corticosteroid absorption and therefore potency.

Topical corticosteroids range in potency from mild (class VII) to superpotent (class I—see Table 72-1). Intrinsic differences in potency are attributable to fluorination or chlorination (halogenation) of the compound.

Topical corticosteroids are generally applied 2 to 3 times daily, but high-potency formulations may require

application only once/day or even less frequently. Most dermatoses are treated with mid-potency to high-potency formulations; mild formulations are better for mild inflammation and for use on the face or intertriginous areas, where systemic absorption is more likely. All agents can cause skin atrophy, striae, and acneiform eruptions when used for > 1 mo. This effect is particularly problematic on the thinner skin of the face or genitals. Corticosteroids also promote fungal growth. Contact dermatitis in reaction to preservatives and additives is also common with prolonged use. Contact dermatitis to the corticosteroid itself may also occur. Perioral dermatitis occurs with mid-potency or high-potency formulations used on the face but is uncommon with mild formulations. High-potency formulations may cause adrenal suppression when used in children, over extensive skin surfaces, or for long periods. Relative contraindications include conditions in which infection plays an underlying role and acneiform disorders.

Noncorticosteroid anti-inflammatory agents include tar preparations. Tar comes in the form of crude coal tar and is indicated for psoriasis. Adverse effects include irritation, folliculitis, staining of clothes and furniture, and photosensitization. Contraindications include infected skin. Several herbal products are commonly used in commercial products, although their effectiveness has not been well established. Among the most popular are chamomile and calendula.

Antimicrobials: Topical antimicrobials include

• Antibiotics

• Antifungals

• Insecticides

• Nonspecific antiseptic agents

Antibiotics have few indications. Topical clindamycin and erythromycin are used as primary or adjunctive treatment for acne vulgaris in patients who do not warrant or tolerate oral antibiotics. Mupirocin has excellent gram-positive (*Staphylococcus aureus*, streptococci) coverage and can be used to treat impetigo when deep tissues are not affected. OTC antibiotics such as bacitracin and polymyxin are often used in postoperative care of a skin biopsy site and to prevent infection in scrapes, minor burns, and excoriations. Topical neomycin causes contact dermatitis more frequently than other antibiotics. The use of topical antibiotics and washing with antiseptic soaps in healing wounds may, however, actually slow healing.

Antifungals are used to treat candidiasis, a wide variety of dermatophytoses, and other fungal infections (see
Table 82-1 on p. 704).

Insecticides (eg, permethrin, malathion) are used treat lice infestation and scabies (see
Table 83-1 on p. 712).

Nonspecific antiseptic agents include iodine solutions (eg, povidone iodine, clioquinol), gentian violet, silver preparations (eg, silver nitrate, silver sulfadiazine), and zinc pyrithione. Iodine is indicated for presurgical skin preparation. Gentian violet is used when an inexpensive chemically and physically stable antiseptic/antimicrobial is needed. Silver preparations are effective in treating burns and ulcers and have strong antimicrobial

[**Table 72-1.** Relative Potency of Selected Topical Corticosteroids]

properties; several wound dressings are impregnated with silver. Zinc pyrithione is an antifungal and a common ingredient in shampoos used to treat dandruff due to psoriasis or seborrheic dermatitis. Healing wounds should generally not be treated with topical antiseptics other than silver because they are irritating and tend to kill fragile granulation tissue.

Keratolytics: Keratolytics soften and facilitate exfoliation of epidermal cells. Examples include 3 to 6% salicylic acid and urea. Salicylic acid is used to treat psoriasis, seborrhea, acne, and warts. Adverse

effects are burning and systemic toxicity if large areas are covered. It should rarely be used in children and infants. Urea is used to treat plantar keratodermas and ichthyosis. Adverse effects are irritation and intractable burning. It should not be applied to large areas.

Astringents: Astringents are drying agents that precipitate protein and shrink and contract the skin. The most commonly used astringents are aluminum acetate (Burow's solution) and aluminum sulfate plus Ca acetate (Domeboro's solution). Usually applied with dressings or as soaks, astringents are used to treat infectious eczema, exudative skin lesions, and pressure ulcers. Witch hazel is a popular OTC astringent.

Antipruritics: Doxepin is a topical antihistamine that is effective in treating itching of atopic dermatitis, lichen simplex chronic dermatitis, and nummular dermatitis. Topical benzocaine and diphenhydramine (present in certain OTC lotions) are sensitizing and not recommended. Other antipruritics include camphor 0.5 to 3%, menthol 0.1 to 0.2%, pramoxine hydrochloride, and eutectic mixture of local anesthetics (EMLA), which contain equal parts lidocaine and prilocaine in an oil-in-water vehicle. Topical antipruritics are preferred over systemic drugs (eg, oral antihistamines) when smaller surface areas of skin are affected and pruritus is not intractable. Calamine lotion is soothing but not specifically antipruritic.

Chapter 73. Acne and Related Disorders

Introduction

Acne vulgaris is a common skin problem, affecting most adolescents and many adults. Perioral dermatitis and rosacea can produce similar lesions.

Acne Vulgaris

Acne vulgaris (acne) is the formation of comedones, papules, pustules, nodules, and/or cysts as a result of obstruction and inflammation of pilosebaceous units (hair follicles and their accompanying sebaceous gland). It most often affects adolescents. Diagnosis is by examination. Treatment is a variety of topical and systemic agents intended to reduce sebum production, infection, and inflammation and to normalize keratinization.

Pathophysiology

Acne occurs when pilosebaceous units become obstructed with plugs of sebum and desquamated keratinocytes, then colonized and sometimes infected with the normal skin anaerobe *Propionibacterium acnes*. Manifestations differ depending on whether *P. acnes* stimulates inflammation in the follicle; acne can be noninflammatory or inflammatory.

Comedones, uninfected sebaceous plugs impacted within follicles, are the signature of noninflammatory acne. Comedones are termed open or closed depending on whether the follicle is dilated or closed at the skin surface. Inflammatory acne comprises papules, pustules, nodules, and cysts.

Papules appear when lipases from *P. acnes* metabolize triglycerides into free fatty acids (FFA), which irritate the follicular wall. Pustules occur when active *P. acnes* infection causes inflammation within the follicle. Nodules and cysts occur when rupture of follicles due to inflammation, physical manipulation, or harsh scrubbing releases FFAs, bacteria, and keratin into tissues, triggering soft-tissue inflammation.

Etiology

The most common trigger is puberty, when surges in androgen stimulate sebum production and hyperproliferation of keratinocytes. Other triggers include hormonal changes that occur with pregnancy or throughout the menstrual cycle; occlusive cosmetics, cleansing agents, and clothing; and humidity and sweating. Associations between acne exacerbation and diet (eg, chocolate), inadequate face washing, masturbation, and sex are unfounded. Some studies question an association with milk products. Acne may improve in summer months because of sunlight's anti-inflammatory effects. Proposed associations between acne and hyperinsulinism require further investigation.

Symptoms and Signs

Cystic acne can be painful; other types cause no physical symptoms but can be a source of significant emotional distress. Lesion types frequently coexist at different stages.

Comedones appear as whiteheads or blackheads. Whiteheads (closed comedones) are flesh-colored or whitish palpable lesions 1 to 3 mm in diameter; blackheads (open comedones) are similar in appearance but with a dark center.

Papules and pustules are red lesions 2 to 5 mm in diameter. In both, the follicular epithelium becomes damaged with accumulation of neutrophils and then lymphocytes. When the epithelium ruptures, the comedo contents elicit an intense inflammatory reaction in the dermis. Relatively deep inflammation produces papules. Pustules are more superficial.

Nodules are larger, deeper, and more solid than papules. Such lesions resemble inflamed epidermoid cysts, although they lack true cystic structure.

Cysts are suppurative nodules. Rarely cysts become infected and form abscesses. Long-term cystic acne can cause scarring that manifests as tiny, deep pits (icepick scars), larger pits, shallow depressions, or areas of hypertrophic scar.

Acne conglobata is the most severe form of acne vulgaris, affecting men more than women. Patients have abscesses, draining sinuses, fistulated comedones, and keloidal and atrophic scars. The back and chest are severely involved. The arms, abdomen, buttocks, and even the scalp may be affected.

Acne fulminans is acute, febrile, ulcerative acne, characterized by the sudden appearance of confluent abscesses leading to hemorrhagic necrosis. Leukocytosis and joint pain and swelling may also be present.

Pyoderma faciale (also called rosacea fulminans) occurs suddenly on the midface of young women. It may be analogous to acne fulminans. The eruption consists of erythematous plaques and pustules, involving the chin, cheeks, and forehead.

Diagnosis

• Assessment for contributing factors (eg, hormonal, mechanical, or drug-related)

• Determination of severity (mild, moderate, severe)

• Assessment of psychosocial impact

Diagnosis is by examination. Differential diagnosis includes rosacea (in which no comedones are seen), corticosteroid-induced acne (which lacks comedones and in which pustules are usually in the same stage of development), perioral dermatitis (usually with a more perioral and periorbital distribution), and acneiform drug eruptions. Acne severity is graded mild, moderate, or severe based on the number and type of lesions; a standardized system is outlined in
Table 73-1.

Prognosis

Acne of any severity usually remits spontaneously by the early to mid-20s, but a substantial minority of patients, usually women, may have acne into their 40s; options for treatment may be limited because of child-bearing. Many adults occasionally develop mild, isolated acne lesions. Noninflammatory and mild inflammatory acne usually heals without scars. Moderate to severe inflammatory acne heals but often leaves scarring. Scarring is not only physical; acne may be a huge emotional stressor for adolescents who may withdraw, using the acne as an excuse to avoid difficult personal adjustments. Supportive counseling for patients and parents may be indicated in severe cases.

Treatment

• Comedones: Topical tretinoin

• Mild inflammatory acne: Topical antibiotics, benzoyl peroxide, or both

• Moderate acne: Oral antibiotics

• Severe acne: Oral isotretinoin

• Cystic acne: Intralesional triamcinolone

Treatments are directed at reducing sebum production, comedone formation, inflammation, and infection (see
Fig. 73-1). Selection of

[**Table 73-1.** Classification of Acne Severity]

[**Fig. 73-1.** How various drugs work in treating acne.]

treatment is generally based on severity; options are summarized in Table 73-2. Affected areas should be cleansed daily, but extra washing, use of antibacterial soaps, and scrubbing confer no added benefit. Changes in diet are also unnecessary and ineffective, although moderation of milk intake might be considered for treatment-resistant adolescent acne. Peeling agents such as sulfur, salicylic acid, and resorcinol are minor therapeutic adjuncts.

Treatment should involve educating the patient and tailoring the plan to one that is realistic for the patient. Treatment failure can frequently be attributed to lack of adherence to the plan and also to lack of follow-up. Consultation with a specialist may be necessary.

Mild acne: Single-agent therapy is generally sufficient for comedonal acne; papulopustular acne generally requires dual therapy (eg, the combination of tretinoin with benzoyl peroxide or topical antibiotics). Treatment should be continued for 6 wk or until lesions respond. Maintenance treatment may be necessary to maintain control.

A mainstay of treatment for comedones is daily topical tretinoin as tolerated. Daily adapalene gel, tazarotene cream or gel, azelaic acid cream, and glycolic or salicylic acid in propylene glycol are alternatives for patients who cannot tolerate topical tretinoin. Adverse effects include erythema, burning, stinging, and peeling. Adapalene and tazarotene are retinoids; like tretinoin, they tend to be somewhat irritating and photosensitizing. Azelaic acid has comedolytic and antibacterial properties by an unrelated mechanism and may be synergistic with retinoids.

Mild inflammatory acne should be treated with topical benzoyl peroxide, topical antibiotics (eg, erythromycin, clindamycin), glyolic acid, or a combination. Combination preparations of these agents may help limit development of resistance. None have significant adverse effects other than drying and irritation (and rare allergic reactions to benzoyl peroxide). Topical retinoids are often used concomitantly.

Physical extraction of comedones using a comedo extractor is an option for patients unresponsive to topical treatment. Comedo extraction may be done by a physician, nurse, or physician assistant. One end of the comedo extractor is like a blade or bayonet that punctures the closed comedo. The other end exerts pressure to extract the comedo.

Oral antibiotics (eg, tetracycline, minocycline, doxycycline, erythromycin) can be used when wide distribution of lesions makes topical therapy impractical.

Moderate acne: Moderate acne responds best to oral systemic therapy with antibiotics. Antibiotics effective for acne include tetracycline, minocycline, erythromycin, and doxycycline. Full benefit takes ≥ 12 wk. Topical therapy as for mild acne is usually used concomitantly with oral antibiotics.

Tetracycline is usually a good first choice: 250 or 500 mg bid (between meals and at bedtime) for 4 wk or until lesions respond, after which it may be reduced to the lowest effective dose. Rarely, dosage must be increased to

[**Table 73-2.** Drugs Used to Treat Acne]

500 mg qid. After control is achieved, it is reasonable to attempt to taper and discontinue the oral antibiotic and continue topical therapy for control. Because relapse often follows short-term treatment, therapy may need to be continued for months to years, although for maintenance tetracycline 250 or 500 mg once/day is often sufficient. Minocycline 50 or 100 mg bid causes fewer GI adverse effects, is easier to take, and is less likely to cause photosensitization, but it is the most costly option. Erythromycin and doxycycline are considered 2nd-line drugs because both can cause GI adverse effects, and doxycycline is a frequent photosensitizer. Subantimicrobial doses of doxycycline have also been proven effective for acne and rosacea.

Long-term use of antibiotics may cause a gram-negative pustular folliculitis around the nose and in the center of the face. This uncommon superinfection may be difficult to clear and is best treated with oral isotretinoin after discontinuing the oral antibiotic. Ampicillin is an alternative treatment for gram-negative folliculitis. In women, prolonged antibiotic use can cause candidal vaginitis; if local and systemic therapy does not eradicate this problem, antibiotic therapy for acne must be stopped.

Severe acne: Oral isotretinoin is the best treatment for patients with moderate acne in whom antibiotics are unsuccessful and for those with severe inflammatory acne. Dosage of isotretinoin is usually 1 mg/kg once/day for 16 to 20 wk, but the dosage may be increased to 2 mg/kg once/day. If adverse effects make this dosage intolerable, it may be reduced to 0.5 mg/kg once/day. After therapy, acne may continue to improve. Most patients do not require a 2nd course of treatment; when needed, it should be resumed only after the drug has been stopped for 4 mo. Retreatment is required more often if the initial dosage is low (0.5 mg/kg). With this dosage (which is very popular in Europe), fewer adverse effects occur, but prolonged therapy is usually required.

Isotretinoin is nearly always effective, but use is limited by adverse effects, including dryness of conjunctivae and mucosae of the genitals, chapped lips, arthralgias, depression, elevated lipid levels, and the risk of birth defects if treatment occurs during pregnancy. Hydration with water followed by petrolatum application usually alleviates mucosal and cutaneous dryness. Arthralgias (mostly of large joints or the lower back) occur in about 15% of patients. Increased risk for depression and suicide is much publicized but probably rare. CBC; liver function; and fasting glucose, triglyceride, and cholesterol levels should be determined before treatment. Each should be reassessed at 4 wk and, unless abnormalities are noted, need not be repeated until the end of treatment. Triglycerides rarely increase to a level at which the drug should be stopped. Liver function is seldom affected. Because isotretinoin is teratogenic, women of childbearing age are urged to use 2 methods of contraception for 1 mo before treatment, during treatment, and for at least 1 mo after stopping treatment. Pregnancy tests should be done before beginning therapy and monthly until 1 mo after therapy stops.

Intralesional injection of 0.1 mL triamcinolone acetonide suspension 2.5 mg/mL (the 10 mg/mL suspension must be diluted) is indicated for patients with firm (cystic) acne who seek quick clinical improvement and to reduce scarring. Local atrophy may occur but is usually transient. For isolated, very boggy lesions, incision and drainage are often beneficial but may result in residual scarring.

Other forms of acne: Pyoderma faciale is treated with oral corticosteroids and isotretinoin. Acne fulminans is treated with oral corticosteroids and systemic antibiotics. Acne conglobata is treated with oral isotretinoin if systemic antibiotics fail. For acne with endocrine abnormalities, antiandrogens are indicated. Spironolactone, which has some antiandrogen effects, is sometimes prescribed to treat acne at a dose of 50 to 100 mg po once/day. Cyproterone acetate is used in Europe. When other measures fail, an estrogen-progesterone-containing contraceptive may be tried; therapy ≥ 6 mo is needed to evaluate effect.

Scarring: Small scars can be treated with chemical peels, laser resurfacing, or dermabrasion. Deeper, discrete scars can be excised. Wide, shallow depressions can be treated with subcision or collagen injection. Collagen implants are temporary and must be repeated every few years.

Perioral Dermatitis

Perioral dermatitis is an erythematous, papulopustular facial eruption that resembles acne and/or rosacea but typically starts around the mouth.

A variety of causes have been proposed, including exposure to topical corticosteroids and/or fluoride in water and toothpaste, but the etiology is unknown. Despite its name, perioral dermatitis is not a true dermatitis. It primarily affects women of childbearing age and children. The eruption classically starts at the nasolabial folds and spreads perioralally sparing a zone around the vermilion border of the lips. But the eruption can also spread periorbitally and to the forehead.

Diagnosis is by appearance; perioral dermatitis is distinguished from acne by the absence of comedones and from rosacea by the latter's lack of lesions around the mouth and eyes. Seborrheic dermatitis and

contact dermatitis must be excluded. Biopsy, which is generally not clinically necessary, shows spongiosis and a lymphohistiocytic infiltrate affecting vellus hair follicles. In the lupoid variant, granulomas may be present.

Treatment is to stop fluorinated dental products and topical corticosteroids (if being used) and then either use topical antibiotics (eg, erythromycin 2% or metronidazole 0.75% gel or cream bid), or oral tetracycline 250 to 500 mg po bid (between meals) for 4 wk, tapered to the lowest effective dose. Alternative oral antibiotics include doxycycline 50 to 100 mg bid and minocycline 50 to 100 mg bid. In contrast to acne, antibiotics can usually be stopped. Reasons for efficacy of antibiotics are unclear given the absence of evidence of infection. Isotretinoin has been successfully used to treat granulomatous perioral dermatitis.

Rosacea

Rosacea (acne rosacea) is a chronic inflammatory disorder characterized by facial flushing, telangiectasias, erythema, papules, pustules, and in severe cases, rhinophyma (see Plate 43). Diagnosis is based on the characteristic appearance and history. Treatment depends on severity and includes topical metronidazole, topical and oral antibiotics, rarely isotretinoin, and, for severe rhinophyma, surgery.

Rosacea most commonly affects patients aged 30 to 50 with fair complexions, most notably those of Irish and Northern European descent, but it affects and is probably under-recognized in darker-skinned patients.

Etiology

The etiology is unknown, although associations with abnormal vasomotor control, impaired facial venous drainage, an increase in follicle mites (*Demodex folliculorum*), and *Helicobacter pylori* infection have been proposed. People with rosacea may have elevated levels of small antimicrobial peptides that are part of the body's natural defense system. People with rosacea may also have higher than normal levels of cathelicidin as well as another group of enzymes called stratum corneum tryptic enzymes.

Symptoms and Signs

Rosacea is limited to the face and scalp and manifests in 4 phases:

• Prerosacea phase

• Vascular phase

• Inflammatory phase

• Late stage

In the prerosacea phase, patients describe embarrassing flushing and blushing, often accompanied by uncomfortable stinging. Common reported triggers for these flares include sun exposure, emotional stress, cold or hot weather, alcohol, spicy foods, exercise, wind, cosmetics, and hot baths or hot drinks. These symptoms persist throughout other phases of the disorder.

In the vascular phase, patients develop facial erythema and edema with multiple telangiectases, possibly as a result of persistent vasomotor instability.

An inflammatory phase often follows, in which sterile papules and pustules (leading to the designation of rosacea as adult acne) develop.

Some patients go on to develop late-stage rosacea, characterized by coarse tissue hyperplasia of the cheeks and nose (rhinophyma) caused by tissue inflammation, collagen deposition, and sebaceous gland hyperplasia.

The phases of rosacea are usually sequential. Some patients go directly into the inflammatory stage, bypassing the earlier stages. Treatment may cause rosacea to return to an earlier stage. Progression to the late stage is not inevitable.

Ocular rosacea often accompanies facial rosacea and manifests as some combination of blepharoconjunctivitis, iritis, scleritis, and keratitis, causing itching, foreign body sensation, erythema, and edema of the eye.

Diagnosis

• Clinical evaluation

Diagnosis is based on the characteristic appearance; there are no specific diagnostic tests. The age of onset and absence of comedones help distinguish rosacea from acne. Differential diagnosis includes acne vulgaris, SLE, sarcoidosis, photodermatitis, drug eruptions (particularly from iodides and bromides), granulomas of the skin, and perioral dermatitis.

Treatment

• Avoidance of triggers

• Consideration of topical or oral antibiotics

• Consideration of isotretinoin if antibiotics are unsuccessful

• Consideration of dermabrasion and tissue excision for rhinophyma

Primary initial treatment of rosacea involves avoidance of triggers (including use of sunscreen). Antibiotics may be used for inflammatory disease. The objective of treatment is control of symptoms, not cure.

Metronidazole cream 1%, lotion (0.75%), or gel (0.75%) and azelaic acid 20% cream, applied bid, are equally effective; 2.5% benzoyl peroxide, applied once/day or bid, can be added for improved control. Less effective alternatives include sodium sulfacetamide 10%/sulfur 5% lotion; clindamycin 1% solution, gel, or lotion; and erythromycin 2% solution, all applied bid. Many patients require indefinite treatment for chronic control.

Oral antibiotics are indicated for patients with multiple papules or pustules and for those with ocular rosacea; options include tetracycline 250 to 500 mg bid, doxycycline 50 to 100 mg bid, minocycline 50 to 100 mg bid, and erythromycin 250 to 500 mg bid. Dose should be reduced to the lowest one that controls symptoms once a beneficial response is achieved. Recalcitrant cases may respond to oral isotretinoin. Subantimicrobial doses of doxycycline are also effective for acne and rosacea.

Techniques for treatment of rhinophyma include dermabrasion and tissue excision; cosmetic results are good.

Chapter 74. Bullous Diseases

Introduction

Bullae are elevated, fluid-filled blisters ≥ 5 mm in diameter. Bullous diseases include bullous pemphigoid, dermatitis herpetiformis, epidermolysis bullosa acquisita, herpes gestationis (pemphigoid gestationis—see p. 2666), linear IgA disease, pemphigus vulgaris, and pemphigus foliaceus. Staphylococcal scalded skin syndrome (see p. 701) and toxic epidermal necrolysis (see p. 689) also cause bullae.

Bullous Pemphigoid

Bullous pemphigoid is an autoimmune skin disorder causing chronic, pruritic bullous eruptions in elderly patients. Diagnosis is by skin biopsy. Corticosteroids are used initially. Most patients require long-term maintenance therapy, for which a variety of drugs can be used.

In bullous pemphigoid, antibodies are directed against the basement membrane zone of the epidermis, causing separation between the epidermis and dermis. Bullous pemphigoid must be distinguished from pemphigus vulgaris (see p. 658), a much more serious disease.

Symptoms and Signs

Characteristic tense bullae develop on normal-appearing or erythematous skin, most often in flexural areas. Nikolsky's sign, in which lateral pressure on skin adjacent to a blister causes epidermal detachment, is negative. Bullous pemphigoid can manifest initially as hives with annular, dusky-red, edematous lesions, with or without peripheral vesicles. Itching is common, usually without other symptoms. Oral lesions occur in about one third of patients but heal rapidly.

Diagnosis

• Skin biopsy and antibody titers

Patients should have a skin biopsy and serum antibody titers for hemidesmosomal BP antigens BP230 (BPAg1) and BP180 (BPAg2).

Bullous pemphigoid must be differentiated from pemphigus vulgaris (see Table 74-1), linear IgA disease, erythema multiforme, drug-induced eruptions, benign mucous membrane pemphigoid, paraneoplastic pemphigoid, dermatitis herpetiformis, and epidermolysis bullosa acquisita.

Prognosis

Prognosis is good, and the disorder usually subsides within months to years; however, the disorder is potentially fatal, especially in the elderly and debilitated patients, with death being caused by infection and sepsis or the effects of the drugs.

Treatment

• Corticosteroids, topical or oral

• Anti-inflammatory drugs

Mild bullous pemphigoid sometimes resolves without treatment, but resolution usually

[**Table 74-1.** Distinguishing Pemphigoid from Pemphigus Vulgaris]

takes months or years. Patients with more severe disease receive prednisone 60 to 80 mg po once/day, which can be tapered to a maintenance level of ≤ 10 to 20 mg/day after several weeks. Most patients achieve remission after 2 to 10 mo. Occasional new lesions in elderly patients do not require increasing the prednisone dosage.

The disorder occasionally responds to a combination of tetracycline or minocycline and nicotinamide. Other treatment options include dapsone, sulfapyridine, erythromycin, and tetracycline used alone for their anti-inflammatory rather than their antibiotic properties. IV immune globulin has been used occasionally. For patients with generalized and recalcitrant disease, immunosuppressants such as azathioprine, cyclophosphamide, rituximab, and cyclosporine may be used. However, use of immunosuppressants for bullous pemphigoid is controversial.

Dermatitis Herpetiformis

Dermatitis herpetiformis is a cutaneous manifestation associated with gluten sensitivity. It produces a chronic eruption characterized by clusters of intensely pruritic vesicles, papules, and urticaria-like lesions. The cause is autoimmune. Diagnosis is by skin biopsy with direct immunofluorescence testing. Treatment is usually with dapsone or sulfapyridine and a gluten-free diet.

This disease usually manifests in patients 30 to 40 yr old (but may occur from age 2 to 90 yr) and is rare in blacks and Asians.

More than 90% of affected patients have a gluten-sensitive enteropathy, which is often asymptomatic. Dermatitis herpetiformis develops in 15 to 25% of patients with celiac sprue. Patients have a slightly higher incidence of other autoimmune disorders, including type 1 diabetes mellitus, sarcoidosis, SLE, and thyroid abnormalities. The incidence of enteropathy-associated T-cell lymphoma is also increased.

The term herpetiformis refers to the clustered appearance of the lesions rather than a relationship to herpesvirus.

Symptoms and Signs

Onset is usually gradual. Vesicles, papules, and urticaria-like lesions are usually distributed symmetrically on extensor aspects (elbows, knees, sacrum, buttocks, occiput). Vesicles and papules occur in about one third of patients. Itching and burning are severe, and scratching often obscures the primary lesions with eczematization of nearby skin, leading to an erroneous diagnosis of eczema. NSAIDs and iodides may worsen the rash.

Diagnosis

• Skin biopsy

Diagnosis is based on skin biopsy and direct immunofluorescence testing of a lesion and adjacent normal-appearing skin. Granular IgA deposition in the dermal papillary tips is invariably present and important for diagnosis. Patients should be evaluated for celiac sprue (see p. 158).

Treatment

• Gluten-free diet

• Dapsone

Strict adherence to a gluten-free diet for a prolonged time (eg, 6 to 12 mo) controls the disease in some patients, obviating or reducing the need for drug therapy. When drugs are needed, dapsone generally results in remarkable improvement. Initial dosages of dapsone are 25 to 50 mg po once/day in adults and 0.5 mg/kg in children. Usually, this dose dramatically relieves symptoms, including itching, within 1 to 3 days; if it does, the dose is continued. If no improvement occurs, the dose can be increased every week, up to 300 mg/day. Most patients can be maintained on 50 to 150 mg/day, and some require as little as 25 mg/wk. After initial therapy and stabilization of the disease, the majority of patients can be maintained on a strict gluten-free diet. Although less effective, sulfapyridine may be used as an alternative for patients who cannot tolerate dapsone. Initial oral dosage is 500 mg bid, increasing by 1 g/day q 1 to 2 wk until

disease is controlled. Maintenance dosage varies from 500 mg twice/wk to 1000 mg once/day. Colchicine is another treatment option. Treatment continues until lesions resolve.

In patients with G6PD deficiency, dapsone may cause severe hemolysis. Patients receiving dapsone or sulfapyridine should have a baseline CBC; CBC is then done weekly for 4 wk, then every 2 to 3 wk for 8 wk, and every 12 to 16 wk thereafter. Hemolytic anemia and methemoglobinemia are the most frequently encountered adverse effects. CNS or liver toxicity is rare. If dapsone therapy causes considerable hemolysis, significant cardiopulmonary problems, or peripheral neuropathy, sulfapyridine may be used. Sulfapyridine usually does not induce significant hemolysis.

Epidermolysis Bullosa Acquisita

Epidermolysis bullosa acquisita is a chronic autoimmune mucocutaneous disease causing blistering and skin fragility.

Epidermolysis bullosa acquisita usually appears in adults. Bullous lesions may develop on normal-appearing skin spontaneously or may be caused by minor trauma. The trauma-prone areas of the skin, such as the extensor surfaces of elbows, knees, ankles, and buttocks, are most commonly affected. Pain and scarring are common. Because the hands and feet are often involved, disability can be significant. Occasionally, mucosa of eyes, mouth, or genitals is involved. Laryngeal and esophageal involvement also occurs. Diagnosis is by skin biopsy. Lesions respond poorly to corticosteroids. Mild disease may be treated with colchicine, but more severe disease may require cyclosporine or immune globulin.

Linear Immunoglobulin A Disease

Linear immunoglobulin A (IgA) disease is an uncommon bullous disease distinguished from bullous pemphigoid and dermatitis herpetiformis by the linear deposits of IgA in the basement membrane zone.

Linear IgA disease occurs in adults and children. The childhood form is most frequently termed chronic bullous disease of childhood.

In linear IgA disease, vesicular or bullous skin lesions occur frequently in a clustered (herpetiform) arrangement. There is a predilection for flexural areas (eg, inguinal crease). As in dermatitis herpetiformis, severe burning and pruritus of cutaneous lesions are prominent features. It was previously considered a form of dermatitis herpetiformis but has no concomitant gluten-sensitive enteropathy and immunopathology. Also, genetic studies indicate that linear IgA disease is a separate disorder. Drug-induced linear IgA disease, most commonly associated with vancomycin, has been reported.

Diagnosis is by skin biopsy. Dapsone is the treatment of choice. Doses should be similar to those used for dermatitis herpetiformis (see p. 657), and CBC monitoring should follow the same parameters. Other treatment options include glucocorticoids (systemic, topical, and intralesional), cyclophosphamide, azathioprine, colchicine, tetracycline and nicotinamide, and cyclosporine.

Pemphigus Vulgaris

Pemphigus vulgaris is an uncommon, potentially fatal, autoimmune disorder characterized by intraepidermal blisters and extensive erosions on apparently healthy skin and mucous membranes. Diagnosis is by skin biopsy with direct immunofluorescence testing. Treatment is with corticosteroids and sometimes immunosuppressants.

Pemphigus vulgaris usually occurs in middle-aged or elderly patients and is rare in children. One variant, paraneoplastic pemphigus, occurs in older patients with cancer (primarily lymphoreticular); outcome is poor.

The disorder is characterized by the presence of autoantibodies directed against intercellular adhesion molecules desmoglein-1 and desmoglein-3 in the epidermis. They are Ca-dependent cadherins, involved in adhesion and cell signaling between epidermal cells. Acantholysis results from either direct inhibition of

function of the desmogleins by autoantibody binding or from autoantibody-induced cell signaling that results in down-regulation of cell-cell adhesion and formation of blisters. These autoantibodies are present in both serum and skin during active disease. Any area of stratified squamous epithelium may be affected, including mucosal surfaces.

Symptoms and Signs

The primary lesions are flaccid bullae of various sizes (see Plate 41), but often skin or mucosa just shears off, leaving painful erosions. Lesions typically occur first in the mouth, where they rupture and remain as chronic, often painful, erosions for variable periods before the skin is affected; dysphagia and poor oral intake are common. Lesions also may occur in the upper esophagus. Cutaneous bullae typically arise from normal-appearing skin, rupture, and leave a raw area and crusting. Itching is usually absent. Open skin lesions often become infected. If large portions of the body are affected, fluid and electrolyte loss may be significant.

Diagnosis

• Clinical evaluation

• Biopsy with direct immunofluorescence testing

• Sometimes titers of antibodies against desmoglein-3 or desmoglein-1

Pemphigus vulgaris should be suspected in patients with any bullous disorder or chronic mucosal ulceration. It must be differentiated from other chronic oral ulcers and from other bullous dermatoses (eg, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid, drug eruptions, toxic epidermal necrolysis, erythema multiforme, dermatitis herpetiformis, bullous contact dermatitis). Two physical signs in pemphigus vulgaris are helpful:

• Lateral pressure on skin adjacent to a blister causes epidermal detachment (Nikolsky's sign).

• Pressure on a blister can cause the blister to extend to adjacent skin (Asboe-Hansen sign).

Biopsy of the edge of a fresh lesion and of a nearby area of normal skin is required; light microscopy and direct immunofluorescence testing are usually diagnostic. Serum antibodies (eg, to desmoglein-3) can be used for diagnosis and for differentiating from pemphigus foliaceus; serial titers can help follow disease activity.

Prognosis

Before systemic corticosteroids were used, pemphigus vulgaris was usually fatal; most patients died within 5 yr of disease onset. Even with treatment, pemphigus vulgaris is a serious disorder with an inconsistent and unpredictable response to treatment, a prolonged course, and virtually inevitable adverse drug effects.

Treatment

• Corticosteroids, oral or IV

• Sometimes immunosuppressants

• Sometimes plasmapheresis and IV immune globulin (IVIG)

Referral to a dermatologist with expertise in treating this disorder is recommended. Hospitalization is required initially for all but the most minor cases. Cleansing and dressing of open skin lesions is similar to that done for partial-thickness burns (eg, reverse isolation, hydrocolloid or silver sulfadiazine dressings —see p. 3246).

Drug treatment aims to decrease the production of autoantibodies and stop the eruption of new lesions. The mainstay is systemic corticosteroids. Some patients with few lesions may respond to oral prednisone 20 to 30 mg once/day, but most require 1.0 mg/kg once/day as an initial dose. Some clinicians begin with even higher doses, which may slightly hasten initial response but does not appear to improve outcome. If new lesions continue to appear after 5 to 7 days, IV pulse therapy with methylprednisolone 1 g once/day can be tried.

Immunosuppressants such as methotrexate, cyclophosphamide, azathioprine, gold, mycophenolate mofetil, cyclosporine, or rituximab can reduce the need for corticosteroids and thus minimize the undesirable effects of long-term corticosteroid use. Plasmapheresis and high-dose IVIG to reduce antibody titers have also been effective.

Once no new lesions have appeared for 7 to 10 days, corticosteroid dose should be tapered monthly by about 10 mg/day (tapering continues more slowly once 20 mg/day is reached). A relapse requires a return to the starting dose. If the patient has been stable after a year, a trial without treatment can be attempted but must be closely monitored.

Pemphigus Foliaceus

Pemphigus foliaceus is a generally benign blistering disorder. It is characterized by splitting high in the epidermis, causing erosions to form on the skin.

Pemphigus foliaceus usually occurs in middle-aged patients. Foci of high incidence occur in South America, especially Brazil.

The primary lesion is a flaccid bulla. However, because splitting occurs high in the epidermis, bullae are rarely seen; the blisters are so fragile that they rupture. Clinically, scaly, crusted cutaneous erosions, often on an erythematous base, can be seen. Mucosal surfaces are not usually involved. In one variant, pemphigus erythematosus, lesions occur on light-exposed skin and are often similar to those of cutaneous lupus erythematosus.

Diagnosis is by biopsy of a lesion and neighboring normal skin and by serum antibody titers against the cell adhesion molecule desmoglein 1 (160 kd). Because the disorder is much more benign than pemphigus vulgaris, treatment is generally less aggressive. Superpotent topical corticosteroids may be sufficient in some patients. Others require oral prednisone and additional immunosuppressants. A combination of tetracycline 500 mg qid and nicotinamide 1.5 g/day has been effective in some patients. Plasmapheresis is an option for severe disease.

Chapter 75. Cornification Disorders

Introduction

Cornification disorders include calluses, corns, ichthyosis, and keratosis pilaris.

Calluses and Corns

(Tylomas; Helomas; Clavi)

Calluses and corns are circumscribed areas of hyperkeratosis at a site of intermittent pressure or friction. Calluses are more superficial, cover broader areas of skin, and usually asymptomatic. Corns are deeper, more focal, and frequently painful. Diagnosis is by appearance. Treatment is with manual abrasion with or without keratolytics. Prevention involves altering biomechanics, such as changing footwear. Rarely, surgery is required.

Calluses and corns are caused by intermittent pressure or friction, usually over a bony prominence (eg, heel, metatarsal heads).

Corns consist of a sharply circumscribed keratinous plug, pea-sized or slightly larger, which extends through most of the underlying dermis. An underlying adventitial bursitis may develop. Hard corns occur over prominent bony protuberances, especially on the toes and plantar surface. Soft corns occur between the toes. Most corns result from poorly fitting footwear, but small seed-sized corns on non-weight-bearing aspects of the soles and palms may represent inherited keratosis punctata.

Calluses lack a central plug and have a more even appearance. They usually occur on the hands or feet but may occur elsewhere, especially in a person whose occupation entails repeated trauma to a particular area (eg, the mandible and clavicle of a violinist).

Symptoms and Signs

Calluses are usually asymptomatic but, if friction is extreme, may become irritated, causing mild burning discomfort. At times, the discomfort may mimic that of interdigital neuralgia.

Corns may be painful or tender when pressure is applied. A bursa or fluid-filled pocket sometimes forms beneath a corn.

Diagnosis

• Clinical evaluation

A corn may be differentiated from a plantar wart or callus by paring away the horny skin. After paring, a callus shows smooth translucent skin, whereas a wart (see p. 715) appears sharply circumscribed, sometimes with soft macerated tissue or with central black dots (bleeding points) representing thrombosed capillaries. A corn, when pared, shows a sharply outlined yellowish to tan translucent core that interrupts the normal architecture of the papillary dermis. Interdigital neuralgia can be ruled out by the absence of interspace pain on palpation.

Treatment

• Manual removal

• Keratolytics

• Cushioning

• Altering foot biomechanics

A nail file, emery board, or pumice stone used immediately after bathing is often a practical way to manually remove hyperkeratotic tissue. Keratolytics (eg, 17% salicylic acid in collodion, 40% salicylic acid plasters, 40% urea) can also be used, taking care to avoid applying the agents to normal skin. Normal skin may be protected by covering it with petrolatum before application of the keratolytic.

Cushioning and altering foot biomechanics can help prevent corns and help treat existing corns. Although difficult to eliminate, pressure on the affected surface should be reduced and redistributed. For foot lesions, soft, well-fitting shoes are important; they should have a roomy toe box so that toes can move freely in the shoe. Stylish shoes often prevent this freedom of motion. Shoes that increase discomfort of a lesion should be eliminated from the wardrobe. Pads or rings of suitable shapes and sizes, moleskin or foam-rubber protective bandages, arch inserts (orthotics), or metatarsal plates or bars may help redistribute the pressure. For corns and calluses on the ball of the foot, an orthotic should not be full length but should extend only to the ball or part of the shoe immediately behind the corn or callus. Surgical off-loading or removal of the offending bone is rarely necessary.

Patients who have a tendency to develop calluses and corns may need the regular services of a podiatrist. Patients with impaired peripheral circulation, especially if associated with diabetes, require expert care.

Ichthyosis

Ichthyosis is scaling and flaking of skin ranging from mild but annoying dryness (xeroderma) to severe disfiguring disease (inherited ichthyosis). Ichthyosis can also be a sign of systemic disease. Diagnosis is clinical. Treatment involves emollients and sometimes oral retinoids.

Xeroderma: Xeroderma (xerosis), or dry skin, is neither inherited nor associated with systemic abnormalities. Dry skin results from loss of the water content of the skin, resulting in fine white scales. Risk factors for xerosis include the following:

• Residence in a dry, cold climate

• Older age

• Atopic dermatitis

• Frequent bathing, particularly if using harsh soaps

Inherited ichthyoses: Inherited ichthyoses, which are characterized by excessive accumulation of scale on the skin surface, are classified according to clinical and genetic criteria (see Table 75-1). Some occur in isolation without

[**Table 75-1.** Clinical and Genetic Features of Some Inherited Ichthyoses]

associated abnormalities (eg, ichthyosis vulgaris, X-linked ichthyosis, lamellar ichthyosis, epidermolytic hyperkeratosis [bullous congenital ichthyosiform erythroderma]). Other ichthyoses are part of a syndrome that involves multiple organs. For instance, Refsum's disease (see p. 3024) and Sjogren-Larsson syndrome (hereditary intellectual disability and spastic paralysis caused by a defect in fatty aldehyde dehydrogenase) are autosomal recessive conditions with skin and extracutaneous organ involvement. A dermatologist should assist in diagnosis and management, and a medical geneticist should be consulted for genetic counseling.

Acquired ichthyosis: Ichthyosis may be an early manifestation of some systemic disorders (eg, leprosy, hypothyroidism, lymphoma, AIDS). Some drugs cause ichthyosis (eg, nicotinic acid, triparanol, butyrophenones). The dry scaling may be fine and localized to the trunk and legs, or it may be thick and widespread. Biopsy of ichthyotic skin is usually not diagnostic of the systemic disorder; however, there are exceptions, most notably sarcoidosis, in which a thick scaling may appear on the legs, and biopsy usually shows the typical granulomas.

Treatment

• Minimization of exacerbating factors

• Moisturization and keratolytics

• Sometimes infection prophylaxis

When ichthyosis is caused by a systemic disorder, abatement is greatest if the primary disorder can be corrected. Otherwise, treatment is symptomatic, including using emollients and keratolytics and avoiding drying.

Moisturization and keratolytics: In any ichthyosis, there is impaired epidermal barrier function, and moisturizers should be applied immediately after bathing. Substances that are applied to the skin may have increased absorption. For example, hexachlorophene products should not be used because of increased absorption and toxicity.

An emollient, preferably plain petrolatum, mineral oil, or lotions containing urea or α-hydroxy acids (eg, lactic, glycolic, and pyruvic acids), should be applied twice daily, especially after bathing while the skin is still wet. Blotting with a towel removes excess applied material.

Ichthyosis typically responds well to propylene glycol. To remove scale (eg, if ichthyosis is severe), patients can apply a preparation containing 40 to 60% propylene glycol in water under occlusion (eg, a thin plastic film or bag), every night after hydrating the skin (eg, by bathing or showering); in children, the preparation should be applied twice daily without occlusion. Occlusion should be maintained overnight. After scaling has decreased, less frequent application is required. Other useful keratolytics include ceramide-based creams, 6% salicylic acid gel, hydrophilic petrolatum and water (in equal parts), and the α-hydroxy acids in various bases. Topical calcipotriol cream has been used with success; however, this vitamin D derivative can result in hypercalcemia when used over broad areas, especially in small children.

Retinoids are effective in treating ichthyosis. Oral synthetic retinoids are effective for most ichthyoses. Acitretin (see p. 679) is effective in treating most forms of inherited ichthyosis. In lamellar ichthyosis, 0.1% tretinoin cream or oral isotretinoin may be effective. The lowest effective dose should be used. Long-term (1 yr) treatment with oral isotretinoin has resulted in bony exostoses in some patients, and other long-term adverse effects may arise. (CAUTION: *Oral retinoids are contraindicated in pregnancy because of their teratogenicity, and acitretin should be avoided in women of childbearing potential because of its teratogenicity and long half-life.)*

Infection prophylaxis: Patients with epidermolytic hyperkeratosis may need long-term treatment with cloxacillin 250 mg po tid or qid or erythromycin 250 mg po tid or qid, as long as thick intertriginous scaling is present, to prevent bacterial superinfection from causing painful, foul-smelling pustules. Regularly using soaps containing chlorhexidine may also reduce the bacteria, but these soaps tend to dry the skin.

Keratosis Pilaris

Keratosis pilaris is a disorder of keratinization in which horny plugs fill the openings of hair follicles.

Keratosis pilaris is common. The cause is unknown, but there is often an autosomal dominant inheritance. Multiple small, pointed, keratotic follicular papules appear mainly on the lateral aspects of the upper arms, thighs, and buttocks. Facial lesions may also occur, particularly in children. Lesions are most prominent in cold weather and sometimes abate in the summer. Skin may appear red. The problem is mainly cosmetic, but the disorder may cause itching or, rarely, follicular pustules.

Treatment is usually unnecessary and often unsatisfactory. Hydrophilic petrolatum and water (in equal parts), cold cream, or petrolatum with 3% salicylic acid may help flatten the lesions. Buffered lactic acid (ammonium lactate) lotions or creams, urea creams, 6% salicylic acid gel, or 0.1% tretinoin cream may also be effective. Acid creams should be avoided in young children because of burning and stinging.

Pulse-dye laser has been used successfully to treat facial redness.

Chapter 76. Dermatitis

Introduction

Dermatitis is superficial inflammation of the skin characterized by redness, edema, oozing, crusting, scaling, and sometimes vesicles. Pruritus is common. Eczema is a term often used interchangeably with dermatitis.

Atopic Dermatitis

Atopic dermatitis (AD) is an immune-mediated inflammation of the skin arising from an interaction between genetic and environmental factors. Recent research suggests that a heritable epidermal barrier defect is a primary cause, and defects in the *filaggrin* gene have been specifically implicated. Pruritus is the primary symptom; skin lesions range from mild erythema to severe lichenification. Diagnosis is by history and examination. Treatment is moisturizers, avoidance of allergic and irritant triggers, and often topical corticosteroids. Atopic dermatitis frequently resolves completely by age 30.

Etiology

AD primarily affects children in urban areas or developed countries; at least 5% of children in the US are affected. Like asthma, it may be linked to proallergic/proinflammatory T-cell immune responses. Such responses are becoming more common in developed countries because trends toward smaller families, cleaner indoor environments, and early use of vaccinations and antibiotics deprive children of the early exposure to infections and allergens that otherwise suppress proallergic T cells and thereby induce tolerance to various antigens.

Pathophysiology

AD can be divided into 2 forms:

• Extrinsic: IgE-mediated (70 to 80% of cases)

• Intrinsic: Non-IgE-mediated (20 to 30% of cases)

Extrinsic AD: This form occurs when environmental exposures trigger immunologic, usually allergic (ie, IgE-mediated), reactions in genetically susceptible people. Common environmental triggers include

• Foods (eg, milk, eggs, soy, wheat, peanuts, fish)

• Airborne allergens (eg, dust mites, molds, dander)

• *Staphylococcus aureus* colonization on skin due to deficiencies in endogenous antimicrobial peptides

• Topical products (eg, cosmetics)

AD is common within families, suggesting a genetic component. Many patients with AD have a mutation in the gene encoding for the filaggrin protein, which is a component of the cornified cell envelope produced by differentiating keratinocytes. Also, research has shown that skin affected by AD is deficient in ceramides, which increases transepidermal water loss.

Intrinsic AD: This form is not mediated by IgE. Intrinsic AD is nonfamilial and idiopathic, and its pathophysiology is generally not well understood.

Symptoms and Signs

Manifestations of intrinsic and extrinsic AD are similar. AD usually appears in infancy, typically by 3 mo. In the acute phase, lasting 1 to 2 mo (see

Plate 27), red, weeping, crusted lesions appear on the face and spread to the neck, scalp, extremities, and abdomen. In the chronic phase (see
Plate 28), scratching and rubbing create skin lesions (typically erythematous macules and papules that lichenify with continued scratching). Lesions typically appear in antecubital and popliteal fossae and on the eyelids, neck, and wrists and may occasionally become generalized. Lesions slowly resolve to dry scaly macules (xerosis) that can fissure and facilitate exposure to irritants and allergens. In older children and adults, intense pruritus is the key feature. Patients have a reduced threshold for perceiving itch, and itch worsens with allergen exposures, dry air, sweating, local irritation, wool garments, and emotional stress.

Complications: Secondary bacterial infections, especially staphylococcal and streptococcal, and regional lymphadenitis are common.

Eczema herpeticum (Kaposi's varicelliform eruption) is a diffuse herpes simplex infection occurring in patients with AD. It manifests as grouped vesicles in areas of active or recent dermatitis, although normal skin can be involved. High fever and adenopathy may develop after several days. Occasionally, this infection can become systemic, which may be fatal. Sometimes the eye is involved, causing a painful corneal lesion.

Fungal and nonherpetic viral skin infections (eg, common warts, molluscum contagiosum) can also occur.

Patients with long-standing AD may develop cataracts in their 20s or 30s.

Frequent use of topical products exposes the patient to many potential allergens, and contact dermatitis may aggravate and complicate AD, as may the generally dry skin that is common among these patients.

Diagnosis

• Clinical evaluation

• Sometimes testing for allergic triggers with skin prick testing or radioallergosorbent testing levels

Diagnosis is clinical (see
Table 76-1). AD is often hard to differentiate from other dermatoses (eg, seborrheic dermatitis, contact dermatitis, nummular dermatitis, psoriasis), although a family history of atopy and the distribution of lesions are helpful. For example, psoriasis is usually extensor rather than flexurally distributed, may involve the fingernails, and has a shinier (micaceous) scale. Seborrheic dermatitis affects the face (eg, nasolabial folds, eyebrows, glabellar region, scalp) most commonly. Nummular dermatitis is not flexural, and lichenification is rare. Because patients can still develop other skin disorders, not all subsequent skin problems should be attributed to AD.

There is no definitive laboratory test for AD. However, allergic precipitants of AD can be identified with skin testing, measurement of allergen-specific IgE levels, or both.

Prognosis

AD in children often abates by age 5 yr, although exacerbations are common throughout adolescence and into adulthood. Girls and patients with severe disease, early age of onset, family history, and associated rhinitis or asthma are more likely to have prolonged disease. Even in these patients, AD frequently resolves completely by age 30. AD may have long-term psychologic sequelae as children confront many challenges of living with a visible, sometimes disabling, skin disease during formative years.

[**Table 76-1.** Clinical Findings in Atopic Dermatitis*]

Treatment

• Supportive care (eg, moisturizers, symptomatic treatment for pruritus)

• Avoidance of precipitating factors

• Topical corticosteroids

• Sometimes immune modulators (most often topical but sometimes oral)

• Sometimes ultraviolet (UV) therapy

Treatment can usually be given at home, but patients who have exfoliative dermatitis (see p. 668), cellulitis, or eczema herpeticum may need to be hospitalized.

Supportive care: Skin care involves moisturizing. Bathing and hand washing should be infrequent, and lukewarm (not hot) water should be used; soap use should be minimized on dermatitic areas because it may be drying and irritating. Colloidal oatmeal baths can be helpful. When toweling dry, the skin should be blotted or patted dry rather than rubbed.

Body oils or emollients such as white petrolatum, vegetable oil, or hydrophilic petrolatum (unless the patient is allergic to lanolin) applied immediately after bathing may help retain skin moisture and reduce itching. Continuously wet dressings (not wet-to-dry) are an alternative for severe lesions. Coal tar cream or oil can be an effective topical anti-pruritic but also can be inconvenient because it stains clothing.

Antihistamines can help relieve pruritus. Options include hydroxyzine 25 mg po tid or qid (for children, 0.5 mg/kg q 6 h or 2 mg/kg in a single bedtime dose) and diphenhydramine 25 to 50 mg po at bedtime. Low-sedating H_1 receptor blockers, such as loratadine 10 mg po once/day, fexofenadine 60 mg po bid or 180 mg po once/day, and cetirizine 5 to 10 mg po once/day, may be useful, although their efficacy has not been defined. Doxepin (a tricyclic antidepressant also with H_1 and H_2 receptor blocking activity) 25 to 50 mg po at bedtime may also help, but its use is not recommended for children < 12 yr. Fingernails should be cut short to minimize excoriations and secondary infections.

Avoidance of precipitating factors: Household antigens can be controlled by using synthetic fiber pillows and impermeable mattress covers; washing bedding in hot water; removing upholstered furniture, soft toys, carpets, and pets (to reduce dust mites and animal dander); using air circulators equipped with high-efficiency particulate air (HEPA) filters in bedrooms and other frequently occupied living areas; and using dehumidifiers in basements and other poorly aerated damp rooms (to reduce molds). Reduction of emotional stress is useful but often difficult. Antistaphylococcal antibiotics, both topical (eg, mupirocin, fusidic acid) and oral (eg, dicloxacillin, cephalexin, erythromycin [all 250 mg qid]), can control *S. aureus* nasal colonization and are indicated in patients with severe disease unresponsive to specific therapies and positive nasal cultures. Extensive dietary changes intended to eliminate exposure to allergenic foods are unnecessary and probably ineffective; food hypersensitivities rarely persist beyond childhood.

Corticosteroids: Corticosteroids are the mainstay of therapy. Creams or ointments applied twice daily are effective for most patients with mild or moderate disease. Emollients are applied between corticosteroid applications and can be mixed with them to decrease the corticosteroid amount required to cover an area. Systemic corticosteroids (prednisone 60 mg or, for children 1 mg/kg, po once/day for short courses of 7 to 14 days) are indicated for extensive or refractory disease but should be avoided whenever possible, because disease often recurs and topical therapy is safer. Prolonged, widespread use of high-potency corticosteroid creams or ointments should be avoided in infants because adrenal suppression may ensue.

Other therapies: Tacrolimus and pimecrolimus are T-cell inhibitors effective for AD. They should be used when patients do not respond to corticosteroids and tar or when corticosteroid adverse effects such as skin atrophy, striae formation, or adrenal suppression is a concern. Tacrolimus or pimecrolimus cream is applied twice daily. Burning or stinging after application is usually transient and abates after a few days. Flushing is less common.

Repair of the stratum corneum and barrier function may help alleviate AD. Research has shown that skin affected by AD is particularly deficient in ceramides and that a deficiency in ceramides increases transepidermal water loss. Several ceramide-containing emollient products are considered helpful for AD

control.

Phototherapy is helpful for extensive AD. Natural sun exposure ameliorates disease in many patients, including children. Alternatively, therapy with ultraviolet A (UVA) or B (UVB) may be used. Narrowband UVB therapy is proving more effective than traditional broadband UVB therapy and is also effective in children. Psoralen plus UVA (PUVA—see p. 679) therapy is reserved for extensive, refractory AD. Adverse effects include sun damage (eg, PUVA lentigines, nonmelanoma skin cancer). Because of these adverse effects, PUVA is rarely indicated for children or young adults.

Systemic immune modulators effective in at least some patients include cyclosporine, interferon gamma, mycophenolate, methotrexate, and azathioprine. All downregulate or inhibit T-cell function and have anti-inflammatory properties. These agents are indicated for widespread, recalcitrant, or disabling AD that fails to abate with topical therapy and phototherapy.

Eczema herpeticum is treated with acyclovir. Infants receive 10 to 20 mg/kg IV q 8 h; older children and adults with mild illness may receive 200 mg po 5 times/day. Involvement of the eye is considered an ophthalmic emergency, and if eye involvement is suspected, an ophthalmology consult should be obtained.

Contact Dermatitis

Contact dermatitis (CD) is acute inflammation of the skin caused by irritants or allergens. The primary symptom is pruritus. Skin changes range from erythema to blistering and ulceration, often on or near the hands but occurring on any exposed skin surface. Diagnosis is by exposure history, examination, and sometimes skin patch testing. Treatment entails antipruritics, topical corticosteroids, and avoidance of causes.

Pathophysiology

CD is caused by irritants or allergens.

Irritant contact dermatitis (ICD): ICD accounts for 80% of all cases of CD. It is a nonspecific inflammatory reaction to substances contacting the skin; the immune system is not activated. Numerous substances are involved, including

• Chemicals (eg, acids, alkalis, solvents, metal salts)

• Soaps (eg, abrasives, detergents)

• Plants (eg, poinsettias, peppers)

• Body fluids (eg, urine, saliva)

Properties of the irritant (eg, extreme pH, solubility in the lipid film on skin), environment (eg, low humidity, high temperature, high friction), and patient (eg, very young or old) influence the likelihood of developing ICD. ICD is more common among patients with atopic disorders, in whom ICD also may initiate immunologic sensitization and hence allergic CD.

Phototoxic dermatitis (see p. 675) is a variant in which topical (eg, perfumes, coal tar) or ingested (eg, psoralens) agents generate damaging free radicals and inflammatory mediators only after absorption of ultraviolet light.

Allergic contact dermatitis (ACD): ACD is a type IV cell-mediated hypersensitivity reaction that has 2 phases:

• Sensitization to an antigen

• Allergic response after reexposure

In the sensitization phase, allergens are captured by Langerhans' cells (dendritic epidermal cells), which migrate to regional lymph nodes where they process and present the antigen to T cells. The process may be brief (6 to 10 days for strong sensitizers such as poison ivy) or prolonged (years for weak sensitizers such as sunscreens, fragrances, and glucocorticoids). Sensitized T cells then migrate back to the epidermis and activate on any reexposure to the allergen, releasing cytokines, recruiting inflammatory cells, and leading to the characteristic symptoms and signs of ACD.

In **autoeczematization**, epidermal T cells activated by an allergen migrate locally or through the circulation to cause dermatitis at sites remote from the initial trigger. However, contact with fluid from vesicles or blisters cannot trigger a reaction elsewhere on the patient or on another person.

Multiple allergens cause ACD (see Table 76-2), and cross-sensitization among agents is common (eg, between benzocaine and paraphenylenediamine). Cross-sensitization means that exposure to one substance can result in an allergic response after exposure to a different but related substance.

ACD variants include photoallergic CD and systemically induced ACD. In photoallergic CD (see p. 675), a substance becomes sensitizing only after it undergoes structural change triggered by ultraviolet light. Typical causes include aftershave lotions, sunscreens, and topical sulfonamides. Reactions may extend to non-sun-exposed skin. In systemically induced ACD, ingestion of an allergen after topical sensitization causes diffuse dermatitis (eg, oral diphenhydramine after sensitization with topical diphenhydramine).

Symptoms and Signs

ICD: ICD is more painful than pruritic. Signs range from mild erythema to hemorrhage, crusting, erosion, pustules, bullae, and edema.

ACD: In ACD, the primary symptom is intense pruritus; pain is usually the result of excoriation or infection. Skin changes range from transient erythema through vesiculation to severe swelling with bullae, ulceration, or both. Changes often occur in a pattern, distribution, or combination that suggests a specific exposure, such as linear streaking on an arm or leg (eg, from brushing against poison ivy) or circumferential erythema (under a wristwatch or waistband). Any surface may be involved, but hands are the most common surface due to handling and touching potential allergens. With airborne exposure (eg,

[**Table 76-2.** Causes of Allergic Contact Dermatitis]

perfume aerosols), areas not covered by clothing are predominantly affected. The dermatitis is typically limited to the site of contact but may later spread due to scratching and autoeczematization. In systemically induced ACD, skin changes may be distributed over the entire body.

Diagnosis

• Clinical evaluation

• Sometimes patch testing

CD can often be diagnosed by skin changes and exposure history. The patient's occupation, hobbies, household duties, vacations, clothing, topical drug use, cosmetics, and spouse's activities must be considered. The "use" test, in which a suspected agent is applied far from the original area of dermatitis, usually on the flexor forearm, is useful when perfumes, shampoos, or other home agents are suspected.

Patch testing is indicated when ACD is suspected and does not respond to treatment. In patch testing, standard contact allergens are applied to the upper back using adhesive-mounted patches containing minute amounts of allergen or plastic (Finn) chambers containing allergen held in place with porous tape. Thin-layer rapid use epicutaneous (TRUE) patch testing involves 2 adhesive strips that can be applied and interpreted by any provider. Skin under the patches is evaluated 48 and 96 h after application. False-positive results occur when concentrations provoke an irritant rather than an allergic reaction, when

reaction to one antigen triggers a nonspecific reaction to others, or with cross-reacting antigens. False-negative results occur when patch allergens do not include the offending antigen. Definitive diagnosis requires a history of exposure to the test agent in the original area of dermatitis.

Prognosis

Resolution may take up to 3 wk. Reactivity is usually lifelong. Patients with photoallergic CD can have flares for years when exposed to sun (persistent light reaction).

Treatment

• Avoidance of offending agents

• Supportive care (eg, cool compresses, dressings, antihistamines)

• Corticosteroids (most often topical but sometimes oral)

CD is prevented by avoiding the trigger; patients with photosensitive CD should avoid exposure to sun.

Topical treatment includes cool compresses (saline or Burow's solution) and corticosteroids; patients with mild to moderate ACD are given mid-potency topical corticosteroids (eg, triamcinolone 0.1% ointment or betamethasone valerate cream 0.1%). Oral corticosteroids (eg, prednisone 60 mg once/day for 7 to 14 days) can be used for severe blistering or extensive disease. Systemic antihistamines (eg, hydroxyzine, diphenhydramine) help pruritus; antihistamines with low anticholinergic potency, such as low-sedating H_1 blockers, are not as effective. Wet-to-dry dressings can soothe oozing blisters, dry the skin, and promote healing.

Exfoliative Dermatitis

(Erythroderma)

Exfoliative dermatitis is widespread erythema and scaling of the skin caused by preexisting skin disorders, drugs, cancer, or unknown causes. Symptoms and signs are pruritus, diffuse erythema, and epidermal sloughing. Diagnosis is clinical. Treatment involves corticosteroids and correction of the cause.

Exfoliative dermatitis is a manifestation of rapid epidermal cell turnover. Its cause is unknown, but it most often occurs in the context of preexisting skin disorders (eg, atopic dermatitis, contact dermatitis, seborrheic dermatitis, psoriasis, pityriasis rubra pilaris), use of drugs (eg, penicillin, sulfonamides, isoniazid, phenytoin, barbiturates), and cancer (eg, mycosis fungoides, leukemia, and, rarely, adenocarcinomas). Up to 25% of patients have no identifiable underlying disease.

Symptoms and Signs

Symptoms include pruritus, malaise, and chills. Diffuse erythema initially occurs in patches but spreads and involves all or nearly all of the body. Extensive epidermal sloughing leads to abnormal thermoregulation, nutritional deficiencies because of extensive protein losses, increased metabolic rate with a hypercatabolic state, and hypovolemia due to transdermal fluid losses.

Diagnosis

• Clinical evaluation

Diagnosis is by history and examination. Preexisting skin disease may underlie the extensive erythema and suggest a cause. Biopsy is often nonspecific but is indicated when mycosis fungoides is suspected. Blood tests may reveal hypoproteinemia, hypocalcemia, and iron deficiency, each a consequence of extensive protein, electrolyte, and RBC loss; however, these findings are not diagnostic.

Treatment

• Supportive care (eg, rehydration)

• Topical care (eg, emollients, colloidal oatmeal baths)

• Systemic corticosteroids for severe disease

The disease may be life threatening; hospitalization is often necessary. Any known cause is treated. Supportive care consists of correction of dehydration, correction of electrolyte abnormalities and nutritional deficiencies, and comprehensive wound care and dressings to prevent bacterial superinfection. Because drug eruptions and contact dermatitis cannot be ruled out by history alone, all drugs should be stopped if possible or changed. Skin care is with emollients and colloidal oatmeal baths. Weak topical corticosteroids (eg, 1 to 2.5% hydrocortisone ointment) may be used. Corticosteroids (prednisone 40 to 60 mg po once/day for 10 days, then tapered) are used for severe disease.

Prognosis depends on the cause. Cases related to drug reactions have the shortest duration, lasting 2 to 6 wk after the drug is withdrawn.

Hand and Foot Dermatitis

Hand and foot dermatitis is not a single disorder. Rather, it is a categorization of dermatitis that affects the hands and feet selectively due to one of several causes.

Patients often present with isolated dermatitis of the hands or feet. Causes include

• Contact dermatitis

• Fungal infection

• Psoriasis

• Scabies

Other causes include systemic viral infection in children (hand-foot-and-mouth disease—see p. 1426) or certain chemotherapies (hand-foot syndrome). Some cases are idiopathic.

Diagnosis can sometimes be inferred from location and appearance of the skin lesions (see Table 76-3).

Treatment of all forms of hand and foot dermatitis should be directed at the cause when possible. Topical corticosteroids or antifungals may be tried empirically. Patients should also avoid prolonged contact with water that would otherwise remove protective oils and lead to paradoxical drying of the skin.

Dyshidrotic dermatitis: Pruritic vesicles or bullae on the palms, sides of the fingers, or soles are characteristic of this disorder. Scaling, redness, and oozing often follow vesiculation. Pompholyx is a severe form with bullae. The cause is unknown, but fungal infection, contact dermatitis, and id reactions to tinea pedis can cause a similar clinical appearance and should be ruled out. Treatment includes topical corticosteroids, tacrolimus or pimecrolimus, oral antibiotics, and ultraviolet light.

Keratolysis exfoliativa: Painless patchy peeling of the palms, soles, or both is characteristic of this disorder. The cause is unknown; treatment is unnecessary because the condition is self-resolving.

Hyperkeratotic eczema: Thick yellow-brown plaques on the palms and sometimes soles are characteristic of this disorder. The cause is unknown. Treatment is with topical corticosteroids and keratolytics, oral psoralen plus ultraviolet A (PUVA), and retinoids.

Id reaction: The appearance of vesicles usually on the sides of the fingers in response to active

dermatitis elsewhere is characteristic of this disorder. The cause may be an allergic reaction.

Housewives' eczema: This irritant contact dermatitis affects people whose hands are frequently immersed in water. It is worsened by washing dishes, clothes, and babies because repeated exposure to even mild detergents and water or prolonged sweating under rubber gloves may irritate dermatitic skin or cause an irritant contact dermatitis.

Hand-foot syndrome: This disorder (also called acral erythema or palmar-plantar eryth-rodysesthesia) represents cutaneous toxicity caused by certain systemic chemotherapies (eg, capecitabine, cytarabine, fluorouracil, idarubicin, doxorubicin, taxanes, methotrexate, cisplatin, tegafur). Manifestations include pain, swelling, numbness, tingling, redness, and sometimes flaking or blistering of the palms or soles. Treatment is with oral or topical corticosteroids, topical dimethylsulfoxide, oral vitamin B_6 (pyridoxine), OTC analgesics (eg, acetaminophen, ibuprofen), and supportive measures (eg, cool compresses, minimizing manual tasks).

Lichen Simplex Chronicus

(Neurodermatitis)

Lichen simplex chronicus is eczema caused by repeated scratching; by several mechanisms, chronic scratching causes further itching, creating a vicious circle. Diagnosis is by examination.

[Table 76-3. Differential Diagnosis of Hand Dermatitis]

Treatment is through education and behavioral techniques to prevent scratching and corticosteroids and antihistamines.

Etiology

Lichen simplex chronicus is thickening of the skin with variable scaling that arises secondary to repetitive scratching or rubbing. Lichen simplex chronicus is not a primary process. Perceived pruritus in a specific area of skin (with or without underlying pathology) provokes rubbing and mechanical trauma, resulting in secondary lichenification and further pruritus. Lichen simplex chronicus frequently occurs in people with anxiety disorders and nonspecific emotional stress as well as in patients with any type of underlying chronic dermatitis.

Pathophysiology

The underlying pathophysiology is unknown but may involve alterations in the way the nervous system perceives and processes itchy sensations. Skin that tends toward eczematous conditions (eg, atopic dermatitis) is more prone to lichenification.

Symptoms and Signs

Lichen simplex chronicus is characterized by pruritic, dry, scaling, hyperpigmented, lichenified plaques in irregular, oval, or angular shapes. It involves easily reached sites, most commonly the legs, arms, neck, and upper trunk.

Diagnosis

• Clinical evaluation

Diagnosis is by examination. A fully developed plaque has an outer zone of discrete, brownish papules and a central zone of confluent papules covered with scales. Look-alike conditions include tinea corporis, lichen planus, and psoriasis; lichen simplex chronicus can be distinguished from these by potassium hydroxide wet mount and biopsy.

Treatment

• Education and behavioral techniques

• Corticosteroids (most often topical but sometimes intralesional)

• Antihistamines

Primary treatment is patient education about the effects of scratching and rubbing. Secondary treatment is topical corticosteroids (eg, triamcinolone acetonide, fluocinonide); surgical tape impregnated with flurandrenolide (applied in the morning and replaced in the evening) may be preferred because occlusion prevents scratching. Small areas may be locally infiltrated (intralesional injections) with a long-acting corticosteroid such as triamcinolone acetonide 2.5 mg/mL (diluted with saline), 0.3 mL/cm^2 of lesion; treatment can be repeated every 3 to 4 wk. Oral H_1-blocking antihistamines may be useful. Emollients may also be helpful.

Nummular Dermatitis

Nummular (discoid) dermatitis is inflammation of the skin characterized by coin-shaped or disc-shaped lesions. Diagnosis is clinical. Treatment may include antibiotics, corticosteroids, and ultraviolet light therapy.

Nummular dermatitis is most common among middle-aged patients and is often associated with dry skin, especially during the winter. The cause is unknown.

Symptoms and Signs

Discoid lesions often start as patches of confluent vesicles and papules that later ooze serum and form crusts. Lesions are eruptive, widespread, and pruritic. They are often more prominent on the extensor aspects of the extremities and on the buttocks but also appear on the trunk. Exacerbations and remissions may occur, and when they do, new lesions tend to reappear at the sites of healed lesions.

Diagnosis

Diagnosis is clinical based on the characteristic appearance and distribution of the skin lesions.

Treatment

• Supportive care

• Antibiotics

• Corticosteroids (most often topical, but sometimes intralesional or oral)

• Ultraviolet light therapy

No treatment is uniformly effective. Oral antibiotics (eg, dicloxacillin or cephalexin 250 mg qid) may be given, along with use of tap water compresses, especially when weeping and pus are present. Less inflamed lesions may respond to tetracycline 250 mg po qid, which has a beneficial (although not necessarily antibacterial) effect. Corticosteroid cream or ointment should be rubbed in 3 times daily. An occlusive dressing with a corticosteroid cream under polyethylene film or with flurandrenolide-impregnated tape can be applied at bedtime. Intralesional corticosteroid injections may be beneficial for the few lesions that do not respond to therapy. In more widespread, resistant, and recurrent cases, ultraviolet B radiation alone or oral psoralen plus ultraviolet A (PUVA) radiation may be helpful. Occasionally, oral corticosteroids are required, but long-term use should be avoided; a reasonable starting dose is prednisone 40 mg every other day.

Seborrheic Dermatitis

Seborrheic dermatitis (SD) is inflammation of skin that has a high density of sebaceous glands (eg, face, scalp, upper trunk). The cause is unknown, but *Pityrosporum ovale*, a normal skin organism, plays some role. SD occurs with increased frequency in patients with HIV and in those with certain neurologic disorders. SD causes occasional pruritus, dandruff, and yellow, greasy scaling along the hairline and on the face. Diagnosis is made by examination. Treatment is tar or other medicated shampoo and topical corticosteroids and antifungals.

Despite the name, the composition and flow of sebum are usually normal. The pathogenesis of SD is unclear, but its activity has been linked to the number of *Pityrosporum* yeasts present on the skin. The incidence and severity of disease seem to be affected by genetic factors, emotional or physical stress, and climate (usually worse in cold weather). SD may precede or be associated with psoriasis (called seborrhiasis). SD may be more common and more severe among patients with neurologic disorders (especially Parkinson's disease) or HIV/AIDS. Very rarely, the dermatitis becomes generalized.

Symptoms and Signs

Symptoms develop gradually, and the dermatitis is usually apparent only as dry or greasy diffuse scaling of the scalp (dandruff) with variable pruritus. In severe disease, yellow-red scaling papules appear along the hairline, behind the ears, in the external auditory canals, on the eyebrows, in the axillae, on the bridge of the nose, in the nasolabial folds, and over the sternum. Marginal blepharitis with dry yellow crusts and conjunctival irritation may develop. SD does not cause hair loss.

Neonates may develop SD with a thick, yellow, crusted scalp lesion (cradle cap); fissuring and yellow scaling behind the ears; red facial papules; and stubborn diaper rash. Older children may develop thick, tenacious, scaly plaques on the scalp that may measure 1 to 2 cm in diameter.

Diagnosis

• Clinical evaluation

Diagnosis is made by physical examination. SD may occasionally be difficult to distinguish from other disorders, including psoriasis, atopic dermatitis or contact dermatitis, tinea, and rosacea.

Treatment

• Topical therapy

Adults: In adults, zinc pyrithione, selenium sulfide, sulfur and salicylic acid, or tar shampoo should be used daily or every other day until dandruff is controlled and twice/wk thereafter. A corticosteroid lotion (eg, 0.01% fluocinolone acetonide solution, 0.025% triamcinolone acetonide lotion) can be rubbed into the scalp or other hairy areas twice daily until scaling and redness are controlled. For SD of the postauricular areas, nasolabial folds, eyelid margins, and bridge of the nose, 1% hydrocortisone cream is rubbed in 2 or 3 times daily, decreasing to once/day when SD is controlled; hydrocortisone cream is the safest corticosteroid for the face because fluorinated corticosteroids may cause adverse effects (eg, telangiectasia, atrophy, perioral dermatitis). In some patients, 2% ketoconazole cream or other topical imidazoles applied twice daily for 1 to 2 wk induce a remission that lasts for months. For eyelid margin seborrhea, a dilution of 1 part baby shampoo to 9 parts water is applied with a cotton swab.

Infants and children: In infants, a baby shampoo is used daily, and 1% hydrocortisone cream is rubbed in twice daily. For thick lesions on the scalp of a young child, 2% salicylic acid in olive oil or a corticosteroid gel is applied at bedtime to affected areas and rubbed in with a toothbrush. The scalp is shampooed daily until the thick scale is gone.

Stasis Dermatitis

Stasis dermatitis is inflammation of the skin of the lower legs caused by chronic venous insufficiency. Symptoms are itching, scaling, hyperpigmentation, and sometimes ulceration.

Diagnosis is clinical. Treatment is directed at the chronic venous insufficiency and preventing occurrence or progression of associated ulcers.

Stasis dermatitis occurs in patients with chronic venous insufficiency (see p. 2231) because pooled venous blood in the legs compromises the endothelial integrity in the microvasculature, resulting in fibrin leakage, local inflammation, and local cell necrosis.

Symptoms and Signs

Initially, hyperpigmentation and red-brown discoloration from RBC extravasation appear. Later, eczematous changes develop and manifest as erythema, scaling, weeping, and crusting (see Plate 46), all of which can be made worse by bacterial superinfection or by contact dermatitis caused by the many topical treatments often applied. When chronic venous insufficiency and stasis dermatitis are both inadequately treated, stasis dermatitis progresses to frank skin ulceration (see Plate 47), chronic edema, thickened fibrotic skin, or lipodermatosclerosis (a painful induration resulting from panniculitis, which, if severe, gives the lower leg an inverted bowling pin shape with enlargement of the calf and narrowing at the ankle).

Diagnosis

Diagnosis is clinical based on the characteristic appearance of the skin lesions and other signs of chronic venous insufficiency.

Treatment

• Elevation, compression, and dressings

• Sometimes topical or oral antibiotics

Chronic venous insufficiency must be adequately treated with leg elevation and compression stockings (see p. 2232). For acute stasis dermatitis (characterized by crusts, exudation, and superficial ulceration), continuous and then intermittent tap water compresses should be applied. For a weeping lesion, a hydrocolloid dressing may be best. For less acute dermatitis, a corticosteroid cream or ointment should be applied 3 times/day or incorporated into zinc oxide paste.

Ulcers are best treated with compresses and bland dressings (eg, zinc oxide paste); other dressings (eg, hydrocolloids) are also effective (see also p. 740). Ulcers in ambulatory patients may be healed with Unna's paste boot (zinc gelatin), the less messy zinc gelatin bandage, or a colloid dressing (all are available commercially). Colloid-type dressings used under elastic support are more effective than Unna's paste boot. It may be necessary to change the dressing every 2 or 3 days, but as edema recedes and the ulcer heals, once or twice/wk is sufficient. After the ulcer heals, an elastic support should be applied before the patient rises in the morning. Regardless of the dressing used, reduction of edema (usually with compression) is paramount for healing.

Oral antibiotics (eg, cephalosporins, dicloxacillin) are used to treat superimposed cellulitis. Topical antibiotics (eg, mupirocin, silver sulfadiazine) are useful for treating erosions and ulcers. When edema and inflammation subside, split-thickness skin grafts may be needed for large ulcers.

Complex or multiple topical drugs or OTC remedies should not be used. The skin in stasis dermatitis is more vulnerable to direct irritants and to potentially sensitizing topical agents (eg, antibiotics; anesthetics; vehicles of topical drugs, especially lanolin or wool alcohols).

Chapter 77. Reactions to Sunlight

Introduction

The skin may respond to excessive sunlight in several ways: various chronic changes (eg, dermatoheliosis, actinic keratoses), photosensitivity, or sunburn.

Ultraviolet (UV) radiation: Although the sun emits a wide range of UV electromagnetic radiation (ie, UVA, 320 to 400 nm; UVB, 280 to 320 nm; UVC, 100 to 280 nm), only UVA and UVB reach the earth's surface. The character and amount of such radiation vary greatly with the seasons and with changing atmospheric conditions. Exposure of skin to sunlight depends on multiple lifestyle factors, (eg, clothing, occupation), geographic factors (eg, altitude, latitude), and time of year (UV intensity is higher in summer).

Sunburn-producing rays (primarily wavelengths < 320 nm) are filtered out by glass and to a great extent by smoke and smog. Sunburn-producing rays may pass through light clouds, fog, or 30 cm of clear water, causing severe burns in unsuspecting people. Snow, sand, and water enhance exposure by reflecting the rays. Stratospheric ozone, which filters out shorter wavelengths of UV, is depleted by man-made chlorofluorocarbons (eg, in refrigerants and aerosols). A decreased ozone layer increases inadvertent exposure to UVA and UVB.

Sun-tanning lamps use artificial light that is more UVA than UVB. This UVA use is often advertised as a "safer" way to tan; however, many of the same long-term deleterious effects may occur as with UVB exposure, including photoaging and skin cancer. Quite simply, there is no "safe tan."

Pathophysiology

After exposure to sunlight, the epidermis thickens, and melanocytes produce the pigment melanin at an increased rate, causing tanning. Tanning provides some natural protection against future exposure. Exposure leads to both inactivation and loss of epidermal Langerhans' cells, which are immunologically important.

People differ greatly in their sensitivity and response to sunlight based on the amount of melanin in their skin. Skin is classified into 6 types (I to VI) in decreasing order of susceptibility to sun injury. Classification is based on skin color, UV sensitivity, and response to sun exposure. Skin type I is white to lightly pigmented, very sensitive to UV light, has no immediate pigment darkening, always burns easily, and never tans. Skin type VI is dark brown or black, least sensitive to UV light, has significant immediate pigment darkening, and tans profusely (deep black). Dark-skinned people are not immune to the effects of the sun and can become sunburned with strong or prolonged exposure. Long-term effects of UV exposure in dark-skinned people are the same as those in light-skinned people but are often delayed and less severe. People with blonde or red hair are especially susceptible to the acute and chronic effects of UV radiation. Uneven melanocyte activation occurs in many fair-haired people and results in freckling. There is no skin pigmentation in people with albinism (see p. 719) because of a defect in melanin metabolism. Patchy areas of depigmentation are present in patients with vitiligo (see p. 720) because of immunologic destruction of melanocytes.

Prevention

Avoidance: Simple precautions help prevent sunburn and the chronic effects of sunlight. These precautions are recommended for people of all skin types, particularly those who are fair skinned and burn easily. Exposure to bright midday sun should not be > 30 min, even for people with dark skin. In temperate zones, exposure is less hazardous before 10 AM and after 3 PM because more sunburn-producing wavelengths are filtered out. Fog and clouds do not reduce risk, and risk is increased at high altitude.

Clothing: Skin should be covered. Fabrics with a tight weave block the sun better than do those with a loose weave. Special clothing that provides high sun protection is commercially available. Broad-brimmed hats protect the face, ears, and neck. Regular use of UV-protective, wrap-around sunglasses helps shield

the eyes.

Sunscreens: Although sunscreens help protect the skin from sunburn and chronic sun damage, they do not always prevent damage. Older sunscreens tended to filter only UVB light, but many newer sunscreens are now "full spectrum" and effectively filter UVA light as well. In the US, the FDA rates sunscreens by sun protection factor (SPF): the higher the number, the greater the protection. Agents with SPF ≥ 15 are recommended. The SPF, however, only quantifies the protection against UVB exposure; there is no scale for UVA protection.

Sunscreens are available in a wide variety of formulations, including creams, gels, foams, sprays, and sticks. Self-tanning products do not provide significant protection from UV exposure.

Most sunscreens contain several agents that function as chemical screens, absorbing light or providing a physical screen that reflects or scatters light. Common chemical sunscreen agents mostly absorb UVB rays and include the aminobenzoates, which include *p*-aminobenzoic acid (PABA), salicylates, cinnamates, benzophenones (eg, avobenzone), and the anthrilates (an aminobenzoate derivative). Of these, the benzophenones are particularly effective at screening UVA rays.

Other sunscreens, called sunblocks, contain zinc oxide and titanium dioxide, which physically block both UVB and UVA rays. Micronized formulations of these products have significantly improved their cosmetic acceptability.

Sunscreen failure is common and usually results from insufficient application of the product, application too late (sunscreens should optimally be applied 30 min before exposure), or failure to reapply after swimming or exercise.

Allergic or photoallergic reactions to sunscreens must be distinguished from other photosensitive skin eruptions. Patch or photopatch testing with sunscreen components may be necessary to make the diagnosis. This testing is usually done by dermatologists with a particular expertise in allergic contact dermatitis.

Chronic Effects of Sunlight

Aging: Chronic exposure to sunlight ages the skin (dermatoheliosis, extrinsic aging), producing both fine and coarse wrinkles, rough leathery texture, mottled pigmentation, and telangiectasia. The atrophic effects in some people may resemble those seen after x-ray therapy (chronic radiation dermatitis).

Actinic keratoses: Actinic keratoses are precancerous changes in skin cells (keratinocytes) that are a frequent, disturbing consequence of many years of sun exposure. People with blonde or red hair, blue eyes, and skin type I or II are particularly susceptible.

The keratoses are usually pink or red, poorly marginated, and scaly on palpation, although some are light gray or pigmented, giving them a brown appearance. They should be differentiated from seborrheic keratoses (see p. 746), which increase in number and size with aging. Seborrheic keratoses tend to appear waxy and stuck-on but can often take on an appearance similar to actinic keratoses. Close inspection usually reveals distinguishing characteristics of the lesion. Unlike actinic keratoses, seborrheic keratoses also occur on non-sun-exposed areas of the body and are not premalignant.

Skin cancers (see p. 748)**:** The incidence of squamous cell carcinoma and basal cell carcinoma in fair, light-skinned people is directly proportional to the total annual sunlight in the area. Such lesions are especially common among people who were extensively exposed to sunlight as children and adolescents and among those who are chronically exposed to the sun as part of their profession or recreational activities (eg, athletes, farmers, ranchers, sailors, frequent sunbathers). Sun exposure also substantially increases the risk of malignant melanomas.

Treatment

Various combination therapies, including chemical peels, 5-fluorouracil (5-FU), topical α-hydroxy acids,

imiquimod, photodynamic therapy, and tretinoin, have been used to reduce carcinogenic changes and improve the cosmetic appearance of chronically sun-damaged skin. These therapies are often effective in ameliorating superficial skin changes (eg, coarse and fine wrinkles, irregular pigmentation, sallowness, roughness, minor laxity) but have a much less pronounced effect on deeper changes (eg, telangiectasias). Lasers are capable of treating both superficial and deep changes in the dermis and are used to treat cosmetic and precancerous skin changes. Many chemicals are used in OTC cosmetic products without significant evidence that they improve chronic changes of the skin caused by sunlight.

Actinic keratoses: There are several options, depending on the number and location of lesions.

• Liquid nitrogen

• Topical 5-FU

• Topical imiquimod

If only a few actinic keratoses are present, cryotherapy (freezing with liquid nitrogen) is the most rapid and satisfactory treatment.

If there are too many lesions to freeze, topical 5-FU applied to the affected area nightly or twice daily for 2 to 6 wk often clears the majority of lesions. Several strengths and formulations of 5-FU are commercially available. Many patients tolerate 0.5% 5-FU cream applied once/day for 4 wk on the face better than stronger concentrations. Actinic keratoses on the arms may require stronger concentrations, such as 5% cream. Topical 5-FU produces a brisk reaction, with redness, scaling, and burning, often affecting areas with no visible actinic keratoses. If the reaction is too brisk, application may be suspended for 1 to 3 days. Topical 5-FU has few significant adverse effects except for this unsightly and uncomfortable reaction, which can be masked by cosmetics and, when necessary, suppressed with topical corticosteroids. 5-FU should not be used to treat basal cell carcinomas, except those shown by biopsy to be of the superficial type.

A relatively new drug, imiquimod, is often used for treatment of actinic keratoses and superficial basal cell carcinomas. It stimulates the immune system to recognize and destroy cancerous skin lesions. For treatment of skin cancers, see Ch. 90.

Photosensitivity

Photosensitivity is a poorly understood cutaneous reaction to sunlight probably involving the immune system. It may be idiopathic or occur after exposure to certain drugs or chemicals, and it is sometimes a feature of systemic disorders (eg, SLE, porphyria, pellagra, xeroderma pigmentosum). Diagnosis is clinical. Treatment varies by type.

In addition to the acute and chronic effects of sunlight, a variety of unusual reactions may occur soon after only a brief sun exposure. Unless the cause is obvious, patients with pronounced photosensitivity should be evaluated for systemic or cutaneous disorders associated with light sensitivity such as SLE (see p. 305) and porphyria (see p. 807). Treatment for chemical photosensitivity is topical corticosteroids and avoidance of the causative substance.

Solar urticaria: In certain patients, urticaria develops at a site of sun exposure within a few minutes. Rarely, if large areas are involved, syncope, dizziness, wheezing, and other systemic symptoms may develop. Etiology is unclear but may involve endogenous skin constituents functioning as photoallergens, leading to mast cell degranulation as in other types of urticaria. Solar urticaria can be distinguished from other types of urticaria in that wheals in solar urticaria occur only on exposed skin after ultraviolet (UV) light exposure. Solar urticaria can be classified based on the component of the UV spectrum (UVA, UVB, and visible light) that produces them. Treatment can be difficult and may include H_1 blockers, antimalarial drugs, topical corticosteroids, sunscreens, and psoralen UV light (PUVA). The wheals of solar urticaria usually last just minutes to hours, but the disorder is chronic and can wax and wane over years.

Chemical photosensitivity: Over 100 substances, ingested or applied topically, are known to

predispose to cutaneous reactions following sun exposure. A limited number are responsible for most reactions (see Table 77-1). Reactions are divided into phototoxicity and photoallergy.

In **phototoxicity**, light-absorbing compounds directly generate free radicals and inflammatory mediators, causing tissue damage manifesting as pain and erythema (like sunburn). This reaction does not require prior sun exposure and can appear in any person, although reaction is highly variable. Typical causes of phototoxic reactions include topical (eg, perfumes, coal tar) or ingested (eg, tetracyclines, psoralen-containing plants) agents. Phototoxic reactions do not generalize to non-sun-exposed skin.

Photoallergy is a type IV (cell-mediated) immune response; light absorption causes structural changes in the drug or substance, allowing it to bind to tissue protein and function as a hapten. Prior exposure is required. Typical causes of photoallergic reactions include aftershave lotions, sunscreens, and sulfonamides. Reaction may extend to non-sun-exposed skin. Symptoms include erythema, pruritus, and sometimes vesicles.

[**Table 77-1.** Some Substances that Sensitize the Skin to Sunlight]

Polymorphous light eruption: These eruptions are unusual reactions to light that do not seem to be associated with systemic disease or drugs. Eruptions appear on sun-exposed areas, usually 30 min to several hours after exposure. Lesions are pruritic, erythematous, and often papular but may be papulovesicular or plaquelike. They are most common among women and people from northern climates when first exposed to spring or summer sun than among those exposed to sun year-round. Lesions subside within several days to 1 wk or so. Actinic prurigo is a similar (perhaps related) phenomenon with more nodular-appearing lesions that may persist year-round, worsening with sun exposure.

Diagnosis is made by history, skin findings, and exclusion of other sun-sensitivity disorders. Diagnosis sometimes requires reproduction of the lesions with artificial or natural sunlight when the patient is not using any potentially sensitizing drugs.

Often, lesions are self-limited and spontaneously improve as summer progresses. Treatment is by moderating sun exposure and applying topical corticosteroids. More severely affected patients may benefit from desensitization by graduated exposure to UV light with PUVA (see p. 679) or narrow band UVB (312 nm) phototherapy. Patients with disabling disease may require a course of oral immunosuppressive therapy such as prednisone, azathioprine, cyclosporine, or hydroxychloroquine.

Sunburn

Sunburn is characterized by erythema and sometimes pain and blisters caused by exposure to solar ultraviolet radiation. Treatment is similar to that for thermal burns, including cool compresses, NSAIDs, and, for severe cases, sterile dressings and topical antimicrobials. Prevention by sun avoidance and use of sunscreens is crucial.

Sunburn results from overexposure of the skin to ultraviolet (UV) radiation; wavelengths in the UVB spectrum (280 to 320 nm) cause the most pronounced effects.

Symptoms and Signs

Symptoms and signs appear in 1 to 24 h and, except in severe reactions, peak within 72 h. Skin changes range from mild erythema, with subsequent superficial scaling, to pain, swelling, skin tenderness, and blisters. Constitutional symptoms (eg, fever, chills, weakness, shock), similar to a thermal burn, may develop if a large portion of the body surface is affected; these symptoms may be caused by the release of inflammatory cytokines such as IL-1.

Secondary infection, blotchy pigmentation, and miliaria-like eruptions are the most common late complications. Exfoliated skin may be extremely vulnerable to sunlight for several weeks.

Treatment

• Supportive measures

Further exposure should be avoided until sunburn has completely subsided. Cold tap water compresses and oral NSAIDs help relieve symptoms, as may topical aloe vera. Topical corticosteroids are no more effective than cool compresses. Blistered areas should be managed similarly to other partial-thickness burns (see p. 3246), with sterile dressings and topical bacitracin or silver sulfadiazine. Ointments or lotions containing local anesthetics (eg, benzocaine) should be avoided because of the risk of allergic contact dermatitis.

Early treatment of extensive, severe sunburn with a systemic corticosteroid (eg, prednisone 20 to 30 mg po bid for 4 days for adults or teenagers) may decrease the discomfort, but this use is controversial.

Prevention

Simple precautions (eg, avoiding the sun especially during midday, wearing tightly woven clothing, using sunscreens) usually prevent most cases of sunburn (see p. 673).

Chapter 78. Psoriasis and Scaling Diseases

Introduction

Psoriasis, parapsoriasis, pityriasis rosea, pityriasis rubra pilaris, pityriasis lichenoides, lichen planus, and lichen sclerosus are dissimilar disorders grouped together because their primary lesions have similar characteristics: sharply marginated, scaling papules or plaques without wetness, crusts, fissures, and excoriations. Lesion appearance and distribution distinguish these diseases from each other.

Psoriasis

Psoriasis is an inflammatory disease that manifests most commonly as well-circumscribed, erythematous papules and plaques covered with silvery scales. Cause is unclear but seems to involve the immune system. Common triggers include trauma, infection, and certain drugs. Symptoms are usually minimal with occasional mild itching, but cosmetic implications may be major. Some people develop severe disease with painful arthritis. Diagnosis is based on appearance and distribution of lesions. Treatment is with emollients, vitamin D analogs, retinoids, tar, anthralin, corticosteroids, phototherapy, and, when severe, methotrexate, retinoids, immunomodulatory agents (biologics), or immunosuppressants.

Psoriasis is hyperproliferation of epidermal keratinocytes combined with inflammation of the epidermis and dermis. It affects about 1 to 5% of the population worldwide; light-skinned people are at greater risk. Peak onset is roughly bimodal, most often at ages 16 to 22 and at ages 57 to 60, but the disorder can occur at any age.

Etiology

The cause is unclear but involves immune stimulation of epidermal keratinocytes; T cells seem to play a central role. Family history is common, and certain genes and HLA antigens (Cw6, B13, B17) are associated with psoriasis. An environmental trigger is thought to evoke an inflammatory response and subsequent hyperproliferation of keratinocytes.

Well-identified triggers include

- Injury (Koebner phenomenon)
- Sunburn
- HIV
- β-Hemolytic streptococcal infection
- Drugs (especially β-blockers, chloroquine, lithium, ACE inhibitors, indomethacin, terbinafine, and interferon alfa)
- Emotional stress
- Alcohol consumption

Symptoms and Signs

Lesions are either asymptomatic or pruritic and are most often localized on the scalp, extensor surfaces of the elbows and knees, sacrum, buttocks, and penis. The nails, eyebrows, axillae, umbilicus, and perianal region may also be affected. The disease can be widespread, involving confluent areas of skin extending between these regions. Lesions differ in appearance depending on type.

Among the various subtypes (see Table 78-1), plaque psoriasis (psoriasis vulgaris or chronic plaque psoriasis) is the most common pattern;

lesions are discrete, erythematous papules or plaques covered with thick, silvery, shiny scales. Lesions appear gradually and remit and recur either spontaneously or with appearance and resolution of triggers.

Arthritis develops in 5 to 30% of patients and can be disabling (see p. 344); joint destruction may ultimately occur.

Psoriasis is rarely life-threatening but can affect a patient's self-image. Besides image, the sheer amount of time required to treat extensive skin or scalp lesions and to maintain clothing and bedding may adversely affect quality of life.

Diagnosis

• Clinical evaluation

• Rarely biopsy

Diagnosis is most often by clinical appearance and distribution of lesions. Differential diagnosis includes seborrheic dermatitis, dermatophytoses, cutaneous lupus erythematosus, eczema, lichen planus, pityriasis rosea, squamous cell carcinoma in situ (Bowen's disease, especially when on the trunk), lichen simplex chronicus, and secondary syphilis. Biopsy is rarely necessary and may not be diagnostic.

Disease is graded as mild, moderate, or severe based on the body surface area affected and how the lesions affect patients' quality of life. There are many more complex scoring systems for disease severity (eg, the Psoriasis Area and Severity Index), but these systems are useful mainly in research protocols.

Treatment

• Topical treatments

• Systemic treatments

• Ultraviolet (UV) light therapy

Treatment options are extensive and include emollients, salicylic acid, coal tar, anthralin, corticosteroids, vitamin D_3 analogs, methotrexate, topical and oral retinoids, topical and oral calcineurin inhibitors, immunosuppressants, immunomodulatory agents (biologics), and ultraviolet light therapy.

Topical treatments: Emollients include emollient creams, ointments, petrolatum, paraffin, and even hydrogenated vegetable (cooking) oils. They reduce scaling and are most effective when applied twice daily and immediately after bathing. Lesions may appear redder as scaling decreases or becomes more transparent. Emollients are safe and should probably always be used for mild to moderate plaque psoriasis.

Salicylic acid is a keratinolytic that softens scales, facilitates their removal, and increases absorption of other topical agents. It is especially useful as a component of scalp treatments; scalp scale can be quite thick.

Coal tar ointments, solutions, or shampoos are anti-inflammatory and decrease keratinocyte hyperproliferation via an unknown mechanism. They are typically applied at night and washed off in the morning. They can be used in combination with topical corticosteroids or with exposure to natural or artificial broad-band UVB light (280 to 320 nm) in slowly increasing increments (Goeckerman regimen).

Anthralin is a topical antiproliferative, anti-inflammatory agent. Its mechanism is unknown. Effective dose is 0.1% cream or ointment increased to 1% as tolerated. Anthralin may be irritating and should be used with caution in intertriginous areas; it also stains. Irritation and staining can be avoided

[**Table 78-1.** Subtypes of Psoriasis]

by washing off the anthralin 20 to 30 min after application. Using a liposome-encapsulated preparation may also avoid some disadvantages of anthralin.

Corticosteroids are usually used topically but may be injected into small or recalcitrant lesions. (CAUTION: *Systemic corticosteroids may precipitate exacerbations or development of pustular psoriasis and should not be used to treat psoriasis.*) Topical corticosteroids are used twice daily, sometimes with anthralin or coal tar applied at bedtime. Corticosteroids are most effective when used overnight under occlusive polyethylene coverings or incorporated into tape; a corticosteroid cream is applied without occlusion during the day. Corticosteroid potency (see p. 647) is selected according to the extent of involvement. As lesions abate, the corticosteroid should be applied less frequently or at a lower potency to minimize local atrophy, striae formation, and telangiectases. Ideally, after about 3 wk, an emollient should be substituted for the corticosteroid for 1 to 2 wk (as a rest period); this substitution limits corticosteroid dosage and prevents tachyphylaxis. Topical corticosteroid use can be expensive because large quantities (about 1 oz or 30 g) are needed for each application when a large body surface area is affected. Topical corticosteroids applied for long duration to large areas of the body may cause systemic effects and exacerbate psoriasis. For small, thick, localized, or recalcitrant lesions, high-potency corticosteroids are used with an occlusive dressing or flurandrenolide tape; these dressings are left on overnight and changed in the morning. Relapse after topical corticosteroids are stopped is often faster than with other agents.

Vitamin D_3 analogs (eg, calcipotriol, calcitriol) are topical vitamin D analogs that induce normal keratinocyte proliferation and differentiation; they can be used alone or in combination with topical corticosteroids. Some clinicians have patients apply calcipotriol on weekdays and corticosteroids on weekends.

Calcineurin inhibitors (eg, tacrolimus, pimecrolimus) are available in topical form and are generally well-tolerated. They are not as effective as corticosteroids but may avoid the complications of corticosteroids when treating facial and intertriginous psoriasis. They may be associated with an increased risk of lymphoma and skin cancer.

Tazarotene is a topical retinoid. It is less effective than corticosteroids as monotherapy but is a useful adjunct.

Systemic treatments: Methotrexate taken orally is the most effective treatment for severe disabling psoriasis, especially severe psoriatic arthritis or widespread erythrodermic or pustular psoriasis unresponsive to topical agents or psoralen plus ultraviolet A (PUVA) light therapy. Methotrexate seems to interfere with the rapid proliferation of epidermal cells. Hematologic, renal, and hepatic function should be monitored. Dosage regimens vary, so only physicians experienced in its use for psoriasis should undertake methotrexate therapy.

Systemic retinoids (eg, acitretin, isotretinoin) may be effective for severe and recalcitrant cases of psoriasis vulgaris, pustular psoriasis (in which isotretinoin may be preferred), and hyperkeratotic palmoplantar psoriasis. Because of the teratogenic potential and long-term retention of acitretin in the body, women who use it must not be pregnant and should be warned against becoming pregnant for at least 2 yr after treatment ends. Pregnancy restrictions also apply to isotretinoin, but the agent is not retained in the body beyond 1 mo. Long-term treatment may cause diffuse idiopathic skeletal hyperostosis (DISH—see p. 342).

Immunosuppressants can be used for severe psoriasis. Cyclosporine is a commonly used immunosuppressant. It should be limited to courses of several months (rarely, up to 1 yr) and alternated with other therapies. Its effect on the kidneys and potential long-term effects on the immune system preclude more liberal use. Other immunosuppressants (eg, hydroxyurea, 6-thioguanine, mycophenolate mofetil) have narrow safety margins and are reserved for severe, recalcitrant psoriasis.

Immunomodulatory agents (biologics—see p. 1086) include tumor necrosis factor (TNF)-α inhibitors (etanercept, adalimumab, infliximab) and the T-cell modulator alefacept. TNF-α inhibitors lead to clearing of psoriasis, but their safety profile is still under study. Efalizumab is no longer available in the US due to increased risk of progressive multifocal

leukoencephalopathy.

Phototherapy: UV light therapy is typically used in patients with extensive psoriasis. The mechanism of action is unknown, although UVB light reduces DNA synthesis and can induce mild systemic immunosuppression. In PUVA, oral methoxypsoralen, a photosensitizer, is followed by exposure to long-wave UVA light (330 to 360 nm). PUVA has an antiproliferative effect and also helps to normalize keratinocyte differentiation. Doses of light are started low and increased as tolerated. Severe burns can result if the dose of drug or UVA is too high. Although the treatment is less messy than topical treatment and may produce remissions lasting several months, repeated treatments may increase the incidence of UV-induced skin cancer and melanoma. Less UV light is required when used with oral retinoids (the so-called re-PUVA regimen). Narrow-band UVB light (311 to 312 nm) used without psoralens is similar in effectiveness to PUVA. Excimer laser therapy is a type of phototherapy using extremely pure wavelengths.

Choice of therapy: Choice of specific agents and combinations requires close cooperation with the patient, always keeping in mind the untoward effects of the treatments. There is no single ideal combination or sequence of agents, but treatment should be kept as simple as possible. Monotherapy is preferred, but combination therapy is the norm. Rotational therapy refers to the substitution of one therapy for another after 1 to 2 yr to reduce the adverse effects caused by chronic use and to circumvent disease resistance. Sequential therapy refers to initial use of potent agents (eg, cyclosporine) to quickly gain control followed by use of agents with a better safety profile.

Mild plaque psoriasis can be treated with emollients, keratolytics, tar, topical corticosteroids, vitamin D_3 analogs, or anthralin alone or in combination. Exposure to sunlight is beneficial, but sunburn can induce exacerbations.

Moderate to severe plaque psoriasis should be treated with topical agents and either phototherapy or systemic agents. Immunosuppressants are used for quick, short-term control (eg, in allowing a break from other modalities) and for the most severe disease. Immunomodulatory agents (biologics) are used for moderate to severe disease unresponsive to other agents.

Scalp plaques are notoriously difficult to treat because they resist systemic therapy, and because hair blocks application of topical agents and scale removal and shields skin from UV light. A suspension of 10% salicylic acid in mineral oil may be rubbed into the scalp at bedtime manually or with a toothbrush, covered with a shower cap (to enhance penetration and avoid messiness), and washed out the next morning with a tar (or other) shampoo. More cosmetically acceptable corticosteroid solutions can be applied to the scalp during the day. These treatments are continued until the desired clinical response is achieved. Resistant skin or scalp patches may respond to local superficial intralesional injection of triamcinolone acetonide suspension diluted with saline to 2.5 or 5 mg/mL, depending on the size and severity of the lesion. Injections may cause local atrophy, which is usually reversible.

Special treatment needs for subtypes are described in Table 78-1.

For psoriatic arthritis, treatment with systemic therapy is important to prevent joint destruction; methotrexate or a TNF-α inhibitor may be effective.

Parapsoriasis

Parapsoriasis describes a poorly understood and poorly distinguished group of diseases that share clinical features. There are 2 general forms: a small-plaque type, which is usually benign, and a large-plaque type, which is a precursor of cutaneous T-cell lymphoma (CTCL). It is extremely rare for small-plaque parapsoriasis to transform into CTCL.

The plaques are usually asymptomatic; their typical appearance is thin, scaling, dull pink patches and plaques with a slightly atrophic or wrinkled appearance. Small-plaque parapsoriasis is defined by lesions < 5 cm in diameter, whereas large-plaque parapsoriasis has lesions > 6 cm in diameter. Sometimes digitate plaques develop along the dermatomes, especially on the flanks and abdomen, in small-plaque parapsoriasis.

Treatment of small-plaque parapsoriasis is unnecessary but can include emollients, topical tar preparations or corticosteroids, phototherapy, or a combination. Treatment of large-plaque parapsoriasis is phototherapy or topical corticosteroids.

Course for both types is unpredictable; periodic clinical follow-up and biopsies give the best indication of risk of developing CTCL.

Pityriasis Rosea

Pityriasis rosea (PR) is an inflammatory disease characterized by diffuse, scaling papules or plaques. Treatment is usually unnecessary.

PR most commonly occurs between ages 10 and 35. It affects women more often and peaks in incidence in cooler months in temperate climates. The cause may be viral infection (some research has implicated human herpesviruses 6 and 7). Drugs may cause a PR-like reaction.

Symptoms and Signs

The condition classically begins with a single, primary, 2- to 10-cm herald patch that appears on the trunk or proximal limbs (see Plate 42). A general centripetal eruption of 0.5- to 2-cm rose- or fawn-colored oval papules and plaques follows within 7 to 14 days. The lesions have a scaly, slightly raised border (collarette) and resemble ringworm (tinea corporis). Most patients itch, occasionally severely. Papules may dominate with little or no scaling in blacks, children, and pregnant women. The rose or fawn color is not as evident in blacks; blacks also more commonly have inverse PR (lesions in the axillae or groin that spread centrifugally). Classically, lesions orient along skin lines, giving PR a Christmas tree-like distribution when multiple lesions appear on the back. A prodrome of malaise and headache precedes the lesions in a minority of patients.

Diagnosis

• Clinical evaluation

Diagnosis is based on clinical appearance and distribution. Differential diagnosis includes tinea corporis, tinea versicolor, drug eruptions, psoriasis, parapsoriasis, pityriasis lichenoides chronica, lichen planus, and secondary syphilis. Serologic testing for syphilis is indicated when the palms or soles are affected, when a herald patch is not seen, or when lesions occur in an unusual sequence or distribution.

Treatment

• Antipruritic therapy

No specific treatment is necessary because the eruption usually remits within 5 wk and recurrence is rare. Artificial or natural sunlight may hasten resolution. Antipruritic therapy such as topical corticosteroids, oral antihistamines, or topical measures may be used as needed.

Pityriasis Rubra Pilaris

Pityriasis rubra pilaris is a rare chronic disorder that causes hyperkeratotic yellowing of the palms and soles and red follicular papules that merge to form red-orange scaling plaques and confluent areas of erythema with islands of normal skin between lesions.

The cause of pityriasis rubra pilaris is unknown.

The 2 most common forms of the disorder are

• Juvenile classic (characterized by autosomal dominant inheritance and childhood onset)

• Adult classic (characterized by no apparent inheritance and adult onset)

Atypical forms exist in both age groups. Sunlight can trigger a flare.

Diagnosis is by clinical appearance and may be supported by biopsy. Differential diagnosis includes seborrheic dermatitis (in children) and psoriasis when disease occurs on the scalp, elbows, and knees.

Treatment is exceedingly difficult and empiric. The disorder may be ameliorated but almost never cured; classic forms of the disorder resolve slowly over 3 yr, whereas non-classic forms persist. Scaling may be reduced with emollients or 12% lactic acid under occlusive dressing, followed by topical corticosteroids. Oral vitamin A may be effective. Oral retinoids or methotrexate is an option when a patient is resistant to topical treatment.

Pityriasis Lichenoides

Pityriasis lichenoides is a clonal T-cell disorder that may develop in response to foreign antigens (eg, infections or drugs) and may be associated with cutaneous T-cell lymphoma.

Pityriasis lichenoides has acute and chronic forms existing in a clinical continuum. The acute form typically appears in children and young adults, with crops of asymptomatic chickenpox-like lesions that typically resolve within weeks to months. Antibiotics (eg, tetracycline, erythromycin) or phototherapy may help.

The chronic form initially manifests as flatter, reddish brown, scaling papules that may take months or longer to resolve. No treatment has proved effective.

Lichen Planus

Lichen planus (LP) is a recurrent, pruritic, inflammatory eruption characterized by small, discrete, polygonal, flat-topped, violaceous papules that may coalesce into rough scaly patches, often accompanied by oral lesions. Diagnosis is usually clinical and supported by skin biopsy. Treatment generally requires topical or intralesional corticosteroids. Severe cases may require phototherapy or systemic immunosuppressants.

Etiology

LP is thought to be caused by a T cell-mediated autoimmune reaction against basal epithelial keratinocytes in people with genetic predisposition. Drugs (especially β-blockers, NSAIDs, ACE inhibitors, sulfonylureas, gold, antimalarial drugs, penicillamine, and thiazides) can cause LP; drug-induced LP (sometimes called lichenoid drug eruption) may be indistinguishable from nondrug-induced LP or may have a pattern that is more eczematous. Associations with hepatitis C-induced liver insufficiency, primary biliary cirrhosis, and other forms of hepatitis have been reported.

Symptoms and Signs

Typical lesions are pruritic, purple, polygonal, flat-topped papules and plaques (see Plate 39). Lesions initially are 2 to 4 mm in diameter, with angular borders, a violaceous color, and a distinct sheen in cross-lighting. They are usually symmetrically distributed, most commonly on the flexor surfaces of the wrists, legs, trunk, glans penis, and oral and vaginal mucosae but can be widespread. The face is rarely involved. Onset may be abrupt or gradual. Children are affected infrequently. During the acute phase, new papules may appear at sites of minor skin injury (Koebner phenomenon), such as a superficial scratch. Lesions may coalesce or change over time, becoming hyperpigmented, atrophic, hyperkeratotic (hypertrophic LP), or vesiculobullous. Although pruritic, lesions are rarely excoriated or crusted. If the scalp is affected, patchy scarring alopecia (lichen planopilaris) may occur.

The oral mucosa is involved in about 50% of cases; oral lesions may occur without cutaneous lesions and usually persist for life. Reticulated, lacy, bluish-white, linear lesions (Wickham's striae) are a hallmark

of oral LP, especially on the buccal mucosae. Tongue margins and gingival mucosae in edentulous areas may also be affected. An erosive form of LP may occur in which the patient develops shallow, often painful, recurrent oral ulcers, which, if long-standing, rarely become cancerous. Chronic exacerbations and remissions are common. Vulvar and vaginal mucosae are often involved. Up to 50% of women with oral mucosal findings have undiagnosed vulvar LP. In men, genital involvement is common, especially of the glans penis.

Nails are involved in up to 10% of cases. Findings vary in intensity with nail bed discoloration, longitudinal ridging and lateral thinning, and complete loss of the nail matrix and nail, with scarring of the proximal nail fold onto the nail bed (pterygium formation).

Diagnosis

• Clinical evaluation

• Biopsy

Although diagnosis is suggested by appearance of the lesions, similar lesions may result from any of the papulosquamous disorders, lupus erythematosus, and secondary syphilis, among others. Oral or vaginal LP may resemble leukoplakia, and the oral lesions must also be distinguished from candidiasis, carcinoma, aphthous ulcers, pemphigus, cicatricial pemphigoid, and chronic erythema multiforme. Typically, biopsy is done.

If LP is diagnosed, some clinicians do laboratory testing for liver dysfunction, including hepatitis B and C infections.

Prognosis

Many cases resolve without intervention, presumably because the inciting agent is no longer present. Recurrence after years may be due to reexposure to the trigger or some change in the triggering mechanism. Sometimes treatment of a previously occult infection, such as a dental abscess, results in resolution.

Vulvovaginal LP may be chronic and refractory to therapy, causing decreased quality of life.

Treatment

• Topical treatments

• Systemic treatments

• Sometimes light therapy

Asymptomatic LP does not require treatment. Drugs suspected of triggering LP should be stopped.

Few controlled studies have evaluated treatments. Options differ by location and extent of disease. Most cases of LP on the trunk or extremities can be treated with local drugs. Topical corticosteroids are first-line treatment for most cases of localized disease. High-potency ointments or creams (eg, clobetasol, fluocinonide) may be used on the thicker lesions on the extremities; lower-potency drugs (eg, triamcinolone, desonide) may be used on the face, groin, and axillae. As always, courses should be limited to reduce risk of corticosteroid atrophy. Potency may be enhanced with use of polyethylene wrapping or flurandrenolide tape. Intralesional corticosteroids (triamcinolone acetonide solution diluted with saline to 5 to 10 mg/mL) can be used every 4 wk for hyperkeratotic plaques and those resistant to other therapies.

Topical therapy is impractical for generalized LP; oral drugs or phototherapy is used. Oral corticosteroids (eg, prednisone 20 mg once/day for 2 to 6 wk followed by a taper) may be used for severe cases. The disease may rebound when therapy ceases; however, long-term systemic corticosteroids should not be

used.

Oral retinoids (eg, acitretin 30 mg once/day for 8 wk) are indicated for otherwise recalcitrant cases. Griseofulvin 250 mg po bid given for 3 to 6 mo may be effective. Cyclosporine (1.25 to 2.5 mg/kg bid) can be used when corticosteroids or retinoids fail. Light therapy using psoralen plus ultraviolet A (PUVA) or narrow-band UVB is an alternative to oral therapies, especially if they have failed or are contraindicated for medical reasons.

Treatment of oral LP differs slightly. Viscous lidocaine may help relieve symptoms of erosive ulcers. Tacrolimus 0.1% ointment applied twice daily may induce lasting remission, although it has not been fully evaluated. Other treatment options include topical (in an adhesive base), intralesional, and systemic corticosteroids. Erosive oral LP may respond to oral dapsone or cyclosporine. Cyclosporine rinses also may be helpful.

Dapsone, hydroxychloroquine, azathioprine, systemic cyclosporine, and topical tretinoin may also be useful. As with any disease with so many therapies, individual drugs have not been uniformly successful.

Lichen Sclerosus

Lichen sclerosus is an inflammatory dermatosis of unknown cause, possibly autoimmune, that usually affects the anogenital area.

The earliest signs are skin fragility, bruising, and sometimes blistering. Lesions typically cause mild to severe itching. When lichen sclerosus manifests in children, the appearance may be confused with sexual abuse. With time, the involved tissue becomes atrophic, thinned, hypopigmented (there may be flecks of postinflammatory hyperpigmentation), fissured, and scaly. Hyperkeratotic and fibrotic forms exist. Severe and longstanding cases cause scarring and distortion of normal anogenital architecture. In women, this distortion can even lead to total absorption of the labia minora and fusion over the clitoris. In men, phimosis or fusion of the foreskin to the coronal sulcus can occur.

Diagnosis can usually be based on appearance, especially in advanced cases; however, biopsy should be done on any anogenital dermatosis that does not resolve with mild conventional therapy (eg, topical hydrocortisone, antifungal drug). It is especially important to biopsy any area that becomes thickened or ulcerated, because lichen sclerosus is a precursor of squamous cell carcinoma.

Treatment

• Topical corticosteroids

Treatment consists of potent topical corticosteroids (drugs that otherwise should be used with extreme caution in this area). The disease is generally intractable, so long-term follow-up, especially to monitor for squamous cell carcinoma and sexual function and for psychologic support, is indicated.

Chapter 79. Hypersensitivity and Inflammatory Disorders

Introduction

The immune system plays a significant role in a large number of skin disorders, including dermatitis, sunlight reactions, and bullous diseases. Although all of these disorders involve some level of inflammation, certain skin disorders are primarily characterized by their inflammatory component or as a hypersensitivity reaction, be it to a drug, infection, or cancer.

Acute Febrile Neutrophilic Dermatosis

(Sweet's Syndrome)

Acute febrile neutrophilic dermatosis is characterized by tender, indurated, dark-red papules and plaques with prominent edema in the upper dermis and dense infiltrate of neutrophils. Cause is not known. It frequently occurs with underlying cancer, especially hematologic cancers.

Etiology

Acute febrile neutrophilic dermatosis may occur with various disorders, including

• Acute respiratory illness

• GI infection

• Cancer

• Drug exposure

• Inflammatory or autoimmune disorders

• Pregnancy

About 25% of patients have an underlying cancer, 75% of which are hematologic cancers, especially myelodysplastic syndromes and acute myeloid leukemia. When not due to cancer, acute febrile neutrophilic dermatosis affects mostly women ages 30 to 50, with a female: male ratio of 3:1. In contrast, men who develop the condition tend to be older (60 to 90).

The cause is unknown; however, type 1 helper T-cell cytokines, including IL-2 and interferon-γ, are predominant and may play a role in lesion formation.

Symptoms and Signs

Patients are febrile, with an elevated neutrophil count, and have tender, dark-red plaques or papules, most often on the face, neck, and upper extremities, especially the dorsum of hands. Oral lesions can also occur. Rarely, bullous and pustular lesions are present. The lesions often develop in crops. Each crop is preceded by fever and persists for days to weeks.

Extracutaneous manifestations can involve the eyes (eg, conjunctivitis, episcleritis, iridocyclitis), joints (eg, arthralgia, myalgia, arthritis), and internal organs (eg, neutrophilic alveolitis; sterile osteomyelitis; psychiatric or neurologic changes; transient kidney, liver, and pancreatic insufficiency).

Diagnosis

• Clinical evaluation

• Skin biopsy

Diagnosis is suggested by the appearance of the lesions and is supported by the presence of associated conditions. Differential diagnosis includes erythema multiforme, erythema elevation diutinum, acute cutaneous lupus erythematosus, pyoderma gangrenosum, and erythema nodosum. If diagnosis is unclear, skin biopsy should be done. The histopathologic pattern is that of edema in the upper dermis with a dense infiltrate of neutrophils in the dermis. Vasculitis may be present but is secondary.

Treatment

• Corticosteroids

Treatment involves systemic corticosteroids, chiefly prednisone 0.5 to 1.5 mg/kg po once/day tapered over 3 wk. Antipyretics are also recommended. In difficult cases, dapsone 100 to 200 mg po once/day, indomethacin 150 mg po once/day for 1 wk and 100 mg po once/day for 2 additional wk, or K iodide 900 mg po once/day or 300 mg po tid can be given.

Drug Eruptions and Reactions

Drugs can cause multiple skin eruptions and reactions. The most serious of these are discussed elsewhere in THE MANUAL and include Stevens-Johnson syndrome and toxic epidermal necrolysis, hypersensitivity syndrome, serum sickness, exfoliative dermatitis, angioedema and anaphylaxis, and drug-induced vasculitis. Drugs can also be implicated in hair loss, lichen planus, erythema nodosum, pigmentation changes, SLE, photosensitivity reactions, pemphigus, and pemphigoid. Other drug reactions are classified by lesion type (see Table 79-1).

[**Table 79-1.** Types of Drug Reactions and Typical Causative Agents]

Symptoms and Signs

Symptoms and signs vary based on the cause and the specific reaction (see Table 79-1).

Diagnosis

• Clinical evaluation and drug exposure history

• Sometimes skin biopsy

A detailed history is often required for diagnosis, including recent use of OTC drugs. Because the reaction may not occur until several days or even weeks after first exposure to the drug, it is important to consider all new drugs and not only the one that has been most recently started. No laboratory tests reliably aid diagnosis, although biopsy of affected skin is often suggestive. Sensitivity can be definitively established only by rechallenge with the drug, which may be hazardous and unethical in patients who have had severe reactions.

Treatment

• Discontinuation of offending drug

• Sometimes antihistamines and corticosteroids

Most drug reactions resolve when drugs are stopped and require no further therapy. Whenever possible, chemically unrelated compounds should be substituted for suspect drugs. If no substitute drug is available and if the reaction is a mild one, it might be necessary to continue the treatment under careful watch despite the reaction. Pruritus can be controlled with antihistamines and topical corticosteroids. For IgE-mediated reactions (eg, urticaria), desensitization (see p. 1124) can be considered when there is critical need for a drug.

When progression from urticaria to anaphylaxis is a concern, treatment is with aqueous epinephrine (1:1000) 0.2 mL sc or IM and with the slower-acting but more persistent soluble hydrocortisone 100 mg IV, which may be followed by an oral corticosteroid for a short period (see also p. 1121).

Erythema Multiforme

Erythema multiforme (EM) is an inflammatory reaction, characterized by target or iris skin lesions. Oral mucosa may be involved. Diagnosis is clinical. Lesions spontaneously resolve but frequently recur. Erythema multiforme can occur as reaction to a drug or an infectious agent such as herpes simplex virus or mycoplasma. Suppressive antiviral therapy may be indicated for patients with frequent or symptomatic recurrence due to herpes simplex virus.

For years, EM was thought to represent the milder end of a spectrum of drug hypersensitivity disorders that included Stevens-Johnson syndrome and toxic epidermal necrolysis. Recent evidence suggests that EM is different from these other disorders.

Etiology

The majority of cases are caused by herpes simplex virus (HSV) infection (HSV-1 more so than HSV-2), although it is unclear whether EM lesions represent a specific or nonspecific reaction to the virus. Current thinking holds that EM is caused by a T-cell-mediated cytolytic reaction to HSV DNA fragments present in keratinocytes. A genetic disposition is presumed given that EM is such a rare clinical manifestation of HSV infection, and several HLA subtypes have been linked with the predisposition to develop lesions. Less commonly, cases are caused by drugs, vaccines, other viral diseases (especially hepatitis C), or possibly SLE. EM that occurs in patients with SLE is sometimes referred to as Rowell's syndrome.

Symptoms and Signs

EM manifests as the sudden onset of asymptomatic, erythematous macules, papules, wheals, vesicles, bullae, or a combination on the distal extremities (including palms and soles) and face. The classic lesion is annular, with a violaceous center and pink halo separated by a pale ring (target or iris lesion). Distribution is symmetric and centripetal; spread to the trunk is common. Some patients have itching. Oral lesions include target lesions on the lips and vesicles and erosions on the palate and gingivae.

Diagnosis

• Clinical evaluation

Diagnosis is by clinical appearance; biopsy is rarely necessary. Differential diagnosis includes essential urticaria, vasculitis, bullous pemphigoid, pemphigus, linear IgA dermatosis, acute febrile neutrophilic dermatosis, and dermatitis herpetiformis; oral lesions must be distinguished from aphthous stomatitis, pemphigus, herpetic stomatitis, and hand-foot-and-mouth disease. Patients with widely disseminated purpuric macules and blisters and prominent involvement of the trunk and face are likely to have Stevens-Johnson syndrome rather than EM.

Treatment

• Supportive care

• Sometimes prophylactic antivirals

EM spontaneously resolves, so treatment is usually unnecessary. Topical corticosteroids and anesthetics may ameliorate symptoms and reassure patients. Recurrences are common, and empiric oral maintenance therapy with acyclovir 400 mg po q 12 h, famciclovir 250 mg po q 12 h, or valacyclovir 1000 mg po q 24 h can be attempted if symptoms recur more than 5 times/yr and HSV association is suspected or if recurrent EM is consistently preceded by herpes flares.

Panniculitis

Panniculitis describes inflammation of the subcutaneous fat that can result from multiple causes. Diagnosis is by clinical evaluation and biopsy. Treatment depends on the cause.

Etiology

There are multiple causes of panniculitis, including

• Infections (the most common)

• Physical factors (eg, cold, trauma)

• Proliferative disorders

• Connective tissue disorders (eg, SLE, systemic sclerosis)

Idiopathic panniculitis is sometimes referred to as Weber-Christian disease.

Symptoms and Signs

Panniculitis is characterized by tender and erythematous subcutaneous nodules located over the extremities and sometimes over the posterior thorax, abdominal area, breasts, face, or buttocks. Rarely, nodules can involve the mesentery, lungs, scrotum, and cranium. Signs of systemic inflammation can accompany panniculitis. In Weber-Christian disease, systemic involvement can result in fever as well as signs of organ dysfunction, including hepatic, pancreatic, and bone marrow insufficiency, which is potentially fatal.

Diagnosis

• Clinical evaluation

• Excisional biopsy

Diagnosis is by usually by clinical appearance and can be confirmed by excisional biopsy.

Treatment

• Supportive care

• Anti-inflammatory drugs

• Immunosuppressants

There is no specific definitive treatment for panniculitis. A variety of strategies have been used with modest results, including NSAIDs, antimalarials, dapsone, and thalidomide. Corticosteroids (1 to 2 mg/kg po or IV once/day) and other immunosuppressive or chemotherapeutic drugs have been used to treat patients with progressive symptoms or signs of systemic involvement. Surgical abdominal panniculectomy has been used with varying levels of success in morbidly obese patients but should be reserved for patients with serious disease that does not respond to other measures.

Erythema Nodosum

Erythema nodosum (EN) is a specific form of panniculitis (see p. 687) characterized by tender, red or violet, palpable, subcutaneous nodules on the shins and occasionally other locations. It often occurs with an underlying systemic disease, notably streptococcal infections, sarcoidosis, inflammatory bowel disease, and TB. Diagnosis is by clinical evaluation and biopsy. Treatment depends on the cause.

Etiology

EN primarily affects people in their 20s and 30s but can occur at any age; women are more often affected. Etiology is unknown, but an immunologic reaction is suspected because EN is frequently accompanied by other disorders; the most common are

- Streptococcal infection (especially in children)
- Sarcoidosis
- Inflammatory bowel disease
- TB

Other possible triggers include

- Other bacterial infections (eg, *Yersinia*, *Salmonella*, mycoplasma, chlamydia, leprosy, lymphogranuloma venereum)
- Fungal infections (eg, coccidioidomycosis, blastomycosis, histoplasmosis)
- Rickettsial infections
- Viral infections (eg, Epstein-Barr, hepatitis B)
- Use of drugs (eg, sulfonamides, iodides, bromides, oral contraceptives)
- Hematologic and solid cancers
- Pregnancy

Up to one third of cases of EN are idiopathic.

Symptoms and Signs

EN is a subset of panniculitis that manifests as erythematous, tender plaques or nodules, primarily in the pretibial region (see
Plate 34), accompanied by fever, malaise, and arthralgia.

Diagnosis

- Clinical evaluation
- Excisional biopsy

Diagnosis is usually by clinical appearance and can be confirmed by excisional biopsy of a nodule when necessary. A diagnosis of EN should prompt evaluation for causes. Evaluation might include biopsy, skin testing (PPD or anergy panel), antinuclear antibodies, CBC, chest x-ray, and antistreptolysin O titer or pharyngeal culture. ESR is often high.

Treatment

- Supportive care
- Anti-inflammatory drugs
- Corticosteroids

EN almost always resolves spontaneously. Treatment includes bed rest, elevation, cool compresses, and NSAIDs. K iodide 300 to 500 mg po tid can be given to decrease inflammation. Systemic corticosteroids are effective but are an intervention of last resort as they can worsen an occult infection. If an underlying disorder is identified, it should be treated.

Granuloma Annulare

Granuloma annulare is a benign, chronic, idiopathic condition characterized by papules or nodules that spread peripherally to form a ring around normal or slightly depressed skin.

Etiology

Etiology is unclear but proposed mechanisms include cell-mediated immunity (type IV), immune complex vasculitis, and an abnormality of tissue monocytes. Granuloma annulare is not associated with systemic disorders, except that the incidence of abnormal glucose metabolism is increased among adults with many lesions. In some cases, exposure to sunlight, insect bites, TB skin testing, BCG vaccination, trauma, *Borrelia* infection, and viral infections have induced disease flares. The condition is twice as prevalent among women.

Symptoms and Signs

Lesions are erythematous, yellowish tan, bluish, or the color of the surrounding skin; one or more lesions may occur, most often on dorsal feet, legs, hands, or fingers. They are usually asymptomatic but may occasionally be tender. The lesions often expand or join to form rings. The center of each ring may be a slightly depressed, pale or light brown. In some cases, lesions may become generalized and widespread.

Diagnosis

Diagnosis is usually clinical but can be confirmed by skin biopsy.

Treatment

• Sometimes corticosteroids, anti-inflammatory drugs, or psoralen plus ultraviolet A (PUVA) therapy

Usually no treatment is necessary; spontaneous resolution is common. For patients with more widespread or bothersome lesions, quicker resolution may be promoted by the use of high-strength topical corticosteroids under occlusive dressings every night, flurandrenolide-impregnated tape, and intralesional corticosteroids. PUVA therapy is also effective and practical for patients with widespread disease. Recent reports have suggested that tumor necrosis factor-α inhibitors (eg, infliximab, adalimumab), 595-nm pulsed dye laser, and fractional photothermolysis are useful in managing disseminated and recalcitrant lesions.

Pyoderma Gangrenosum

Pyoderma gangrenosum is a chronic progressive skin necrosis of unknown etiology often associated with systemic illness.

Etiology

Etiology is unknown, but pyoderma gangrenosum can be associated with vasculitis, gammopathies, RA, leukemia, lymphoma, hepatitis C virus infection, SLE, sarcoidosis, polyarthritis, and especially inflammatory bowel disease and is thought to be caused by an abnormal immune response.

Pathophysiology

Pathophysiology is poorly understood but may involve problems with neutrophil chemotaxis. Ulcerations of pyoderma gangrenosum may occur after trauma or injury to the skin in 30% of patients; this process is termed pathergy.

Symptoms and Signs

Pyoderma gangrenosum begins as an inflamed erythematous papule, pustule, or nodule. The lesion, which may resemble a furuncle or an arthropod bite at this stage, then ulcerates and expands rapidly, developing a swollen necrotic base and a raised dusky to violaceous border. An undermined border is common, if not pathognomonic. Systemic symptoms such as fever, malaise, and arthralgias are common. The ulcers coalesce to form larger ulcers, often with cribriform or sieve-like scarring.

Diagnosis

Diagnosis is clinical. Biopsies of lesions are not often diagnostic but may be supportive; 40% of biopsies from a leading edge show vasculitis with neutrophils and fibrin in superficial vessels.

Treatment

• Corticosteroids

• Sometimes other anti-inflammatory drugs or immunosuppressants

• Avoidance of surgical debridement

Prednisone 60 to 80 mg po once/day is still the mainstay of treatment, although cyclosporine 3 mg/kg po once/day is also quite effective. Dapsone, clofazimine, thalidomide, tumor necrosis factor-α inhibitors (eg, infliximab), and mycophenolate mofetil have also been used successfully. Surgical treatments are avoided because of the risk of wound extension.

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe cutaneous hypersensitivity reactions. Drugs, especially sulfa drugs, antiepileptics, and antibiotics, are the most common causes. Macules rapidly spread and coalesce, leading to epidermal blistering, necrosis, and sloughing. Diagnosis is usually obvious by appearance of initial lesions and clinical syndrome. Treatment is supportive care; corticosteroids, cyclophosphamide, and other drugs may be tried. Prognosis depends on how early the disorders are diagnosed and treated. Mortality can be as high as 7.5% in children and 20 to 25% in adults.

SJS and TEN are clinically similar except for their distribution. By one commonly accepted definition, changes affect < 10% of body surface area in SJS and > 30% of body surface area in TEN; involvement of 15 to 30% of body surface area is considered SJS-TEN overlap.

The disorders affect between 1 and 5 people/million. Incidence, severity, or both of these disorders may be higher in bone-marrow transplant recipients, in *Pneumocystis jirovecii*-infected HIV patients, in patients with SLE, and in patients with other chronic rheumatologic diseases.

Etiology

Drugs precipitate over 50% of SJS cases and up to 95% of TEN cases. The most common drug causes include

• Sulfa drugs (eg, cotrimoxazole, sulfasalazine)

• Other antibiotics (eg, aminopenicillins, fluoroquinolones, cephalosporins)

• Antiepileptics (eg, phenytoin, carbamazepine, phenobarbital, valproate, lamotrigine)

• Miscellaneous individual drugs (eg, piroxicam, allopurinol, chlormezanone)

Cases that are not caused by drugs are attributed to

• Infection (mostly with *Mycoplasma pneumoniae*)

• Vaccination

• Graft-vs-host disease

Rarely, a cause cannot be identified.

Pathophysiology

Exact mechanism is unknown; however, one theory holds that altered drug metabolism in some patients causes formation of reactive metabolites that bind to and alter cell proteins, triggering a T-cell-mediated cytotoxic reaction to drug antigens in keratinocytes.

Another possible mechanism involves interactions between Fas (a cell-surface receptor that induces apoptosis) and its ligand, particularly a soluble form of Fas ligand released from mononuclear cells. Recent findings suggest that granulysin released from cytotoxic T cells and natural killer cells might play a role in keratinocyte death.

Symptoms and Signs

Within 1 to 3 wk after the start of the offending drug, patients develop a prodrome of malaise, fever, headache, cough, and conjunctivitis. Macules, often in a target configuration, then appear suddenly, usually on the face, neck, and upper trunk. These macules simultaneously appear elsewhere on the body, coalesce into large flaccid bullae, and slough over a period of 1 to 3 days. Nails and eyebrows may be lost along with epithelium.

In severe cases of TEN, large sheets of epithelium slide off the entire body at pressure points (Nikolsky's sign), exposing weepy, painful, and erythematous skin. Painful oral crusts and erosions, keratoconjunctivitis, and genital problems (eg, phimosis, vaginal synechiae) accompany skin sloughing in up to 90% of cases. Bronchial epithelium may also slough, causing cough, dyspnea, pneumonia, pulmonary edema, and hypoxemia. Glomerulonephritis and hepatitis may develop.

Diagnosis

• Clinical evaluation

• Often skin biopsy

Diagnosis is often obvious from appearance of lesions and rapid progression of symptoms. Histologic examination of sloughed skin shows necrotic epithelium, a distinguishing feature.

Differential diagnosis in SJS and early TEN includes erythema multiforme, viral exanthems, and drug rash; and, in later stages of TEN, paraneoplastic pemphigus, toxic shock syndrome, exfoliative erythroderma, and thermal burn. In children, TEN is less common and must be distinguished from staphylococcal scalded skin syndrome.

Prognosis

Severe TEN is similar to extensive burns; patients are acutely ill, may be unable to eat or open their eyes, and suffer massive fluid and electrolyte losses. They are at high risk of infection, multiorgan failure, and death. With early therapy, survival rates approach 90%. The severity-of-illness score for TEN (see Table 79-2) systematically scores 7 independent risk factors within the first 24 h of presentation to the hospital to determine the mortality rate for a particular patient.

Treatment

• Supportive care

• Possibly immune modulator treatment

• Possibly plasmapheresis

Treatment is most successful when SJS or TEN is recognized early and treated in an inpatient dermatologic or ICU setting; treatment in a burn unit may be needed for severe disease. Ophthalmology consultation is mandatory for patients with ocular involvement. Drugs should be stopped immediately. Patients

[**Table 79-2.** Severity-of-Illness Score for Toxic Epidermal Necrolysis (Scorten)]

are isolated to minimize exposure to infection and are given fluids, electrolytes, blood products, and nutritional supplements as needed. Skin care includes prompt treatment of secondary bacterial infections. Prophylactic antibiotics are controversial.

Drug treatment of STS and TEN is controversial. High-dose systemic corticosteroids (eg, methylprednisolone 80 to 200 mg IV or prednisone 80 mg po once/day for 7 to 10 days or until progression stops) or cyclophosphamide (300 mg IV q 24 h for 7 days or until significant improvement) can be given to inhibit T-cell-mediated cytolysis. Cyclosporine (3 to 5 mg/kg po once/day) inhibits CD8 cells and has been shown to decrease the duration of active disease by 2 to 3 days in some instances. However, corticosteroids are controversial and are thought by some to increase mortality. Plasmapheresis can remove reactive drug metabolites or antibodies. Early high-dose IV immune globulin (IVIG) 2.7 g/kg over 3 days blocks antibodies and Fas ligand. Despite some remarkable results using high-dose IVIG for TEN, clinical trials involving small cohorts have reported conflicting results.

Chapter 80. Sweating Disorders

Introduction

There are two types of sweat glands: apocrine and eccrine.

Apocrine glands are clustered in the axillae, areolae, genitals, and anus; modified apocrine glands are found in the external auditory meatus. Apocrine glands become active at puberty; their excretions are oily and viscid and are presumed to play a role in sexual olfactory messages. The most common disorders of apocrine glands are bromhidrosis and hidradenitis suppurativa (see p. 698).

Eccrine glands are sympathetically innervated, distributed over the entire body, and active from birth. Their secretions are watery and serve to cool the body in hot environments or during activity. Disorders of eccrine glands include hyperhidrosis, hypohidrosis, and miliaria.

Bromhidrosis

Bromhidrosis is excessive or abnormal body odor caused by decomposition by bacteria and yeasts of apocrine secretions and cellular debris.

Apocrine secretions are lipid-rich, sterile, and odorless but become odoriferous when decomposed. Eccrine bromhidrosis is not as fragrant because eccrine sweat is nearly 100% water. The cause of apocrine bromhidrosis is poor hygiene of skin and clothing.

In some people, a few days of washing with an antiseptic soap, which may be combined with use of antibacterial creams containing clindamycin or erythromycin, may be necessary. Shaving the hair in the armpits may also help control odor.

Hyperhidrosis

Hyperhidrosis is excessive sweating, which can be focal or diffuse and has multiple causes. Sweating of the axillae, palms, and soles is most often due to stress; diffuse sweating is usually idiopathic but should raise suspicions for cancer, infection, and endocrine disease. Diagnosis is obvious, but tests for underlying causes may be indicated. Treatment is topical aluminum chloride, tap water iontophoresis, botulinum toxin, and, in extreme cases, surgery.

Etiology

Hyperhidrosis can be focal or generalized.

Focal sweating: Emotional causes are common, causing sweating on the palms, soles, axillae, and forehead at times of anxiety, excitement, anger, or fear. It may be due to a generalized stress-increased sympathetic outflow. Although such sweating is a normal response, patients with hyperhidrosis sweat excessively and under conditions that do not cause sweating in most people.

Gustatory sweating occurs around the lips and mouth when ingesting foods and beverages that are spicy or hot in temperature. There is no known cause in most cases, but gustatory sweating can be increased in diabetic neuropathy, facial herpes zoster, cervical sympathetic ganglion invasion, CNS injury or disease, or parotid gland injury. In the case of parotid gland injury, surgery, infection, or trauma may disrupt parotid gland innervation and lead to regrowth of parotid parasympathetic fibers into sympathetic fibers innervating local sweat glands in skin where the injury took place, usually over the parotid gland. This condition is called Frey's syndrome.

Other causes of focal sweating include pretibial myxedema (shins), hypertrophic osteoarthropathy (palms), and blue rubber bleb nevus syndrome and glomus tumor (over lesions). Compensatory sweating is intense sweating after sympathectomy.

Generalized sweating: Generalized sweating involves most of the body. Although most cases are

idiopathic, numerous conditions can be involved (see Table 80-1).

Symptoms and Signs

Sweating is often present during examination and sometimes is extreme. Clothing can be soaked, and palms or soles may become macerated and fissured. Hyperhidrosis can cause emotional distress to patients and may lead to social withdrawal. Palmar or plantar skin may appear pale.

Diagnosis

• History and examination

• Iodine and starch test

• Tests to identify a cause

Hyperhidrosis is diagnosed by history and examination but can be confirmed with the iodine and starch test (apply iodine solution to the affected area, let dry, dust on corn starch: areas of sweating appear dark). Testing is necessary only to confirm foci of sweating (as in Frey's syndrome or to locate the

[**Table 80-1.** Some Causes of Generalized Sweating]

area needing surgical or botulinum toxin treatment) or in a semiquantitative way when following the course of treatment.

Tests to identify a cause of hyperhidrosis are guided by a review of symptoms and might include CBC to detect leukemia, serum glucose to detect diabetes, and thyroid-stimulating hormone to screen for thyroid dysfunction.

Treatment

• Aluminum chloride hexahydrate solution

• Tap water iontophoresis

• Botulinum toxin type A

• Surgery

Initial treatment of focal and generalized sweating is similar.

Aluminum chloride hexahydrate 6 to 20% solution in absolute ethyl alcohol is indicated for topical treatment of axillary, palmar, and plantar sweating; these preparations require a prescription. The solution blocks sweat ducts and is most effective when applied nightly and covered tightly with a thin polyvinylidene or polyethylene film; it should be washed off in the morning. Sometimes an anticholinergic drug is taken before applying to prevent sweat from washing the aluminum chloride away. Initially, several applications weekly are needed to achieve control, then a maintenance schedule of once or twice weekly is followed. If treatment under occlusion is irritating, it should be tried without occlusion. This solution should not be applied to inflamed, broken, wet, or recently shaved skin. High-concentration, water-based aluminum chloride solutions may provide adequate relief in milder cases. Topical alternatives to aluminum chloride, including glutaraldehyde, formaldehyde, and tannic acid, are effective but can cause contact dermatitis and skin discoloration. A solution of methenamine also may help.

Tap water iontophoresis, in which salt ions are introduced into the skin using electric current, is an option for patients unresponsive to topical treatments. The affected areas (typically palms or soles) are placed in 2 tap water basins each containing an electrode across which a 15- to 25-mA current is applied for 10 to 20 min. This routine is done daily for 1 wk and then repeated weekly or bimonthly. Treatments may be

made more effective with topical or oral anticholinergic drugs. Although the treatments are usually effective, the technique is time-consuming and somewhat cumbersome, and some patients tire of the routine.

Botulinum toxin type A is a neurotoxin that decreases the release of acetylcholine from sympathetic nerves serving eccrine glands. Injected directly into the axillae, palms, or forehead, botulinum toxin inhibits sweating for about 5 mo depending on dose. Complications include local muscle weakness and headache. Injections are effective but painful and expensive.

Surgery is indicated if more conservative treatments fail. Patients with axillary sweating can be treated with surgical excision of axillary sweat glands either through open dissection or by liposuction (the latter seems to have lower morbidity). Patients with palmar sweating can be treated with endoscopic transthoracic sympathectomy. The potential morbidity of surgery must be considered, especially in sympathectomy. Potential complications include phantom sweating, compensatory sweating, gustatory sweating, neuralgia, and Horner's syndrome.

Hypohidrosis

Hypohidrosis is inadequate sweating.

Hypohidrosis due to skin abnormalities is rarely clinically significant. It is most commonly focal and caused by local skin injury (eg, from trauma, radiation, infection [eg, leprosy], or inflammation) or by atrophy of glands from connective tissue disease (eg, systemic sclerosis, SLE, Sjogren's syndrome). Hypohidrosis may be caused by drugs, especially those with anticholinergic properties. It is also caused by diabetic neuropathy and a variety of congenital syndromes. Heatstroke causes inadequate sweating but is a CNS rather than a skin disorder (see p. 3265). A rare presentation is fever of unknown origin.

Diagnosis is by clinical observation of decreased sweating or by heat intolerance. Treatment is by cooling measures (eg, air-conditioning, wet garments).

Miliaria

In miliaria, sweat flow is obstructed and trapped within the skin, causing papular lesions.

Miliaria most often occurs in warm humid weather but may occur in cool weather in an overdressed patient. Lesions vary depending on the depth of tissue at which the sweat duct is obstructed.

- **Miliaria crystallina** is ductal obstruction in the uppermost epidermis, with retention of sweat subcorneally. It causes clear droplike vesicles that rupture with light pressure.

- **Miliaria rubra** (prickly heat) is ductal obstruction in the mid-epidermis with retention of sweat in the epidermis and dermis. It causes irritated, pruritic papules (prickling).

- **Miliaria pustulosa** is similar to miliaria rubra but manifests as pustules rather than papules.

- **Miliaria profunda** is ductal obstruction at the entrance of the duct into the dermal papillae at the dermo-epidermal junction, with retention of sweat in the dermis. It causes papules that are larger and more deeply seated than those of miliaria pustulosa. Papules are frequently painful.

Diagnosis is by clinical appearance in the context of hot environment.

Treatment is cooling and drying of the involved areas and avoidance of conditions that may induce sweating; an air-conditioned environment is ideal. Once the rash develops, corticosteroid creams or lotions are used, sometimes with a bit of menthol added.

Chapter 81. Bacterial Skin Infections

Introduction

Bacterial skin infections may be uncomplicated or complicated. Uncomplicated infections usually respond promptly to systemic antibiotics and local wound care. A skin infection is considered complicated when it meets 2 of the following 5 criteria:

- Involves a preexisting wound or ulceration of the skin
- Involves the deeper soft tissues
- Requires surgical intervention
- Is caused or exacerbated by underlying comorbid disease states (eg diabetes, systemic immunosuppression)
- Is unresponsive to conventional antibiotic therapy or is recurrent

All uncomplicated skin infections have the potential to become complicated. Complicated skin and soft-tissue infections may require multidrug therapy and the assistance of other consultants (eg, surgeons, infectious disease specialists), particularly in light of resistance in many strains of bacteria and the rapid loss of efficacy among more potent antibiotics. Recurrent skin infections should raise suspicion of colonization (eg, staphylococcal nasal carriage), resistant strains of bacteria (eg, methicillin-resistant *Staphylococcus aureus* [MRSA]), cancer, poorly controlled diabetes, or other reasons for immunocompromise (eg, HIV, hepatitis, advanced age, congenital susceptibility). Bacteria are involved in the pathophysiology of acne, but acne is not primarily considered a bacterial skin infection.

Cellulitis

Cellulitis is acute bacterial infection of the skin and subcutaneous tissue most often caused by streptococci or staphylococci. Symptoms and signs are pain, rapidly spreading erythema, and edema; fever may occur, and regional lymph nodes may enlarge. Diagnosis is by appearance; cultures are sometimes helpful but awaiting culture results should not delay empiric therapy. Treatment is with antibiotics. Prognosis is excellent with timely treatment.

Etiology

- *Streptococcus pyogenes*
- *Staphylococcus aureus*

Cellulitis is most often caused by group A β-hemolytic streptococci (eg, *Streptococcus pyogenes*) or *Staphylococcus aureus*. Streptococci cause diffuse, rapidly spreading infection because enzymes produced by the organism (streptokinase, DNase, hyaluronidase) break down cellular components that would otherwise contain and localize the inflammation. Staphylococcal cellulitis is typically more localized and usually occurs in open wounds or cutaneous abscesses.

Recently, methicillin-resistant *S. aureus* (MRSA) has become more common in the community (community-associated MRSA [CA-MRSA]). Historically, MRSA was typically confined to patients who were exposed to the organism in a hospital or nursing facility. MRSA infection should now be considered in patients with community-acquired cellulitis, particularly in those with cellulitis that is recurrent or unresponsive to monotherapy.

Less common causes are group B streptococci (eg, *Streptococcus agalactiae*) in older patients with diabetes; gram-negative bacilli (eg, *Haemophilus influenzae*) in children; and *Pseudomonas aeruginosa* in patients with diabetes or neutropenia, hot tub or spa users, and hospitalized patients. Animal bites may

result in cellulitis; *Pasteurella multocida* is the cause in cat bites, and *Capnocytophaga* sp is responsible in dog bites. Immersion injuries in fresh water may result in cellulitis caused by *Aeromonas hydrophila*; in warm salt water, by *Vibrio vulnificus*.

Risk factors include skin abnormalities (eg, trauma, ulceration, fungal infection, other skin barrier compromise due to preexisting skin disease), which are common in patients with chronic venous insufficiency or lymphedema. Scars from saphenous vein removal for cardiac or vascular surgery are common sites for recurrent cellulitis, especially if tinea pedis is present. Frequently, no predisposing condition or site of entry is evident.

Symptoms and Signs

Infection is most common in the lower extremities. Cellulitis is typically unilateral; stasis dermatitis closely mimics cellulitis but is usually bilateral. The major findings are local erythema and tenderness, frequently with lymphangitis and regional lymphadenopathy. The skin is hot, red, and edematous (see Plate 31), often with surface appearance resembling the skin of an orange (peau d'orange). The borders are usually indistinct, except in erysipelas (a type of cellulitis with sharply demarcated margins—see p. 696). Petechiae are common; large areas of ecchymosis are rare. Vesicles and bullae may develop and rupture, occasionally with necrosis of the involved skin. Cellulitis may mimic deep venous thrombosis but can often be differentiated by one or more features (see Table 81-1). Fever, chills, tachycardia, headache, hypotension, and delirium may precede cutaneous findings by several hours, but many patients do not appear ill. Leukocytosis is common.

[**Table 81-1.** Differentiating Cellulitis and Deep Venous Thrombosis]

Diagnosis

• Examination

• Blood and sometimes tissue cultures for immunocompromised patients

Diagnosis is by examination. Skin and (when present) wound cultures are generally not indicated because they rarely identify the infecting organism. Blood cultures are useful in immunocompromised patients to detect or rule out bacteremia. Culture of involved tissue may be required in immunocompromised patients if they are not responding to empiric therapy or if blood cultures do not isolate an organism.

Prognosis

Most cellulitis resolves quickly with antibiotic therapy. Local abscesses occasionally form, requiring incision and drainage. Serious but rare complications include severe necrotizing subcutaneous infection (see p. 700) and bacteremia with metastatic foci of infection.

Recurrences in the same area are common, sometimes causing serious damage to the lymphatics, chronic lymphatic obstruction, and lymphedema.

Treatment

• Antibiotics

Treatment is with antibiotics. For most patients, empiric treatment effective against both group A streptococci and *S. aureus* is used. Oral therapy is usually adequate with dicloxacillin 250 mg or cephalexin 500 mg qid for mild infections. Levofloxacin 500 mg po once/day or moxifloxacin 400 mg once/day works well for patients who are unlikely to adhere to multiple daily dosing schedules. For more serious infections, oxacillin or nafcillin 1 g IV q 6 h is given. Use of initial empiric therapy against MRSA is not typically advised unless there is compelling clinical evidence (eg, contact with a documented case or outbreak; culture-documented prevalence of > 10% or 15% in a practice area). For penicillin-allergic patients or those with suspected or confirmed MRSA infection, vancomycin 1 g IV q 12 h is the drug of

choice (see also p. 1230). Linezolid is another option for the treatment of MRSA at a dose of 600 mg IV or po q 12 h for 10 to 14 days. Teicoplanin has a mechanism of action similar to vancomycin. It is commonly used outside the US to treat MRSA; the usual dose is 6 mg/kg IV q 12 h for 2 doses, followed by 6 mg/kg (or 3 mg/kg) IV or IM once/day. Immobilization and elevation of the affected area help reduce edema; cool, wet dressings relieve local discomfort.

Cellulitis in a patient with neutropenia requires empiric antipseudomonal antibiotics (eg, tobramycin 1.5 mg/kg IV q 8 h and piperacillin 3 g IV q 4 h) until blood culture results are available. Penicillin is the drug of choice for cellulitis caused by *P. multocida*; an aminoglycoside (eg, gentamicin) is effective against *A. hydrophila*, and tetracycline is preferred for *V. vulnificus* infections.

Recurrent leg cellulitis is prevented by treating concomitant tinea pedis, which often eliminates the source of bacteria residing in the inflamed, macerated tissue. If such therapy is unsuccessful or not indicated, recurrent cellulitis can sometimes be prevented by benzathine penicillin 1.2 million units IM monthly or penicillin V or erythromycin 250 mg po qid for 1 wk/mo. If these regimens prove unsuccessful, tissue culture may be required.

Erysipelas

Erysipelas is a type of superficial cellulitis (see p. 694) with dermal lymphatic involvement.

Erysipelas should not be confused with erysipeloid, a skin infection caused by *Erysipelothrix* (see p. 1241). Erysipelas is characterized clinically by shiny, raised, indurated, and tender plaque-like lesions with distinct margins (see Plate 33). There is also a bullous form of erysipelas. Erysipelas is most often caused by group A (or rarely group C or G) β-hemolytic streptococci and occurs most frequently on the legs and face. However, other causes have been reported, including *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]), *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Escherichia coli*, *S. warneri*, *Streptococcus pneumoniae*, *S. pyogenes*, and *Moraxella* sp. Erysipelas of the face must be differentiated from herpes zoster, angioedema, and contact dermatitis. It is commonly accompanied by high fever, chills, and malaise; MRSA is more common in facial erysipelas than in lower-extremity erysipelas. Erysipelas may be recurrent and may result in chronic lymphedema.

Diagnosis

Diagnosis is by characteristic appearance; blood culture is done in toxic-appearing patients. Diffuse inflammatory carcinoma of the breast may also be mistaken for erysipelas.

Treatment

• Usually penicillin for lower-extremity erysipelas

• Initially vancomycin for facial erysipelas

Treatment of choice for lower-extremity erysipelas is penicillin V 500 mg po qid for ≥ 2 wk. In severe cases, penicillin G 1.2 million units IV q 6 h is indicated, which can be replaced by oral therapy after 36 to 48 h. Dicloxacillin 500 mg po qid for 10 days can be used for infections with staphylococci. Erythromycin 500 mg po qid for 10 days may be used in penicillin-allergic patients; however, there is growing macrolide resistance in streptococci. In infections resistant to these antibiotics, cloxacillin or nafcillin can be used. In Europe, pristinamycin and roxithromycin have been shown to be good choices for erysipelas. If facial erysipelas is present or if MRSA is otherwise suspected, empiric therapy should be initiated with vancomycin 1 g IV q 12 h (which is active against MRSA). Cold packs and analgesics may relieve local discomfort. Fungal foot infections may be an entry site for infection and may require antifungal treatment to prevent recurrence.

Cutaneous Abscess

A cutaneous abscess is a localized collection of pus in the skin and may occur on any skin

surface. Symptoms and signs are pain and a tender, firm or fluctuant swelling. Diagnosis is usually obvious by examination. Treatment is incision and drainage.

Bacteria causing cutaneous abscesses are typically indigenous to the skin of the involved area. For abscesses on the trunk, extremities, axillae, or head and neck, the most common organisms are *Staphylococcus aureus* and streptococci. In recent years, methicillin-resistant *S. aureus* (MRSA) has become a more common cause.

Abscesses in the perineal (ie, inguinal, vaginal, buttock, perirectal) region contain organisms found in the stool, commonly anaerobes or a combination of aerobes and anaerobes. Carbuncles and furuncles are follicle-based cutaneous abscesses with characteristic features (see p. 697).

Cutaneous abscesses tend to form in patients with bacterial overgrowth, antecedent trauma (particularly when a foreign body is present), or immunologic or circulatory compromise.

Symptoms and Signs

Cutaneous abscesses are painful, tender, indurated, and sometimes erythematous. They vary in size, typically 1 to 3 cm in length, but sometimes much larger. Initially the swelling is firm; later, as the abscess "points," the overlying skin becomes thin and feels fluctuant. The abscess may then spontaneously drain. Local cellulitis, lymphangitis, regional lymphadenopathy, fever, and leukocytosis are variable accompanying features.

Diagnosis

• Examination

• Gram stain and culture to identify MRSA

Diagnosis is usually obvious by examination. Gram stain and culture are recommended, primarily to identify MRSA.

Conditions resembling simple cutaneous abscesses include hidradenitis suppurativa (see p. 698) and ruptured epidermal cysts. Epidermal cysts (often incorrectly referred to as sebaceous cysts) rarely become infected; however, rupture releases keratin into the dermis, causing an exuberant inflammatory reaction sometimes clinically resembling infection. Culture of these ruptured cysts seldom reveals any bacteria. Perineal abscesses may represent cutaneous emergence of a deeper perirectal abscess or drainage from Crohn's disease via a fistulous tract. These other conditions are usually recognizable by history and rectal examination.

Treatment

• Incision and drainage

• Sometimes antibiotics

Some small abscesses resolve without treatment, coming to a point and draining. Warm compresses help accelerate the process. Incision and drainage are indicated when significant pain, tenderness, and swelling are present; it is unnecessary to await fluctuance. Under sterile conditions, local anesthesia is administered as either a lidocaine injection or a freezing spray.

Patients with large, extremely painful abscesses may benefit from IV sedation and analgesia during drainage. A single puncture with the tip of a scalpel is often sufficient to open the abscess. After the pus drains, the cavity should be bluntly probed with a gloved finger or curette to clear loculations, and then irrigated with 0.9% saline solution. Some clinicians pack the cavity loosely with a gauze wick that is removed 24 to 48 h later. Local heat and elevation may hasten resolution of inflammation.

Antibiotics are unnecessary unless the patient has signs of systemic infection, cellulitis, multiple

abscesses, immunocompromise, or a facial abscess in the area drained by the cavernous sinus. In these cases, empiric therapy should be started with a drug active against MRSA (eg, trimethoprim/sulfamethoxazole, clindamycin; for severe infection, vancomycin) pending results of bacterial culture.

Folliculitis

Folliculitis is a bacterial infection of hair follicles.

Folliculitis is usually caused by *Staphylococcus aureus* but occasionally *Pseudomonas aeruginosa* (hot tub folliculitis) or other organisms. Hot tub folliculitis occurs because of inadequate treatment of water with chlorine or bromine.

Symptoms of folliculitis are mild pain, pruritus, or irritation. Signs of folliculitis are a superficial pustule or inflammatory nodule surrounding a hair follicle. Infected hairs easily fall out or are removed, but new papules tend to develop. Growth of stiff hairs into the skin may cause chronic low-grade irritation or inflammation that may mimic infectious folliculitis (pseudofolliculitis barbae—see p. 731).

Treatment

Because most folliculitis is caused by *S. aureus*, clindamycin 1% lotion or gel may be applied topically bid for 7 to 10 days. Alternatively, benzoyl peroxide 5% wash may be used when showering for 5 to 7 days. Extensive cutaneous involvement may warrant systemic therapy (eg, cephalexin 250 to 500 mg po tid to qid for 10 days). If these measures do not result in a cure, or folliculitis recurs, pustules are Gram stained and cultured to rule out gram-negative or methicillin-resistant *S. aureus* (MRSA) etiology, and nares are cultured to rule out nasal staphylococcal carriage. Potassium hydroxide wet mount should be done on a plucked hair to rule out fungal folliculitis.

Treatment for MRSA usually requires 2 oral antibiotics, and the choice of therapeutic drugs should be based on culture and sensitivity reports.

Hot tub folliculitis usually resolves without treatment. However, adequate chlorination of the hot tub is necessary to prevent recurrences and to protect others from infection.

Furuncles and Carbuncles

Furuncles are skin abscesses caused by staphylococcal infection, which involve a hair follicle and surrounding tissue. Carbuncles are clusters of furuncles connected subcutaneously, causing deeper suppuration and scarring. They are smaller and more superficial than subcutaneous abscesses (see p. 696). Diagnosis is by appearance. Treatment is warm compresses and often oral antistaphylococcal antibiotics.

Both furuncles and carbuncles may affect healthy young people but are more common in the obese, the immunocompromised (including those with neutrophil defects), the elderly, and possibly those with diabetes. Clustered cases may occur among those living in crowded quarters with relatively poor hygiene or among contacts of patients infected with virulent strains. Predisposing factors include bacterial colonization of skin or nares, hot and humid climates, and occlusion or abnormal follicular anatomy (eg, comedones in acne). Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common cause.

Furuncles are common on the neck, breasts, face, and buttocks. They are uncomfortable and may be painful when closely attached to underlying structures (eg, on the nose, ear, or fingers). Appearance is a nodule or pustule that discharges necrotic tissue and sanguineous pus. Carbuncles may be accompanied by fever and prostration.

Diagnosis

Diagnosis is by examination. Material for culture should be obtained.

Treatment

• Drainage

• Often antibiotics effective against MRSA

Abscesses are incised and drained. Intermittent hot compresses are used to facilitate drainage. Antibiotics, when used, should be effective against MRSA, pending culture and sensitivity test results. In afebrile patients, treatment of a single lesion < 5 mm requires no antibiotics. If a single lesion is ≥ 5 mm, an oral antibiotic is given for 5 to 10 days; choices include trimethoprim/sulfamethoxazole (TMP/SMX) 160/800 mg to 320/1600 mg bid, clindamycin 300 to 600 mg q 6 to 8 h, and doxycycline or minocycline 100 mg q 12 h. Patients with fever, multiple abscesses, or carbuncles are given 10 days of TMP/SMX 160/800 mg to 320/1600 mg bid plus rifampin 300 mg bid. Systemic antibiotics are also needed for

• Lesions < 5 mm that do not resolve with drainage

• Evidence of expanding cellulitis

• Immunocompromised patients

• Patients at risk of endocarditis

Furuncles frequently recur and can be prevented by applying liquid soap containing either chlorhexidine gluconate with isopropyl alcohol or 2 to 3% chloroxylenol and by giving maintenance antibiotics over 1 to 2 mo. Patients with recurrent furunculosis should be treated for predisposing factors such as obesity, diabetes, occupational or industrial exposure to inciting factors, and nasal carriage of *S. aureus* or MRSA colonization.

Erythrasma

Erythrasma is an intertriginous infection with *Corynebacterium minutissimum* that is most common among patients with diabetes and among people living in the tropics.

Erythrasma resembles tinea or intertrigo. It is most common in the foot, where it manifests as superficial scaling, fissuring, and maceration most commonly confined to the 3rd and 4th web spaces. Erythrasma is also common in the groin, where it manifests as irregular but sharply marginated pink or brown patches with fine scaling. Erythrasma may also involve the axillae, submammary or abdominal folds, and perineum, particularly in obese middle-aged women and in patients with diabetes.

Erythrasma fluoresces a characteristic coral-red color under Wood's light. Absence of hyphae in skin scrapings also distinguishes erythrasma from tinea.

Treatment is erythromycin or tetracycline 250 mg po qid for 14 days. Topical erythromycin or clindamycin is also effective. Recurrence is common.

Hidradenitis Suppurativa

Hidradenitis suppurativa is a chronic, scarring inflammation of apocrine glands of the axillae, groin, and around the nipples and anus.

Blockage of apocrine ducts has been suggested as the cause, leading to subsequent inflammation, bacterial overgrowth, and scarring. *Staphylococcus aureus* is almost always implicated in acute cases, but gram-negative organisms such as *Proteus* may predominate in chronic cases.

Swollen, tender masses resembling cutaneous abscesses develop. Pain, fluctuance, discharge, and sinus tract formation are characteristic in chronic cases. In chronic axillary cases, coalescence of inflamed nodules causes palpable cordlike fibrotic bands. The condition may become disabling because of pain and foul odor.

Diagnosis

Diagnosis is by examination. Bacterial cultures may be helpful if there appears to be a concomitant cellulitis or loculated abscess.

Treatment

Treatment of acute cases consists of high-dose oral tetracycline (500 mg bid), doxycycline (100 to 200 mg once/day), minocycline (100 mg once/day), or erythromycin (250 to 500 mg qid) until the lesions resolve. Topical clindamycin applied bid may be equally effective. Incision and drainage are necessary for an abscess or fluctuance of the affected area but alone do not resolve the problem (unlike in cutaneous abscesses). Isotretinoin 1 mg/kg po bid has also been effective in some patients, but recurrences are common. Intralesional corticosteroid injections (eg, triamcinolone 1 to 10% suspension intradermally) may help with inflammation and pain. Surgical excision and repair or grafting of the affected areas is often necessary if the disease persists. Ablative laser therapy (CO_2 or erbium:YAG) is an alternate surgical treatment. Several studies report success in treating hidradenitis suppurativa with etanercept or infliximab, injectable tumor necrosis factor-α inhibitors. Although not the gold standard, this option may be useful when all other treatment modalities have failed.

Impetigo and Ecthyma

Impetigo is a superficial skin infection with crusting or bullae caused by streptococci, staphylococci, or both. Ecthyma is an ulcerative form of impetigo.

No predisposing lesion is identified in most patients, but impetigo may follow any type of break in the skin. General risk factors seem to be moist environment, poor hygiene, and chronic nasal carriage of staphylococci. Impetigo may be bullous or nonbullous. *Staphylococcus aureus* is the predominant cause of nonbullous impetigo and the cause of all bullous impetigo. Bullae are caused by exfoliative toxin produced by staphylococci. Methicillin-resistant *S. aureus* (MRSA) has been isolated in about 20% of recent cases of impetigo.

Symptoms and Signs

Nonbullous impetigo typically manifests as clusters of vesicles or pustules that rupture and develop a honey-colored crust (exudate from the lesion base) over the lesions (see Plate 35). Bullous impetigo is similar except that vesicles typically enlarge rapidly to form bullae. The bullae burst and expose larger bases, which become covered with honey-colored varnish or crust. Ecthyma is characterized by small, purulent, shallow, punched-out ulcers with thick, brown-black crusts and surrounding erythema.

Impetigo and ecthyma cause mild pain or discomfort. Pruritus is common; scratching may spread infection, inoculating adjacent and nonadjacent skin.

Diagnosis

• Clinical evaluation

Diagnosis is by characteristic appearance. Cultures of lesions are indicated only when the patient does not respond to empiric therapy. Patients with recurrent impetigo should have nasal culture. Persistent infections should be cultured to identify MRSA.

Treatment

• Topical mupirocin or retapamulin

• Sometimes oral antibiotics

The affected area should be washed gently with soap and water several times a day to remove any crusts. Treatment for localized disease is topical mupirocin antibiotic ointment tid for 7 days or retapamulin ointment bid for 5 days. Oral antibiotics (eg, dicloxacillin or cephalexin 250 to 500 mg qid, 12.5 mg/kg qid for children, for 10 days) may be needed in patients with extensive or resistant lesions. Use of initial empiric therapy against MRSA is not typically advised unless there is compelling clinical evidence (eg, contact with a documented case or outbreak; high culture-documented prevalence in a practice area). Treatment of MRSA should be directed by culture and sensitivity test results; typically, clindamycin, rifampin, and trimethoprim/sulfamethoxazole are effective against most strains of community-associated MRSA.

Other therapy includes restoring a normal cutaneous barrier in patients with underlying atopic dermatitis or extensive xerosis using topical emollients and corticosteroids if warranted. Chronic staphylococcal nasal carriers are given topical antibiotics (mupirocin) for 1 wk each of 3 consecutive months.

Prompt recovery usually follows timely treatment. Delay can cause cellulitis, lymphangitis, furunculosis, and hyperpigmentation or hypopigmentation with or without scarring. Children aged 2 to 4 yr are at risk of acute glomerulonephritis if nephritogenic strains of group A streptococci are involved; nephritis seems to be more common in the southern US than in other regions.

Lymphadenitis

(See also Lymphangitis, below.)

Lymphadenitis is an acute infection of one or more lymph nodes.

Lymphadenitis is a feature of many bacterial, viral, fungal, and protozoal infections. Focal lymphadenitis is prominent in streptococcal infection, TB or nontuberculous mycobacterial infection, tularemia, plague, cat-scratch disease, primary syphilis, lymphogranuloma venereum, chancroid, and genital herpes simplex. Multifocal lymphadenitis is common in infectious mononucleosis, cytomegalovirus infection, toxoplasmosis, brucellosis, secondary syphilis, and disseminated histoplasmosis.

Symptoms and Signs

Lymphadenitis typically causes pain, tenderness, and lymph node enlargement. Pain and tenderness typically distinguish lymphadenitis from lymphadenopathy. With some infections, the overlying skin is inflamed, occasionally with cellulitis. Abscesses may form, and penetration to the skin produces draining sinuses. Fever is common.

Diagnosis

The underlying disorder is usually suggested by history and examination. If not, aspiration and culture or excisional biopsy is indicated.

Treatment

• Treatment of cause

Treatment is directed at the cause and is usually empiric. Options include IV antibiotics, antifungals, and antiparasitics depending upon etiology or clinical suspicion. Many patients with lymphadenitis may respond to outpatient therapy with oral antibiotics. However, many also go on to form abscesses, which require surgical drainage; an extensive procedure is done with accompanying IV antibiotics. In children, IV antibiotics are commonly needed. Hot, wet compresses may relieve some pain. Lymphadenitis usually resolves with timely treatment, although residual, persistent, nontender lymphadenopathy is common.

Lymphangitis

(See also Lymphadenitis, above.)

Lymphangitis is acute bacterial infection (usually streptococcal) of peripheral lymphatic channels.

Bacteria enter the lymphatic channels from an abrasion, wound, or coexisting infection (usually cellulitis). Patients with underlying lymphedema are at particular risk. Red, irregular, warm, tender streaks develop on an extremity and extend proximally from a peripheral lesion toward regional lymph nodes, which are typically enlarged and tender. Systemic manifestations (eg, fever, shaking chills, tachycardia, headache) may occur and may be more severe than cutaneous findings suggest. Leukocytosis is common. Bacteremia may occur. Rarely, cellulitis with suppuration, necrosis, and ulceration develops along the involved lymph channels as a consequence of primary lymphangitis.

Diagnosis is clinical. Isolation of the responsible organism is usually unnecessary. Most cases respond rapidly to antistreptococcal antibiotics (see Cellulitis on p. 694).

Necrotizing Subcutaneous Infection

(Necrotizing Fasciitis)

Necrotizing subcutaneous infection (NSI) is typically caused by a mixture of aerobic and anaerobic organisms that cause necrosis of subcutaneous tissue, usually including the fascia. This infection most commonly affects the extremities and perineum. Affected tissues become red, hot, and swollen, resembling severe cellulitis (see p. 694). Without timely treatment, the area becomes gangrenous. Patients are acutely ill. Diagnosis is by history and examination and is supported by evidence of overwhelming infection. Treatment involves antibiotics and surgical debridement. Prognosis is poor without early, aggressive treatment.

Etiology

NSI typically results from infection with group A streptococci (eg, *Streptococcus pyogenes*) or a mixture of aerobic and anaerobic bacteria (eg, *Bacteroides* sp). These organisms typically extend to subcutaneous tissue from a contiguous ulcer, an infection, or after trauma. Streptococci can arrive from a remote site of infection via the bloodstream. Perineal involvement (also called Fournier's gangrene) is usually a complication of recent surgery, perirectal abscess, periurethral gland infection, or retroperitoneal infection from perforated abdominal viscera. Patients with diabetes are at particular risk of NSI.

Pathophysiology

NSI causes tissue ischemia by widespread occlusion of small subcutaneous vessels. Vessel occlusion results in skin infarction and necrosis, which facilitates the growth of obligate anaerobes (eg, *Bacteroides*) while promoting anaerobic metabolism by facultative organisms (eg, *Escherichia coli*), resulting in gangrene. Anaerobic metabolism produces hydrogen and nitrogen, relatively insoluble gases that may accumulate in subcutaneous tissues.

Symptoms and Signs

The primary symptom is intense pain. However, in areas denervated by peripheral neuropathy, pain may be minimal or absent. Affected tissue is red, hot, and swollen and rapidly becomes discolored. Bullae, crepitus (from soft-tissue gas), and gangrene may develop. Subcutaneous tissues (including adjacent fascia) necrose, with widespread undermining of surrounding tissue. Muscles are spared initially. Patients are acutely ill, with high fever, tachycardia, altered mental status ranging from confusion to obtundation, and hypotension. Patients may be bacteremic or septic and may require aggressive hemodynamic support.

Diagnosis

• Clinical examination

• Blood and wound cultures

Diagnosis, made by history and examination, is supported by leukocytosis, soft-tissue gas on x-ray, positive blood cultures, and deteriorating metabolic and hemodynamic status.

NSI must be differentiated from clostridial soft-tissue infections, in which cellulitis, myositis, and myonecrosis often occur (see p. 1295). Such infections are anaerobic. Anaerobic cellulitis produces lots of gas but little pain, edema, or change in skin; it very seldom travels into the muscle. Anaerobic myonecrosis has pronounced skin changes, pain, and edema and usually penetrates into muscle.

Prognosis

Mortality rate is about 30%. Old age, underlying medical problems, delayed diagnosis and therapy, and insufficient surgical debridement worsen prognosis.

Treatment

• Surgical debridement

• Antibiotics

• Amputation if necessary

Treatment of early NSI is primarily surgical. IV antibiotics are adjuncts, usually including 2 or more drugs, but regimens vary depending on results of Gram stain and culture (eg, penicillin G 4 million units q 4 h combined with clindamycin 600 to 900 mg q 8 h or ceftriaxone 2 g q 12 h). Evidence of bullae, ecchymosis, fluctuance, crepitus, and systemic spread of infection requires immediate surgical exploration and debridement. The initial incision should be extended until an instrument or finger can no longer separate the skin and subcutaneous tissue from the deep fascia. The most common error is insufficient surgical intervention; repeat operation every 1 to 2 days, with further incision and debridement as needed, should be carried out routinely. Amputation of an extremity may be necessary.

IV fluids may be needed in large volumes before and after surgery. Antibiotic choices should be reviewed based on Gram stain and culture of tissues obtained during surgery. Hyperbaric O_2 therapy as adjuvant therapy may also be of benefit; however, the evidence is inconclusive.

Staphylococcal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome (SSSS) is an acute epidermolysis caused by a staphylococcal toxin. Infants and children are most susceptible. Symptoms are widespread bullae with epidermal sloughing. Diagnosis is by examination and sometimes biopsy. Treatment is antistaphylococcal antibiotics and local care. Prognosis is excellent with timely treatment.

SSSS almost always affects children < 6 yr (especially infants); it rarely occurs in older patients unless they have renal failure or are immunocompromised. Epidemics may occur in nurseries, presumably transmitted by the hands of personnel who are in contact with an infected infant or who are nasal carriers of *Staphylococcus aureus*. Sporadic cases also occur.

SSSS is caused by group II coagulase-positive staphylococci, usually phage type 71, which elaborate exfoliatin (also called epidermolysin), a toxin that splits the upper part of the epidermis just beneath the granular cell layer (see also p. 1228). The primary infection often begins during the first few days of life in the umbilical stump or diaper area; in older children, the face is the typical site. Toxin produced in these areas enters the circulation and affects the entire skin.

[
Table 81-2. Differentiating Staphylococcal Scalded Skin Syndrome (SSSS) and Toxic Epidermal Necrolysis (TEN)]

Symptoms and Signs

The initial lesion is usually superficial and crusted. Within 24 h, the surrounding skin becomes painful and scarlet, changes that quickly spread to other areas. The skin may be exquisitely tender and have a wrinkled tissue paper-like consistency. Large, flaccid blisters arise on the erythematous skin and quickly break to produce erosions. Intact blisters extend laterally with gentle pressure (Nikolsky's sign). The epidermis may peel easily, often in large sheets (see Plate 45). Widespread desquamation occurs within 36 to 72 h, and patients become very ill with systemic manifestations (eg, malaise, chills, fever). Desquamated areas appear scalded. Loss of the protective skin barrier can lead to sepsis and to fluid and electrolyte imbalance.

Diagnosis

• Biopsy

• Cultures may be useful in adults

Diagnosis is suspected clinically, but confirmation usually requires biopsy (frozen section may give earlier results). Specimens show noninflammatory superficial splitting of the epidermis. In children, skin cultures are seldom positive; in adults, they are frequently positive. Cultures should be taken from the nose, conjunctiva, throat, and nasopharynx.

Differential diagnosis: Differential diagnosis includes drug hypersensitivity, viral exanthemas, scarlet fever, thermal burns, genetic bullous diseases (eg, some types of epidermolysis bullosa), acquired bullous diseases (eg, pemphigus vulgaris, bullous pemphigoid), and toxic epidermal necrolysis (see p. 689 and Table 81-2). Stevens-Johnson syndrome is characterized by mucosal involvement, which is absent in SSSS.

Treatment

• Antibiotics

• Corticosteroids not recommended

• Gel dressings for weeping lesions

With prompt diagnosis and therapy, death rarely occurs; the stratum corneum is quickly replaced, and healing usually occurs within 5 to 7 days after start of treatment.

Penicillinase-resistant antistaphylococcal antibiotics given IV must be started immediately. Nafcillin 12.5 to 25 mg/kg IV q 6 h for neonates > 2 kg and 25 to 50 mg/kg for older children is given until improvement is noted, followed by oral cloxacillin 12.5 mg/kg q 6 h (for infants and children weighing ≤ 20 kg) and 250 to 500 mg q 6 h (for older children). Corticosteroids are contraindicated. Topical therapy and patient handling must be minimized.

If disease is widespread and lesions are weeping, the skin should be treated as for burns (see p. 3245). Hydrolyzed polymer gel dressings may be very useful, and the number of dressing changes should be minimized.

Steps to detect carriers and prevent or treat nursery epidemics are discussed elsewhere (see p. 2828).

Chapter 82. Fungal Skin Infections

Introduction

Fungal skin infections are caused by yeasts (*Candida* sp) or dermatophytes (*Epidermophyton*, *Microsporum*, and *Trichophyton* spp).

Candidiasis

Candidiasis (moniliasis) is skin infection with *Candida* sp, most commonly *Candida albicans*. Infections can occur anywhere and are most common in skinfolds and web spaces and on the genitals, cuticles, and oral mucosa. Symptoms and signs vary by site. Diagnosis is by clinical appearance and potassium hydroxide wet mount of skin scrapings. Treatment is with drying agents and antifungals.

Most candidal infections are of the skin and mucous membranes, but invasive candidiasis is common in immunosuppressed patients and can be life threatening. Systemic candidiasis is discussed in Ch. 142.

Etiology

Candida is a group of about 150 yeast species. *C. albicans* is responsible for about 70 to 80% of all candidal infections. Other significant species include *C. glabrata*, *C. tropicalis*, *C. krusei*, and *C. dubliniensis*.

Candida is a ubiquitous yeast that resides harmlessly on skin and mucous membranes until dampness, heat, and impaired local and systemic defenses provide a fertile environment for it to grow. Risk factors for candidiasis include

- Hot weather
- Restrictive clothing
- Poor hygiene
- Infrequent diaper or undergarment changes in children and elderly patients
- Altered flora from antibiotic therapy
- Inflammatory diseases (eg, psoriasis) that occur in skinfolds
- Immunosuppression resulting from corticosteroids and immunosuppressive drugs, pregnancy, diabetes, other endocrinopathies (eg, Cushing's disease, hypoadrenalism, hypothyroidism), blood dyscrasias, or T-cell defects

Candidiasis occurs most commonly in intertriginous areas such as the axillae, groin, and gluteal folds (eg, diaper rash—see Plate 30), in digital web spaces, in the glans penis, and beneath the breasts. Vulvovaginal candidiasis is common in women (see p. 2544). Candidal nail infections and paronychia may develop after improperly done manicures and in kitchen workers and others whose hands are continually exposed to water (see p. 734). In obese people, candidal infections may occur beneath the pannus (abdominal fold). Oropharyngeal candidiasis (see Plate 32) is a common sign of local or systemic immunosuppression.

Chronic mucocutaneous candidiasis typically affects the nails, skin, and oropharynx. Patients have cutaneous anergy to *Candida*, absent proliferative responses to *Candida* antigen (but normal proliferative responses to mitogens), and an intact antibody response to *Candida* and other antigens. Chronic mucocutaneous candidiasis may occur as an autosomal recessive illness associated with

hypoparathyroidism and Addison's disease (*Candida*-endocrinopathy syndrome).

Symptoms and Signs

Intertriginous infections manifest as pruritic, well-demarcated, erythematous patches of varying size and shape; erythema may be difficult to detect in darker-skinned patients. Primary patches may have adjacent satellite papules and pustules. Perianal candidiasis produces white maceration and pruritus ani. Vulvovaginal candidiasis causes pruritus and discharge (see p. 2544).

Candidal infection is a frequent cause of chronic paronychia, which manifests as painful red periungual swelling. Subungual infections are characterized by distal separation of one or several fingernails (onycholysis), with white or yellow discoloration of the subungual area (see p. 735).

Oropharyngeal candidiasis causes white plaques on oral mucous membranes that may bleed when scraped.

Perleche is candidiasis at the corners of the mouth, which causes cracks and tiny fissures. It may stem from chronic lip licking, thumb sucking, ill-fitting dentures, or other conditions that make the corners of the mouth moist enough that yeast can grow.

Chronic mucocutaneous candidiasis is characterized by red, pustular, crusted, and thickened plaques resembling psoriasis, especially on the nose and forehead, and is invariably associated with chronic oral candidiasis.

Diagnosis

• Clinical appearance

• Potassium hydroxide wet mounts

Diagnosis is based on clinical appearance and identification of yeast and pseudohyphae in potassium hydroxide wet mounts of scrapings from a lesion. Positive culture is usually meaningless because *Candida* is omnipresent.

Treatment

• Sometimes drying agents

• Topical or oral antifungals

Intertriginous infection is treated with drying agents as needed (eg, Burow's solution for oozing lesions, gentian violet for toe web spaces) and topical antifungals (see Table 82-1). Powdered formulations are ideal for dry lesions (eg, miconazole powder bid for 2 to 3 wk). Fluconazole 150 mg po once/wk for 2 to 4 wk is indicated for extensive intertriginous candidiasis; topical antifungal agents may be used at the same time.

Candidal diaper rash is treated with more frequent change of diapers, avoidance of disposable diapers with plastic coverings, and an imidazole cream bid. Oral nystatin is an option for infants with coexisting oropharyngeal candidiasis; 1 mL of suspension (100,000 units/mL) is placed in each buccal pouch qid.

Candidal paronychia is treated by protecting the area from wetness and giving topical or oral antifungals. These infections are often resistant to treatment.

Oral candidiasis is treated with fluconazole 200 mg po on the first day, then 100 mg po once/day for 2 to 3 wk thereafter.

Chronic mucocutaneous candidiasis requires long-term oral antifungal treatment with ketoconazole 400 mg once/day or itraconazole 200 mg once/day.

[Table 82-1. Options for Treatment of Superficial Fungal Infections*]

Dermatophytoses

Dermatophytoses are fungal infections of keratin in the skin and nails (nail infection is called tinea unguium—see p. 734). Symptoms and signs vary by site of infection. Diagnosis is by clinical appearance and by examination of skin scrapings on potassium hydroxide wet mount. Treatment varies by site but always involves topical or oral antifungal drugs.

Dermatophytes are molds that require keratin for nutrition and must live on stratum corneum, hair, or nails to survive. Human infections are caused by *Epidermophyton*, *Microsporum*, and *Trichophyton* spp. These infections differ from candidiasis in that they are rarely if ever invasive. Transmission is person-to-person, animal-to-person, and rarely, soil-to-person. The organism may persist indefinitely. Most people do not develop clinical infection; those who do may have impaired T-cell responses from an alteration in local defenses (eg, from trauma with vascular compromise) or from primary (hereditary) or secondary (eg, diabetes, HIV) immunosuppression.

Symptoms and Signs

Symptoms and signs vary by site (skin, hair, nails). Organism virulence and host susceptibility and hypersensitivity determine severity. Most often, there is little or no inflammation; asymptomatic or mildly itching lesions with a scaling, slightly raised border remit and recur intermittently. Occasionally, inflammation is more severe and manifests as sudden vesicular or bullous disease (usually of the foot) or as an inflamed boggy lesion of the scalp (kerion).

Diagnosis

• Clinical appearance

• Potassium hydroxide wet mount

Diagnosis is based on clinical appearance and site of infection and confirmed by skin scrapings and demonstration of hyphae on potassium hydroxide (KOH) wet mount. Identification of specific organisms by culture is unnecessary except for scalp infection (where an animal source may be identified and treated) and nail infection (which may be caused by a nondermatophyte). Culture may also be useful when overlying inflammation and bacterial infection are severe and/or accompanied by alopecia.

Differential diagnosis includes

• Folliculitis decalvans

• Bacterial pyodermas

• Entities that cause scarring alopecia, such as discoid lupus, lichen planopilaris, and pseudopelade

Treatment

• Topical or oral antifungals

• Sometimes corticosteroids

Topical antifungals are generally adequate (see Table 82-1). In general, OTC terbinafine is best; econazole or ciclopirox may be better if candidal infection cannot be excluded. Oral antifungals are used for most nail and scalp infections, resistant skin infections, and patients unwilling or unable to adhere to prolonged topical regimens; doses and duration differ by site of infection.

Corticosteroid creams can be used to help relieve itching and pain for the first few days. Low-dose

hydrocortisone can be applied separately, or more potent corticosteroids may be added to the antifungal cream. Oral corticosteroids are occasionally used for treatment of severe inflammatory lesions.

Tinea Barbae

(Barber's Itch)

Tinea barbae is a dermatophyte infection of the beard area most often caused by *Trichophyton mentagrophytes* or *T. verrucosum*.

Tinea barbae manifests as superficial annular lesions, but deeper infection similar to folliculitis may occur. It may also occur as an inflammatory kerion that can result in scarring hair loss. Diagnosis is by KOH wet mount, culture, or biopsy.

Treatment is micronized griseofulvin 500 mg to 1 g po once/day until 2 to 3 wk after clinical clearance. Terbinafine 250 mg po once/day and itraconazole 200 mg po once/day have also been used. If the lesions are severely inflamed, a short course of prednisone should be added (to lessen symptoms and perhaps reduce the chance of scarring), starting with 40 mg po once/day (for adults) and tapering the dose over 2 wk.

Tinea Capitis

(Scalp Ringworm)

Tinea capitis is a dermatophyte infection of the scalp.

Tinea capitis mainly affects children, is contagious, and can be epidemic. *T. tonsurans* is the most common cause in the US, followed by *Microsporum canis* and *M. audouinii*; other *Trichophyton* sp (eg, *T. schoenleinii*, *T. violaceum*) are common elsewhere.

Tinea capitis causes the gradual appearance of round patches of dry scale, alopecia, or both. *T. tonsurans* infection causes "black dot ringworm," in which hair shafts break at the scalp surface; *M. audouinii* infection causes "gray patch ringworm," in which hair shafts break above the surface, leaving short stubs. Tinea capitis less commonly manifests as diffuse scaling, like dandruff, or in a diffuse pustular pattern.

Kerion: Dermatophyte infection occasionally leads to formation of a kerion, which is a large, boggy, inflammatory scalp mass (see Plate 48) caused by a severe inflammatory reaction to the dermatophyte. A kerion may have pustules and crusting and can be mistaken for an abscess. A kerion may result in scarring hair loss.

Diagnosis

• Clinical appearance

• KOH wet mount

• Sometimes Wood's light examination

Tinea capitis is diagnosed by clinical appearance and by KOH wet mount of plucked hairs or of hairs and scale obtained by scraping or brushing. Spore size and appearance inside (endothrix) or outside (ectothrix) the hair shaft distinguish organisms and can help guide treatment. Blue-green fluorescence during Wood's light examination is diagnostic for infection with *M. canis* and *M. audouinii* and can distinguish tinea from erythrasma.

Differential diagnosis of tinea capitis includes

• Seborrheic dermatitis

• Psoriasis

Treatment

• Oral antifungals

• Selenium sulfide shampoo

• Sometimes prednisone

Children are treated with micronized griseofulvin suspension 10 to 20 mg/kg po once/day (doses vary by several parameters, but maximum dose is generally 1 g/day) or, if > 2 yr, with ultramicronized griseofulvin 5 to 10 mg/kg (maximum 750 mg/day) po once/day or in 2 divided doses with meals or milk for 4 to 6 wk or until all signs of infection are gone. Terbinafine also may be used; children < 20 kg are given 62.5 mg once/day; those 20 to 40 kg, 125 mg once/day, and those > 40 kg, 250 mg once/day. An imidazole or ciclopirox cream should be applied to the scalp to prevent spread, especially to other children, until tinea capitis is cured; selenium sulfide 2.5% shampoo should also be used at least twice/wk. Children may attend school during treatment.

Adults are treated with terbinafine 250 mg po once/day for 2 to 4 wk, which is more effective for endothrix infections, or itraconazole 200 mg once/day for 2 to 4 wk or 200 mg bid given for 1 wk, followed by 3 wk without the drug (pulsed) for 2 to 3 mo.

For severely inflamed lesions and for kerion, a short course of prednisone should be added (to lessen symptoms and perhaps reduce the chance of scarring), starting with 40 mg po once/day (1 mg/kg for children) and tapering the dose over 2 wk.

Tinea Corporis

(Body Ringworm)

Tinea corporis is a dermatophyte infection of the face, trunk, and extremities.

Common causes are *T. mentagrophytes*, *T. rubrum*, and *M. canis*.

Tinea corporis causes pink-to-red annular patches and plaques with raised scaly borders that expand peripherally and tend to clear centrally (see
Plate 49). A variant form appears as nummular scaling patches studded with small papules or pustules.

Diagnosis

• Clinical evaluation

Differential diagnosis includes

• Pityriasis rosea

• Drug eruptions

• Nummular dermatitis

• Erythema multiforme

• Tinea versicolor

• Erythrasma

• Psoriasis

• Secondary syphilis

Treatment

• Topical or oral antifungals

Treatment of mild-to-moderate lesions is an imidazole, ciclopirox, naftifine, or terbinafine in cream, lotion, or gel. The drug should be rubbed in bid continuing at least 7 to 10 days after lesions disappear, typically at about 2 to 3 wk.

Extensive and resistant lesions occur in patients infected with *T. rubrum* and in people with debilitating systemic diseases. For such cases, the most effective therapy is oral itraconazole 200 mg once/day or terbinafine 250 mg once/day for 2 to 3 wk.

Tinea Cruris

(Jock Itch)

Tinea cruris is a dermatophyte infection of the groin.

Common organisms include *T. rubrum* or *T. mentagrophytes*. The primary risk factors are associated with a moist environment (ie, warm weather, wet and restrictive clothing, obesity causing constant apposition of skin folds). Men are affected more than women because of apposition of the scrotum and thigh.

Typically, a pruritic, ringed lesion extends from the crural fold over the adjacent upper inner thigh (see Plate 50). Infection may be bilateral. Lesions may be complicated by maceration, miliaria, secondary bacterial or candidal infection, and reactions to treatment. In addition, scratch dermatitis and lichenification can occur. Recurrence is common because fungi may repeatedly infect susceptible people. Flare-ups occur more often during summer.

Diagnosis

• Clinical evaluation

Differential diagnosis includes

• Contact dermatitis

• Psoriasis

• Erythrasma

• Candidiasis

Scrotal involvement is usually absent or slight; by contrast, the scrotum is often inflamed in candidal intertrigo or lichen simplex chronicus.

Treatment

• Topical antifungal cream or lotion

Antifungal choices include terbinafine, miconazole, clotrimazole, ketoconazole, econazole, naftifine, and ciclopirox applied bid for 10 to 14 days. Itraconazole 200 mg po once/day or terbinafine 250 mg po once/day for 3 to 6 wk may be needed in patients who have refractory, inflammatory, or widespread infections.

Tinea Pedis

(Athlete's Foot)

Tinea pedis is a dermatophyte infection of the feet.

Tinea pedis is the most common dermatophytosis because moisture from foot sweating facilitates fungal growth. Tinea pedis may occur as any of 4 clinical forms or in combination:

• Chronic hyperkeratotic

• Chronic intertriginous

• Acute ulcerative

• Vesiculobullous

Chronic hyperkeratotic tinea pedis due to *T. rubrum* causes a distinctive pattern of lesion, manifesting as scaling and thickening of the soles, which often extends beyond the plantar surface in a moccasin distribution. Differential diagnosis is sterile maceration (due to hyperhidrosis and occlusive footgear), contact dermatitis (due to type IV delayed hypersensitivity to various materials in shoes, particularly adhesive cement, thiuram compounds in footwear that contains rubber, and chromate tanning agents used in leather footwear), irritant dermatitis, and psoriasis.

Chronic intertriginous tinea pedis is characterized by scaling, erythema, and erosion of the interdigital and subdigital skin of the feet, most commonly affecting the lateral 3 toes.

Acute ulcerative tinea pedis (most often caused by *T. mentagrophytes* var. *interdigitale*) typically begins in the 3rd and 4th interdigital spaces and extends to the lateral dorsum and/or the plantar surface of the arch. These toe web lesions are usually macerated and have scaling borders (see Plate 51). Secondary bacterial infection, cellulitis, and lymphangitis are common complications.

Vesiculobullous tinea pedis, in which vesicles develop on the soles and coalesce into bullae, is the less common result of a flare of interdigital tinea pedis; risk factors are occlusive shoes and environmental heat and humidity.

Diagnosis

Diagnosis is usually obvious based on clinical examination and review of risk factors.

Treatment

• Moisture reduction and drying agents

• Topical and oral antifungals

The safest treatment is topical antifungals, but recurrence is common and treatment must often be prolonged. Alternatives that provide a more durable response include itraconazole 200 mg po once/day for 1 mo (or pulse therapy with 200 mg bid 1 wk/mo for 1 to 2 mo) and terbinafine 250 mg po once/day for 2 to 6 wk. Concomitant topical antifungal use may reduce recurrences.

Moisture reduction on the feet and in footwear is necessary for preventing recurrence. Permeable or open-toe footwear and sock changes are important especially during warm weather. Interdigital spaces should be manually dried after bathing. Drying agents are also recommended; options include antifungal powders (eg, miconazole), gentian violet, Burow's solution (5% aluminum sub-acetate) soaks bid, and 20 to 25% aluminum chloride hexahydrate powder once/day.

Dermatophytid Reaction

Dermatophytid is an inflammatory reaction to dermatophytosis at a cutaneous site distant from the primary infection.

Dermatophytid (identity or id) reactions are protean; they are not related to localized growth of the fungus but rather are an inflammatory reaction elsewhere on the body. Lesions are typically pruritic but may manifest as

• Vesicular eruptions on the hands and feet

• Follicular papules

• Erysipelas-like plaques

• Erythema nodosum

• Erythema annulare centrifugum

• Urticaria

Distribution may be extensive.

Diagnosis is by KOH wet mounts that are negative at the site of the id reaction and positive at the distant site of dermatophyte infection.

Treatment of the primary infection cures dermatophytid; pending cure, topical corticosteroids and/or antipruritics (eg, hydroxyzine 25 mg qid) can be used to relieve symptoms.

Intertrigo

Intertrigo is skinfold changes caused by moisture and infection.

Intertrigo develops when friction and trapped moisture in intertriginous areas cause skin maceration with formation of patches or plaques; bacterial, yeast, and dermatophyte infection is common. Typical locations are the inframammary, infrapannicular, interdigital, axillary, infragluteal, and genitocrural folds.

Diagnosis is based on clinical appearance; potassium hydroxide wet mounts and cultures can guide treatment.

If no bacteria or yeast are detected, drying agents (powders such as talc rather than cornstarch, which can support fungal growth, Burow's solution) to decrease moisture should be therapeutic. If bacteria or yeasts are present, topical antibacterial lotions or antifungal creams are given in addition to drying agents.

Tinea Versicolor

(Pityriasis Versicolor)

Tinea versicolor is skin infection with *Malassezia furfur* that manifests as multiple asymptomatic scaly patches varying in color from white to brown. Diagnosis is based on clinical appearance and skin scrapings. Treatment is topical antifungals.

Malassezia furfur is a dimorphic fungus that is normally a harmless component of normal skin flora but that in some people causes tinea versicolor. The high prevalence of tinea versi-color in young adults suggests a link to increased sebaceous secretions; other risk factors include heat and humidity and immunosuppression due to corticosteroids, pregnancy, undernutrition, diabetes, and other disorders.

Symptoms and Signs

Tinea versicolor usually is asymptomatic. Classically, it causes the appearance of multiple tan, brown, salmon, or white scaling lesions (see Plate 52) on the trunk, neck, abdomen, and occasionally face. The lesions coalesce. In whites, the condition is often diagnosed in summer months because the lesions, which do not tan, become more obvious against tanned skin.

Diagnosis

• Clinical appearance

• Potassium hydroxide wet mount

• Sometimes Wood's light examination

Diagnosis is based on clinical appearance and by identification of hyphae and budding cells ("spaghetti and meatballs") on potassium hydroxide wet mount. Wood's light examination reveals golden-white fluorescence.

Treatment

• Topical antifungals

• Sometimes oral antifungals

Treatment is any topical antifungal drug. Examples include selenium sulfide shampoo 2.5% (in 10-min applications daily for 1 wk or 24-h applications weekly for 1 mo); topical azoles (eg, ketoconazole 2% daily for 2 wk); and bathing with zinc pyrithione soap 2% or sulfur-salicylic shampoo 2% for 1 to 2 wk.

Oral treatment is indicated for patients with extensive disease and those with frequent recurrences. Two convenient regimens are a single 400-mg dose of fluconazole and ketoconazole 200 mg once/day for 1 to 5 days.

Hypopigmentation from tinea versicolor is reversible in months to years after the yeast has cleared. Recurrence is almost universal after treatment because the causative organism is a normal skin inhabitant. Fastidious hygiene, regular use of zinc pyrithione soap, or once-monthly use of topical antifungal therapy lowers the likelihood of recurrence.

Chapter 83. Parasitic Skin Infections

Introduction

Parasitic skin infections can cause severe itching and be distressing. Most skin parasites are insects or worms that burrow into the skin for part or all of their life cycle. Also, some systemic parasitic infections have cutaneous manifestations; these include certain nematodes (ancylostomiasis, dracunculosis, strongyloidiasis, toxocariasis—see p. 1342) and flukes (schistosomiasis—see p. 1358). Very rarely, patients have delusional parasitosis.

Cutaneous Larva Migrans

(Creeping Eruption)

Cutaneous larva migrans (CLM) is the skin manifestation of hookworm infestation.

CLM is caused by *Ancylostoma* sp, most commonly dog or cat hookworm *Ancylostoma braziliense*. Hookworm ova in dog or cat feces develop into infective larvae when left in warm moist ground or sand; transmission occurs when skin directly contacts contaminated soil or sand and larvae penetrate unprotected skin, usually of the feet, legs, buttocks, or back. CLM occurs worldwide but most commonly in tropical environments.

CLM causes intense pruritus; signs are erythema and papules at the site of entry, with a winding, threadlike subcutaneous trail of reddish-brown inflammation. Diagnosis is by history and clinical appearance.

Topical thiabendazole 15% liquid or cream (compounded) bid to tid for 5 days is extremely effective. Oral thiabendazole is not well tolerated and not usually used. Albendazole (400 mg po once/day for 7 days) and ivermectin can cure the infestation and are well tolerated.

CLM may be complicated by a self-limiting pulmonary reaction called Loffler's syndrome (patchy pulmonary infiltrates and peripheral blood eosinophilia).

Cutaneous Myiasis

Cutaneous myiasis is skin infestation by the larvae of certain fly species.

Myiasis involves the larvae of two-winged (dipterous) flies. Three types of cutaneous infestation exist, depending on the species involved:

• Furuncular

• Wound

• Migratory

Other organs sometimes are involved (eg, nasopharynx, GI tract, GU tract). Infestation usually occurs in tropical countries, so most cases in the US occur in people who have recently arrived from endemic areas.

Furuncular myiasis: Many of the common sources are known as bot flies. *Dermatobia hominis*, native to South and Central America, is the most common cause in travelers returning to the US. Other species include *Cordylobia anthropophaga* (in sub-Saharan Africa), and various *Cuterebra* sp (in tropical Africa). Many of the flies do not lay their eggs on humans but on other insects (eg, mosquitoes) or objects (eg, drying laundry) that may contact skin. Eggs on the skin hatch into larvae, which burrow into the skin and develop through successive stages (instars) into mature larvae; mature larvae may be 1 to 2 cm long, depending on the species. If the infestation is untreated, larvae eventually emerge from the skin and drop

to the ground to continue their life cycle.

Typical symptoms include itching, a sensation of movement, and sometimes lancinating pain. The initial lesion may resemble an arthropod bite or bacterial furuncle but may be distinguished by the presence of a central punctum with serosanguineous drainage; sometimes a small portion of the end of the larva is visible.

Because larvae require atmospheric O_2, occlusion of the skin opening may cause them to depart or at least come closer to the surface, facilitating manual removal. The numerous occlusal methods include use of petrolatum, nail polish, bacon, or a paste of tobacco. However, larvae that die during occlusion are difficult to remove and often trigger an intense inflammatory reaction. Other options for removal include manual expression (ie, squeezing) and extraction through a small incision. Ivermectin, oral (200 µg/kg, one dose) or topical, may kill the larvae or induce migration.

Wound myiasis: Open wounds, typically in the homeless, alcoholics, and other people in poor social circumstances, may be infested by fly larvae, most often from green or black blowflies. Unlike larvae of common houseflies, most agents of wound myiasis invade healthy as well as necrotic tissue. Treatment is usually with irrigation and manual debridement.

Migratory myiasis: The most common agents are *Gasterophilus intestinalis* and *Hypoderma* sp. These flies typically infest horses and cattle; people acquire them via contact with infested animals or, less often, via direct egg-laying on their skin. Larvae of these agents burrow under the skin, causing pruritic, advancing lesions, which may be mistaken for cutaneous larva migrans; however, fly larvae are much larger than nematodes, and the lesions created by fly larvae last longer. Treatment is similar to that of furuncular myiasis.

Delusional Parasitosis

In delusional parasitosis, patients mistakenly believe that they are infested with parasites.

Patients have an unshakable belief that they are infested with insects, worms, mites, lice, or other organisms. They often provide vivid descriptions of how the organisms enter their skin and move around their bodies, and bring samples of hair, skin, and debris such as dried scabs, dust, and lint on slides or in containers (the matchbox sign) to prove that the infestation is real. The condition is considered a hypochondriacal psychosis, but the cause is unknown.

Diagnosis is suspected by history. Work-up requires ruling out true infestations and other physiologic disease by physical examination and judicious testing, such as skin scrapings and CBC.

Treatment is with antipsychotic drugs (see p. 1562). Typically, the patient seeks confirmation that the drug treats the infestation itself, and any suggestion that the treatment is for something else is met with resistance and/or rejection. Thus, effective treatment often requires diplomacy and a delicate balance between offering proper treatment and respecting the patient's right to know.

Lice

(Pediculosis)

Lice can infect the scalp, body, pubis, and eyelashes. Head lice are transmitted by close contact; body lice, in cramped, crowded conditions; and pubic lice, by sexual contact. Symptoms, signs, diagnosis, and treatment differ by location of infestation.

Lice are wingless, blood-sucking insects that infest the head (*Pediculus humanus* var. *capitis*), body (*P. humanus* var. *corporis*), or pubis (*Phthirus pubis*). The 3 kinds of lice differ substantially in morphology and clinical features. Head lice and pubic lice live directly on the host; body lice live in garments. All types occur worldwide.

Head lice: Head lice are most common in girls aged 5 to 11 but can affect almost anyone; infestations

are rare in blacks. Head lice are easily transmitted from person to person with close contact (as occurs within households and classrooms) and may be ejected from hair by static electricity or wind; transmission by these routes (or by sharing of combs, brushes, and hats) is likely but unproven. There is no association between head lice and poor hygiene or low socioeconomic status.

Infestation typically involves the hair and scalp, but the eyebrows, eyelashes, and beard may be involved as well. Active infection usually involves ≤ 20 lice and causes severe pruritus. Examination is most often normal but may reveal scalp excoriations and posterior cervical adenopathy.

Diagnosis depends on demonstration of living lice. Lice are detected by a thorough combing-through of wet hair from the scalp with a fine-tooth detection comb; lice are usually found at the back of the head or behind the ears. Nits are ovoid, grayish white eggs fixed to the base of hair shafts (see Plate 38). Each adult female louse lays 3 to 5 eggs/day, so nits typically vastly outnumber lice and are not a measure of severity of infestation.

Treatment is outlined in Table 83-1. Drug resistance is common and should be managed with use of oral ivermectin and by attempting to rotate pediculicides. Termination of live (viable) nits is important in preventing reinfestation; live nits fluoresce on illumination with a Wood's lamp. Most pediculicides also kill nits. Dead nits remain after successful treatment and do not signify active infection; they do not have to be removed. Nits grow away from the scalp with time; the absence of nits less than one fourth of an inch from the scalp rules out current active infection. Hot air has been shown to kill > 88% of eggs but has been variably effective in killing hatched lice. Thirty minutes of hot air, slightly cooler than a blow drier, may be an effective adjunctive measure to treat head lice.

Controversy surrounds the need to clean the personal items of people with lice or nits and the need to exclude children with head lice or nits from school; there are no conclusive data supporting either approach.

Body lice: Body lice primarily live on bedding and clothing, not people, and are most frequently found in cramped, crowded conditions (eg, military barracks) and in people of low socioeconomic status. Transmission is by sharing of contaminated clothing and bedding. Body lice are important vectors of epidemic typhus, trench fever, and relapsing fever.

Body lice cause pruritus; signs are small red puncta caused by bites, usually associated with linear scratch marks, urticaria, or superficial bacterial infection. These findings are especially common on the shoulders, buttocks, and abdomen. Nits may be present on body hairs.

Diagnosis is by demonstration of lice and nits in clothing, especially at the seams.

Primary treatment is thorough cleaning or replacement of clothing and bedding, which is often difficult because affected people often have few resources and little control over their environment.

[**Table 83-1.** Treatment Options for Scabies and Lice]

Pubic lice: Pubic lice ("crabs") are sexually transmitted in adolescents and adults and may be transmitted to children by close parental contact. They may also be transmitted by fomites (towels, bedding, clothing). They most commonly infest pubic and perianal hairs but may spread to thighs, trunk, and facial hair (beard, mustache, and, in children, eyelashes).

Pubic lice cause pruritus. Physical signs are few, but some patients have excoriations and regional lymphadenopathy and/or lymphadenitis. Pale, bluish gray skin macules (maculae caeruleae) on the trunk, buttocks, and thighs are caused by anticoagulant activity of louse saliva while feeding; they are unusual but characteristic of infestation. Eyelash infestation manifests as eye itching, burning, and irritation.

Diagnosis is by demonstration of nits and/or living lice by close inspection (Wood's light) or microscopic analysis. A supporting sign of infestation is scattering of dark brown specks (louse excreta) on skin or undergarments.

Treatment is outlined in Table 83-1. Treatment of eyelid and eyelash infestation is often difficult and involves use of petrolatum, physostigmine ointment, oral ivermectin, or physical removal of lice with forceps. Sex partners should also be treated.

Scabies

Scabies is an infestation of the skin with the mite *Sarcoptes scabiei*. Scabies causes intensely pruritic lesions with erythematous papules and burrows in web spaces, wrists, waistline, and genitals. Diagnosis is based on examination and scrapings. Treatment is with topical scabicides or, rarely, oral ivermectin.

Etiology

Scabies is caused by the mite *Sarcoptes scabiei* var. *hominis*, an obligate human parasite that lives in burrowed tunnels in the stratum corneum. Scabies is easily transmitted from person to person through physical contact; animal and fomite transmission probably also occurs. The primary risk factor is crowded conditions (as in schools, shelters, barracks, and some households); there is no clear association with poor hygiene. For unknown reasons, crusted scabies is more common in immunosuppressed patients (eg, those with HIV infection, hematologic cancer, chronic corticosteroid or other immunosuppressant use), patients with severe physical disabilities or intellectual disability, and Australian Aborigines. Infestations occur worldwide. Patients in warm climates develop small erythematous papules with few burrows. Severity is related to the patient's immune status, not geography.

Symptoms and Signs

The primary symptom is intense pruritus, classically worse at night, although that timing is not specific to scabies.

Classic scabies: Erythematous papules initially appear in finger web spaces, flexor surfaces of the wrist and elbow, axillary folds, along the belt line, or on the lower buttocks. Papules can spread to any area of the body, including the breasts and penis. The face remains uninvolved in adults. Burrows are pathognomonic for disease, manifesting as fine, wavy, and slightly scaly lines several mm to 1 cm long. A tiny dark papule—the mite—is often visible at one end.

Signs of classic scabies may be atypical. In blacks and other people with dark skin, scabies can manifest as granulomatous nodules. In infants, the palms, soles, face, and scalp may be involved, especially in the posterior auricular folds. In elderly patients, scabies can cause intense pruritus with subtle skin findings, making it a challenge to diagnose. In immunocompromised patients, there may be widespread nonpruritic scaling (particularly on the palms and soles in adults and on the scalp in children).

Other forms: Crusted (Norwegian) scabies is due to an impaired host immune response, allowing mites to proliferate and number in the millions. Nodular scabies is more common in infants and young children and may be due to hypersensitivity to retained organisms. Bullous scabies occurs more commonly in children. When it occurs in the elderly, it can mimic bullous pemphigoid, resulting in a delay in diagnosis. Scalp scabies occurs in infants and immunocompromised people and can mimic dermatitis, particularly atopic or seborrheic dermatitis. Scabies incognito is a widespread atypical form resulting from application of topical corticosteroids.

Diagnosis

• Clinical evaluation

• Burrow scrapings

Diagnosis is suspected by physical findings, especially burrows, and confirmed by mites, ova, or fecal pellets on microscopic examination of burrow scrapings. Scrapings should be obtained by placing glycerol, mineral oil, or immersion oil over a burrow or papule (to prevent dispersion of mites and material

during scraping), which is then unroofed with the edge of a scalpel. The material is then placed on a slide and covered with a coverslip; potassium hydroxide should be avoided because it dissolves fecal pellets.

Treatment

• Topical permethrin or lindane

• Sometimes oral ivermectin

Primary treatment is topical or oral scabicides (see Table 83-1). Permethrin is the 1st-line topical drug.

Older children and adults should apply permethrin or lindane to the entire body from the neck down and wash it off after 8 to 14 h. Treatments should be repeated in 7 days.

For infants and young children, permethrin should be applied to the head and neck, avoiding periorbital and perioral regions. Special attention should be given to intertriginous areas, fingernails, toenails, and the umbilicus. Mittens on infants can keep permethrin out of the mouth. Lindane is not recommended in children < 2 yr and in patients with a seizure disorder because of potential neurotoxicity.

Precipitated sulfur 6 to 10% in petrolatum, applied for 24 h for 3 consecutive days, is safe and effective.

Ivermectin is indicated for patients who do not respond to topical treatment, are unable to adhere to topical regimens, or are immunocompromised with Norwegian scabies. Ivermectin has been used with success in epidemics involving close contacts, such as nursing homes.

Close contacts should also be treated, and personal items (eg, towels, clothing, bedding) should be washed or isolated for at least 3 days.

Pruritus can be treated with corticosteroid ointments and/or oral antihistamines (eg, hydroxyzine 25 mg po qid). Secondary infection should be considered in patients with weeping, yellow-crusted lesions and treated with the appropriate systemic or topical antistaphylococcal or antistreptococcal antibiotic.

Symptoms and lesions take up to 3 wk to resolve despite killing of the mites, making failed treatment due to resistance, poor penetration, incompletely applied therapy, reinfection, or nodular scabies difficult to recognize. Skin scrapings can be done periodically to check for persistent scabies.

Chapter 84. Viral Skin Diseases

Introduction

Many systemic viral infections cause skin lesions. Molluscum contagiosum and warts are the 2 most common primary viral skin diseases without systemic manifestations. Herpes simplex virus infection is discussed on p. 1417.

Molluscum Contagiosum

Molluscum contagiosum is clusters of smooth, waxy, or pearly umbilicated papules 1 to 5 mm in diameter caused by molluscum contagiosum virus, a poxvirus.

Molluscum contagiosum virus commonly causes a localized chronic infection. Transmission is by direct contact; spread occurs by autoinoculation and via fomites (eg, towels, bath sponges).

Symptoms and Signs

Molluscum contagiosum can appear anywhere on the skin except the palms and soles. Lesions consist of clusters of flesh-colored papules, which occur most commonly on the face, trunk, and extremities in children and on the pubis, penis, or vulva in adults. Lesions may grow to 10 to 15 mm in diameter, especially among patients with HIV infection and other immunocompromised patients. Lesions are usually not pruritic or painful and may be discovered only coincidentally during a physical examination. However, the lesions can become inflamed and itchy as the body fights off the virus.

Diagnosis

• Clinical evaluation

Diagnosis is based on clinical appearance; hematoxylin and eosin staining of expressed fluid demonstrates inclusion bodies but is necessary only when diagnosis is uncertain. Differential diagnosis includes folliculitis, milia, and warts (for lesions < 2 mm) and juvenile xanthogranuloma and Spitz nevus (for lesions > 2 mm).

Treatment

• Curettage, cryosurgery, laser therapy, or electrocautery

• Topical irritants (eg, trichloroacetic acid, cantharidin, tretinoin, tazarotene), imiquimod, or both

• Sometimes combination therapies

Most lesions spontaneously regress in 1 to 2 yr, but they can remain for 2 to 3 yr. Treatment is indicated for cosmetic reasons or for prevention of sexual spread. Options include curettage, cryosurgery, laser therapy, electrocautery, trichloroacetic acid (25 to 40% solution), cantharidin, tretinoin, tazarotene and imiquimod 5% cream. Especially in children, treatments that cause minimal pain (eg, tretinoin, imiquimod, tazarotene, cantharidin) are used first. Curettage or liquid nitrogen can be used after application of a topical anesthetic such as EMLA (eutectic mixture of local anesthetics) or 4% lidocaine cream. EMLA cream must be applied judiciously because it can cause systemic toxicity, especially in children. In adults, curettage is very effective but painful. Dermatologists often use combination therapy such as liquid nitrogen or cantharidin in the office and imiquimod cream at home. This form of therapy is typically successful, but resolution often takes 1 to 2 mo in some patients.

Nondermatologists should feel comfortable using imiquimod cream. The cream is applied at night, 1 drop to each molluscum lesion and rubbed in well, until the cream turns clear. The area is washed with soap and water. The cream can be applied 3 to 7 times/wk. Molluscum lesions within the orbital rim should not be treated, and those in the genital region can easily become irritated. Lesions should be treated until they develop a scant amount of redness; treatment is then withheld to avoid weeping and crusting.

Cantharidin is safe and effective but can cause blistering. Cantharidin is applied in 1 small drop directly to the molluscum lesion. Areas that patients (especially children) may rub are covered with a bandage because contact with the fingers should be avoided. Cantharidin should not be applied to the face or near the eyes because blistering is unpredictable. If cantharidin comes into contact with the cornea, it can scar the cornea. Cantharidin should be washed off with soap and water in 6 h. Parents should be warned about blistering if their children are prescribed this drug.

Warts

(Verrucae Vulgaris)

Warts are common, benign epidermal lesions caused by human papillomavirus infection. They can appear anywhere on the body in a variety of morphologies. Diagnosis is by examination. Warts are usually self limited but may be treated by excision, cautery, cryotherapy, liquid nitrogen, and topical or injected agents.

Warts are almost universal in the population; they affect all ages but are most common among children and are uncommon among the elderly.

Etiology

Warts are caused by human papillomavirus (HPV) infection; there are over 100 HPV subtypes. Trauma and maceration facilitate initial epidermal inoculation. Spread may then occur by autoinoculation. Local and systemic immune factors appear to influence spread; immunosuppressed patients (especially those with HIV infection or a renal transplant) are at particular risk of developing generalized lesions that are difficult to treat. Humoral immunity provides resistance to HPV infection; cellular immunity helps established infection to regress.

Symptoms and Signs

Warts are named by their clinical appearance and location; different forms are linked to different HPV types (for unusual manifestations, see Table 84-1).

Common warts: Common warts (verrucae vulgaris) are caused by HPV 1, 2, 4, 27, and 29. They are usually asymptomatic but sometimes cause mild pain, especially when they are located on a weight-bearing surface (eg, bottom of the feet). They are sharply demarcated, rough, round or irregular, firm, and light gray, yellow, brown, or gray-black nodules 2 to 10 mm in diameter. They appear most often on sites subject to trauma (eg, fingers, elbows, knees, face) but may spread elsewhere. Variants of unusual shape (eg, pedunculated or resembling a cauliflower) appear most frequently on the head and neck, especially the scalp and beard area.

Filiform warts: These warts are long, narrow, frondlike growths, usually located on the eyelids, face, neck, or lips. They are usually asymptomatic. This morphologically distinct variant of the common wart is benign and easy to treat.

Flat warts: Flat warts, caused by HPV 3, 10, 28, and 49, are smooth, flat-topped, yellow-brown papules, most often located on the face and along scratch marks; they are more common among children and young adults and develop by autoinoculation. They generally cause no symptoms but can be difficult to treat.

Palmar and plantar warts: These warts, caused by HPV 1, occur on the palms and soles; they are flattened by pressure and surrounded by cornified epithelium (see Plate 55). They are

[**Table 84-1.** Wart Variants]

often tender and can make walking and standing uncomfortable. They can be distinguished from corns and calluses by their tendency to pinpoint bleeding when the surface is pared away. Classically, warts hurt with side-to-side pressure, and calluses hurt with direct pressure; in reality, this is not a reliable sign.

Mosaic warts: Mosaic warts are plaques formed by the coalescence of myriad smaller, closely set plantar warts. As with other plantar warts, they are often tender.

Periungual warts: These warts appear as thickened, fissured cauliflower-like skin around the nail plate. Patients frequently lose the cuticle and are susceptible to paronychia. Periungual warts are more common among patients who bite their nails.

Genital warts: Genital warts (see p. 1470) manifest as discrete flat to broad-based smooth to velvety papules on the perineal, perirectal, labial, and penile areas. Infection with high-risk HPV types (most notably types 16 and 18) is the main cause of cervical cancer. These warts are usually asymptomatic.

Diagnosis

• Clinical evaluation

• Rarely biopsy

Diagnosis is based on clinical appearance; biopsy is rarely needed. A cardinal sign of warts is the absence of skin lines crossing their surface and the presence of pinpoint black dots (thrombosed capillaries) or bleeding when warts are shaved. Differential diagnosis includes corns (clavi), lichen planus, seborrheic keratosis, skin tags, and squamous cell carcinomas. DNA typing is available in some medical centers but is generally not needed.

Prognosis

Many warts regress spontaneously; others persist for years and recur at the same or different sites, even with treatment. Factors influencing recurrence appear to be related to the patient's overall immune status as well as local factors. Patients who subject themselves to local trauma (eg, athletes, mechanics, butchers) may have recalcitrant and recurrent HPV infection. Genital HPV infection has malignant potential, but malignant transformation is rare in HPV-induced skin warts, except among immunosuppressed patients.

Treatment

• Topical irritants (eg, salicylic acid, cantharidin, podophyllum resin)

• Destructive methods (eg, cryosurgery, electrocautery, curettage, excision, laser)

Treatment is aimed at eliciting an immune response to HPV. In most instances, this response is achieved by applying an irritant (eg, salicylic acid [SCA], trichloroacetic acid, 5-fluorouracil, podophyllum resin, tretinoin, cantharidin).

These compounds can be used in combination or with a destructive method (eg, cryosurgery, electrocautery, curettage, excision, laser). Direct antiviral effects can be achieved with bleomycin and interferon alfa-2b, but these treatments are reserved for the most recalcitrant warts. Topical imiquimod 5% cream induces skin cells to locally produce antiviral cytokines. Topical cidofovir, HPV vaccines, and contact immunotherapy (eg, squaric acid dibutyl ester and *Candida* allergen) have been used to treat warts. Oral treatments include cimetidine, isotretinoin, and oral zinc. In most instances, modalities should be combined to increase the likelihood of success.

Common warts: In immunocompetent patients, common warts usually spontaneously regress within 2 to 4 yr, but some linger for many years. Numerous treatments are available. Destructive methods include

• Electrocautery

• Cryosurgery with liquid nitrogen

• SCA preparations

Which method is used depends on the location and severity of involvement. For example, 17% liquid SCA can be used on the fingers, and 40% plaster SCA can be used on the soles.

The most common topical agent to be used is SCA. SCA is available in a liquid, plaster, or impregnated within tape. Patients apply SCA to their warts at night and leave on for 8 to 48 h depending on the site.

Cantharidin can be used alone or in combination (1%) with SCA (30%) and podophyllum (5%) in a collodion base. Cantharidin alone is removed with soap and water after 6 h; cantharidin with SCA or podophyllum is removed in 2 h. The longer these agents are left in contact with the skin, the more brisk the blistering response.

Cryosurgery is painful but extremely effective. Electrodesiccation with curettage, laser surgery, or both is effective and indicated for isolated lesions but may cause scarring. Recurrent or new warts occur in about 35% of patients within 1 yr, so methods that scar should be avoided as much as possible.

Filiform warts: Treatment is removal with scalpel, scissors, curettage, or liquid nitrogen. Liquid nitrogen should be applied so that up to 2 mm of skin surrounding the wart turns white. Damage to the skin occurs when the skin thaws, which usually takes 10 to 20 sec. Blisters can occur 24 to 48 h after treatment with liquid nitrogen. Care must be taken when treating cosmetically sensitive sites, such as the face and neck, because hypopigmentation frequently occurs after treatment with liquid nitrogen. Patients with darkly pigmented skin can develop permanent depigmentation.

Flat warts: Treatment is daily tretinoin (retinoic acid 0.05% cream). If peeling is not sufficient for wart removal, another irritant (eg, 5% benzoyl peroxide) or 5% SCA cream can be applied sequentially with tretinoin. Imiquimod 5% cream can be used alone or in combination with topical drugs or destructive measures. Topical 5-fluorouracil (1% or 5% cream) can also be used. Spontaneous resolution may follow unprovoked inflammation of the lesions; however, flat warts are frequently recalcitrant to treatment.

Plantar warts: Treatment is vigorous maceration with 40% SCA plaster kept in place for several days. The wart is debrided while damp and soft, then destroyed by freezing or using caustics (eg, 30 to 70% trichloroacetic acid). Other destructive treatments (eg, CO_2 laser, pulsed-dye laser, various acids) are often effective. Duct tape is effective when applied for 6-day intervals, followed by debridement of macerated tissue.

Periungual warts: Combination therapy with liquid nitrogen and imiquimod 5% cream, tretinoin, or SCA is effective.

Recalcitrant warts: Several methods whose long-term value and risks are not fully known are available for recalcitrant warts. Intralesional injection of small amounts of a 0.1% solution of bleomycin in saline often cures stubborn plantar and periungual warts. However, Raynaud's syndrome or vascular damage may develop in injected digits, especially when the drug is injected at the base of the digit, so caution is warranted. Interferon, especially interferon alfa, administered intralesionally (3 times/wk for 3 to 5 wk) or IM, has also cleared recalcitrant skin and genital warts. Extensive warts sometimes improve or clear with oral isotretinoin or acitretin. Cimetidine at doses up to 800 mg po tid has been used with success but is more effective when combined with another therapy.

Zoonotic Diseases

Two viral skin diseases are rarely transmitted from animals to humans.

Contagious ecthyma: Contagious ecthyma (contagious pustular dermatitis) is caused by orf virus, a poxvirus that infects ruminants (most often sheep and goats). Farmers, veterinarians, zoo caretakers, and others with direct animal contact are at risk. The cutaneous findings pass through 6 stages that together

last about 1 wk:

• Stage 1 (papular): A single red edematous papule on a finger (most commonly right index finder)

• Stage 2 (target): A larger nodule with a red center surrounded by a white ring with a red periphery

• Stage 3 (acute): A rapidly growing infected-looking tumor

• Stage 4 (regenerative): A nodule with black dots covered with a thin transparent crust

• Stage 5 (papillomatous): A nodule with a surface studded with small projections

• Stage 6 (regressive): A flattened nodule with a thick crust

Patients can develop regional adenopathy, lymphangitis, and fever.

Diagnosis is by history of contact; differential diagnosis is extensive depending upon the stage of the lesion. Acute lesions must be differentiated from milker's nodules, *Mycobacterium marinum* infection, and other bacterial infections; regressed lesions must be differentiated from cutaneous tumors, such as Bowen's disease or squamous cell carcinoma. Lesions spontaneously heal; no treatment is necessary.

Milker's nodules: These nodules are caused by paravaccinia virus, a parapoxvirus that causes udder lesions in cows. Infection requires direct contact and produces macules that progress to papules, vesicles, and nodules. This infection has 6 stages, which are similar to those of contagious ecthyma. Fever and lymphadenopathy are uncommon. Diagnosis is by history of contact and cutaneous findings. Differential diagnosis varies depending upon morphology but includes primary inoculation TB, sporotrichosis, anthrax, and tularemia. Lesions heal spontaneously; no treatment is necessary.

Chapter 85. Pigmentation Disorders

Introduction

Pigmentation disorders involve hypopigmentation, depigmentation, or hyperpigmentation. Areas may be focal or diffuse.

Focal hypopigmentation is most commonly a consequence of

- Injury
- Inflammatory dermatoses (eg, atopic dermatitis, psoriasis)
- Burns
- Chemical exposure

Focal hypopigmentation or depigmentation is also a feature of vitiligo (which may involve large areas of skin), leprosy, nutritional deficiencies (kwashiorkor), and genetic conditions (tuberous sclerosis, piebaldism, Waardenburg's syndrome).

Diffuse hypopigmentation is most often caused by

- Albinism
- Vitiligo

Focal hyperpigmentation typically occurs after inflammation of various causes, but it also may occur in patients with a systemic disorder or cancer.

Albinism

Albinism (officially called oculocutaneous albinism) is an inherited defect in melanin formation that causes diffuse hypopigmentation of the skin, hair, and eyes; deficiency of melanin (and hence pigmentary dilution) may be total or partial, but all areas of the skin are involved. Ocular involvement causes strabismus, nystagmus, and decreased vision. Diagnosis is usually obvious from the skin, but ocular evaluation is necessary. No treatment for the skin involvement is available other than protection from sunlight.

Pathophysiology

Oculocutaneous albinism (OCA) is a group of rare inherited disorders in which a normal number of melanocytes are present but melanin production is absent or greatly decreased. Cutaneous and ocular pathologies (ocular albinism) are both present. Ocular albinism involves abnormal optic tract CNS development manifested by foveal hypoplasia with decreased photoreceptors and misrouting of optic chiasmal fibers. Ocular albinism may occur without cutaneous abnormalities.

Most cases are autosomal recessive; autosomal dominant inheritance is rare. There are 4 main genetic forms:

- Type I is caused by absent (OCA1A; 40% of all OCA) or reduced (OCA1B) tyrosinase activity; tyrosinase catalyzes several steps in melanin synthesis.
- Type II (50% of all OCA) is caused by mutations in the P (pink-eyed) gene. The function of the P protein is not yet known. Tyrosinase activity is present.
- Type III occurs only in people with dark skin (skin types III to V). It is caused by mutations in a tyrosinase-related protein 1 gene whose product is important in eumelanin synthesis.

• Type IV is an extremely rare form in which the genetic defect is in a gene that codes a membrane transporter protein. Type IV is the most common form of OCA in Japan.

In a group of inherited diseases, a clinical phenotype of OCA occurs in conjunction with bleeding disorders. In the Hermansky-Pudlak syndrome, OCA-like findings occur with platelet abnormalities and a ceroid-lipofuscin lysosomal storage disease. This syndrome is rare except in people with family origin in Puerto Rico, where its incidence is 1 in 1800. In the Chediak-Higashi syndrome, OCA-like findings occur (hair is silvery gray), and a decrease in platelet-dense granules results in a bleeding diathesis. Patients have severe immunodeficiency due to abnormal lymphocyte lytic granules. Progressive neurologic degeneration occurs.

Symptoms and Signs

The different genetic forms have a variety of phenotypes.

Type I (OCA1A) is classic tyrosinase-negative albinism; skin and hair are milky white, and eyes are blue-gray. Pigmentary dilution in OCA1B ranges from obvious to subtle.

Type II has phenotypes with pigmentary dilution that ranges from minimal to moderate. Pigmented nevi and lentigines may develop if skin is exposed to the sun; some lentigines become large and dark. Eye color varies greatly.

In type III, skin is brown, hair is rufous (reddish), and eye color can be blue or brown.

In type IV, the phenotype is similar to that for type II.

Patients with ocular involvement may have decreased retinal pigmentation (see Plate 25), leading to photophobia. In addition, nystagmus, strabismus, reduced visual acuity, and loss of binocular vision likely result from defective routing of the optic fibers.

Diagnosis

• Clinical evaluation

Diagnosis of all types of OCA is based on examination of the skin. Early ocular examination may detect iris translucency, reduced retinal pigmentation, foveal hypoplasia, reduced visual acuity, and ocular movement disorders (strabismus and nystagmus).

Treatment

• Sun protection

• Sometimes surgical intervention for ocular movement disorders

There is no treatment for albinism. Patients are at high risk of sunburn and skin cancers (especially squamous cell carcinoma) and should avoid direct sunlight, use sunglasses with UV filtration, wear protective clothing, and use sunscreen with an SPF of ≥ 30 that protects against UVA and UVB wavelengths (see p. 673). Some surgical interventions may lessen ocular movement disorders.

Vitiligo

Vitiligo is a loss of skin melanocytes that causes areas of skin depigmentation of varying sizes. Cause is unknown, but the condition may be autoimmune; up to one third of patients have evidence of other autoimmune disease. Diagnosis is often obvious on examination. First-line treatment is topical corticosteroids. Calcineurin inhibitors (tacrolimus and pimecrolimus) and psoralens plus ultraviolet A are commonly used. For severe widespread pigment loss, depigmentation (bleaching) of residual patches of normal skin may be done with hydroquinone.

Vitiligo affects 0.5 to 2% of the population.

Etiology

Etiology is unclear, but melanocytes are lacking in affected areas. It is both familial (autosomal dominant, with incomplete penetrance and variable expression) and acquired. Proposed mechanisms include autoimmune destruction of melanocytes, reduced survival of melanocytes, and primary melanocyte defects. Occasionally, vitiligo occurs after a direct physical injury to the skin (eg, as a response to sunburn). This form of vitiligo is called the Koebner phenomenon. Patients may associate the onset of vitiligo with emotional stress.

Some patients have antibodies to melanin. Up to 30% have other autoimmune antibodies (to thyroglobulin, adrenal cells, and parietal cells) or clinical autoimmune endocrinopathies (Addison's disease, diabetes mellitus, pernicious anemia, and thyroid dysfunction), leading to speculation that vitiligo is an autoimmune disease. However, the relationship is unclear and may be coincidental. The strongest association is with hyperthyroidism (Graves' disease) and hypothyroidism (Hashimoto's thyroiditis).

Symptoms and Signs

Vitiligo is characterized by depigmented areas (see Plate 54), usually sharply demarcated and often symmetric. Depigmentation may be localized, involving 1 or 2 spots or entire body segments (segmental vitiligo); rarely, it may be generalized, involving most of the skin surface (universal vitiligo). However, vitiligo most commonly involves the face (especially around the orifices), digits, dorsal hands, flexor wrists, elbows, knees, shins, dorsal ankles, armpits, inguinal area, anogenital area, umbilicus, and nipples. Cosmetic disfigurement can be especially devastating in dark-skinned patients. Hair in vitiliginous areas is usually white.

Diagnosis

• Clinical evaluation

Depigmented skin is typically obvious on examination. Skin lesions are accentuated under Wood's light. Differential diagnosis includes postinflammatory hypopigmentation, morphea, leprosy, chemical leukoderma, and leukoderma due to melanoma. Additional testing for autoimmune endocrine disease is probably unnecessary unless symptoms or signs suggest a particular disorder.

Treatment

• Protection of affected areas from sunlight

• Topical corticosteroids

• Topical calcineurin inhibitors when face or groin involved

• Sometimes psoralen plus ultraviolet A (PUVA) therapy

Treatment is supportive and cosmetic. Physicians must be aware of individual and ethnic sensibilities regarding uniform skin coloring; the disease can be psychologically devastating. All depigmented areas are prone to severe sunburn and must be protected with clothing or sunscreen.

Small, scattered lesions may be camouflaged with makeup. First-line therapy for more extensive involvement is potent topical corticosteroids, which may cause hypopigmentation or atrophy in normal surrounding skin. Calcineurin inhibitors (tacrolimus and pimecrolimus) may be particularly useful for treating areas of the skin (such as the face and groin) where adverse effects of topical corticosteroid therapy most commonly occur. Oral and topical PUVA is often successful, although hundreds of treatment sessions may be necessary. Narrowband UVB is as effective as topical PUVA and has few adverse effects. Lasers may be useful, particularly for localized disease that does not respond to initial topical

therapy.

Surgery is reasonable only for patients with stable, limited disease when medical therapy has failed. Therapies include autologous micrografting, suction blister grafting, and tattooing; tattooing is especially useful for difficult-to-repigment areas such as the nipples, lips, and fingertips.

Depigmentation of unaffected skin to achieve homogeneous skin tone is possible with 20% monobenzyl ether of hydroquinone applied twice daily and is indicated only when most of the skin is involved and the patient is prepared for permanent pigment loss. This treatment can be extremely irritating, so a smaller test area should be treated before widespread use. Treatment for ≥ 1 yr may be required.

Hyperpigmentation

Hyperpigmentation has multiple causes and may be focal or diffuse. Most cases are due to an increase in melanin production and deposition.

Focal hyperpigmentation is most often postinflammatory in nature, occurring after injury (eg, cuts and burns) or other causes of inflammation (eg, acne, lupus). Focal linear hyperpigmentation is commonly due to phytophotodermatitis, which results from ultraviolet light combined with furocoumarins in limes, celery, and other plants.

Hyperpigmentation also has systemic and neoplastic causes.

Melasma (chloasma): Melasma consists of dark brown, sharply marginated, roughly symmetric patches of hyperpigmentation on the face (usually on the forehead, temples, and cheeks). It occurs primarily in pregnant women (melasma gravidarum, or the mask of pregnancy) and in women taking oral contraceptives. Ten percent of cases occur in nonpregnant women and dark-skinned men. Melasma is more prevalent and lasts longer in people with dark skin.

Because all cases are associated with sun exposure, the mechanism probably involves overproduction of melanin by hyperfunctional melanocytes. Other than sun exposure, aggravating factors include

• Autoimmune thyroid disorders

• Photosensitizing drugs

In women, melasma fades slowly and incompletely after childbirth or cessation of hormone use. In men, melasma rarely fades.

Treatment depends on whether the pigmentation is epidermal or dermal; epidermal pigmentation becomes accentuated with Wood's light or can be diagnosed with biopsy. Only epidermal pigmentation responds to treatment. First-line therapy includes a combination of hydroquinone 2 to 4%, tretinoin 0.05 to 1%, and a class V to VII topical corticosteroid. Hydroquinone 3 to 4% applied twice daily is often effective, but long courses are usually required; 2% hydroquinone is useful as maintenance. Hydroquinone should be tested behind one ear or on a small patch on the forearm for 1 wk before use on the face because it may cause irritation. Bleaching agents, such as 0.1% tretinoin and azelaic acid 15 to 20% cream, can be used in place of or with hydroquinone. Chemical peeling with glycolic acid or 30 to 50% trichloroacetic acid is an option for patients with severe melasma unresponsive to topical bleaching agents.

Lentigines: Lentigines (singular: lentigo) are flat, tan to brown oval spots. They are commonly due to chronic sun exposure (solar lentigines; sometimes called liver spots) and occur most frequently on the face and back of the hands. They typically first appear during middle age and increase in number with age. Although progression from lentigines to melanoma has not been established, lentigines are an independent risk factor for melanoma. They are treated with cryotherapy or laser; hydroquinone is not effective.

Nonsolar lentigines are sometimes associated with systemic disorders, such as Peutz-Jeghers syndrome (in which profuse lentigines of the lips occur), multiple lentigines syndrome (Leopard syndrome), or

xeroderma pigmentosum.

[
Table 85-1. Hyperpigmentation Effects of Some Drugs and Chemicals]

Diffuse hyperpigmentation due to systemic disorders: Common systemic causes include Addison's disease (see p. 792), hemochromatosis (see p. 1032), and primary biliary cirrhosis (see p. 244). Skin findings are nondiagnostic as to cause.

Drug-induced hyperpigmentation: Changes are usually diffuse but sometimes have drug-specific distribution patterns or hues (see Table 85-1). Mechanisms include

• Increased melanin in the epidermis (tends to be more brown)

• Melanin in the epidermis and high dermis (mostly brown with hints of gray or blue)

• Increased melanin in the dermis (tends to be more grayish or blue)

• Dermal deposition of the drug or metabolite (usually slate or bluish gray)

Focal hyperpigmentation frequently follows drug-induced lichen planus (also known as lichenoid drug reactions).

In fixed drug eruptions, red plaques or blisters form at the same site each time a drug is taken; residual postinflammatory hyperpigmentation usually persists. Typical lesions occur on the face (especially the lips), hands, feet, and genitals. Typical inciting drugs include sulfonamides, tetracycline, NSAIDs (especially phenazone derivatives), barbiturates, and carbamazepine.

Chapter 86. Hair Disorders

Introduction

Hair growth in both men and women is regulated by androgens. Testosterone stimulates hair growth in the pubic area and underarms. Dihydrotestosterone stimulates beard hair growth and scalp hair loss.

Hair disorders include alopecia, hypertrichosis, hirsutism, and pseudofolliculitis barbae. Although most hair disorders are not serious, they are often perceived as major cosmetic issues that demand treatment. Dandruff is not a hair disorder but rather a skin disorder (seborrheic dermatitis) of the scalp (see p. 671).

Alopecia

(Baldness)

Alopecia is defined as loss of hair. Hair loss is often a cause of great concern to the patient for cosmetic and psychologic reasons, but it can also be an important sign of systemic disease.

Pathophysiology

Growth cycle: Hair grows in cycles. Each cycle consists of a long growing phase (anagen), a brief transitional apoptotic phase (catagen), and a short resting phase (telogen). At the end of the resting phase, the hair falls out (exogen) and a new hair starts growing in the follicle, beginning the cycle again. Normally, about 100 scalp hairs reach the end of resting phase each day and fall out. When significantly more than 100 hairs/day go into resting phase, clinical hair loss (telogen effluvium) may occur. A disruption of the growing phase causing abnormal loss of anagen hairs is an anagen effluvium.

Classification: Alopecia can be classified as focal or diffuse and by the presence or absence of scarring.

Scarring alopecia is the result of active destruction of the hair follicle. The follicle is irreparably damaged and replaced by fibrotic tissue. Several hair disorders show a biphasic pattern in which nonscarring alopecia occurs early in the course of the disease, and then permanent hair loss occurs as the disease progresses. Scarring alopecias can be subdivided further into primary forms, where the target of inflammation is the follicle itself, and secondary forms, where the follicle is destroyed as a result of nonspecific inflammation (see Table 86-1).

Nonscarring alopecia results from processes that reduce or slow hair growth without irreparably damaging the hair follicle. Disorders that primarily affect the hair shaft also are considered nonscarring alopecia.

Etiology

The alopecias comprise a large group of disorders with multiple and varying etiologies (see Table 86-1).

The **most common cause** of alopecia is

• Androgenetic alopecia (male-pattern or female-pattern hair loss)

Androgenetic alopecia is an androgen-dependent hereditary disorder in which dihydrotestosterone plays a major role.

Other common causes of hair loss are

• Drugs (including chemotherapeutic agents)

• Infection

• Systemic illnesses (particularly those that cause high fever, systemic lupus, endocrine disorders, and nutritional deficiencies)

Less common causes are primary hair shaft abnormalities, autoimmune disease, heavy metal poisoning, and rare dermatologic conditions.

Evaluation

History: History of present illness should cover the onset and duration of hair loss, whether hair shedding is increased, and whether hair loss is generalized or localized. Associated symptoms such as pruritus and scaling should be noted. Patients should be asked about typical hair care practices, including use of braids, rollers, and hair dryers, and whether they routinely pull or twist their hair.

Review of systems should include recent exposures to noxious stimuli (eg, drugs, toxins, radiation) and stressors (eg, surgery, chronic illness, fever, psychologic stressors). Symptoms of possible causes should be sought, including fatigue and cold intolerance (hypothyroidism) and, in women, hirsutism, deepening of the voice, and increased libido (virilizing syndrome). Other features, including dramatic weight loss, dietary practices (including vegetarianism), and obsessive-compulsive behavior, should be noted. In women, a hormonal/gynecologic/obstetric history should be obtained.

Past medical history should note known possible causes of hair loss, including endocrine and skin disorders. Current and recent

[**Table 86-1.** Classification and Causes of Alopecia]

drug use should be reviewed for offending agents (see Table 86-1). A family history of hair loss should be recorded.

Physical examination: Examination of the scalp should note the distribution of hair loss, the presence and characteristics of any skin lesions, and whether there is scarring. Part widths should be measured. Abnormalities of the hair shafts should be noted.

A full skin examination should be done to evaluate hair loss elsewhere on the body (eg, eyebrows, eyelashes, arms, legs), rashes that may be associated with certain types of alopecia (eg, lichen planus, atopy, psoriasis, discoid lupus lesions, hidradenitis, signs of secondary syphilis or of other bacterial or fungal infections), and signs of virilization in women (eg, hirsutism, acne, deepening voice, clitoromegaly). Signs of potential underlying systemic disorders should be sought, and a thyroid examination should be done.

Red flags: The following findings are of particular concern:

• Virilization in women

• Signs of systemic illness or constellations of nonspecific findings possibly indicating poisoning

Interpretation of findings: Hair loss that begins at the temples or vertex and spreads to diffuse thinning or nearly complete hair loss is typical of male-pattern hair loss. Hair thinning in the frontal, parietal, and crown regions is typical of female-pattern hair loss (see Fig. 86-1).

Hair loss that occurs 2 to 4 wk after chemotherapy or radiation therapy (anagen effluvium) can typically be ascribed to those causes. Hair loss that occurs 3 to 4 mo after a major stressor (pregnancy, febrile illness, surgery, medication change, or severe psychologic stressor) suggests a diagnosis of telogen effluvium.

Other findings help suggest alternative diagnoses (see Table 86-2).

Other than hair loss, scalp symptoms (eg, itching, burning, tingling) are often absent and, when present, are not specific to any cause.

Signs of hair loss in patterns other than those described above are nondiagnostic and may require microscopic hair examination or scalp biopsy for definitive diagnosis.

Testing: Evaluation for causative disorders (eg, endocrinologic, autoimmune, toxic) should be done based on clinical suspicion.

Male-pattern or female-pattern hair loss generally requires no testing. When it occurs in young men with no family history, the physician should question the patient about use of anabolic steroids and other drugs. In addition to questions regarding drug and illicit drug use, women with significant hair loss and evidence of virilization should have testosterone and dehydroepiandrosterone sulfate (DHEAS) levels measured (see p. 730).

The **pull test** helps evaluate diffuse scalp hair loss. Gentle traction is exerted on a bunch of hairs (40 to 60) on at least 3 different areas of the scalp, and the number of extracted hairs is counted and examined microscopically. Normally, < 3 telogen-phase hairs should come out with each pull. If at least 3 hairs are obtained with each pull or if > 10 hairs total are obtained, the pull test is positive and suggestive of telogen effluvium.

The **pluck test** pulls individual hairs out abruptly ("by the roots"). The roots of the plucked hairs are examined microscopically to determine the phase of growth and thus help diagnose a defect of telogen or anagen or an occult systemic disease. Anagen hairs have sheaths attached to their roots; telogen hairs have tiny bulbs without sheaths at their roots. Normally, 85 to 90% of hairs are in the

[**Fig. 86-1.** Male-pattern and female-pattern hair loss.]

anagen phase; about 10 to 15% are in telogen phase; and < 1% are in catagen phase. Telogen effluvium shows an increased percentage of telogen-phase hairs on microscopic examination, whereas anagen effluvium shows a decrease in telogen-phase hairs and an increased number of broken hairs. Primary hair shaft abnormalities are usually obvious on microscopic examination of the hair shaft.

Scalp biopsy is indicated when alopecia persists and diagnosis is in doubt. Biopsy may differentiate scarring from nonscarring forms. Specimens should be taken from areas of active inflammation, ideally at the border of a bald patch. Fungal and bacterial cultures may be useful; immunofluorescence studies may help identify lupus erythematosus, lichen planopilaris, and systemic sclerosis.

Daily hair counts can be done by the patient to quantify hair loss when the pull test is negative. Hairs lost in the first morning combing or during washing are collected in clear plastic bags daily for 14 days. The number of hairs in each bag is then recorded. Scalp hair counts of > 100/day are abnormal except after shampooing, when hair counts of up to 250 may be normal. Hairs may be brought in by the patient for microscopic examination.

Treatment

Androgenetic alopecia: Minoxidil (2% for women, 2% or 5% for men) prolongs the anagen growth phase and gradually enlarges miniaturized follicles (vellus hairs) into mature terminal hairs. Topical minoxidil 1 mL bid applied to the scalp is most effective for vertex alopecia in male-pattern or female-pattern hair loss. However, usually only 30 to 40% of patients experience significant hair growth, and minoxidil is generally not effective or indicated for other causes of hair loss except possibly alopecia areata. Hair regrowth can take 8 to 12 mo. Treatment is continued indefinitely because, once treatment is stopped, hair loss resumes. The most frequent adverse effects are mild scalp irritation, allergic contact dermatitis, and increased facial hair.

Finasteride inhibits the 5α-reductase enzyme, blocking conversion of testosterone to dihydrotestosterone, and is useful for male-pattern hair loss. Finasteride 1 mg po once/day can stop hair

loss and can stimulate hair

[Table 86-2. Interpreting Findings in Alopecia]

growth. Efficacy is usually evident within 6 to 8 mo of treatment. Adverse effects include decreased libido, erectile and ejaculatory dysfunction, hypersensitivity reactions, gynecomastia, and myopathy. There may be a decrease in prostate-specific antigen levels in older men, which should be taken into account when that test is used for cancer screening. Common practice is to continue treatment for as long as positive results persist. Once treatment is stopped, hair loss returns to previous levels. Finasteride is not indicated for women and is contraindicated in pregnant women because it has teratogenic effects in animals.

Hormonal modulators such as oral contraceptives or spironolactone may be useful for female-pattern hair loss associated with hyperandrogenemia.

Surgical options include follicle transplant, scalp flaps, and alopecia reduction. Few procedures have been subjected to scientific scrutiny, but patients who are self-conscious about their hair loss may consider them.

Hair loss due to other causes: Underlying disorders are treated.

Multiple treatment options for alopecia areata exist and include topical, intralesional, or, in severe cases, systemic corticosteroids, topical minoxidil, topical anthralin, topical immunotherapy (diphencyprone or squaric acid dibutylester), or psoralen plus ultraviolet A (PUVA).

Treatment for traction alopecia is elimination of physical traction or stress to the scalp.

Treatment for tinea capitis is topical or oral antifungals (see p. 707).

Trichotillomania is difficult to treat, but behavior modification, clomipramine, or an SSRI (eg, fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram) may be of benefit.

Scarring alopecia as seen in central centrifugal scarring alopecia, dissecting cellulitis of the scalp, and acne keloidalis nuchae is best treated by a long-acting oral tetracycline in combination with a potent topical corticosteroid.

Lichen planopilaris and chronic cutaneous lupus lesions may be treated with oral antimalarials, corticosteroids, retinoids, or immunosuppressants.

Hair loss due to chemotherapy is temporary and is best treated with a wig; when hair regrows, it may be different in color and texture from the original hair. Hair loss due to telogen effluvium or anagen effluvium is usually temporary as well and abates after the precipitating agent is eliminated.

Key Points

• Androgenetic alopecia (male-pattern and female-pattern hair loss) is the most common type of hair loss.

• Concomitant virilization in women or scarring hair loss should prompt a thorough evaluation for the underlying disorder.

• Microscopic hair examination or scalp biopsy may be required for definitive diagnosis.

Alopecia Areata

Alopecia areata is sudden patchy hair loss in people with no obvious skin or systemic disorder.

The scalp and beard are most frequently affected, but any hairy area may be involved. Hair loss may affect most or all of the body (alopecia universalis). Alopecia areata is thought to be an autoimmune disorder affecting genetically susceptible people exposed to unclear environmental triggers, such as

infection or emotional stress. It occasionally coexists with autoimmune vitiligo or thyroiditis.

Diagnosis

• Examination

Diagnosis is by inspection. Alopecia areata typically manifests as discrete circular patches of hair loss characterized by short broken hairs at the margins, which resemble exclamation points. Nails are sometimes pitted or display trachyonychia, a roughness of the nail also seen in lichen planus. Differential diagnosis includes tinea capitis, trichotillomania, discoid lupus, and secondary syphilis. Measures of thyroid-stimulating hormone, vitamin B_{12}, and autoantibodies are indicated only when coexisting disease is suspected.

Treatment

• Corticosteroids

• Sometimes topical anthralin, minoxidil or both

Treatment is with corticosteroids. Triamcinolone acetonide suspension (in doses not to exceed 0.1 mL per injection site, eg, 10 mg/mL concentration to deliver 1 mg) can be injected intradermally if the lesions are small. Potent topical corticosteroids (such as betamethasone 0.05% bid) can be used; however, they often do not penetrate to the depth of the hair bulb where the inflammatory process is located. Oral corticosteroids are effective, but hair loss recurs after cessation of therapy and adverse effects limit use. Topical anthralin (0.5 to 1% for 10 to 20 min daily, then washed off, frequency titrated as tolerated up to 30 min bid) and/or minoxidil may be used. Induction of allergic contact dermatitis using diphencyprone or squaric acid dibutylester leads to hair growth due to unknown mechanisms, but this treatment is best reserved for patients with diffuse involvement who have not responded to other therapies.

Alopecia areata may spontaneously regress, become chronic, or spread diffusely. Risk factors for chronicity include extensive involvement, onset before adolescence, atopy, and involvement of the peripheral scalp (ophiasis).

Hirsutism

Hirsutism is the excessive growth of thick or dark hair in women in locations that are more typical of male hair patterns (eg, mustache, beard, central chest, shoulders, lower abdomen, back, inner thigh). The amount of hair growth that is considered excessive may differ depending on ethnic background and cultural interpretation. Men vary significantly in amount of body hair, some being quite hairy, but rarely present for medical evaluation.

Hypertrichosis is a separate condition. It is simply an increase in the amount of hair growth anywhere on the body. Hypertrichosis may be generalized or localized.

Pathophysiology

Hair growth depends on the balance between androgens (eg, testosterone, dehydroepiandrosterone sulfate [DHEAS], dihydrotestosterone [DHT]) and estrogens. Androgens promote thick, dark hair growth, whereas estrogens slow hair growth or modulate it toward finer, lighter hairs.

When caused by increased androgen activity, hirsutism is often accompanied by virilization, which may manifest as loss of menses, increased muscle mass, voice deepening, and clitoral hypertrophy.

Etiology

There are a number of causes of hirsutism (see Table 86-3). Overall, the most common causes are the following:

• Polycystic ovary syndrome

• Familial hirsutism

Androgen excess: Hirsutism typically results from abnormally high androgen activity as a result of increased central production of androgens (eg, from ovarian or adrenal disorders) or increased peripheral conversion of testosterone to DHT by 5α-reductase. Free androgen levels also can increase as a result of decreased production of sex hormone-binding globulin, which can occur in a variety of conditions, including hyperinsulinemia and liver disease. However, the severity of hirsutism does not correlate with the level of circulating

[**Table 86-3.** Some Causes of Hirsutism]

androgens because of individual differences in androgen sensitivity of the hair follicle.

No androgen excess: Hirsutism not associated with androgen excess may be physiologic (eg, postmenopausal, during pregnancy), the result of systemic nonandrogenic endocrine conditions, or a familial phenomenon, especially in people of Mediterranean or Middle Eastern ancestry.

Hypertrichosis involves nonandrogenic hair growth and is usually caused by a drug, systemic illness (see Table 86-4), or paraneoplastic syndrome. It also occurs as part of a rare familial disorder.

Evaluation

History: History of present illness should cover the extent and acuity of hair growth as well as the age of onset.

Review of systems should seek signs of virilization (eg, deepening of the voice, increased libido) and review menstrual and fertility history. Symptoms of causative disorders should be sought, including cold intolerance, fatigue, and weight gain (hypothyroidism); polyuria (diabetes); bingeing and purging (eating disorders); and weight loss and fevers (cancer).

Past medical history should specifically seek known causative disorders such as endocrine disorders, adrenal or ovarian pathology, and cancer.

Family history should inquire about excess hair growth in family members. Drug history should review all prescribed drugs and specifically query for the surreptitious use of anabolic steroids.

Physical examination: The presence of excess coarse and dark hair growth should be assessed at multiple sites, including the face, chest, lower abdomen, back, buttocks, and inner thigh. Signs of virilization should be sought, including clitoromegaly, acne, male-pattern hair loss, breast atrophy, and increased muscle mass.

General physical examination should note signs of potentially causative disorders.

The eyes should be examined for extraocular movements, and the visual fields should be assessed.

The breasts should be examined for galactorrhea.

The abdomen (including pelvic examination) should be examined for masses.

The skin should be examined for velvety, black pigmentation on the axillae and neck and under the breasts (acanthosis nigricans); acne; and striae.

The general habitus should be examined for fat distribution (particularly a round face and accumulation of fat at the base of the neck posteriorly).

[**Table 86-4.** Causes of Hypertrichosis]

Red flags: The following findings are of particular concern:

• Virilization

• Abrupt appearance of hirsutism

• Pelvic or abdominal mass

Interpretation of findings: Excess hair growth beginning after use of an anabolic steroid or other causative drug (see Tables 86-3 and 86-4) in an otherwise healthy female is likely due to that drug. Symptoms and signs sometimes point to a diagnosis (see Table 86-5).

Testing: Diagnostic testing in men with no other signs of illness is unnecessary.

Women should have laboratory measurement of serum hormone levels, including the following:

• Free and total testosterone

• DHEAS

• Follicle-stimulating hormone (FSH) and luteinizing hormone (LH)

• Androstenedione

• Thyroid-stimulating hormone

• Prolactin

High levels of testosterone accompanied by a normal level of DHEAS indicate that the ovaries, and not the adrenal glands, are producing the excess androgen. High levels of testosterone accompanied by moderate elevations in DHEAS suggest an adrenal origin for the hirsutism.

Often, in women with polycystic ovary syndrome, LH levels are elevated and FSH levels are depressed, which results in elevated LH/FSH ratios (> 3 is common).

Imaging: Pelvic ultrasonography, CT, or both should be done to rule out pelvic or adrenal cancer, particularly when a pelvic mass is appreciated, when the total testosterone level is > 200 ng/dL (> 100 ng/dL in postmenopausal women), or when the DHEAS level is > 7000 ng/dL (> 4000 ng/dL in postmenopausal women). However, the majority of patients with elevated DHEAS have adrenal hyperplasia rather than adrenal carcinoma.

Patients with signs of Cushing's syndrome or an adrenal mass on imaging studies should have 24-h urine cortisol levels measured.

Treatment

The underlying disorder should be treated, including stopping or changing causative drugs. Treatment for hirsutism itself is unnecessary if the patient does not find the excess hair cosmetically objectionable.

Nonandrogen-dependent excess hair growth, such as hypertrichosis, is treated primarily with physical hair removal methods. Patients with androgen-dependent hirsutism require a combination of hair removal and medical antiandrogen therapy.

Hair removal: There are several techniques. Depilatory techniques remove hair from the surface of the skin and include shaving and OTC depilatory creams, such as those containing barium sulfate and Ca thioglycolate.

Epilation involves removing intact hairs and the roots and can be achieved via mechanical means (eg, tweezing, plucking, waxing) or home epilating devices. Permanent epilation techniques, including electrolysis, thermolysis, and laser epilation, can result in more long-term hair removal but often require multiple treatments.

As an alternative to hair removal, hair bleaching is inexpensive and works well when hirsutism is not excessive. Bleaches lighten the color of the hair, rendering it less noticeable. There are several types of commercial

[Table 86-5. Some Symptoms and Signs for Diagnosis of Hirsutism]

hair-bleaching products, most of which use hydrogen peroxide as the active ingredient.

Topical eflornithine, applied twice daily, decreases hair growth and, with long-term use, may decrease the need to manually remove hair.

Hormonal treatment: Hirsutism resulting from androgen excess usually requires long-term therapy because the source of excess androgen rarely can be eliminated permanently. Hormonal treatments include

• Oral contraceptives

• Antiandrogenic drugs

• Sometimes other drugs

Oral contraceptives in standard doses often are the initial treatment for hirsutism caused by ovarian hyperandrogenism. Oral contraceptives reduce ovarian androgen secretion and increase sex hormone-binding globulin, thereby decreasing free testosterone levels.

Antiandrogenic therapy is also used and can include finasteride (5 mg po once/day), spironolactone (25 to 100 mg po bid), or flutamide (125 mg po once/day or bid). These drugs are contraindicated during pregnancy as they may cause feminization of a male fetus.

Insulin sensitizers such as metformin decrease insulin resistance, causing a decline in testosterone levels. However, they are less effective than other antiandrogenic drugs. Corticosteroids are used for adrenal suppression. Gonadotropin-releasing hormone agonists (eg, leuprolide acetate, nafarelin, triptorelin) can be used for severe forms of ovarian hyperandrogenism under the direction of a gynecologist or endocrinologist.

Key Points

• Hirsutism may be familial, and the degree of hair growth may vary with ethnicity.

• Polycystic ovary syndrome is the most frequent cause of hirsutism.

• Virilization suggests an androgenic disorder that requires further evaluation.

• Abrupt onset of hirsutism may indicate cancer.

Pseudofolliculitis Barbae

Pseudofolliculitis barbae (PFB) is irritation of the skin due to beard hairs that penetrate the skin before leaving the hair follicle or that leave the follicle and curve back into the skin, causing a foreign-body reaction.

PFB predominantly affects black men. It is most noticeable around the beard and neck. It causes small

papules and pustules that can be confused with bacterial folliculitis.

Diagnosis is by physical examination.

Treatment

Acute PFB can be treated with warm compresses and manual removal of ingrown hairs with a needle or tweezers. Topical hydrocortisone 1% or topical antibiotics can be used for mild inflammation. Oral tetracycline (250 to 500 mg qid) or oral erythromycin (250 to 500 mg qid, 333 mg tid, 500 mg bid) can be used for moderate to severe inflammation. Tretinoin (retinoic acid) liquid or cream or benzoyl peroxide cream may also be effective in mild or moderate cases but may irritate the skin. Topical eflornithine hydrochloride cream may help by slowing hair growth. Hairs should be allowed to grow out; grown hairs can then be cut to about 0.5 cm length. Depilatories are an alternative but may irritate the skin. Hair follicles can be permanently removed by electrolysis or laser treatment.

Chapter 87. Nail Disorders

Introduction

A variety of disorders can affect nails, including deformities, infections of the nail, paronychia, and ingrown toenails. Nail changes may occur in many systemic conditions and genetic syndromes.

Nails may also undergo changes due to local infection or trauma. For example, trauma to the finger may cause changes in the nail. The nail may develop a white coloration that starts at the nail bed and grows up with the nail. Sometimes, if a nail becomes separated from the nail bed, a new nail grows below the existing nail and replaces it when fully grown in.

Most nail infections are fungal (onychomycosis—see p. 734), but bacterial and viral infections can occur (eg, green-nail syndrome [*Pseudomonas*], herpetic whitlow [herpes simplex virus-1]). Paronychia is not actually an infection of the nail but rather of periungual tissues.

Common warts (verrucae vulgaris) result from papillomavirus infection and frequently infect the proximal nail fold and sometimes the subungual area. Onychophagia (nail-biting) can help to spread this infection. Warts involving these areas are especially difficult to treat. Freezing with liquid nitrogen may be effective.

Toenails require special attention in the elderly and in people with diabetes or peripheral vascular disease; a podiatrist can help avoid local breakdown and secondary infections.

Deformities

About 50% of nail deformities result from fungal infection. The remainder result from various causes, including trauma, psoriasis, lichen planus, and occasionally cancer. Diagnosis may be obvious on examination, but sometimes fungal scrapings and culture may be done. Deformities may resolve with treatment of the cause, but if not, manicurists may be able to hide nail deformities with appropriate trimming and polishes. Dystrophies are often considered together with deformities, but the two are slightly different; deformities are generally considered to be gross changes in nail shape, whereas dystrophies are changes in nail texture or composition (eg, onychomycosis).

Congenital deformities: In some congenital ectodermal dysplasias, patients have no nails (anonychia). In pachyonychia congenita, the nail beds are thickened, discolored, and hypercurved with a pincer nail deformity. Nail-patella syndrome (see p. 2910) causes triangular lunulae and partially absent thumb nails. Patients with Darier's disease can have nails with red and white streaks and a distal V-shaped nick.

Deformities associated with systemic problems: In Plummer-Vinson syndrome, 50% of patients have koilonychia (concave, spoon-shaped nails). Yellow nail syndrome (characterized by hard, hypercurved, transversely thickened, yellow nails with loss of the cuticle) occurs in patients with lymphedema of limbs, pleural effusion, and ascites. Half-and-half nails occur with renal failure; the proximal half of the nail is white, and the distal half is pink or pigmented. White nails occur with cirrhosis, although the distal third may remain pinker.

Deformities associated with dermatologic conditions: In psoriasis, nails may have a number of changes, including irregular pits, oil spots (localized areas of tan-brown discoloration), onycholysis, and thickening and crumbling of the nail plate. Lichen planus of the nail matrix causes scarring with early longitudinal ridging and splitting of the nail and later leads to pterygium formation. Pterygium of the nail is characterized by scarring from the proximal nail outward in a V formation, which leads ultimately to loss of the nail. Alopecia areata can be accompanied by regular pits that form a pattern.

Discoloration: Cancer chemotherapy drugs (especially the taxanes) can cause melanonychia (nail plate pigmentation), which can be diffuse or may occur in transverse bands. Some drugs cause characteristic changes in nail coloration. For example, quinacrine can cause nails to appear greenish yellow or white under ultraviolet light. Cyclophosphamide can cause the onychodermal bands (seal formed at the junction of the nail plate and distal nail bed at the free edge of the nail plate) to become slate-gray or bluish. With arsenic intoxication, the nails may turn diffusely brown. Tetracyclines, ketoconazole, phenothiazines,

sulfonamides, and phenindione can all cause brownish or blue discoloration. Gold therapy can turn nails light or dark brown. Tobacco use can result in yellow or brownish discoloration. In argyria, the nails may be diffusely blue-gray.

White transverse lines of the nails (Mees' lines) may occur with chemotherapy, acute arsenic intoxication, malignant tumors, MI, thallium and antimony intoxication, fluorosis, and even during etretinate therapy. They also develop with trauma to the finger, although traumatic white lines usually do not span the entire nail. The fungus *Trichophyton mentagrophytes* causes a chalky white discoloration of the nail plate.

Green-nail syndrome is caused by infection with *Pseudomonas*. It is generally a harmless infection, usually of 1 or 2 nails, and is noteworthy for its striking blue-green color. It often occurs in patients with onycholysis or chronic paronychia whose nails have been immersed in fresh water for a long period. Treatment is most effective with soaks of 1% acetic acid solution or alcohol diluted 1:4 with water. Patients should soak their affected nails twice a day for 10 min and should avoid trauma and excess moisture. Frequent clipping of the nail increases the response to treatment.

Melanonychia striata: Melanonychia striata are hyperpigmented bands that are longitudinal and extend from the proximal nail fold and cuticle to the free distal end of the nail plate. In dark-skinned people, these bands may be a normal physiologic variant requiring no treatment. Other causes include trauma; pregnancy; Addison's disease; post-inflammatory hyperpigmentation; and the use of certain drugs, including doxorubicin, 5-fluorouracil, zidovudine (AZT), and psoralens. Melanonychia striata can also occur in benign melanocytic nevi and malignant melanoma. Hutchinson's sign of the nail (melanin extending through the lunula, cuticle, and proximal nail fold) may signal a melanoma in the nail matrix. Rapid biopsy and treatment are essential.

Onychogryphosis: Onychogryphosis is a nail dystrophy in which the nail, most often on the big toe, becomes thickened and curved. It may be caused by ill-fitting shoes. It is common among the elderly. Treatment consists of trimming the deformed nails.

Onycholysis: Onycholysis is separation of the nail plate from the nail bed or complete nail plate loss. It can occur as a drug reaction in patients treated with tetracyclines (photo-onycholysis), doxorubicin, 5-fluorouracil, cardiovascular drugs (particularly practolol and captopril), cloxacillin and cephaloridine (rarely), trimethoprim/sulfamethoxazole, diflunisal, etretinate, indomethacin, isoniazid, and isotretinoin. Partial onycholysis may also result from infection with *Candida albicans* as a component of onychomycosis or from trauma. Partial onycholysis may occur in patients with psoriasis or thyrotoxicosis.

Onychotillomania: In this disorder, patients pick at and self-mutilate their nails, which can lead to parallel transverse grooves and ridges (washboard deformity or habit-tic nails). It most commonly manifests in patients who habitually push back the cuticle on one finger, causing dystrophy of the nail plate as it grows. Subungual hemorrhages can also develop in onychotillomania.

Pincer nail deformity: Pincer nail deformity is a transverse over-curvature of the nail plate. It can occur in patients with psoriasis, SLE, Kawasaki disease, cancer, end-stage renal disease, and some genetic syndromes. Patients often have pain at the borders of the nail where the nail plate curves into the tips of the fingers.

Subungual hematoma and nail bed trauma: Subungual hematoma occurs when blood becomes trapped between the nail plate and nail bed, usually as a result of trauma. Subungual hematoma causes significant pain and eventual separation of and temporary loss of the nail plate. When the cause is a crush injury, underlying fracture and nail bed damage are common. Nail bed damage may result in permanent nail deformity.

If the injury is acute, nail trephination (eg, creating a hole in the nail plate using a cautery device, 18-gauge needle, or red-hot paperclip) can help relieve pain by draining accumulated blood. It is not clear whether removing the nail and repairing any nail bed damage reduces risk of permanent nail deformity.

Trachyonychia: Trachyonychia (rough, opaque nails) may occur with alopecia areata, lichen planus, atopic dermatitis, and psoriasis. It is most common among children.

Tumors: Benign and malignant tumors can affect the nail unit, causing deformity. These tumors include benign myxoid cysts, pyogenic granulomas, glomus tumors, Bowen's disease, squamous cell carcinoma, and malignant melanoma. When cancer is suspected, expeditious biopsy followed by referral to a surgeon is strongly advised.

Onychomycosis

Onychomycosis is fungal infection of the nail plate, nail bed, or both. The nails typically are deformed and discolored white or yellow. Diagnosis is by appearance, wet mount, culture, PCR, or a combination. Treatment, when indicated, is with selective use of oral terbinafine or itraconazole.

About 10% (range 2 to 14%) of the population has onychomycosis. Risk factors include

- Tinea pedis
- Preexisting nail dystrophy (eg, in patients with psoriasis)
- Older age
- Male sex
- Exposure to someone with tinea pedis or onychomycosis (eg, a family member or through public bathing)
- Peripheral vascular disease or diabetes
- Immunocompromise

Toenails are 10 times more commonly infected than fingernails. About 60 to 80% of cases are caused by dermatophytes (eg, *Trichophyton rubrum*); dermatophyte infection of the nails is called tinea unguium. Many of the remaining cases are caused by nondermatophyte molds (eg, *Aspergillus*, *Scopulariopsis*, *Fusarium*). Immunocompromised patients and those with chronic mucocutaneous candidiasis may have candidal onychomycosis (which is more common on the fingers). Subclinical onychomycosis can also occur in patients with recurrent tinea pedis. Onychomycosis may predispose patients to lower extremity cellulitis.

Symptoms and Signs

Nails have asymptomatic patches of white or yellow discoloration and deformity. There are 3 characteristic manifestations:

- Distal subungual, in which the nails thicken and yellow, keratin and debris accumulate distally and underneath, and the nail separates from the nail bed (onycholysis)
- Proximal subungual, a form that starts proximally and is a marker of immunosuppression
- White superficial, in which a chalky white scale slowly spreads beneath the nail surface

Diagnosis

- Clinical evaluation
- Potassium hydroxide wet mount examination
- Culture

Onychomycosis is suspected by appearance; predictive clinical features include involvement of the 3rd or 5th toenail, involvement of the 1st and 5th toenails on the same foot, and unilateral nail deformity. Subclinical onychomycosis should be considered in patients with recurrent tinea pedis. Differentiation from psoriasis or lichen planus is important, because the therapies differ, so diagnosis is typically confirmed by microscopic examination and culture of scrapings. Scrapings are taken from the most proximal position that can be accessed on the affected nail and are examined for hyphae on potassium hydroxide wet mount and cultured. Obtaining an adequate sample of nail can be difficult because the distal subungual debris, which is easy to sample, often does not contain living fungus. Therefore, removing the distal portion of the nail with clippers before sampling or using a small curette to reach more proximally beneath the nail increases the yield. PCR can also be done on nail clippings if cultures are negative and the cost of finding a definitive diagnosis is warranted.

Treatment

• Sometimes oral terbinafine or itraconazole

Onychomycosis is not always treated because many cases are asymptomatic or mild and unlikely to cause complications, and the oral drugs that are the most effective treatments can potentially cause hepatotoxicity and serious drug interactions. Some proposed indications for treatment include the following:

• Previous ipsilateral cellulitis

• Diabetes or other risk factors for cellulitis

• Presence of bothersome symptoms

• Psychosocial impact

• Desire for cosmetic improvement (controversial)

Treatment is oral terbinafine or itraconazole. Terbinafine 250 mg once/day for 12 wk (6 wk for fingernail) or itraconazole 200 mg bid 1 wk/mo for 3 mo is used and achieves a cure rate of 60 to 75%, but the recurrence rate is estimated to be as high as 10 to 50%. It is not necessary to treat until all abnormal nail is gone because these drugs remain bound to the nail plate and continue to be effective after oral administration has ceased. The affected nail will not revert to normal; however, newly growing nail will appear normal. Topical antifungal nail lacquer containing ciclopirox 8% or amorolfine 5% (not available in the US) is rarely effective as primary treatment but can improve cure rate when used as an adjunct with oral drugs, particularly in resistant infections.

To limit relapse, the patient should trim nails short, dry feet after bathing, wear absorbent socks, and use antifungal foot powder. Old shoes may harbor a high density of spores and, if possible, should not be worn.

Paronychia

Paronychia is infection of the periungual tissues. Acute paronychia causes redness, warmth, and pain along the nail margin. Diagnosis is by inspection. Treatment is with antistaphylococcal antibiotics and drainage of any pus.

Paronychia is usually acute, but chronic cases occur. In acute paronychia, the causative organisms are usually *Staphylococcus aureus* or streptococci and, less commonly, *Pseudomonas* or *Proteus* spp. Organisms enter through a break in the epidermis resulting from a hangnail, trauma to a nail fold, loss of the cuticle, or chronic irritation (eg, resulting from water and detergents). Biting or sucking the fingers can also predispose people to developing the infection. In toes, infection often begins at an ingrown toenail (see p. 736).

In patients with diabetes and those with peripheral vascular disease, toe paronychia can threaten the

limb.

Symptoms and Signs

Paronychia develops along the nail margin (lateral and proximal nail folds), manifesting over hours to days with pain, warmth, redness, and swelling. Pus usually develops along the nail margin and sometimes beneath the nail. Infection can spread to the fingertip pulp, causing a felon. Rarely, infection penetrates deep into the finger, sometimes causing infectious flexor tenosynovitis.

Diagnosis

Diagnosis is by inspection. Several skin conditions can cause changes that mimic paronychia and should be considered, particularly when treatment is not effective initially. These conditions include squamous cell carcinoma, proximal onychomycosis, pyogenic granuloma, pyoderma gangrenosum, and herpetic whitlow.

Treatment

• Antistaphylococcal antibiotics

• Drainage of pus

Early treatment is warm compresses or soaks and an antistaphylococcal antibiotic (eg, dicloxacillin or cephalexin 250 mg po qid, clindamycin 300 mg po qid). In areas where methicillin-resistant *S. aureus* is common, antibiotics that are effective against this organism (eg, trimethoprim/sulfamethoxazole) should be chosen based on results of local sensitivity testing. In patients with diabetes and others with peripheral vascular disease, toe paronychia should be monitored for signs of cellulitis or more severe infection (eg, extension of edema or erythema, lymphadenopathy, fever).

Fluctuant swelling or visible pus should be drained with a Freer elevator, small hemostat, or #11 scalpel blade inserted between the nail and nail fold. Skin incision is unnecessary. A thin gauze wick should be inserted for 24 to 48 h to allow drainage.

Chronic Paronychia

Chronic paronychia is recurrent or persistent nail fold inflammation, typically of the fingers.

Chronic paronychia occurs almost always in people whose hands are chronically wet (eg, dishwashers, bartenders, housekeepers), particularly if they are diabetic or immunocompromised. *Candida* is often present, but its role in etiology is unclear; fungal eradication does not always resolve the condition. The condition may be an irritant dermatitis with secondary fungal colonization.

The nail fold is painful and red as in acute paronychia, but there is almost never pus accumulation. Eventually, there is loss of the cuticle and separation of the nail fold from the nail plate. This forms a space that allows entry of irritants and microorganisms. The nail becomes distorted.

Diagnosis is clinical.

Treatment

• Keeping hands dry

• Topical corticosteroid or tacrolimus

Primary treatment is to keep the hands dry and to assist the cuticle in reforming to close the space between the nail fold and nail plate. Gloves or barrier creams are used if water contact is necessary. Topical drugs that may help include corticosteroids and, for their corticosteroid-sparing effects, immunosuppressants (eg, tacrolimus). Antifungal treatments are helpful only in reducing colonizing fungal

organisms. Thymol 3% in ethanol applied several times a day to the space left by loss of cuticle aids in keeping this space dry and free of microorganisms. If there is no response to therapy, squamous cell carcinoma should be considered and a biopsy should be done.

Ingrown Toenail

(Onychocryptosis)

An ingrown toenail is incurvation or impingement of a nail border into its adjacent nail fold, causing pain.

Causes include tight shoes, abnormal gait (eg, toe-walking), bulbous toe shape, excessive trimming of the nail plate, or congenital variations in nail contour (congenital pincer nail deformity). Sometimes an underlying osteochondroma is responsible, especially in the young. In the elderly, peripheral edema is a risk factor. Eventually, infection can occur along the nail margin (paronychia—see p. 735).

Symptoms and Signs

Pain occurs at the corner of the nail fold or, less commonly, along its entire lateral margin. Initially only mild discomfort may be present, especially when wearing certain shoes. In chronic cases, granulation tissue becomes visible, more often in the young.

Diagnosis

• Clinical evaluation

Redness, swelling, and pain suggest paronychia. In young patients (eg, < 20 yr) with ingrown toenails, x-rays should be considered to exclude underlying osteochondroma. In the elderly, apparent granulation tissue around the toe suggests the possibility of amelanotic melanoma, which is often overlooked; biopsy is necessary.

Treatment

• Usually nail excision and destruction of adjacent nail matrix

In mild cases, inserting cotton between the ingrown nail plate and painful fold (using a thin toothpick) may provide immediate relief and, if continued, correct the problem. If the shoes are too tight, a larger toe box is indicated. In most cases, however, particularly with paronychia, excision of the ingrown toenail after injecting a local anesthetic is the only effective treatment. If ingrown toenails recur, permanent destruction of the nearby lateral nail matrix by applying phenol or trichloroacetic acetic acid or by surgical excision is indicated. Phenol should not be used if there is arterial insufficiency.

Chapter 88. Pressure Ulcers

Introduction

(Pressure Sores; Bedsores; Decubitus Ulcers; Decubiti)

Pressure ulcers (PUs) are areas of necrosis and ulceration where tissues are compressed between bony prominences and hard surfaces; they result from pressure alone or pressure in combination with friction, shearing forces, or both. Risk factors include old age, impaired circulation, immobilization, undernutrition, and incontinence. Severity ranges from nonblanchable skin erythema to full-thickness skin loss with extensive soft-tissue necrosis. Diagnosis is clinical. Prognosis is excellent for early-stage ulcers; neglected and late-stage ulcers pose risk of serious infection and nutritional stress and are difficult to heal. Treatment includes pressure reduction, avoidance of friction and shearing forces, local care, and sometimes skin grafts or myocutaneous flaps.

Etiology

An estimated 1.3 to 3 million patients in the US have PUs; incidence is highest in older patients, especially those who are hospitalized or in long-term care facilities. Aging increases risk, in part because of reduced subcutaneous fat and decreased capillary blood flow. Immobility and comorbidities increase risk further.

Patients who are cognitively impaired, immobile, or both are at increased risk. Immobility—because of decreased spontaneous movement (eg, due to stroke, sedation, or severe illness) or inability to change position frequently because of weakness—is the most important factor. Other risk factors include urinary and fecal incontinence; poor nutritional status, including dehydration; diabetes; and cardiovascular disease. Clinical assessment is sufficient to identify patients at risk; several scales (eg, Norton, Braden —see
Fig. 88-1) are useful for predicting risk. The National Pressure Ulcer Advisory Panel has also issued guidelines for the prediction and prevention of PUs.

Pathophysiology

PUs develop when soft tissues are compressed between bony prominences and contact surfaces

[**Fig. 88-1.** Braden scale for predicting risk for pressure ulcers.]

[
Table 88-1. Pressure Ulcer Staging]

or when friction (eg, rubbing against clothing or bedding) or shearing forces (which develop when skin clings to surfaces) cause erosion, tissue ischemia, and infarction. PUs most frequently develop over the sacrum, ischial tuberosities, trochanters, malleoli, and heels, but they can develop elsewhere, including behind the ears when nasal cannulae are used for prolonged periods. Also, poorly fitting prosthetic devices can cause PUs to develop over bony prominences. Increased force and duration of pressure directly influence risk and severity, but PUs can develop in as little as 3 to 4 h in some settings (eg, trauma patients who are immobilized on rigid spine-immobilization boards). Ulcers worsen when skin is overly moist and macerated (eg, from perspiration or incontinence).

Other causes of skin ulcers: Chronic arterial and venous insufficiency can result in skin ulcers, particularly on the lower extremities. Although the underlying mechanism is vascular, the same forces that cause PUs can worsen these ulcers, and principles of treatment are similar.

Symptoms and Signs

Several staging systems exist; the most common classifies ulcers according to the depth of soft-tissue damage (see Table 88-1). PUs do not always present as Stage I and then progress to higher stages.

Sometimes the first sign of a PU is a deep, necrotic stage III or IV ulcer. In a rapidly developing PU, subcutaneous tissue can become necrotic before the epidermis erodes. A small ulcer might, like an iceberg, be quite large under the surface.

Stage I PUs manifest as nonblanchable erythema, usually over a bony prominence. Color changes may not be as visible in darkly pigmented skin. The lesion may also be warmer, cooler, firmer, softer, or more tender than adjacent or contralateral tissue. This stage is a misnomer in the sense that an actual ulcer (a defect of skin into the dermis) is not yet present. However, ulceration will occur if the course is not arrested and reversed.

Stage II PUs involve loss of epidermis with or without erosion (defect of epidermis) or true ulceration (partial-thickness loss of dermis); subcutaneous tissue is not exposed. The ulcers are shallow with a reddish base. Intact or partially ruptured blisters due to pressure are also stage II PUs. (NOTE: Non-pressure-related causes of erosion, ulceration, or blistering—eg, skin tears, tape burns, perineal dermatitis, maceration, excoriation—are excluded from stage II description.)

Stages III and IV PUs have deeper involvement of underlying tissue with more extensive destruction.

Ulcers covered with debris or eschar are by definition unstageable. However, stable, nonfluctuant heel lesions with dry eschar should not be debrided for the sake of staging. Bruising of an apparent stage II ulcer should raise the suspicion of a deeper-stage PU. PUs at any stage may be painful or pruritic but may not be noticed by patients with blunted awareness or sensation. Tenderness, erythema of surrounding skin, exudate, or foul odor suggests infection. Fever should raise suspicion of bacteremia or underlying osteomyelitis.

Complications

Nonhealing ulcers may be due to inadequate treatment but should raise suspicion of osteomyelitis or, rarely, squamous cell carcinoma within the ulcer (Marjolin's ulcer). Other complications of nonhealing PUs include sinus tracts, which can be superficial or connect the ulcer to deep adjacent structures (eg, to the bowel in sacral ulcers), and tissue calcification. In addition, PUs are a reservoir for hospital-acquired antibiotic-resistant organisms, which can slow healing and cause bacteremia and sepsis.

Diagnosis

• Clinical evaluation with continuous assessment

• Sometimes bone scan or MRI

Diagnosis is usually apparent clinically, but depth and extent can be difficult to determine. PUs are always colonized by bacteria, so wound surface cultures are uninterpretable. Underlying osteomyelitis is diagnosed with radionuclide bone scanning or gadolinium-enhanced MRI, but both techniques have poor sensitivity and specificity. Diagnosis may require bone biopsy and culture.

Continuous assessment is mandatory for effective management. Serial photographs can also document healing.

Prognosis

Prognosis for early-stage PUs is excellent with timely, appropriate treatment, but healing typically requires weeks. PUs often develop in patients with suboptimal care. If care cannot be improved, long-term outcome is poor, even if short-term wound healing is accomplished.

Treatment

• Pressure reduction

• Direct ulcer care

• Management of pain, infection, and undernutrition

• Sometimes adjunctive therapy or surgery

Treatment requires multiple simultaneous elements.

Reducing pressure: Reducing tissue pressure is accomplished through careful positioning of the patient, protective devices, and variation of support surfaces.

Frequent repositioning (and selection of the proper position) is most important. A written schedule should be used to direct and document repositioning. Bedbound patients should be turned a minimum of every 2 h, should be placed at a 30° angle to the mattress when on their side (ie, lateral decubitus) to avoid direct trochanteric pressure, and should be elevated as minimally as possible to avoid the shear forces on tissues that result from sliding down the bed. For repositioning patients, lifting devices (eg, a Stryker frame) or bed linen should be used instead of dragging the patient (which causes friction and shear forces). Patients placed in chairs should be repositioned every hour, and they should be encouraged to change position on their own every 15 min.

Protective padding includes pillows or foam wedges placed between knees, ankles, and heels when patients are on their side and pillows, foam, or heel protectors when patients are supine. Windows should be cut out of plaster casts at pressure sites in patients immobilized by fractures. Soft seat cushions should be provided for patients able to sit in a chair. Donut-shaped devices and sheepskins should be avoided as a treatment for PUs.

Support surfaces under bedbound patients can be changed to reduce pressure. A change from standard mattresses is indicated when patients are unable to reposition themselves and periodic repositioning care is unavailable.

Support surfaces are static or dynamic.

Static surfaces, which do not require electricity, include air, foam, gel, and water overlays and mattresses. Old-fashioned "egg crate" mattresses offer no advantage. In general, static surfaces increase surface support areas and decrease pressure and shear forces; they are indicated for high-risk patients without PUs and for patients with stage I PUs.

Dynamic surfaces require electricity. Alternating-air mattresses have air cells that are alternately inflated and deflated by a pump, thus shifting supportive pressure from site to site. Low-air-loss mattresses are giant air-permeable pillows that are continuously inflated with air; the air flow has a drying effect on tissues. These specialized mattresses are indicated for patients with stage I ulcers who develop hyperemia on static surfaces and for patients with stage III or IV ulcers. Air-fluidized (high-air-loss) mattresses contain silicone-coated beads that liquefy when air is pumped through the bed. Advantages include reduction of moisture on surfaces and cooling. They are indicated for patients with nonhealing stage III and IV ulcers or numerous truncal ulcers (see Table 88-2). Although specialized mattresses are designed to shift

[**Table 88-2.** Options for Support Surfaces]

pressure and reduce forces that lead to PUs, they are best thought of as an adjunct to comprehensive care.

Ulcer care: Appropriate ulcer care involves cleaning, debridement, and dressings.

Cleaning should be done initially and with each dressing change; ordinary soap and water (not hot) is usually best. Cleaning often involves irrigation with saline solution at pressures sufficient to remove bacteria without traumatizing tissue; commercial syringes, squeeze bottles, or electrically pressurized systems can be used. Alternatively, a 35-mL syringe and an 18-gauge IV catheter can be used. Irrigation should continue until no further debris can be loosened. Antiseptics (eg, iodine, hydrogen peroxide) and

antiseptic washes interfere with tissue healing and should be avoided. Rubbing of skin should be minimized, and moisturizer should be applied gently after each cleansing.

Debridement is necessary to remove dead tissue. Methods include

- Autolytic debridement: Synthetic occlusive dressings are used to facilitate digestion of dead tissues by enzymes normally present in wound fluids. Autolytic debridement may be used for small wounds with simple accumulation of tissue proteins and wounds that need to be sealed off anyway (eg, for protection from feces or urine). DuoDERM or Contreet (which is impregnated with silver and thus offers antimicrobial effects) are commonly applied. Infected wounds, however, should not be occluded.

- Mechanical debridement: Hydrotherapy (whirlpool baths), ultrasound, medical maggots, wound irrigation, or dextranomers (small carbohydrate-based beads that help absorb exudate and liquid debris) should be used to remove thick exudate or loose necrotic tissue. A scalpel or scissors can be used to remove eschar (except in heel ulcers, in which dry eschar in the absence of edema, erythema, fluctuance, or drainage can be safely left alone) or extensive areas of dead tissue. Modest amounts of eschar or tissue can be debrided at the patient's bedside, but extensive or deep areas should be debrided in the operating room. Urgent debridement is indicated in advancing cellulitis or sepsis. Debridement with wet-to-dry dressings should be done only for wounds with very loose exudate and only with great care because it is often painful and it may remove healthy tissue or overdry the wound.

- Enzymatic debridement (using collagenase, papain, fibrinolysin, or streptokinase/streptodornase): This method can be used for patients whose caretakers are not trained to do mechanical debridement or for patients unable to tolerate surgery. It is most effective after careful and judicious cross-hatching of the wound with a scalpel to improve penetration. Collagenase is especially effective as collagen comprises 75% of the dry weight of skin.

Dressings should be used for stage I ulcers that are subject to friction or incontinence and for all other ulcers (see
Table 88-3). Objectives are to keep the ulcer bed moist to retain tissue growth factors while allowing some evaporation and inflow of O_2, to keep surrounding skin

[**Table 88-3.** Options for Pressure Ulcer Dressings]

dry, to facilitate autolytic debridement, and to establish a barrier to infection. Transparent films (eg, OpSite, Tegaderm, Bioclusive) are sufficient for ulcers with limited exudate; they should not be used over cavities and must be changed every 3 to 7 days. Some experts recommend a small amount of triple antibiotic ointment under the dressing. Hydrogels (Clear-Site, Vigilon, FlexiGel), which are cross-linked polymer dressings that come in sheets or gels, are indicated for very shallow wounds, such as re-epithelializing wounds with minimal exudate.

Hydrocolloids (eg, RepliCare, DuoDERM, Restore, Tegasorb), which combine gelatin, pectin, and carboxymethylcellulose in the form of wafers, powders, and pastes, are indicated for light-to-moderate exudate; some have adhesive backings and others are typically covered with transparent films to ensure adherence to the ulcer and must be changed every 3 days. Alginates (polysaccharide seaweed derivatives containing alginic acid), which come as pads, ropes, and ribbons (AlgiSite, Sorbsan, Curasorb), are indicated for absorbing extensive exudate and for controlling bleeding after surgical debridement. Foam dressings (Allevyn, LYOfoam, Hydrasorb, Mepilex, Curafoam, Contreet) are useful as they can handle various levels of exudate and provide a moist environment for wound healing. Waterproof versions protect the skin from incontinence. Dressings with adhesive backings stay in place longer and need less frequent changing.

Pain management: Primary treatment of pain is treatment of the PU itself, but NSAIDs or acetaminophen is used for mild-to-moderate pain. Opioids should be avoided if possible because sedation promotes immobility. Opioids may be necessary during dressing changes and debridement. In cognitively impaired patients, changes in vital signs can be used as an indication of pain.

Infection management: PUs should be continually reassessed for bacterial infection using clinical signs