

Box 17-3**CAUSES OF CHEMICAL AND DRUG-INDUCED HEPATITIS****Dose-Related (Predictable)**

Acetaminophen (analgesic; suicide attempts)

Alcohol

Amanita phalloides (poisonous mushroom)

Anabolic steroids

Aspirin

Benzene, toluene

Carbon tetrachloride

Chloroform (anesthetic)

Methotrexate (antineoplastic agent)

Oral contraceptives

Organic pesticides

Penicillin

Tetracyclines (antibiotic)

Trichloroethylene

Vinyl chloride

Idiosyncratic (Unpredictable)

α -Methyldopa (antihypertensive)

Halothane (anesthetic)

Isoniazid (antitubercular)

Minocycline (antibiotic)

Monoamine oxidase inhibitors (antidepressant)

Nitrofurantoin

Phenytoin (Dilantin) (anticonvulsant)

Rifampin (antitubercular)

Quinidine (antiarrhythmic)

Sulfonamides (antibiotic)

Sulindac (NSAID)

Valproate (anticonvulsant)

NSAID, Nonsteroidal antiinflammatory drug.

Pathogenesis

Drugs and toxins can result in liver injury via numerous mechanisms.⁶² Some of these mechanisms include programmed cell death (apoptosis) as a result of tumor necrosis factor (TNF); binding of drug to cellular proteins, which causes an immunologic response, leading to cell death¹³⁷; inhibiting metabolism of drugs; and mitochondrial dysfunction with formation and accumulation of reactive oxidative species.¹²³

The pattern of injury is often drug dependent. Patterns of liver injury include hepatocellular, cholestatic, mixed, hypersensitivity (or immunologic), and mitochondrial injury. Hepatocellular injury is defined by inflammation of the hepatocytes, breakup of the hepatic lobule (comprised of the central vein, the portal vein, hepatic artery, bile duct, and hepatic cords), and hepatocellular necrosis.

Isoniazid is an example of a drug that can cause this type of injury. Cholestatic injury is demonstrated by mild bile duct injury with pooling of bile in the hepatocytes. Amoxicillin-clavulanic acid is one drug that can cause this type of injury. Mixed patterns exhibit both hepatocellular and cholestatic patterns. Hypersensitivity reactions often

show an eosinophilic infiltration of the portal triad; phenytoin can lead to this type of response. Mitochondrial injury is demonstrated by small droplets of fat (or microvesicular steatosis) within the hepatocyte. Valproic acid has been known to cause this type of cellular change.

Clinical Manifestations

The manifestations of drug-related liver disease can range from mild symptoms to fulminant liver failure. Vague symptoms, including fatigue, nausea, and right upper quadrant pain or discomfort, may be the first indications of hepatotoxicity. Other symptoms associated with liver injury are jaundice, pruritus, and dark urine. Fever and rash are often present with a hypersensitivity reaction. As discussed, drugs often cause a specific pattern of injury. The most readily identifiable patterns are hepatocellular and cholestatic.

Hepatocellular liver disease frequently presents with abdominal discomfort/pain, fatigue, and jaundice; the clinical course is acute and can be severe. Cholestatic liver disease is manifested clinically by jaundice and pruritus. In contrast to the hepatocellular pattern, cholestatic disease is often less acutely serious, but healing may be prolonged and chronic, taking weeks to months.

MEDICAL MANAGEMENT

DIAGNOSIS. Since drug-induced hepatotoxicity is uncommon, people who present with symptoms consistent with liver disease should have a complete evaluation to avoid missing more common causes. This includes laboratory testing for viral hepatitis, autoimmune liver diseases, Wilson's disease, hemochromatosis, and α -antitrypsin deficiency. Ultrasonography, computed tomography (CT) scanning, magnetic resonance imaging (MRI), or endoscopic retrograde cholangiopancreatography (ERCP) are useful to identify biliary obstruction. A history of heavy alcohol consumption may be consistent with alcohol-related hepatitis.

A review of medications taken, remembering to question exposures to chemicals, herbals, and OTC medications, may point toward drug-related liver disease. Although many drugs have more immediate effects, unpredictable injury may not exhibit symptoms for months.

Tests used to detect liver injury include ALT, bilirubin, and ALP. ALT values that are at least three times normal are suggestive of liver injury, whereas ALP values of two times normal are considered abnormal. A bilirubin more than twice the upper limit of normal and associated with an abnormal ALT or ALP suggests disease. An elevation in the ALT value, with minimal changes in ALP, is consistent with hepatocellular damage, whereas a predominantly elevated ALP is associated with cholestatic disease.

Significant elevations in these laboratory values are not predictive of prognosis since the liver has the prodigious ability to heal. Function is often a better indicator of prognosis. Several laboratory tests indicate how well the liver is functioning. Prothrombin/international normalized ratio (INR) and albumin demonstrate the liver's ability to synthesize proteins, and total bilirubin and conjugated bilirubin reflect the liver's ability to move bilirubin from the blood into bile.¹¹²

The liver also has the ability to adapt to some medications. This ability is demonstrated when the introduction of a drug leads to transient elevations in liver enzyme tests, but there is no progression of injury. In these cases the drug does not have to be stopped. For example, isoniazid often causes a transient, minor increase in liver enzymes but is permanently stopped in only 1 in 1000 affected clients.¹¹⁵

TREATMENT AND PROGNOSIS. Treatment for drug-related hepatotoxicity most often consists of removal of the causative agent and providing supportive care. Two exceptions include the usage of N-acetylcysteine soon after toxic ingestion of acetaminophen and intravenous carnitine for valproate-induced hepatotoxicity. Reexposure or rechallenge of the offending agent should be avoided, particularly if the drug has an unpredictable liver toxicity and the hepatotoxicity was immune-related. Reexposure could lead to an even more severe and serious reaction.

Liver injury accompanied by increases in liver enzyme levels may worsen for days to weeks before improvement. In some severe cases, improvement of liver enzyme levels suggests liver failure rather than healing of injury caused by severe necrosis and loss of hepatocytes. In this setting, laboratory values indicative of liver function (such as prothrombin time/INR and albumin) and symptoms (such as encephalopathy) are better indicators of hepatic function.

Chronic liver disease can also develop; up to 5% to 6% of drug-induced liver disease can become chronic (principally with a cholestatic pattern of injury). Methyl-dopa, minocycline, and nitrofurantoin are drugs that have been associated with this problem. A poor prognosis is seen in clients who develop jaundice, impaired liver function, and encephalopathy within 26 weeks of the onset of symptoms.¹¹⁴ Prognosis is the most serious and poor for those people with hepatocellular damage accompanied by jaundice, with a mortality of 10% to 50% (known as *Hy's law*). This type of injury is more likely than others to require liver transplantation.¹¹⁵

SPECIAL IMPLICATIONS FOR THE THERAPIST 17-8

Drug-Related Hepatotoxicity

PREFERRED PRACTICE PATTERNS

See *Viral Hepatitis*.

Therapists should be alert to the possibility of drug toxicity or drug reactions in clients taking multiple medications or reactions in people who are combining prescription medications or OTC medications with complementary or alternative medications. Many people do not consider OTC drugs as medications and may take the same drug with different names or combine OTC drugs with prescription medications. People with memory loss or short-term memory deficits may take multiple doses in a short amount of time because they cannot remember when or whether they took their medication. Other guiding principles for the recovery process are as mentioned for viral hepatitis.

Autoimmune Hepatitis Overview and Incidence

Autoimmune hepatitis is a chronic progressive, inflammatory disorder of the liver of unknown cause. It occurs in adults and children and is characterized by the presence of abnormal liver histology, autoantibodies, elevated levels of serum immunoglobulins, and frequent association with other autoimmune diseases. Autoimmune hepatitis is one of the three major autoimmune liver diseases, along with primary biliary cirrhosis and primary sclerosing cholangitis. Variant forms of autoimmune hepatitis have been termed *overlap syndromes* because they share features of several liver diseases.

The International Autoimmune Hepatitis Group has classified two types of autoimmune hepatitis: type 1 and type 2.¹ Both forms are more common among women than men and have similar clinical and serum biochemical features. Type 2 is rare and most often seen in childhood and in young adulthood; it is associated with more severe and advanced disease at presentation. Autoimmune hepatitis is seen worldwide and in various ethnic groups, although type 2 is uncommon in North America.

Etiologic Factors and Pathogenesis

The cause and pathogenesis of autoimmune hepatitis are not known. The disease appears to occur among genetically predisposed individuals on exposure to as-yet unidentified environmental agents, triggering a cascade of T cell-mediated events directed at liver antigens.⁶⁷

Purported triggering agents include viruses (such as measles, hepatitis, CMV, and Epstein-Barr viruses) and drugs (such as methyl-dopa, nitrofurantoin, diclofenac, interferon, pemoline, minocycline, and atorvastatin). It is uncertain if drugs actually trigger autoimmune hepatitis or merely cause a drug-mediated hepatitis with features similar to autoimmune hepatitis. Most people with autoimmune hepatitis, however, have no identifiable trigger. Factors that predispose an individual to autoimmune hepatitis are not certain, but specific HLA genes have been linked to the development of autoimmune hepatitis and probably play a major role.

Type 1 is associated with human leukocyte antigen (HLA)-DR3 and HLA-DR4. Studies have shown that HLA-DR3-associated disease correlates to earlier onset, particularly in girls and young women, and more severe disease; whereas HLA-DR4 is associated with milder disease (although extrahepatic findings are more common) and better response to treatment.⁶⁷ HIA-DR2 may be protective.³⁵

Autoreactive T cells and their proinflammatory response appear to cause the liver destruction seen in autoimmune hepatitis. Research continues to identify the antigens that are targeted by T cells, but one possibility is the asialoglycoprotein receptor, which is a liver membrane protein found in hepatocytes.

Continued T-cell response with chronic liver damage may ensue because of a failure of CD4+CD25+ regulatory

T cells (T-reg) to regulate the response of CD8+ and CD4+CD25 cells (autoreactive T cells). Normally, T-reg control the adaptive immune response of CD8+ and CD4+CD25-T cells by suppressing the proliferation and function of these T cells, which allows for self-tolerance maintenance. In autoimmune hepatitis, the low number and defective function of T-reg leads to a change in cytokine production, proliferation, and apoptosis of autoreactive T cells.⁸⁷

Antibodies are also produced and vary, depending on the type of autoimmune hepatitis. Antinuclear antibodies (ANA), smooth-muscle antibodies, atypical perinuclear antineutrophilic cytoplasmic antibodies (pANCA), and antiactin antibodies are seen with type 1 autoimmune hepatitis. Type 2 is associated with liver-kidney microsome 1 (LKM-1) and liver cytosol 1 (ALC-1) antibodies. Although present in the serum, there is little evidence to support the theory that these autoantibodies cause the disease.⁶⁷ Yet measurement of these antibodies can be helpful in the diagnosis of autoimmune hepatitis.

Clinical Manifestations

Autoimmune hepatitis is represented by a wide spectrum of clinical manifestations. While most clients present with nonspecific, mild, or chronic liver symptoms, up to 40% present with acute symptoms of hepatitis, including fulminant hepatitis with cirrhosis and liver failure. Autoimmune hepatitis is usually progressive and chronic, although a minority of cases are characterized by a fluctuating course.

The most common presenting symptoms are fatigue (85%), jaundice (46%), anorexia (30%), myalgias (30%), and diarrhea (28%). Other symptoms include abdominal pain, arthralgias (particularly small joints), and malaise. Weight loss is uncommon and should prompt an evaluation for another disorder.

The presence of another autoimmune disorder, such as thyroiditis, ulcerative colitis, type 1 diabetes, rheumatoid arthritis, and celiac disease,¹ is seen in one-third of affected individuals. Physical examination may be normal, but 78% of clients present with hepatomegaly. Individuals with fulminant hepatitis often have profound jaundice.

Complications of autoimmune hepatitis are similar to other chronic liver diseases, particularly the development of cirrhosis. Although occurring less frequently than hepatitis associated with a virus, another serious complication is the development of HCC.

MEDICAL MANAGEMENT

DIAGNOSIS. The diagnosis of autoimmune hepatitis can be difficult since no one test is diagnostic for the disease. The diagnosis is based on a synthesis of clinical, biochemical, and histologic information. Laboratory findings consistent with autoimmune hepatitis include elevated aminotransferase values, hypergammaglobulinemia, elevated bilirubin and ALP values, and the presence of autoantibodies. At presentation aminotransferase values are typically between 150 U/L and 500 U/L, but people with severe disease at presentation can have significantly elevated aminotransferase values in the thousands.

Over 80% of affected people have hyperbilirubinemia, although this is typically mild with values less than 3 mg/dl. Serum ALP values are usually elevated, but values twice the upper limit of normal are likely indicative of another disease. Serum globulins are elevated up to three times normal, particularly gamma globulin and IgG.

As discussed, autoantibodies are produced and can be helpful in making the diagnosis of autoimmune hepatitis, but 10% of cases do not exhibit autoantibody production. The most common autoantibodies seen in type 1 are ANA and smooth muscle. Titers of at least 1:80 in adults are considered a positive value.⁶⁷ Anti-LKM-1 and anti-ALC-1 antibodies are more specific to type 2.

The magnitude of the elevations of aminotransferase and gamma globulin does not necessarily correlate with the extent of liver damage, making liver biopsy important. Although histologic appearance of autoimmune hepatitis is similar to chronic hepatitis (can also be seen in other liver diseases), there are characteristic findings of autoimmune hepatitis that include a mononuclear-cell infiltrate of the interface around the portal triad, particularly with plasma cells. Fibrosis is another common finding.

TREATMENT. The mainstay of therapy is immunosuppression. Over 80% of clients achieve remission with prednisone or prednisone plus azathioprine. Serum aminotransferases and gamma globulin levels can be used to monitor response to treatment. Therapy can be withdrawn once in remission, although relapse is high, occurring in 50% to 85% of affected people, particularly during the first 6 months.

Therapy for relapsed disease is the same as that used for the initial treatment and can successfully induce remission of the disease. Individuals who experience repeated relapses tend to have a poorer prognosis.¹⁰⁵ Maintenance therapy with azathioprine is often needed and life-long maintenance therapy is frequently used in persons with type 2 disease or cirrhosis at diagnosis.

Liver transplantation may be required for clients who develop end-stage liver disease because of intolerance to therapy (and have progression of the disease) or who have progression of the disease while receiving adequate therapy. Five-year survival rates after liver transplantation are 80% to 90%, and the 10-year survival rate is approximately 75%.³⁷ Autoimmune hepatitis reoccurs in about 40% of clients who undergo liver transplantation,¹³³ although this is often mild and related to the immunosuppressive medications used after transplantation.

PROGNOSIS. Prognosis depends on the stage of disease at the time of diagnosis and initiation of therapy, but 10-year survival rates (meaning not requiring liver transplantation or causing death) surpass 90%, whereas 20-year survival rates are probably less than 80%. People that respond to treatment often have lifespans similar to healthy persons.²⁷ Individuals who present with cirrhosis have 20-year survival rates of only 40%.

SPECIAL IMPLICATIONS FOR THE THERAPIST

17-9

Autoimmune Hepatitis**PREFERRED PRACTICE PATTERNS***See Viral Hepatitis.*

Management of a client who has an autoimmune disease with liver involvement is a challenge. Energy conservation and maintaining quiet body functions during active liver disease must be balanced by activities to prevent musculoskeletal deconditioning with accompanying loss of strength, flexibility, and/or mobility.

Alcohol-Related Liver Disease**Overview, Incidence, and Risk Factors**

Although over two-thirds of Americans drink alcohol, only a minority develop problems leading to chronic alcohol abuse and severe liver disease. Yet alcohol problems result in significant morbidity and mortality; over 40% of deaths from cirrhosis are alcohol-related and 30% of HCC cases are a result of alcohol-related liver disease.

More men than women acquire liver disease, but women develop the disease after a shorter exposure to alcohol and while consuming lower quantities of alcohol as compared to men. In men 6 to 8 alcohol-containing beverages daily (60 to 80 g/day) over a 5-year period can lead to liver disease, while only 3 to 4 drinks/day are needed to cause the same effect in women.

Women are more vulnerable to the effects of alcohol than men. Women produce substantially less of the gastric enzyme alcohol dehydrogenase, which breaks down ethanol in the stomach. As a result, women absorb 75% more alcohol into the bloodstream. Other effects and gender differences are discussed further in Chapter 2.

About 90% of heavy drinkers develop fat accumulation in the liver (the first sign of alcohol abuse), yet although many persons are heavy drinkers for long periods of time, only a minority progress to develop alcoholic hepatitis and alcoholic cirrhosis. Research suggests that genetics may play an important role in preventing liver damage despite chronic alcohol exposure.

Alcohol-related liver disease encompasses alcoholic hepatitis and alcoholic cirrhosis. Alcoholic hepatitis occurs in only 10% to 35% of heavy drinkers and is the precursor for the development of alcoholic cirrhosis. People with alcoholic hepatitis are nine times more likely than people with fatty liver infiltration to develop cirrhosis.⁸¹

Some cofactors that may predispose to cirrhosis include coexisting HCV, smoking, and obesity. Although much progress has been made in understanding potential causes, many questions remain such as determining which factors lead to severe liver damage and the mechanisms that protect other heavy drinkers.

Pathogenesis

The initial physiologic change observed in the liver with alcohol exposure is the accumulation of fat, which is reversible with abstinence. In some people, with continued exposure to alcohol, there is a progression of damage to the liver consisting of inflammation, necrosis of individual cells, and early fibrosis, termed *alcoholic hepatitis*. With continued heavy drinking, micronodular fibrosis (small bands of fibers) can develop and eventually progress to large bands of fibrosis, creating large nodules of fibrotic liver tissue (macronodular cirrhosis). Once cirrhosis has developed, HCC may result.

Research has demonstrated that heavy quantities of alcohol can have significant detrimental effects. Many mechanisms have been described that may be responsible for liver injury caused by alcohol consumption. Damage most likely requires several of these processes to be present, and genetic factors probably play a role in prevention or progression of liver injury. A few of these mechanisms include the toxic buildup of acetaldehyde, inflammatory reaction of immune cells, overproduction of reactive oxidative species (ROS) and reduction of antioxidants, mitochondrial dysfunction, and abnormal metabolism of methionine and S-adenosylmethionine (SAM).

Acetaldehyde is an intermediate product in the metabolism of alcohol. Typically, alcohol is converted to acetaldehyde by the enzymes alcohol dehydrogenase and cytochrome P450 2E1 (CYP2E1); acetaldehyde is in turn metabolized to acetate by aldehyde dehydrogenase. When the metabolism process is overwhelmed by alcohol, acetaldehyde can build up. Acetaldehyde is a reactive molecule and is able to modify proteins. These altered proteins are then not only unable to function appropriately in the hepatocyte but may also elicit an immune response, bringing inflammatory leukocytes into the liver and contributing to cellular injury.

Alcohol can also alter the balance between pro-oxidants and antioxidants, causing oxidative stress and liver injury. When the enzyme CYP2E1 is activated, it leaks electrons. These electrons create reactive species (such as superoxide anions), which then react with proteins, lipids, and DNA, or deplete antioxidants, leading to the inability of the hepatocyte to function. Reactive molecules can also signal other pathways, such as activating transcription factors, to produce TNF. Hepatocytes can be very sensitive to the damaging effects of TNF as a result of the abnormally increased level of acetaldehyde.⁸²

Another factor contributing to oxidative stress is alcohol-related mitochondrial dysfunction. Mitochondria utilize oxygen and produce ROS but are protected from oxidative stress by glutathione (which is transported from the cytosol). In the presence of alcohol, hepatic mitochondria produce increased amounts of superoxide molecules, but the transport of glutathione into the mitochondria does not function, leaving the mitochondria to the damaging effects of ROS.

Alcohol also interrupts the important metabolism of methionine to SAM. The enzyme responsible for this conversion is methionine adenosyltransferase (MAT), which is depressed by alcohol.⁸³ SAM is a necessary

molecule, donating methyl groups in many enzymatic reactions involving DNA, RNA, phospholipids, and proteins. SAM is the precursor of glutathione and may be hepatoprotective; the depletion of SAM can result in abnormal functioning of hepatocytes and sensitization of hepatocytes to destructive cytokines.

Clinical Manifestations

The initial histologic change noted in heavy drinkers is fatty liver infiltrate. This is often asymptomatic and detected only on laboratory evaluation. Even clients with alcoholic hepatitis and/or cirrhosis may be asymptomatic. Others may present with nausea, vomiting, abdominal pain, jaundice, anorexia, fever, and weight loss.

The most common sign in people with fatty liver or alcoholic hepatitis is hepatomegaly; 60% of all people with alcohol-related liver disease exhibit jaundice and ascites (typically in clients with severe disease). Splenomegaly is more common as the disease worsens and hepatic encephalopathy can exist in varying degrees, ranging from mild cognitive impairment to coma. Clients with alcoholic hepatitis or cirrhosis often display spider angioma, liver tenderness, and edema.⁹⁷

MEDICAL MANAGEMENT

DIAGNOSIS. The diagnosis of alcoholic hepatitis is made using the appropriate history of heavy drinking, consistent laboratory values, and no evidence of other diseases that could cause liver injury. Because alcohol can worsen preexisting diseases, such as viral hepatitis, the diagnosis of alcohol-related liver disease should not be made without a thorough evaluation.

A history of heavy drinking may not be present because of client denial. Only 50% of clients who abuse alcohol are identified by their physician. Elevated levels of aminotransferases (AST and ALT) are the most common abnormalities seen in alcohol-related liver disease. The AST is rarely over 300 to 500 U/L, while the ALT is typically only slightly elevated, giving an AST/ALT ratio of greater than 2. Serum ALP and bilirubin can range from normal to 1000 U/L and 20 to 40 mg/dL, respectively.

Often, despite advanced disease, laboratory levels may be only mildly elevated. Alcohol-related liver disease is usually accompanied by malnutrition and is evident in the low albumin levels and elevated prothrombin time (PT). Erythrocyte count is often low (anemia) and thrombocytopenia may be present; the white blood cell (WBC) count frequently is elevated. Because the diagnosis of alcohol-related liver disease can competently be made using history, physical, and laboratory information, liver biopsy is rarely needed.

TREATMENT AND PROGNOSIS. Treatment of alcoholic hepatitis centers on cessation of alcohol, nutritional support and education, and prevention of the complications of end-stage disease. Corticosteroids can be used for severe cases of alcoholic hepatitis, whereas SAM, an antioxidant, may reduce mortality and decrease the need for liver transplantation.⁹⁸

Anti-TNF- α agents, such as etanercept, may be beneficial⁹⁹; however, only preliminary data are available from pilot studies and these medications are not used

routinely. Alcoholic hepatitis carries a poor prognosis if the person continues to drink alcohol. Frequently, the disease will stabilize if the person stops drinking.

Clients who develop cirrhosis (but are asymptomatic) and are able to abstain from alcohol have a prognosis of 80% at 5 years. Liver transplantation is offered to clients who have end-stage liver disease and are able to stop drinking, typically for at least a period of 6 months. This often allows for sufficient improvement to the point of not requiring a liver transplant. Outcomes of transplantation for alcohol-related liver disease are similar to other groups requiring transplantation,¹⁵⁶ with a 7-year survival of 60%.

Prognosis depends on the severity of disease, other coexisting illnesses (i.e., HCV), nutritional status, the client's ability to abstain from alcohol, and the presence of end-stage liver disease. The prognosis and severity of disease can be determined using the discriminant function (DF) equation; the more recent model for end-stage disease (MELD) predicts survival and is often used in allocating livers for transplantation.³⁸ People with a DF score greater than 32 have a 50% mortality within 30 days.

SPECIAL IMPLICATIONS FOR THE THERAPIST 17-10

Alcohol-Related Liver Disease

PREFERRED PRACTICE PATTERNS

See Viral Hepatitis.

Follow the same guidelines regarding liver protection as are discussed in Special Implications for the Therapist: Viral Hepatitis. Increased susceptibility to infections requires careful handwashing before treating this client. (See also Special Implications for the Therapist: Cirrhosis.) The presence of coagulopathy requires additional precautions. (See the discussion, Special Implications for the Therapist: Signs and Symptoms of Hepatic Disease.)

Primary Biliary Cirrhosis

Overview and Incidence

Primary biliary cirrhosis (PBC) is a chronic, progressive liver disorder with uncertain cause. Similar to autoimmune hepatitis, PBC has an autoimmune basis, but unlike autoimmune hepatitis, the areas of destruction involve the small bile ducts. The incidence of PBC has been stable over time although the prevalence has been increasing, which is most likely a result of earlier diagnosis and prolonged survival. PBC occurs most frequently in women (80% to 90% of cases) between the ages of 40 to 60 years.

PBC is a slowly progressive (irreversible), chronic liver disease that causes inflammatory destruction of the small intrahepatic bile ducts, decreased bile secretion, cirrhosis, and ultimately, liver failure. An autoimmune attack against the bile duct is probably an important pathogenic element, but the precipitating event and contribution of genetic and environmental factors are uncertain.

The disease is associated with other autoimmune disorders, including scleroderma, Sjogren's syndrome, thyroiditis, pernicious anemia, and renal tubular acidosis. Although it is most common in whites from North America and Europe, cases have occurred in all races.

Etiologic Factors and Pathogenesis

The underlying cause of primary biliary cirrhosis has a basis in aberrant autoimmunity. People affected with PBC express antimitochondrial antibodies (90% to 95% of cases). These are specifically targeted toward large enzyme complexes associated with oxidative phosphorylation (pyruvate dehydrogenase complex-E2 [PDC-E2]).⁴⁵

Although these enzymes occur throughout the body, only the epithelial cells of the small bile ducts in the liver are affected. This may be related to how a bile duct epithelial cell processes glutathione once the bile duct cell undergoes apoptosis.⁶¹ Autoreactive T cells then respond to these antibodies, causing inflammation. As the ducts are destroyed, toxic substances build up in the liver, intensifying the damage. Chronic inflammation leads to fibrosis, cirrhosis, and eventually, without treatment, liver failure.

Research has also been investigating factors that lead to the production of antimitochondrial antibodies. Several hypotheses are centered on molecular mimicry.⁶¹ Evidence suggests that antibodies made against bacteria have similarities to the PDC-E2 in mitochondrial cells, thus producing antibodies that target bile duct cells. Some of the bacteria proposed to play a role in this process are *E. coli*, *Novosphingobium aromaticivorans*, lactobacilli, and *Chlamydia*.⁶¹ Other possible environmental factors include chemicals, such as halogenated hydrocarbons found in pesticides and detergents, but more research is needed to verify this association.^{19,76}

Clinical Manifestations

Most people with PBC are asymptomatic (50% to 60%) at diagnosis; the remainder may present with symptoms ranging from minor annoyances to advanced disease. The most common presenting symptom is fatigue, which is noted in over 20% of affected clients at diagnosis. With progression of the disease, fatigue becomes more significant, occurring in about 80% of people,⁴³ and may be disabling.¹²⁸

Pruritus is frequently present (20% to 70%), particularly in the perineal area and the palmar and plantar surfaces of the hands and feet, although it can be diffuse. Pruritus often worsens at night or when the environment is warm. Contact with fibers, such as wool, can also aggravate the pruritus. Less commonly noted is the presence of right upper quadrant pain (about 10%).

Other symptoms of the disease include hyperlipidemia, osteopenia, and the presence of other autoimmune diseases (i.e., Sjogren's and scleroderma).^{78,168} In the later stages of the disease, clients may exhibit portal hypertension, malabsorption, fat-soluble vitamin deficiencies, and steatorrhea (the result of impairment of excretion of bile into the intestine). Complications from advanced liver disease include ascites, bleeding from esophageal varices, and hepatic encephalopathy.

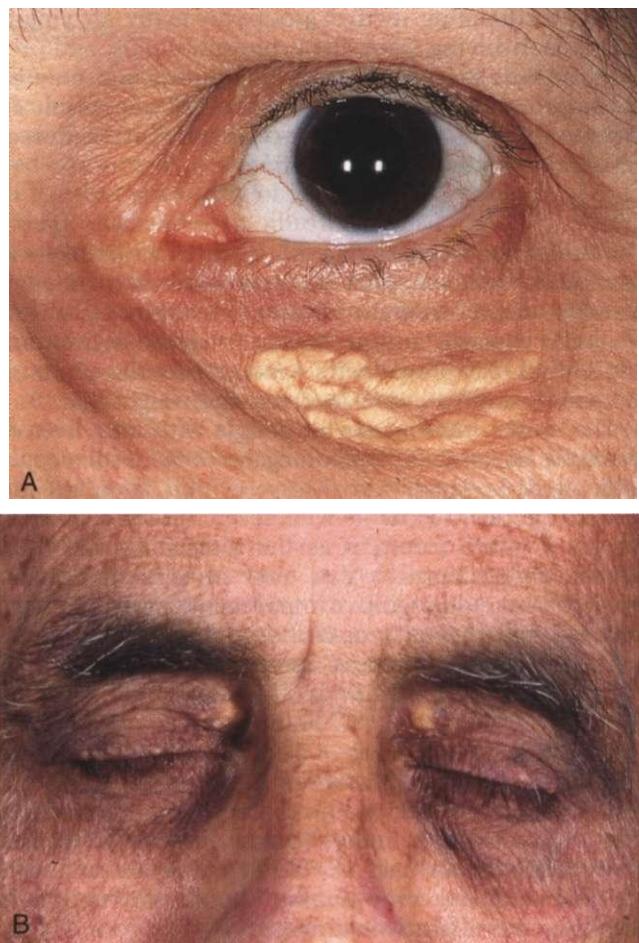


Figure 17-6

Xanthelasma. Multiple, soft yellow plaques involving the eyelid (lower and upper). Lipid-laden foam cells seen in the dermis tend to cluster around blood vessels. Lipid deposits can also be seen along the extensor surfaces of the body (not shown) such as the heels, elbows, and dorsum of the hands. (A, From Yanoff M: Ophthalmology, ed 2, St. Louis, 2004, Mosby; B, from Rakel RE: Textbook of family medicine, ed 7, Philadelphia, 2007, WB Saunders.)

The physical examination is typically normal in asymptomatic people, but skin manifestations often occur as the disease progresses. Pruritus frequently leads to excoriations of the skin, and spider nevi, thickening of the skin, and increased skin pigmentation are often detected with advancement. Xanthelasmata are seen in 5% to 10% of persons with the disease (Fig. 17-6). Hepatomegaly is noted in 70% of clients, yet splenomegaly is uncommon at presentation, often developing only near the end stages of PBC. Jaundice is observed later in the illness, often months to years after diagnosis. Muscle wasting, edema, and ascites often herald liver failure.

MEDICAL MANAGEMENT

DIAGNOSIS. The diagnosis of PBC is based on a triad of criteria: presence and elevation of antimitochondrial antibodies (titer 1:40 or more), elevated levels of serum liver enzymes (particularly serum ALP and y-

glutamyltransferase) for more than 6 months, and liver biopsy histology consistent with PBC. A probable diagnosis of PBC can be made with only the presence of antimitochondrial antibodies and elevated liver enzymes, but a definite diagnosis requires a liver biopsy. A liver biopsy may be beneficial for several reasons. First, the stage of the disease can be defined since the magnitude of the elevation of antimitochondrial titers is not indicative of the severity of the disease. Second, 5% to 10% of clients with PBC do not manifest antimitochondrial antibodies. Third, liver biopsy gives a baseline with which to compare response to treatment.

The histology of PBC is divided into four successive stages referred to as stages 1 to 4, as seen on evaluation of the liver biopsy. As the liver is affected asymmetrically, a biopsy may not give a complete picture of the disease process. If more than one stage is observed on biopsy, the stage assigned is the highest of those seen. The hallmark of PBC is asymmetric inflammation and destruction of the bile duct within the portal triads. In stage 1 the damage is confined to the portal triad. Stage 2 is characterized by a reduction in the number of bile ducts and an inflammatory involvement of the surrounding parenchyma. Stage 3 disease demonstrates fibrosis, which connects the affected portal triads, whereas stage 4 manifests frank cirrhosis with regenerative nodules and accompanying liver failure.

The clinical course of the disease is variable and early diagnosis is important in order to initiate therapeutic measures before the development of advanced disease.

TREATMENT. Most people with PBC are now treated with ursodeoxycholic acid (UDCA), or ursodiol, a bile acid taken in capsules. It is currently the only drug approved by the Food and Drug Administration (FDA) for the treatment of PBC. Twenty-five to thirty percent of clients will have a complete response with UDCA,⁷⁷ which can reduce serum liver enzymes, cholesterol, and IgM; it also reduces pruritus.¹²¹

UDCA has also been shown to reduce the risk of death or need of liver transplantation after 4 years of therapy and can be effective for up to 10 years.^{126,129} It appears to be safe and has few adverse effects. If used in clients with early-stage disease, it may delay the development of hepatic fibrosis and esophageal varices, with survival rates slightly lower than that seen in an age-sex-matched control population.^{24,25,127}

UDCA has little effect in clients with advanced disease, and better options are still needed for this subgroup. Clients who have a complete response to UDCA require indefinite therapy. Progression, however, occurs in many people, requiring additional medical treatment or liver transplantation. Colchicine and methotrexate are two drugs that are often utilized when UDCA is no longer efficacious; other drugs are under investigation.¹³⁴

Liver transplantation is considered for clients with end-stage liver disease (i.e., hepatorenal syndrome, diuretic-resistant edema, bleeding esophageal varices, and hepatic encephalopathy), unacceptable quality of life caused by intractable symptoms, or anticipated death in less than 1 year.⁹¹

Many laboratory values and factors are followed to aid in determining the appropriate time for liver transplantation such as the bilirubin, AST/ALT ratio, serum albumin, prothrombin time, and presence of complications from portal hypertension. Clients who receive a liver transplant often have difficulty weaning from immunosuppressants, and evidence of recurrent disease appears in 15% of clients at 3 years and 30% at 10¹¹³ years.

Complications of PBC, such as fatigue, pruritus, osteoporosis, fat-soluble vitamin deficiencies, portal hypertension, and hyperlipidemia, also receive treatment. Fatigue is difficult to treat and can be debilitating. One preliminary study showed some improvement in daytime drowsiness with the use of modafinil in people who were able to tolerate the drug.⁶⁰

Cholestyramine and rifampin are the principal drugs used to relieve pruritus, although side effects may not be tolerable. PBC-associated osteoporosis occurs in up to one-third of clients with PBC, but severe bone disease (i.e., with multiple fractures) is uncommon except in more advanced disease. Treatment with alendronate may increase bone mineral density, but long-term studies are needed to demonstrate efficacy.⁵⁴

Liver transplantation leads to an initial worsening of osteopenia, but bone mineral density typically returns to baseline after 1 year and can subsequently continue to improve. Because of a lack of bile acid secretion, fat-soluble vitamins (i.e., vitamins D, A, and K) are not absorbed in the intestine. This typically occurs in the later stages of the disease and clients can be given supplements as needed.

Many clients with PBC have significantly elevated serum lipids, yet they appear not to be at increased risk for cardiovascular complications, usually making treatment with a cholesterol-lowering agent unnecessary.⁸⁸ People with PBC may have early esophageal bleeding, which cause portal hypertension leading to later esophageal bleeds.

Treatment consists of placement of a distal splenorenal shunt by endoscopic rubber-band ligation. If this is not successful, a transjugular intrahepatic portosystemic stent-shunt is placed. Survival is not significantly altered by treatment and many people are stable for years without requiring liver transplant.

PROGNOSIS. Clients who are diagnosed with stage 1 or 2 disease typically have a better response to treatment. In one study, people with stage 1 or 2 disease who were treated with UDCA for a mean average of 8 years demonstrated a survival rate similar to healthy controls. However, in this same study, those people with stage 3 or 4 disease were at significantly higher risk of requiring a liver transplant.²⁵

Liver transplantation offers persons with liver failure improved survival. The survival rate at 1 year is 92%, and the 5-year rate is 85%. Clients with an elevated bilirubin level above 10 mg/dL have an average life expectancy of 2 years without liver transplantation. Death is usually a result of hepatic failure or complications of portal hypertension associated with cirrhosis.

SPECIAL IMPLICATIONS FOR THE THERAPIST 17-11

Primary Biliary Cirrhosis**PREFERRED PRACTICE PATTERNS**

- 4A:** Primary Prevention/Risk Reduction for Skeletal Demineralization (osteoporosis)
- 4B:** Impaired Posture (osteoporosis)
- 4C:** Impaired Muscle Performance (osteoporosis)
- 5D:** Impaired Motor Function and Sensory Integrity Associated with Nonprogressive Disorders of the Central Nervous System Acquired in Adolescence or Adulthood (encephalopathy)
- 5F:** Impaired Peripheral Nerve Integrity and Muscle Performance Associated with Peripheral Nerve Injury (toxic neuropathy)
- 5G:** Impaired Motor Function and Sensory Integrity Associated with Acute or Chronic Polyneuropathies (alcoholic polyneuropathy)

The most significant clinical problem for PBC clients is bone disease characterized by impaired osteoblastic activity and accelerated osteoclastic activity. Calcium and vitamin D should be carefully monitored and appropriate replacement instituted. Physical activity after an osteoporosis protocol should be encouraged but with proper pacing and energy conservation. (See also Special Implications for the Therapist: Signs and Symptoms of Hepatic Disease, and Special Implications for the Therapist: Liver Transplantation in Chapter 21, and Special Implications for the Therapist: Osteoporosis and Osteomalacia in Chapter 24.)

Occasionally, sensory neuropathy (xanthomatous neuropathy) of the hands and/or feet may occur as a result of increased serum cholesterol levels and an abnormal lipoprotein X. Cholesterol-laden macrophages accumulate in the subcutaneous tissues and create local lesions, termed *xanthomas*, around the eyelids and over skin, tendons, nerves, joints, and other locations. Treatment and precautions are as listed for this condition associated with diabetes mellitus or other etiologies (see Special Implications for the Therapist: Diabetes Mellitus in Chapter 11).

Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis (suppression of bile flow) of pregnancy is characterized by pruritus and cholestatic jaundice; it usually occurs in the last trimester of each pregnancy and promptly resolves after delivery. Most women present with pruritus, since clinical jaundice is evident in only a minority of women. Of the women who develop pregnancy-induced intrahepatic cholestasis, up to 50% have other family members who have experienced jaundice during pregnancy or after the use of oral contraceptives. Women who have experienced cholestatic jaundice of pregnancy should avoid contraceptives because of a high risk of disease recurrence.

Cholestasis of pregnancy is most likely related to the inhibitory effect estrogen has on bile formation in susceptible women. Maternal health is unaffected by this condition, but the effects on the unborn child can be serious, including fetal distress, stillbirth, prematurity, and an increased risk of intracranial hemorrhage during delivery. UDCA can be used to relieve symptoms and is well tolerated by both mother and fetus. No significant effects are apparent on the liver of the mother, although the risk of developing gallstones is increased.

Vascular Disease of the Liver

Congestive heart failure is the major cause of liver congestion, especially in the Western world, where ischemic heart disease is so prevalent. Backward congestion of the liver and the decreased perfusion of the liver secondary to decline in cardiac output result in abnormal liver function tests. Hepatic encephalopathy may contribute to the altered mentation seen with severe congestive heart failure. Decreased cerebral perfusion, hypoxemia, and electrolyte imbalance are usually the major contributors to the confused state that can be seen in people with severe congestive heart failure.

Portal vein obstruction can be the result of thrombosis, infection, constriction, or invasion. Thrombosis of the portal system is typically caused by a hypercoagulable state or secondary to inflammation, cirrhosis, trauma, or cancer. Inflammatory diseases that affect thrombosis of the portal vein include pancreatitis and inflammatory bowel disease. HCC and pancreatic cancer are the two most common malignancies to cause thrombosis; they also lead to constriction and invasion of the vein.

Ischemic hepatitis or hypoxic hepatitis results when tissue of the liver does not receive adequate oxygen. This may occur in any disease process that reduces blood flow (cardiac failure), reduces oxygen supply (respiratory failure), or increases oxygen requirements (sepsis).

The Budd-Chiari syndrome is an uncommon disease manifested by a thrombosis in and on the hepatic veins where the veins open into the inferior vena cava. Symptoms include pain, ascites, and impaired liver function. Hypercoagulable states, cancer, and infections are the most common causes.

Liver Neoplasms

Hepatic neoplasms can be divided into three groups: benign neoplasms, primary malignant neoplasms, and metastatic malignant neoplasms. Cancer arising from the liver itself is called *primary*; liver cancer that has spread from somewhere else is labeled *secondary* or *metastatic*.

Primary liver tumors may arise from hepatocytes, connective tissue, blood vessels, or bile ducts and are either benign or malignant (Table 17-5). Primary malignant cancer is almost always found in a cirrhotic liver and is considered a late complication of cirrhosis. Benign and malignant neoplasms can also occur in women taking oral contraceptives. A few rare tumors arise from the bile ducts within the liver and are associated with certain hormonal drugs and cancers. *Cholangiocarcinomas* are discussed later in this chapter.

Table 17-5 Classification of Primary Liver Neoplasms

Origin	Benign	Malignant
Hepatocytes	Adenoma	Hepatocellular carcinoma
Connective tissue	Fibroma	Sarcoma
Blood vessels	Hemangioma	Hemangioendothelioma
Bile ducts	Cholangioma	Cholangiocarcinoma

Benign Liver Neoplasms

Cavernous Hemangioma. About 7% of autopsied livers contain hemangiomas, making this lesion the most common benign liver tumor. It is of unknown etiology and occurs in all age groups, more commonly among women. The pathology is similar to that of hemangiomas anywhere in the body; it is a blood-filled mass of variable size and can be located anywhere in the liver. Multiple lesions are observed in about 10% of cases. Areas of thrombosis are common, and older lesions may begin to calcify. The end stage is a fibrous scar.

Most hepatic hemangiomas are asymptomatic until they become large enough to cause a sense of fullness or upper abdominal pain. Hepatomegaly or an abdominal mass is the most common physical finding. About 10% of clients with clinically detectable lesions are febrile. Hepatic hemangiomas are often discovered coincidentally on CT scan, by MRI, or during laparotomy; otherwise the diagnosis is made by contrast-enhanced serial CT, MRI (particularly if small), or single-photon emission CT (SPECT). Needle aspiration or biopsy is avoided because of the risk of hemorrhage.

Treatment is not usually recommended because most hepatic hemangiomas have a benign course with negligible risk of malignancy and minimal chance of spontaneous hemorrhage. Surgical resection may be performed if the hemangioma is consistently symptomatic, producing pain or fever, or if the tumor is large enough for traumatic rupture to be considered a risk (e.g., a palpable lesion in an athlete). Other methods, such as radiofrequency ablation, arterial embolization, and systemic glucocorticoids, have had limited success.

SPECIAL IMPLICATIONS FOR THE THERAPIST 17-12

Cavernous Hemangioma

Most liver hemangiomas are small and found incidentally and require no special precautions. In the case of a known large liver hemangioma, the client must be cautioned to avoid activities and positions that will increase intraabdominal pressure to avoid risk of rupture (see Box 16-1). For the same reason, throughout therapy and especially during exercise, the client must be instructed in proper breathing techniques.

Liver Adenomas. Liver cell adenomas occur most commonly in the third and fourth decades, almost exclusively in women. The incidence of adenomas before the marketing of oral contraceptives was very low. Although

it remains low in men, oral contraceptives have significantly increased the incidence in women. Most remain asymptomatic, although with growth, right upper quadrant abdominal pain may be present. Although classified as benign tumors, they are highly vascular and carry a risk for rupture and subsequent hemorrhage. The clinical presentation is often one of acute abdominal disease because of necrosis of the tumor with hemorrhage. Pain, fever, and circulatory collapse occur in the presence of hemorrhage. Most adenomas are evaluated with hepatic angiography, MRI, or CT. Liver function test results are usually within normal limits. Because of the risk of rupture and rarely, malignant transformation to HCC, resection is usually recommended. Affected women should refrain from taking oral contraceptives.

SPECIAL IMPLICATIONS FOR THE THERAPIST 17-13

Liver Adenomas

The therapist is most likely to see this client postoperatively after the danger of rupture and hemorrhage has passed. Standard postoperative protocols are usually sufficient.

Malignant Liver Neoplasms

Primary Hepatocellular Carcinoma

Overview and Incidence. Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world; it is also the most common primary liver cancer, constituting about 90% to 95% of primary liver cancers in adults. The geographic locations with the highest incidence include China and sub-Saharan Africa. In Western countries, HCC is linked to cirrhosis, particularly HBV- and HCV-related cirrhosis. HCC is seen more often in men and the incidence increases with age. In many countries, including the United States, a definite increase in the incidence of HCC has been reported, largely attributable to the increasing incidence of HCV infection.¹⁰⁸

Etiologic and Risk Factors. Epidemiologic and laboratory studies have firmly established a strong and specific association between HBV and HCV with HCC. Over 80% of HCC is related to chronic HBV in Africa and China, whereas HCV is causal for 80% of HCC in Japan, Italy, and Spain. In the United States, HCV is emerging as a principal cause of HCC, particularly when associated with alcohol. Cirrhosis is typically prerequisite for HCC development in association with HCV.

In all parts of the world, there is a strong correlation between HCC and cirrhosis (of any cause). Another risk factor is dietary exposure to anatoxin B₁, which is derived from the fungi *Aspergillus flavus* and *Aspergillus parasiticus*. This is a major concern in Africa and Asia. Up to 45% of individuals with hemochromatosis (an iron overload disease) can develop HCC. Although the tumor is more likely to arise with the development of cirrhosis, it is not necessarily true (i.e., HCC can develop in the absence of cirrhosis).

Other diseases, such as Wilson's disease and α₁-antitrypsin deficiency, also display an increased risk with the development of cirrhosis. Epidemiologic studies have demonstrated an increase risk with the long-term use of oral contraceptives,²³ although the number of cases involved is extremely small.

Pathogenesis and Clinical Manifestations. The exact events leading to malignant transformation of the hepatic cell remain unknown. HBV appears to be an oncogenic virus that can integrate its viral DNA sequences into the cellular genome. Whether this integration is a necessary step for the mentioned transformation is still uncertain; but it does appear that HBV is both directly and indirectly carcinogenic.

Indirect carcinogenic effects are the result of the chronic necroinflammatory hepatic disease. Continuous turnover of cells with cycles of inflammation and regeneration can lead to tumor formation. HCV does not integrate into human DNA but appears to be directly oncogenic. Aflatoxin appears to cause HCC by inactivating a tumor suppressor gene.

Most people who develop HCC are unaware of it until advanced stages. Abdominal pain (60% to 95%) and weight loss (35% to 70%) are the most common initial symptoms. Other symptoms include weakness, fatigue, poor appetite, early satiety, fullness of the abdomen, diarrhea, and constipation. Jaundice is observed in only 5% to 25% of cases. Metastases occur to the bone and lungs, resulting in back pain and cough. Physical examination may demonstrate an enlarged liver, ascites, or splenomegaly. Unfortunately, many of these signs and symptoms may already be present because of cirrhosis and not distinguished as HCC.

Rarely, paraneoplastic syndromes (a result of a bioactive substance produced by the tumor) can be associated with this tumor. Hypoglycemia, caused by the defective processing of a precursor to insulin-like growth factor II, can occur early in the disease process and may be the presenting symptom. Polycythemia (an increase in erythrocytosis) occurs in less than 10% of cases of HCC but may warn of the presence of the tumor.

Uncommon complications include rupture of tumor with associated hemoperitoneum, thrombosis of portal or hepatic vein, and tumor embolism.

MEDICAL MANAGEMENT

DIAGNOSIS. Changes in liver transaminases are not helpful in distinguishing HCC from cirrhosis or other masses. One tumor marker that can be useful is serum α-fetoprotein. In high-risk populations, an elevation in α-fetoprotein is 80% to 90% sensitive and 90% specific.

Ultrasonography and CT scans are the most commonly used imaging tests and can be used to guide and obtain a percutaneous liver biopsy. If these approaches are inappropriate because of location of the tumor, laparoscopic-mediated biopsy may be performed. CT most often is able to reveal tumor size and extent (tumor often involves the portal blood vessels), although occasionally laparoscopic visualization may be needed to verify the presence of peritoneal seeding. Some physicians do not biopsy the tumor if it is deemed resectable because of the possibility

of seeding tumor. Definitive diagnosis is based on histologic findings in resected hepatic tumors or biopsy specimens.

PREVENTION AND TREATMENT. The use of vaccination to prevent infection with HBV is expected to reduce the incidence of HCC associated with HBV. This is the only malignancy for which an effective prophylactic immunization is available. In the meantime, early screening of high-risk populations using α-fetoprotein and ultrasonography remains the key to successful treatment of this malignancy.

Surgical resection (partial or total hepatectomy) has been the primary treatment if no nodal involvement or distant spread is present; but only 15% of cases are feasibly resectable at presentation. Liver transplantation is a viable option if fewer than three lesions are present (with the largest being less than 3 cm) or one lesion that is less than 5 cm. This may be the optimal therapy for individuals with cirrhosis who cannot tolerate resection.

Newer treatment techniques take advantage of the fact that intrahepatic tumors derive their blood supply from the hepatic artery. Transarterial chemoembolization (angiography to embolize the tumor arterial supply associated with chemotherapy or chemotherapy eluting beads) for unresectable HCC can reduce the size of large tumors and may prolong survival.⁸⁴

Percutaneous ethanol injection (alcohol injection into the tumor) or radiofrequency thermal ablation are beneficial in connection with small tumors with a 5-year survival rate of 40% to 50% (rarely curative for small tumors). Tyrosine kinase inhibitors and antiangiogenic agents are newer agents currently undergoing clinical trials.⁸⁵

Several radioembolization techniques are being employed; yttrium-90 (Y-90) microspheres, or iodine-131 (I-131) or rhenium-188 (Re-188) labeled lipiodol are injected into the hepatic artery. Holmium-166 (Ho-166) loaded poly (L-lactic acid) microspheres have also been developed.¹⁶⁴

This method of treatment targets the tumor with radiation while decreasing radiation dose to the body. Criteria are currently lacking on which clients benefit most from this type of therapy, and more study is required to determine optimal dosing in individuals with cirrhosis.¹⁴⁵ Systemic chemotherapy can be administered as palliative treatment (response rates are less than 20%).

PROGNOSIS. Symptomatic HCC has a very poor prognosis, especially in clients with multiple tumor nodules. Factors affecting the prognosis favorably include early detection, tumor size (less than 5 cm), tumor location, presence of a tumor capsule, well-differentiated tumor, lack of vascular invasion, and absence of cirrhosis. Successful treatment with liver resection has increased 5-year survival rates to 68%, but tumor recurrence is very frequent. Tumor resection in the presence of cirrhosis is accompanied by risk of tumor recurrence or death from the remaining underlying liver dysfunction. If treatment fails to eradicate the tumor process, the expected survival is no more than 4 to 6 months.

SPECIAL IMPLICATIONS FOR THE THERAPIST 17-14

Primary Hepatocellular Carcinoma**PREFERRED PRACTICE PATTERNS**

6E: Impaired Ventilation and Respiration/Gas Exchange Associated with Ventilatory Pump Dysfunction or Failure (elevated diaphragm)

7A: Primary Prevention/Risk Reduction for Integumentary Disorders (edema)

Liver tumors that cause elevation of the diaphragm can cause right shoulder pain or symptoms of respiratory involvement. Peripheral edema associated with developing ascites may be observed first by the therapist (see the section on Ascites in this chapter). As the tumor grows, pain may radiate to the back (midthoracic region). Paraneoplastic syndromes (see Chapter 9) resulting from ectopic hormone may occur, including polycythemia, hypoglycemia, and hypercalcemia. (See Special Implications for the Therapist: Oncology in Chapter 9).

markers and the clinical usefulness of CEA throughout the different stages of management in both animal and human studies.

Treatment is the same as for unresectable liver cancer; see the section on Hepatocellular Carcinoma in this chapter. Other ongoing research is investigating the use of a totally implantable pump for hepatic arterial infusion (HAI) therapy for those with unresectable hepatic metastases and for posthepatic resection. This enables oncologists to give much higher doses of chemotherapy directly into the blood supply of the tumors, as well as use a continuous infusion schedule. This approach may offer more successful treatment of people with metastatic colorectal carcinoma to the hepatic system.^{63,66}

Liver Abscess

Liver abscess most often occurs among individuals with other underlying disorders. Most common underlying causes include *bacterial cholangitis* secondary to obstruction of the bile ducts by stone or stricture; *portal vein bacteremia* secondary to bacterial seeding via the portal vein from infected viscera following bowel inflammation or organ perforation; *liver flukes*, a parasitic infestation; or *amebiasis*, an infestation with amebae from tropical or subtropical areas.

Other predisposing factors are diabetes mellitus, infected hepatic cysts, metastatic liver tumors with secondary infection, and diverticulitis. Pyogenic (pus-filled) abscesses may be single or multiple; liver cirrhosis is a strong risk factor for single pyogenic liver abscess, and multiple abscesses often arise from a biliary source of infection.

Clinical manifestations are commonly right-sided abdominal and shoulder pain, nausea, vomiting, rapid weight loss, high fever, and diaphoresis. The liver's close proximity to the base of the right lung may contribute to the development of right pleural effusion. Complications of hepatic abscess relate to rupture and direct spread of infection. Pleuropulmonary involvement from the rupture of an abscess through the diaphragm and peritonitis from leakage into the abdominal cavity can occur.

Diagnosis is accomplished by a variety of possible tests including liver function tests, chest x-ray, contrast-enhanced CT scan of the abdomen, ultrasonography of the right upper quadrant, liver scan, or arteriography. Treatment may consist of antimicrobial therapy alone or percutaneous aspiration of the abscess with antimicrobial therapy. Surgery may be required to relieve biliary tract obstruction and to drain abscesses that do not respond to percutaneous drainage and antibiotics.

Unrecognized and untreated, pyogenic liver abscess is universally fatal. The mortality from hepatic abscess in treated cases remains high, ranging from 40% to 80%. Amebic abscesses are an exception; when treated, the mortality rate is less than 3%. Early diagnosis and aggressive treatment can significantly reduce the mortality in some cases. Specific antibiotics are required whenever abscess is caused by amebic infestation.

Metastatic Malignant Tumors

The liver is one of the most common sites of metastasis from other primary cancers (e.g., colorectal, stomach, pancreas, esophagus, lung, breast, melanoma, Hodgkin's disease, and non-Hodgkin's lymphoma). Metastatic tumors occur twenty times more often than primary liver tumors and constitute the bulk of hepatic malignancy.

As with other types of cancers, secondary liver cancer can occur as a result of local invasion from neighboring organs, lymphatic spread, spread across body cavities, and spread via the vascular system. The liver filters blood from anywhere else in the body, but because all blood from the digestive organs passes through the liver before joining the general circulation, the liver is the first organ to filter cancer cells released from the stomach, intestine, or pancreas.

Metastatic tumors to the liver originating in some organs (e.g., stomach or lung) never give rise to hepatic symptoms, whereas others produce hepatic symptoms or jaundice with less than 60% replacement of the liver. Certain tumors (colon, breast, or melanoma) typically replace 90% of the liver before jaundice develops. Melanomas are associated with such minimal tissue reaction that almost complete hepatic replacement occurs before hepatic symptoms develop.

Clinical manifestations, diagnosis, and treatment are the same as for the primary (original) neoplasm. Experimental and clinical data show evidence of a correlation between elevated blood levels of carcinoembryonic antigen (CEA) and the development of liver metastases from colorectal carcinomas. A cause-effect relationship between these two observations has not been identified. Investigations continue to explore the use of tumor

SPECIAL IMPLICATIONS FOR THE THERAPIST 17-15**Liver Abscess****PREFERRED PRACTICE PATTERNS**

6E: Impaired Ventilation and Respiration/Gas Exchange Associated with Ventilatory Pump Dysfunction or Failure (decreased lung capacity; elevated diaphragm)

6F: Impaired Ventilation and Respiration/Gas Exchange Associated with Respiratory Failure (pleural effusion)

7A: Primary Prevention/Risk Reduction for Integumentary Disorders (high fever; immobility)

Clients with liver abscess are very ill and usually are seen only by the therapist assigned to an intensive care unit team. In such situations, vital signs are assessed regularly to detect high fever and rapid pulse, which are early signs of sepsis (a common complication). Movement, coughing, and deep breathing are important to prevent or limit pulmonary complications related to hepatic abscess, and skin care in the presence of high fever is essential. Careful disposal of feces and careful handwashing to avoid transmission are required when abscess is caused by amebic infestation.

Liver Injuries

Toxic liver injury can occur as a result of drugs or from occupational exposure to chemicals and toxins. Hepatotoxic chemicals produce liver cell necrosis, a consequence of the metabolism of the compound by the oxidase system of the liver. Agents responsible for toxic liver injury include yellow phosphorus, carbon tetrachloride, phalloidin (mushroom toxin), and acetaminophen (analgesic). Reye's syndrome in children may be related to aspirin toxicity. In addition to jaundice, other symptoms of liver toxicity may occur (e.g., cholestasis or chronic hepatitis).

Toxic liver injury produces toxic hepatitis (discussed earlier in this chapter). The prognosis is usually good if the toxin is withdrawn and never reintroduced. Whatever drug is responsible, it is well documented that liver toxicity becomes more severe with advancing age.

Liver injury by trauma may be either penetrating or blunt, leading to laceration and hemorrhage. Penetrating injuries are usually knife or missile wounds (gunshot). A knife wound leaves a sharp clear incision, whereas gunshot wounds enter and exit with greater damage. Blunt trauma from a fall or from hitting a steering wheel has varying effects, from small hematomas to large lacerations as a result of severe impact forces.

The therapist will likely be treating clients with liver injury secondary to trauma postoperatively in the trauma unit. The common postoperative problems include pulmonary infections and abscess formation. Clients are assessed postoperatively for manifestations of infection (e.g., fever, chills, or difficulty breathing). Physical therapy intervention is focused on prevention of respiratory complications, especially pneumonia and provision of skin care and extremity movement, until the client can begin progressive transfer and mobility skills.

PANCREAS**Diabetes Mellitus**

The pancreas has dual functions, acting as both an endocrine gland in secreting hormones insulin and glucagon and as an exocrine gland in producing digestive enzymes. The cells of the pancreas that function in the endocrine capacity are the islets of Langerhans, constituting 1% to 2% of the pancreatic mass. Defective endocrine function of the pancreas resulting in ineffective insulin (whether deficient or defective in action within the body) characterizes diabetes mellitus (see Chapter 11).

Pancreatitis

Pancreatitis is a potentially serious inflammation of the pancreas that may result in autodigestion of the pancreas by its own enzymes. Pancreatitis may be acute or chronic; the acute form is brief, usually mild, and reversible, whereas the chronic form is recurrent or persisting. Because the hormones and enzymes provided by the pancreas perform many vital functions, acute pancreatitis causes systemic problems and complications that affect the entire body. Approximately 15% of all cases of acute pancreatitis develop into chronic pancreatitis.

Acute Pancreatitis

Incidence and Etiologic Factors. Acute pancreatitis is an inflammatory process of the pancreas that can involve surrounding organs, as well as cause a systemic reaction. Pancreatitis can arise from a variety of factors and conditions (Box 17-4) or as a result of an unknown cause (10% of cases). The most common cause is gallstones, followed by chronic alcohol consumption. Other causes include hypertriglyceridemia (levels over 1000 mg/dL), trauma, duct obstruction (neoplasms), and medications. The incidence has increased over the past few decades, but the mortality rate has remained fairly constant at 7%.

Pancreatitis can involve only the interstitium of the pancreas, termed *interstitial pancreatitis*, or have necrosis of pancreatic tissue, called *necrotizing pancreatitis*. Interstitial pancreatitis accounts for 80% of cases and has a milder course and few complications, whereas necrotizing pancreatitis occurs in 20% of cases and can result in significant complications and higher mortality.

Pathogenesis. Acute pancreatitis is thought to result from the inappropriate activation of trypsinogen within

SPECIAL IMPLICATIONS FOR THE THERAPIST 17-16**Liver Injuries****PREFERRED PRACTICE PATTERNS**

6A: Primary Prevention/Risk Reduction for Cardiovascular/Pulmonary Disorders

7A: Primary Prevention/Risk Reduction for Integumentary Disorders

Box 17-4**CONDITIONS ASSOCIATED WITH ACUTE PANCREATITIS**

- Alcohol abuse*
- Autoimmune diseases
- Cystic fibrosis
- Gallstones*
- Hereditary (familial) pancreatitis
- Hypercalcemia
- Hyperlipidemia (hypertriglyceridemia)
- Infection
- Ischemia
- Medications (oral estrogens, antibiotics, AZT, thiazide diuretic, corticosteroids)
- Neoplasm
- Peptic ulcers
- Post-ERCP
- Postoperative inflammation
- Pregnancy (third trimester)
- Blunt or penetrating trauma (including ischemia/perfusion that occurs during some surgical procedures)
- Vasculitis
- Viral infections
- Unknown

ERCP, Endoscopic retrograde cholangiopancreatography.

*Most common causes.

acinar cells to the enzyme trypsin. Trypsin is the principal enzyme responsible for activating other pancreatic enzymes. The buildup of pancreatic enzymes can trigger pancreatic autodigestion. In the development of pancreatitis, the conversion of trypsinogen to trypsin occurs in sufficient quantities to overwhelm the normal mechanisms of eliminating trypsin from the cells. The release of enzymes leads to acinar cell and vascular damage, resulting in an out-of-proportion inflammatory response with associated edema and inflammation.¹⁶⁹

Pancreatitis becomes severe when cytokines (interleukin 1 [IL-1], IL-6, IL-8, TNF, and platelet-activating factor) and free radicals mediate a systemic response,^{13,143} leading to multiorgan failure and occasionally death. Severe ischemia and inflammation can disrupt the ducts, resulting in the leakage of pancreatic fluid and the formation of fluid collections and pseudocysts. A pseudocyst is a liquefied collection of necrotic debris and pancreatic enzymes surrounded by a rim of pancreatic tissue or adjacent tissues; it contains no true epithelial lining. Complications of pseudocysts include infection, bleeding, and rupture into the peritoneum.

Infection can occur secondary to the breakdown of normal barriers in the gut because of hypoperfusion of the colon. Multiple genes are also under investigation, which, coupled with the appropriate environmental conditions, may be responsible for the development of pancreatitis.¹⁷⁰

Clinical Manifestations. Symptoms in clients presenting with acute pancreatitis can vary from mild, non-specific abdominal pain to profound pain accompanied by systemic symptoms. Most people with mild-to-moderate disease present with pain, nausea, anorexia, and vomiting. Abdominal pain, the cardinal symptom of

acute pancreatitis, may be dull at first but can increase in quality and intensity to sharp and severe.

Quality of pain can vary, depending on the cause and severity of disease, but often involves the entire upper abdomen. Right upper quadrant pain with radiation to the back may be more prevalent with gallstones. The pain is typically steady and at maximal intensity within 10 to 20 minutes. Pain can be triggered or made worse by eating fatty meals or drinking alcohol. Position changes usually do not alleviate the discomfort. Nausea and vomiting occur in 90% of people with pancreatitis and can be severe.

A minority of cases develops into severe pancreatitis with serious complications. Symptoms that warn of worsening condition include tachycardia, hypoxia, tachypnea, and changes in mental status. Complications of pancreatitis include pancreatic fluid-filled collections (57% of cases), pseudocysts, and necrosis. These fluid collections can enlarge, leading to worsening pain. Bacteria can infect these collections and necrotic areas, resulting in pain, leukocytosis, fever, hypotension, and hypovolemia. Often the first sign of a complication is the failure to improve followed by unexpected deterioration. Ascites and pleural effusions are rare complications.

MEDICAL MANAGEMENT

DIAGNOSIS. Diagnosis is based on clinical presentation, laboratory tests, and imaging studies. Early in the disease process (within 24 to 72 hours), pancreatic enzymes released from injured acinar cells result in elevated serum amylase and lipase levels, which are diagnostic for acute pancreatitis. The amylase level is typically three times the upper limit of normal, whereas lipase increases proportionately with the amylase level. Amylase rises early (within 2 hours of symptom onset), but decreases quickly (within 36 hours). Amylase levels may not be very helpful unless the person seeks medical attention very early on.

Lipase levels are more specific to acute pancreatitis, rising in 4 to 8 hours, peaking around 24 hours, and staying elevated for at least 14 days. Lipase levels at least three times the normal range (10 to 140 U/L) indicate acute pancreatitis.⁵⁷ An elevated ALT is suggestive of pancreatitis caused by gallstones (where alcohol abuse is not a factor).

Other tests may demonstrate hypertriglyceridemia or hypercalcemia. Imaging studies include CT scan to evaluate the pancreas (possibly serial examinations if symptoms fail to resolve with treatment) and transabdominal ultrasound to evaluate the gallbladder and cystic duct for possible gallstones. The CT is also able to demonstrate necrotizing pancreatitis, which provides management and prognostic information.

In clients who have contraindications for CT with contrast, an MRI can be obtained that can reveal necrosis when present. If gallstones in the common bile duct are suspected but are not seen on CT scan, endoscopic ultrasound (EUS) or magnetic resonance cholangiopancreatography (MRCP) can be employed.

TREATMENT. For most persons (about 80% of cases), acute pancreatitis is a mild disease that subsides spontaneously within several days. Treatment for mild

pancreatitis is largely symptomatic and designed to preserve normal pancreatic function while preventing complications and includes intravenous fluids for hydration, analgesics for pain control, and eating nothing by mouth to allow the pancreas to rest. If after 2 to 3 days, there is no improvement, a CT scan should be obtained to determine if complications are present.

Clients are allowed to return home once the pain is under control and they are able to eat, drink, and take oral analgesics. Food intake progresses from clear liquids for 24 hours to small, low-fat meals with a slow increase in quantity over several days as tolerated.¹⁶⁹ If pancreatitis is secondary to gallstones, laparoscopic cholecystectomy can be performed before discharge from the hospital (if pancreatic fluid collections or other complications are not present).

If fluid collections are present, surgery should be delayed until they have resolved. If after 6 weeks the collections have not resolved, laparoscopic cholecystectomy with fluid collection drainage can be performed.⁷¹ ERCP with endoscopic sphincterotomy may be performed post-operatively if common bile duct stones are present or for clients who are not surgical candidates.

Severe pancreatitis is defined by the presence of organ failure, local complications, or both. It is important to identify clients with severe pancreatitis at admission to provide aggressive care and close observation for complications. The Acute Physiology and Chronic Health Evaluation score (APACHE II) is an accurate predictor of severity of disease, complications, and death. An elevated C-reactive protein value, elevated hematocrit (above 44%), and obesity (body mass index greater than 30) are factors that predict severe disease.

People admitted to the hospital with severe pancreatitis require admittance to an intensive care unit, aggressive intravenous hydration, and pain control. Enteral nutrition (within 2 to 3 days) is preferred to parenteral feeding in most cases of severe pancreatitis because it has been shown to decrease infectious complications.⁹² Evidence has failed to show a benefit of medications designed to improve the course of severe pancreatitis; some of these medications include inhibitors of platelet-activating factor, somatostatin, and protease inhibitors.^{59,169}

Severe pancreatitis can be accompanied by significant complications, including the formation of pancreatic fluid collections, pseudocysts, necrosis, bacterial cholangitis, and infected fluid collections and necrotic areas. Fluid collections should be followed by serial CT scans to verify improvement.

ERCP with sphincterotomy should be performed early in the course of severe pancreatitis caused by bile duct stones. This procedure has been shown to decrease the risk for complications.¹² If the person's medical condition allows, surgery should be avoided in cases of severe pancreatitis since there is a high rate of death if done within the first few days of onset.¹⁶¹

Fluid collections that are infected can be treated with antibiotics and drained; necrotic areas that are not infected can be watched. If necrotic areas become infected, a necrosectomy can be performed or the area can be drained percutaneously once the client is stable.⁷¹ Prophylactic antibiotics are controversial for severe pancreatitis.

PROGNOSIS. Prognosis of acute pancreatitis depends on the severity of the condition. Individuals with mild pancreatitis (80% of cases) have a better outcome than those with necrotizing or severe disease. The clinical course of mild disease follows a self-limiting pattern, resolving within 2 weeks of onset. The risk of dying from severe pancreatitis is between 10% and 30% and is the result of complications such as infection. Yet most people who experience severe pancreatitis are able to recover and at 6 years, about 65% of people are able to work full time. Recurrences and the development of diabetes mellitus are common in alcoholic pancreatitis, particularly with continued drinking of alcohol.

SPECIAL IMPLICATIONS FOR THE THERAPIST 17-17

Acute Pancreatitis

PREFERRED PRACTICE PATTERNS

See Acute (Adult) Respiratory Distress Syndrome in Chapter 15 and Tetany in Chapter 5.

The therapist is most likely to see acute pancreatitis either when the early presentation is back pain (undiagnosed) or when acute respiratory distress syndrome (ARDS) develops as a complication, necessitating assisted respiration and pulmonary care. Pancreatic inflammation and scarring occurring as part of the acute pancreatic process can result in decreased spinal extension, especially of the thoracolumbar junction. This problem is difficult to treat and requires the therapist to make reasonable goals (e.g., maintain function and current range of motion), especially when the pancreatitis is in an active, ongoing phase.

Even with client compliance with treatment intervention and subsiding of inflammation, the residual scarring is difficult to reach or affect with mobilization techniques and continues to reduce mechanical motion. Back pain associated with acute pancreatitis may be accompanied by GI symptoms such as diarrhea, pain after a meal, anorexia, and unexplained weight loss. The client may not see any connection between GI symptoms and back pain and may not report the additional symptoms.

The pain may be relieved by heat initially (decreases muscular tension); preferred positions include leaning forward, sitting up, or lying motionless on the left side in a fetal-flexed position. Promoting comfort and rest as part of the medical rehabilitation process may necessitate teaching the client positioning (side-lying, knee-chest position with a pillow pressed against the abdomen, or sitting with the trunk flexed may be helpful) and relaxation techniques.

For the client who is restricted from eating or drinking to rest the GI tract and decrease pancreatic stimulation, even ice chips can stimulate enzymes and increase pain. In such cases, the therapist must be careful not to give in to the client's repeated requests for food, water, or ice chips unless approved by nursing or medical staff. Clients with acute pancreatitis are allowed to resume oral intake when all abdominal pain and tenderness have resolved. (See also Chapter

5 for care of the client with fluid or electrolyte imbalance.)

Monitor the individual with acute pancreatitis for signs and symptoms of bleeding; alert the health care team about bruising or prolonged bleeding.

Chronic Pancreatitis

Overview, Incidence, and Etiology. Chronic pancreatitis is characterized by the development of irreversible changes in the pancreas secondary to chronic inflammation. The principal causes are chronic alcohol consumption, a history of severe acute pancreatitis, autoimmune, hereditary, and idiopathic. In Western industrialized nations, the most common cause of chronic pancreatitis is alcohol abuse, accounting for more than 50% of cases.

The typical person with alcohol-related chronic pancreatitis is male, between the ages of 35 and 45, and has consumed large quantities (150 g or more) for more than 6 years. Hereditary pancreatitis is found in clients who have two or more relatives with the disease, including cystic fibrosis.

Several mutations have been discovered that are associated with the disease although the specific pathogenesis is under investigation. The *PRSS1* and *R122H* are cationic trypsinogen genes,²⁶ the *PSTI/SPINK1* are pancreatic secretory trypsin inhibitor genes, and the *CFTR* gene is a cystic fibrosis transmembrane conductance regulator gene.

Autoimmune chronic pancreatitis occurs most frequently in the Far East and is associated with an elevated IgG level, diffuse involvement of the pancreas, a mass in the pancreas, an irregular main pancreatic duct, and the presence of autoantibodies.¹¹⁶ It is occasionally related to other autoimmune diseases such as Sjogren's syndrome, ulcerative colitis, and systemic lupus erythematosus.

Pathogenesis. Several hypotheses have been published to explain the development of chronic pancreatitis. Most are directed toward alcohol-related chronic pancreatitis but have some applicability to other types. The first one suggests that alcohol consumption leads to release of pancreatic fluid that is high in protein but low in volume and bicarbonate. These characteristics result in the precipitation of protein, creating plugs in the pancreatic ducts, which may calcify and produce pancreatic stones. Plugs and stones can obstruct the ducts, causing an increased pressure and damage to pancreatic tissue and ducts. Pancreatic stones are seen in several types of chronic pancreatitis, although damage is noted in areas without obstruction.

A second hypothesis proposes that alcohol or one of its metabolites acts as a direct toxin on pancreatic tissue or sensitizes the acinar cells to the effects of pathologic stimuli. Alcohol may also stimulate the release of cholecystokinin (CCK), which, in the presence of alcohol, leads to the transcription of inflammatory enzymes.¹²⁰

A third hypothesis explains that after repeated bouts of acute pancreatitis, areas of necrosis heal with the

formation of scar tissue or fibrosis. In persons without a history of acute episodes, the pathogenesis of chronic pancreatitis may relate to persistent necrosis and insidious scarring, similar to the progression of cirrhosis of the liver. Several genetic mutations have also been implicated; many occur in the trypsinogen gene, which renders trypsin resistant to inactivation.²⁶ Theories continue to evolve, and the pathogenesis most likely depends on both genetic and environmental factors.

Clinical Manifestations. Most clients with chronic pancreatitis present with abdominal pain, which is also the most significant problem. Chronic pain often leads to an abuse of opioids, decreased appetite, weight loss, and poor quality of life; it is also the most common reason for surgery in people with this disease. Pain is typically epigastric in location, often with radiation to the back. It is made worse with meals but can be relieved by bringing the knees to the chest or bending forward. Nausea and vomiting are often associated with the pain. Pain during the course of the disease varies; many people will experience acute attacks followed by periods of feeling well. As the number of attacks increases and occurs more frequently, pain becomes more chronic in nature. Others have continual pain, which gradually increases in intensity.

Chronic destruction of pancreatic tissue contributes to the loss of pancreatic function, resulting in diarrhea, steatorrhea, and diabetes mellitus. Once the production of lipase is reduced to less than 10% of normal, fat malabsorption occurs, producing bulky, foul-smelling, oily stools (steatorrhea). This complication is seen in late stages of the disease, signifying the destruction of most of the acinar cells.

Diabetes is also seen later in the course of the disease, particularly after surgical removal of the pancreas. Unlike type 1 diabetes, there is destruction of both beta-cells (which produce insulin) and alpha-cells (which produce glucagon). This can lead to severe and prolonged hypoglycemia with the use of insulin.

History is often significant for alcohol abuse; other clients may have a history of pancreatitis or family history of chronic pancreatitis. Physical examination is usually significant for abdominal tenderness, with few other findings.

MEDICAL MANAGEMENT

DIAGNOSIS. The diagnosis of chronic pancreatitis may be difficult to make, particularly in the early stages of the disease when the pancreas lacks significant functional or structural changes. Routine laboratory tests, such as lipase and amylase, are often not elevated except during an acute episode of pancreatitis. Bilirubin may only be abnormal if there is significant compression of the bile duct by a pseudocyst or fibrosis.

More specialized functional tests are available, which either directly measure pancreatic enzymes produced by the pancreas or indirectly measure a product from the action of a pancreatic enzyme or its presence in the serum or stool (such as stool fat or serum trypsinogen). These functional tests are not well tolerated and not widely available.

Imaging tests can demonstrate structural changes. Some of the changes seen in chronic pancreatitis include dilated pancreatic ducts (both large and small), strictures, pancreatic stones, lobularity, and atrophy. *Large duct disease*, which is disease characterized by involvement of the large pancreatic duct by imaging) is often seen with alcohol abuse and is associated with functional problems as well. *Small duct disease* is often difficult to diagnose, and the cause is often idiopathic. Various imaging modalities can be used to diagnose chronic pancreatitis. Often the least invasive test is utilized such as transabdominal ultrasonography or CT.

Other tests are used as needed, such as EUS, endoscopic retrograde cholangiopancreatography (ERCP), or magnetic resonance cholangiopancreatography (MRCP)/MRI.

TREATMENT. The treatment of chronic pancreatitis is directed toward prevention of further pancreatic injury, pain relief, and replacement of lost endocrine/exocrine function. Cessation of alcohol intake is essential in the management of chronic pancreatitis in clients with alcohol-related pancreatitis. Smoking has also been linked with increased risk of mortality in people with alcohol-related pancreatitis and should be avoided.⁹⁰

Pain can be initially treated with nonnarcotics and advanced to narcotics as needed. Narcotics are useful for persons with established chronic pancreatitis, but the risk for addiction is about 10% to 30%. High-dose pancreatic enzyme therapy can reduce pain in some people with small duct disease but not for large duct disease. Nerve blocks can also aid in the reduction of pain.

Treatment of a dominant stricture in the pancreatic duct with stents and pancreatic duct sphincterotomy improves pain in over half of the clients with large duct disease¹³⁹; yet the long-term management of stents is controversial. Surgical drainage for persistent pseudocysts, as well as surgical intervention to eliminate obstruction of pancreatic ducts, may be indicated for severe pain, although the pain often returns.

A pancreatectomy may be performed as a last means of relieving refractory pain. People who undergo pancreatectomy can consider islet cell autotransplantation,²² which has been successful in a small group of clients. Oral enzyme replacements are taken before, during, and after meals to correct enzyme deficiencies and to prevent malabsorption. Insulin may be required in the case of islet cell dysfunction but used with care secondary to the loss of glucagon-producing cells.

PROGNOSIS. Complications include the development of large pseudocysts, bleeding from pseudoaneurysms, splenic vein thrombosis, and fistula formation. Pancreatic cancer develops in about 3% to 4% of people with chronic pancreatitis and is often difficult to distinguish from chronic changes of pancreatitis. Chronic pancreatitis is a serious disease, often leading to chronic disability. Alcohol-related chronic pancreatitis has a poor prognosis without alcohol cessation and increases the risk of mortality by 60%. Overall, the 10-year survival of chronic pancreatitis is 70%, and the 20-year survival rate is 45%.⁹⁰

SPECIAL IMPLICATIONS FOR THE THERAPIST 17-18

Chronic Pancreatitis

PREFERRED PRACTICE PATTERNS

Patterns associated with chronic pancreatitis are determined by the presence of associated complications, such as diabetes, neuropathy, and osteoporosis, and complications of alcohol abuse (e.g., malnutrition, cirrhosis, and ascites). Each client must be assessed individually.

Back pain in the upper thoracic area or pain at the thoracolumbar junction may be the presenting symptom for some individuals with chronic pancreatitis, but past medical history including the presence of pancreatitis should raise a red flag and suggest that careful screening is required in these cases. People with alcohol-related chronic pancreatitis often have peripheral neuropathy.

The clinical presentation with aggravating and relieving factors (e.g., alcohol consumption, food intake, or positional changes noted) or failure to improve with therapy intervention adds additional red flag symptoms.⁴⁷ The person with known pancreatitis and/or pancreatectomy may need monitoring of vital signs and/or blood glucose levels depending on complications present. Education about the effects of malabsorption and associated osteoporosis should be included. See also Special Implications for the Therapist: Malabsorption Syndrome in Chapter 16.

Pancreatic Cancer Overview and Incidence

Pancreatic cancer represents the fourth leading cause of cancer mortality in the United States, with more than 32,000 deaths each year.^{57a} It also has the lowest 5-year survival rate (3% to 5%) of any type of cancer.

Most pancreatic neoplasms (90%) arise from exocrine cells and are *adenocarcinoma* (70% in the proximal or head of the pancreas, 10% in the pancreas body, and 15% in the tail). The remaining primary pancreatic neoplasms include cystic neoplasms, intraductal papillary mucinous tumors, and neuroendocrine tumors. Adenocarcinoma is the focus of this discussion.

Pancreatic cancer is more common in black men and women than in whites, occurs in the Western world most often, and has a peak incidence in the seventh and eighth decades.

Etiologic and Risk Factors

Clear evidence of increased risk of pancreatic cancer has been shown related to advancing age. Pancreatic adenocarcinoma is rare in people under the age of 45 years; however, the risk increases after the age of 50 years. Seven to eight percent of people with pancreatic adenocarcinoma have a family history; other genetic syndromes with an increased risk include adenomatous polyposis, Peutz-Jeghers syndrome, and von Hippel-Lindau syndrome.

Tobacco use, exposure to certain chemicals (such as benzidine), obesity, diets high in fats and meat, history of familial chronic pancreatitis, history of nonfamilial chronic pancreatitis, and a history of partial gastrectomy are also risk factors.⁶⁸ The presence of adult-onset diabetes mellitus and impaired glucose tolerance (especially in women), chronic pancreatitis, and prior gastrectomy may be contributing factors. Obesity and physical activity (both linked with abnormal glucose metabolism) are associated with increased risk of pancreatic cancer. Higher consumption of red and processed meat is also associated with elevated pancreatic cancer risk.⁶⁸

No support exists for any direct effect from exposure to radiation, socioeconomic status, alcohol intake, or coffee consumption, although these risk factors remain under investigation.⁶²

Pathogenesis

Although the specific cause of pancreatic cancer is unknown, many genes are under investigation as possibly linked to its development. The *K-ras* mutation has been found in over 90% of tested pancreatic adenocarcinomas. *K-ras* is believed to be an oncogene, along with AKT2. Genes that inactivate tumor suppressor genes include p16, p53, and DPC4, while *hMLH1* and *hMLH2* are defective DNA repair genes. Mutations in the epidermal growth factor receptor (EGFR) have also been described⁶⁹ with investigations into EGFR-targeted agents.¹³⁸

Microscopically, adenocarcinomas contain infiltrative glands of various sizes and shapes surrounded by dense, reactive fibrous tissue. Many adenocarcinomas infiltrate into vascular spaces, lymphatic spaces, and perineural spaces. Pancreatic cancer appears to progress from flat ductal lesions to papillary ductal lesions without irregularities then with irregularities (atypia) and finally to infiltrating adenocarcinoma. The existence of such a progression suggests that it may be possible to detect a curable precursor lesion and early cancer with a molecular test in the future.⁸²

Clinical Manifestations

The clinical features of pancreatic cancer are initially non-specific and vague, which contribute to the delay in diagnosis. Most clients are seen for pain (80% to 85%), weight loss (60%), and jaundice (47%). These symptoms suggest advanced disease. Typically, people with significant pain have tumor in the body or tail of the pancreas, whereas jaundice and weight loss are more suggestive of tumor in the head of the pancreas.

Pain is a common symptom of pancreatic carcinoma because of invasion of tumor into nerves. In later stages of the disease, pain may be intractable. Pain is often epigastric in location, radiating to the back (thoracic or lumbar regions). Jaundice accompanied by pruritus, dark urine, and acholic stools occurs caused by compression of the biliary tree by tumor.

Pancreatitis may also develop from obstruction of the duct. In some people, pancreatitis may be the first sign of the disease. Deep venous thrombosis can occur as a result of tumor presence. In one-third of people with pancreatic adenocarcinoma, the gallbladder may be palpable on physical examination.

Metastasis. Pancreatic adenocarcinomas metastasize via the hematologic and lymphatic systems to the liver, peritoneum, lungs and pleura, and adrenal glands. These metastasized tumors may grow by direct extension, causing further involvement of the duodenum, stomach, spleen, and colon. Tumors of the body and tail of the pancreas are twice as likely to metastasize to the peritoneum compared with tumors in the head of the pancreas.

MEDICAL MANAGEMENT

PREVENTION. At the present time, the best advice to reduce the risk of pancreatic cancer is to avoid tobacco use, maintain a healthful weight, remain physically active, and eat five or more 1/2-cup servings of vegetables and fruits each day.⁶⁸

DIAGNOSIS. Spiral CT with intravenous contrast of the abdomen is the most common test in the assessment of pancreatic adenocarcinoma, with 90% sensitivity and 95% specificity. These CT scans also provide staging information that aids in determining resectability. One common sign noted on CT scan is the "double duct" sign, which occurs secondary to obstruction of both the bile and pancreatic ducts. EUS is helpful in viewing pancreatic tumors that may not be seen on CT and is accurate in detecting local lymph nodes.

If a tumor is felt to be resectable by CT and is in the body or tail of the pancreas, laparoscopy may be performed with washing samples, since CT is unable to discern small liver and peritoneal metastases in 20% to 30% of cases (false negative).¹⁴² Biopsy is not required for the diagnosis, but in some cases is helpful. This can be done percutaneously but EUS-guided fine-needle aspiration may cause less seeding of tumor.¹⁰⁰

Laboratory tests can be abnormal, including elevated bilirubin level if biliary tree obstruction is present. The serum tumor marker CA 19-9 may be increased, but this is nonspecific for pancreatic cancer and should not be relied on as diagnostic. This marker can be useful, however, in monitoring treatment.

The TNM staging system (tumor, node, metastases) (see Chapter 9) classifies pancreatic carcinoma according to tumor size, extent of local invasion, presence or absence of regional lymph node metastases, and presence or absence of distant nonnodal metastatic disease. Preoperative staging provides information required for determining surgical resectability and prognosis.

TREATMENT. Treatment of pancreatic adenocarcinoma is based on the stage of the tumor and is often divided into three broad categories: resectable (15% to 20%), locally advanced (often encasing major blood vessels) (40% to 45%), and metastatic (40% to 45%). Surgical resection provides the only curative therapy, yet this is only appropriate for a minority of clients. For those people with resectable disease, pancreaticoduodenectomy (Whipple procedure) is the procedure of choice and should be performed by an experienced surgeon. Since the 1960s the surgical mortality rate has dropped significantly and in experienced hospitals approaches 3%.^{14,155}

Chemoradiation can be provided to people with locally advanced disease and chemotherapy for those with metastatic disease. Neoadjuvant therapy (given before surgery) consists of chemoradiation and can be given for local tumors that have a high probability of not being entirely resectable (microscopic tumor is often seen at the margins of the surgical incision or tumor in the tail of the pancreas). The goal is to reduce tumor size to increase the likelihood of complete resection at surgery.⁵⁶ However, more studies are needed to verify this approach since some studies show no improvement in survival.

Much of the therapy offered to clients with pancreatic carcinoma is palliative to improve quality of life. Pain control is a significant part of therapy. Long-lasting opioids and celiac plexus neurolysis can substantially improve quality of life. Pancreatic enzyme replacement aids clients with malabsorption and steatorrhea problems. For clients who experience jaundice and will receive neoadjuvant therapy or may not be a candidate for surgery, ERCP-guided stent placement in the biliary ducts can help relieve obstruction or biliary bypass surgery can be performed.

Return of hepatic function after relief of obstruction is variable. Bile secretion may return to normal within hours; immunologic dysfunction may take weeks to normalize; jaundice characteristically improves dramatically within the first several days but may not disappear for weeks, and some of the other symptoms, such as pruritus, loss of appetite, and malaise, correct within hours or days after relief of the obstruction.

PROGNOSIS. Surgical resection is currently the only treatment that provides long-term survival; yet only 20% of people with tumor deemed to be resectable are alive at 5 years; this is most likely related to microfoci of tumor still present outside the main mass. For clients with locally advanced or metastatic disease, long-term survival is rare and the mortality rate is nearly 100%. Chemoradiation therapy can prolong survival to a median of 1 year for people with locally advanced disease, whereas chemotherapy offers clients with metastatic disease approximately 6 months.

Factors associated with a more favorable outcome include tumor size less than 3 cm, lymph nodes without tumor, surgical margins free of tumor, and pathology consistent with a well-differentiated tumor.

SPECIAL IMPLICATIONS FOR THE THERAPIST 17-19

Pancreatic Cancer

PREFERRED PRACTICE PATTERNS (ASSOCIATED WITH INTRACTABLE REFERRED BACK PAIN)

4B: Impaired Posture

4C: Impaired Muscle Performance

4F: Impaired Joint Mobility, Motor Function, Muscle Performance, Range of Motion, and Reflex Integrity Associated with Spinal Disorders

Vague back pain may be the first symptomatic presentation, and cervical lymphadenopathy (called Virchow's node) may be the first sign of distant metastases.

The therapist is most likely to palpate an enlarged supraclavicular lymph node (usually left-sided), a finding that should always alert the therapist to the need to screen for medical disease. Paraneoplastic syndrome (see Chapter 9) associated with pancreatic carcinoma may present as neuromyopathy, dermatomyositis, or thrombophlebitis associated with abnormalities in blood coagulation (coagulopathy). The presence of coagulopathy represents a precaution in the administration of certain therapeutic interventions. See Special Implications for the Therapist: Signs and Symptoms of Hepatic Disease in this chapter.

The therapist is most likely to be involved with the client with diagnosed pancreatic cancer who experiences intractable back pain. Referral to chronic pain clinics or hospice centers likely includes physical therapy services. Repeated nerve blocks may be performed after a reasonable effort to manage pain through the use of transcutaneous electrical nerve stimulation (TENS), biofeedback, analgesics, or other pain control techniques. Indwelling infusion pumps implanted to deliver analgesics directly to the site of visceral afferent nerves in the epidural or intrathecal spaces may be used for short periods (i.e., 1 to 3 months).

Cystic Fibrosis

Cystic fibrosis is a disease of the exocrine glands that results in the production of excessive, thick mucus that obstructs the digestive and respiratory systems. When the disease was first being differentiated from other conditions, it was given the name cystic fibrosis of the pancreas, because cysts and scar tissue on the pancreas were observed during autopsy. This term describes a secondary rather than primary characteristic (in-depth discussion of this disorder is found in Chapter 15).

BILIARY

See Table 17-6.

Cholelithiasis (Gallstone Disease) Overview, Definition, and Incidence

Cholelithiasis, or gallstone disease, is one of the most common gastrointestinal diseases in the United States, occurring in an estimated 20 million people (about 14 million women and 6 million men). Most gallstones are asymptomatic and are only detected on radiologic examinations performed for other reasons. Yet, in about 25% of cases, significant symptoms and complications develop because of the presence of gallstones, requiring surgery or other treatment. Age appears to play a role in the development of cholelithiasis so that gallstones are present in 20% to 35% of people by age 55 years.

Cholelithiasis occurs when stones form in the bile. These gallstones form in the gallbladder as a result of changes in the normal components of bile. Two types are

Table 17-6 Biliary Tract Terminology

Term	Definition
Chole-	Pertaining to bile
Cholang-	Pertaining to bile ducts
Cholangiography	X-ray study of bile ducts
Cholangitis	Inflammation of bile duct
Cholecyst-	Pertaining to the gallbladder
Cholecystectomy	Removal of gallbladder
Cholecystitis	Inflammation of gallbladder
Cholecystography	X-ray study of gallbladder
Cholecystostomy	Incision and drainage of gallbladder
Choledoco-	Pertaining to common bile duct
Choledocholithiasis	Stones in common bile duct
Choledochostomy	Exploration of common bile duct
Cholelith-	Gallstones
Cholelithiasis	Presence of gallstones
Cholescintigraphy	Radionuclide imaging of biliary system
Cholestasis	Stoppage or suppression of bile flow

classified according to composition: 80% consist primarily of cholesterol (cholesterol stones), whereas 20% are composed of bilirubin salts (e.g., calcium bilirubinate and other calcium salts), called *pigment stones* (black and brown). Symptoms occur when these stones block bile flow in any of the ducts, the most common being the cystic duct.

Etiologic and Risk Factors

Many risk factors are associated with the development of gallstones (Box 17-5). Advancing age is a significant risk factor. Older people experience an increase in cholesterol secretion into bile with a simultaneous decrease in bile salt production. Genetics plays a role in gallstone formation; in some ethnic populations the risk for gallstone disease is high. For example, 70% of the Native American women in the Pima tribe in Arizona develop gallstones by the age of 25 years. Alternately, African Americans have less than half the rate of Caucasian Americans.

Obesity is a well-known risk factor, particularly in women. One study demonstrated a linear increase in the incidence of cholelithiasis as the body mass increased.¹⁵⁷ Women are also more than twice as likely to develop gallstones as men. This trend is seen until the fifth decade when the risk for women approaches that of men, suggesting estrogen may be the principal factor.

Because of the prevalence of gastric bypass surgery and other methods of extreme weight loss, rapid weight loss has emerged as a risk for cholelithiasis. One study demonstrated the development of gallstones in up to 50% of people within the first 6 months of gastric bypass surgery; 40% became symptomatic.¹⁵⁸

People who receive total parenteral nutrition (TPN) often develop cholelithiasis; after 3 to 4 months of TPN about 45% of people form gallstones. Pregnancy is another common factor in cholelithiasis. As pregnancy progresses, the bile is more lithogenic (i.e., more prone to stone formation); up to 2% of pregnant women develop gallstones.

Many drugs contribute to the formation of gallstones. Estrogen is the most studied (i.e., oral contraceptives

Box 17-5**RISK FACTORS ASSOCIATED WITH GALLSTONES**

- Age (increasing incidence with increasing age)
- Genetic factors
 - Deficiency in ABCG5/G8
 - Pima women
 - Sickle cell anemia
- Decreased physical activity
- Pregnancy
- Obesity
- Diabetes mellitus
- Hypertriglyceridemia/low HDL cholesterol
- Rheumatoid arthritis
- Diseases of the terminal ileum
- TPN
- Rapid weight loss
- Liver disease
- Biliary strictures
- Drugs
 - Clofibrate
 - Estrogen (oral contraceptives, estrogen replacement therapy)
 - Octreotide

HDL, High-density lipoprotein; TPN, total parenteral nutrition.

[excluding newer, low-dose products], estrogen replacement therapy),¹⁶² but reports have shown ceftriaxone, clofibrate, and octreotide are also lithogenic.

Pathogenesis

In the formation of cholesterol gallstones, the cholesterol is obtained principally from the diet (only 20% is synthesized by the liver). Cholesterol is absorbed into the liver from the blood by receptors; each lipoprotein has its own receptor. The apo B,E receptor binds and removes low-density lipoproteins (LDLs) from the blood, while the scavenger receptor BI removes high-density lipoproteins (HDLs). A series of reactions and protein interactions regulate this process.

The liver produces bile to aid in excreting excess cholesterol. Bile is composed of biliary lipids (bile salts, phospholipids, and cholesterol), which are secreted from the liver into bile by specific transporter proteins. Each biliary lipid has a specific transporter; for example, cholesterol is transported by a protein known as ABCG5/G8. Once these biliary lipids have been secreted into the bile, the phospholipids and cholesterol form vesicles (fused together) while the bile salts form simple micelles. These vesicles and micelles interact, forming mixed micelles as they pass into the gallbladder.

Cholesterol requires the detergent properties of the phospholipids and bile salts to remain in solution. If the bile contains more cholesterol than is able to aggregate into mixed micelles, the bile becomes oversaturated with cholesterol and forms cholesterol crystals. In the presence of gallbladder-secreted mucin glycoproteins, there is a precipitation of the crystal aggregates, and gallstones are formed.⁵³

Some of the common mechanisms associated with cholesterol gallstone formation include stasis of bile in

the gallbladder (gallbladder hypomotility), changes in mucin glycoproteins in the gallbladder, or processes that may increase the amount of cholesterol or reduce the amount of bile salts or phospholipids that are secreted into the bile.

Gallbladder hypomotility is presumed to occur when insoluble or supersaturated cholesterol is absorbed into the gallbladder wall, making it difficult for the smooth muscle of the gallbladder to contract.¹⁶⁶ This is seen during pregnancy, after a period of rapid weight loss, in rheumatoid arthritis clients, and when a person is receiving TPN.^{53,119}

Although there are many proteins that interact with the mixed micelles during the transport process from the liver to the gallbladder, only mucin glycoproteins have been shown to enhance the formation of cholesterol gallstones. People who experience rapid weight loss may have, among other factors, an increase in mucin glycoprotein production. Although more research is needed to understand the factors that alter this glycoprotein, there are preliminary data in animals to show that aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) may inhibit the production of mucin glycoproteins.⁷³ Yet in one study following people who take NSAIDs chronically, there appeared to be no protective benefit.¹²²

Environmental, as well as genetic, factors most likely affect the amount of biliary cholesterol. There are several genes that code for transporters of biliary lipids and receptors for lipoproteins. A deficiency in one of these, such as the ABCG5/G8 transporter protein, may be responsible for excess cholesterol secretion into bile.^{52,53}

Excess dietary cholesterol consumption may lead to an increase in the amount absorbed into the liver from the blood, but studies are conflicting.^{64,101} Obese people may express an overactive enzyme required for cholesterol synthesis (3-hydroxy-3-methylglutaryl coenzyme A [HMG CoA] reductase), leading to excessive cholesterol production. Because of elevated levels of estrogen, pregnancy can also increase the amount of cholesterol secreted into bile and reduce bile acid production.

Black pigment stones are formed by an increased production of unconjugated bilirubin that precipitates as calcium bilirubinate in bile to form stones. This type of stone occurs in clients who experience chronic hemolysis (such as sickle cell anemia) or have end-stage liver disease or pancreatitis. *Brown pigment stones* are less common than black pigment stones in the United States and typically found in geographic areas where biliary infections are prevalent (more frequent among Asians). These stones can form in the gallbladder or in the ducts. Brown pigment stones form secondary to the anaerobic bacterial infection. Bacteria are postulated to produce unconjugated bilirubin and bile acids, and release phospholipids through the production of enzymes. These products combine with calcium, forming stones.

Clinical Manifestations

The majority of gallstones remain asymptomatic once formed in the gallbladder. Only a minority (approximately 25%) cause painful symptoms. This occurs when the stone attempts to pass down the ducts leading to the

duodenum, becoming wedged. The most common location of obstruction is the cystic duct (Fig. 17-7). This causes abdominal pain (often referred to as *biliary colic*). Obstruction of the cystic duct distends the gallbladder while the muscles in the duct wall contract, trying to expel the stone. The pain of biliary colic may be intermittent or steady; it is usually severe and is located in the right upper quadrant just below or slightly to the right of the sternum with abdominal tenderness and muscle guarding. In more severe cases, rebound pain may be present. Painful symptoms are frequently related to meals, although not exclusively postprandial. The pain often radiates to the right shoulder and upper back (60% of cases) and is associated with nausea and vomiting. Radiating pain to the midback and scapula occurs as a result of splanchnic (visceral) fibers synapsing with adjacent phrenic nerve fibers (major branch of the cervical plexus innervating the diaphragm).

Episodes can last from 20 minutes to several hours and may develop daily or as infrequently as once every few years. Complicated cases often feature jaundice, fever, nausea and vomiting, and leukocytosis.

Other symptoms are vague, including heartburn, belching, flatulence, epigastric discomfort, and food intolerance (especially for fats). Gallstones in the older adult may not cause pain, fever, or jaundice; instead, mental confusion may be the only manifestation of gallstones.

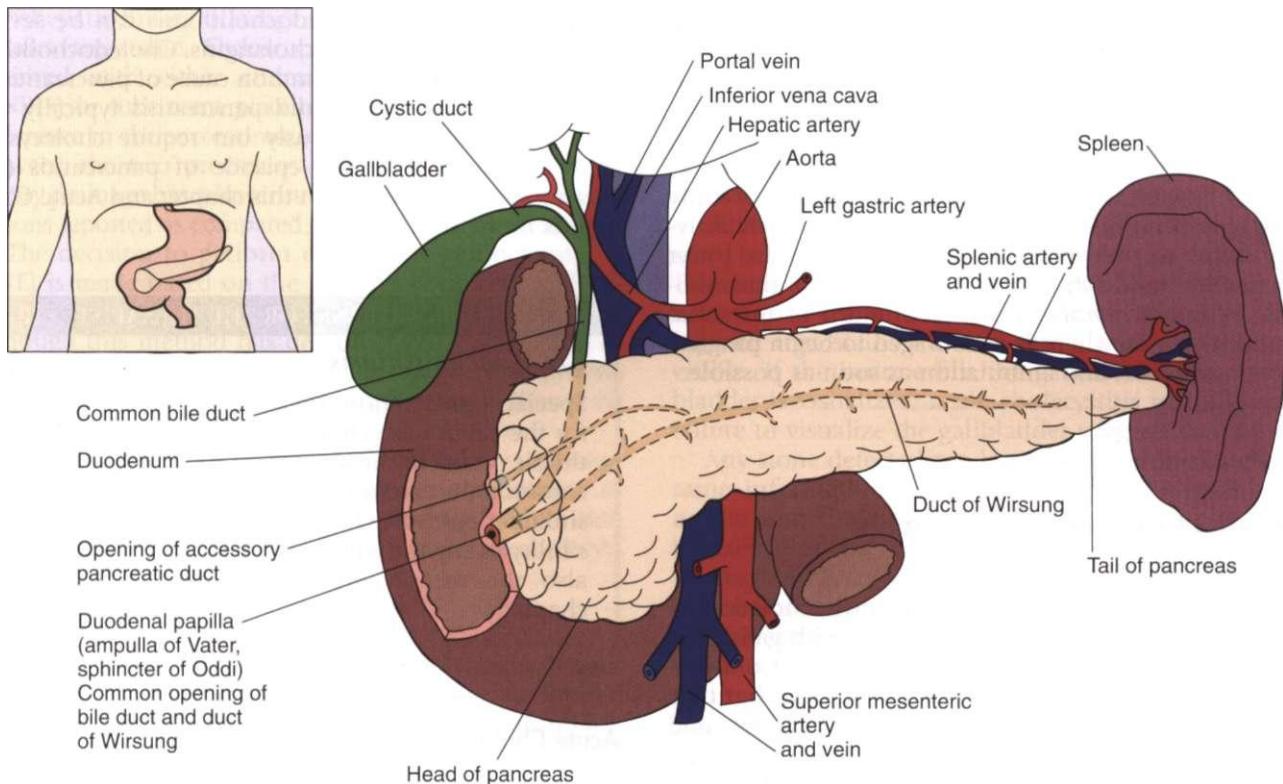
Serious complications occur in 20% of cases when a stone becomes lodged in the lower end of the common bile duct, causing inflammation (cholangitis) leading to bacterial infection and jaundice (indicating the stone is in the common bile duct). Sometimes acute pancreatitis develops when the duct from the pancreas that joins the common bile duct also becomes blocked (see Fig. 17-7). About 15% of clients with gallstones also have stones in the common bile duct (choledocholithiasis).

MEDICAL MANAGEMENT

DIAGNOSIS. Diagnosis is based on history, physical examination, and radiographic evaluation. Physical examination often reveals tenderness to palpation in the right upper quadrant of the abdomen. The radiologic test of choice is the transabdominal ultrasound. Ultrasonography reveals gallstones in more than 95% of cases (when 1.5 mm or greater in size). Ultrasound can also provide information concerning the gallbladder and ducts and can aid in predicting possible technical difficulties during surgery.¹²⁵

EUS can be used to detect stones too small for typical transabdominal ultrasound, and functional ultrasonography (gallbladder volumes with fasting and postprandial) is used to assess gallbladder motility. These latter tests are not routinely employed since transabdominal ultrasound is frequently sufficient for diagnosis. Other tests are available to detect the location of stones if they are not in the cystic duct and are discussed in the next section.

TREATMENT AND PROGNOSIS. Asymptomatic gallstones typically do not require treatment, except in populations at high risk, such as the women of the Pima tribe or people with sickle cell anemia. Prophylactic

**Figure 17-7**

The pancreas (located behind the stomach) and gallbladder are anterior to the L1-L3 vertebral bodies. Attaching to the duodenum to the right, the pancreas extends horizontally across to the spleen in the left abdomen, coming in contact with the duodenum, kidneys, liver, and spleen. Obstruction of either the hepatic or common bile duct by stone or spasm blocks the exit of bile from the liver, where it is formed, and prevents bile from ejecting into the duodenum. [From Black JM, Matassarin-Jacobs E, eds: *Luckmann and Sorensen's medical-surgical nursing*, ed 4, Philadelphia, 1993, WB Saunders.]

cholecystectomy may be recommended in these cases. Other groups requiring prophylactic treatment include those experiencing rapid weight loss or receiving TPN. People who experience rapid weight loss can receive prophylactic UDCA¹⁵² and those needing prolonged TPN can be treated with cholecystokinin-octapeptide.

Once gallstones cause pain, there is a 1% to 2% annual risk of developing complications, and 50% of people with symptomatic cholelithiasis will have a recurrent episode. Cholecystectomy therefore is recommended for most symptomatic clients. Laparoscopic cholecystectomy is the preferred surgical approach since the complication rate is decreased when compared to an open procedure. When the gallbladder is removed, bile drains directly from the liver into the intestine, eliminating the opportunity for stone formation.

Medical treatment is used only in select clients and consists of oral dissolution with UDCA, with or without extracorporeal shock-wave lithotripsy. Characteristics that deem a client a candidate for medical therapy include presence of small cholesterol stones; reversible cause of gallstone formation (such as medication use); infrequent, mild pain attacks; functioning gallbladder; and a patent cystic duct for the passage of stones. Even with successful medical treatment, 30% to 50% of stones recur within 5 years.

SPECIAL IMPLICATIONS FOR THE THERAPIST 17-20

Cholelithiasis (Gallstone Disease)

Physical activity may play an important role in the prevention of symptomatic gallstone disease in up to a third of all cases. Based on a limited number of studies, increasing exercise to 30 minutes of endurance-type training five times per week is recommended.^{74,75} When the gallbladder has been removed (or is blocked by a stone) a small amount of less concentrated bile is still secreted into the intestine. The loss of a gallbladder itself does not appear to have an impact on physical activity and exercise.

In the past, gallbladder removal required a significant incision with muscle disruption, scarring, and frequently, postoperative back pain associated with the formation of deep scar tissue. Now the closed procedure (laparoscopic cholecystectomy) can be performed as outpatient (day) surgery without these complications.

Air introduced into the abdomen during this operative technique is removed after the procedure, thereby reducing the postoperative abdominal pain. However, many individuals still experience referred pain to the right shoulder for 24 to 48 hours. Deep breathing,

Continued.

physical movement and activity as tolerated, and application of a heating pad to the abdomen (if approved by the surgeon) can help ease the discomfort.

The usual postoperative exercises (e.g., breathing, turning, coughing, wound splinting, compressive stockings, and leg exercises) for any surgical procedure apply, especially in case of complications. Early activity helps to prevent pooling of blood in the lower extremities and subsequent development of thrombosis. Early activity also assists the return of intestinal motility, so the client is encouraged to begin progressive movement and ambulation as soon as possible.

Complications of Cholelithiasis

Choledocholithiasis

Defined as calculi in the common bile duct, choledocholithiasis occurs in 5% to 10% of persons with gallstones and has the same etiology and pathogenesis. Common duct stones usually originate in the gallbladder, but they also may form spontaneously in the common duct and can therefore occur after a person has had a cholecystectomy (10% to 15%). Stones that occur in the absence of a gallbladder are referred to as *primary common duct stones*. Approximately 30% to 40% of duct stones are asymptomatic; they are typically small enough to pass through without causing an obstruction. When symptomatic, duct stones produce right upper quadrant pain often with radiating pain to the shoulder and/or back (see previous section on Clinical Manifestations under Cholelithiasis). Liver enzymes are frequently elevated; in some cases the values can be similar to those seen in hepatitis. Serum aminotransferase, ALP, and bilirubin values are usually elevated at least twofold.

Diagnosis is based on clinical picture and radiologic or endoscopic evidence of dilated bile ducts, ductal stones, or impaired bile flow. Although transabdominal ultrasonography is very sensitive for identifying stones in the gallbladder, it is the least sensitive method for detecting stones in the common bile duct (identifying only 30% to 50%).

Helical CT has a sensitivity nearing 80% in imaging common bile duct stones, whereas EUS has a sensitivity of greater than 90%. But ERCP is very sensitive and provides the means to extract the stone during the procedure.⁴¹ ERCP consists of introduction of radiopaque medium into the biliary system by percutaneous puncture of a bile duct to provide x-ray examination of the bile ducts. ERCP is the test of choice for clients with choledocholithiasis associated with cholangitis or pancreatitis but may be contraindicated in clients who have had GI reconstructive surgery (such as a Billroth II procedure) or stones greater than 1 cm or those who have a biliary stricture. Laparoscopic transcystic bile duct exploration can detect and remove common bile duct stones in greater than 90% of clients, and laparoscopic choledochotomy can be performed if transcystic bile duct exploration is not successful.

Complications of choledocholithiasis can be severe, including pancreatitis and cholangitis. Choledocholithiasis is currently the most common cause of pancreatitis in the world. Clients with mild pancreatitis typically will pass the stone spontaneously but require cholecystectomy to prevent another episode of pancreatitis (see Acute Pancreatitis section in this chapter and Acute Cholangitis in the next section).

SPECIAL IMPLICATIONS FOR THE THERAPIST 17-21

Choledocholithiasis

Special considerations for the therapist are the same as for the client with cholelithiasis. When choledocholithiasis occurs in the absence of a gallbladder (primary common duct stones), the presenting symptom can be shoulder pain. The therapist must be alert to this possibility in anyone who has had a cholecystectomy. (See also the section on Obstructive faudice in this chapter.)

Acute Cholangitis

In 6% to 9% of cholelithiasis cases, obstruction and stasis of bile leads to a suppurative infection of the biliary tree, termed *acute cholangitis*. Acute cholangitis symptoms include those of cholelithiasis plus fever and jaundice. These three symptoms of pain, fever, and jaundice are referred to as Charcot's triad and are noted in 50% to 100% of people with cholangitis.

Reynolds' pentad (seen in only 14% of cases) includes Charcot's triad plus hypotension and mental confusion. The presence of Reynolds' pentad is an ominous sign, with mortality approaching 100% unless there is emergent decompression of the biliary tree. Acute cholangitis can be categorized into three stages: mild grade I (responds to medical therapy), moderate grade II (no organ dysfunction but not responding to initial medical treatment), and severe grade III (at least one new organ dysfunction).¹⁶⁵

The total bilirubin is typically elevated greater than two times normal, although it may be in the normal range early in the infection process. Bacteria are isolated in the bile in more than 80% of cases and in the blood in anywhere from 20% to 80% of cases (reports vary widely). Aerobic and anaerobic gram-negative bacilli and enterococci are the most common organisms isolated.

CT scans and ultrasonography can aid in discerning cholecystitis from cholangitis, as well as identify possible abscesses in the liver. EUS can identify stones in the common bile duct.

Treatment is given according to the grade of illness. Grade 1 is mild and can typically be treated with appropriate antibiotics with subsequent laparoscopic cholecystectomy. Clients with grade II disease are treated with antibiotics and early biliary drainage. Once stable, this therapy is followed by open or laparoscopic cholecystectomy. Stage III disease requires appropriate intensive care support with urgent endoscopic or percutaneous

transhepatic biliary drainage once the person's hemodynamics are stable. Endoscopic biliary drainage can be achieved with either endoscopic nasobiliary drainage (ENBD) or tube stent placement. There is no significant difference in the success rate, effectiveness, and morbidity between the two procedures. Percutaneous transhepatic biliary drainage has a lower success rate with more complications reported as compared to endoscopic methods.¹⁶⁰

The decision to perform endoscopic sphincterotomy (EST) is made based on the person's condition and the number and diameter of common bile duct stones,¹⁶⁷ although this method has demonstrated higher rates of hemorrhaging and pancreatitis. As the client improves, delayed elective cholecystectomy can then be performed.¹⁶²

A complication of cholangitis and biliary drainage includes biliary peritonitis. This can occur because of perforation of the gallbladder with leakage of bile into the abdominal cavity. This requires immediate cholecystectomy and/or drainage.

Cholecystitis

Cholecystitis is the most common complication of gallstone disease, with 700,000 cholecystectomies performed in the United States each year.¹⁵³ Cholecystitis, or inflammation of the gallbladder, may be acute or chronic and occurs most often as a result of impaction of gallstones in the cystic duct (see Fig. 17-7), causing obstruction to bile flow and painful distention of the gallbladder.

Acute cholecystitis caused by gallstones accounts for the majority of cases, and acalculous cholecystitis (i.e., gallstones not present) makes up the remaining 10%. Acute cholecystitis from stones is most common during middle age (particularly in women), whereas the acute acalculous form is most common among older adult men and carries a worse prognosis.

Some of the causes for acalculous cholecystitis include ischemia; chemicals that enter biliary secretions; motility disorders associated with drugs; infections with microorganisms, protozoa, and parasites; collagen disease; and allergic reactions. Acute acalculous cholecystitis is associated with a recent operation, trauma, burns, multisystem organ failure, and TPN.⁶⁵

Gallbladder attacks are usually caused by gallbladder and/or cystic duct distention as the stone causes obstruction to the flow of bile. The increased pressure and stasis of bile leads to damage of the mucosa with subsequent release of inflammatory enzymes. Gallbladder inflammation causes prolonged pain characterized as steady right upper quadrant abdominal pain with abdominal tenderness, muscle guarding, and rebound pain. Upper quadrant pain often radiates to the upper back (between the scapulae) and into the right scapula or right shoulder. Murphy's sign (interruption of deep breathing with deep palpation under the right costal arch) is a fairly sensitive and specific sign for gallbladder disease. Accompanying GI symptoms usually include nausea, anorexia, and vomiting and there may be signs of visceral or peritoneal inflammation (e.g., pain worse with movement and locally tender to touch).

Diagnosis is made on the basis of clinical history, examination, laboratory findings, and imaging. The WBC

count is usually elevated (12,000 to 15,000/ml). Total serum bilirubin, serum aminotransferase, and ALP levels are often elevated in the acute disease, but they are normal or minimally elevated in the chronic form. X-ray films of the abdomen show radiopaque gallstones in only 15% of cases. Abdominal ultrasonography often shows stones, thickened gallbladder wall, and pericholecystic fluid.

Biliary scintigraphy (hepatobiliary iminodiacetic acid [HIDA] scan) is useful in demonstrating an obstructed cystic duct. The client swallows a long thin, lighted flexible tube connected to a computer and a monitor. A special dye is injected that stains the bile ducts, making them more visible. If the isotope fills the gallbladder and the gallbladder is visualized, acute cholecystitis is unlikely. But failure to visualize the gallbladder suggests cholecystitis.

Any stone detected can be removed immediately. The same information can be obtained by passing a thin needle into the abdominal wall through which dye is injected into the ducts, a procedure called *percutaneous transhepatic cholangiography*.

Laparoscopic cholecystectomy (gallbladder resection) is the treatment and procedure of choice, since it is less invasive than an open procedure and healing and hospital time are reduced.¹⁷ It is often performed during the first hospitalization for acute cholecystitis, although the exact timing depends on the surgeon's judgment; the presence of complications may delay surgery.

Prognosis for both acute and chronic cholecystitis is good with medical intervention. Acute attacks may resolve spontaneously, but recurrences are common, requiring cholecystectomy. Complications can be serious and usually are associated with cholangitis. The mortality of acute cholecystitis is 5% to 10% for clients older than 60 years with serious associated diseases.

An infrequent complication of laparoscopic cholecystectomy is injury to the bile duct (0.4% to 0.6% of all cases), causing leakage of bile into the abdomen. Symptoms postoperatively include fever, abdominal pain, ascites, nausea, elevated bilirubin levels, and rarely, frank jaundice. Intraperitoneal bile fluid collections can be seen on ultrasonography, CT scanning, or HIDA scan. ERCP can be utilized to detect the site of injury and treat the obstruction. Prompt repair requires less treatment than delayed diagnosis, which often requires a more complex reconstruction.

SPECIAL IMPLICATIONS FOR THE THERAPIST

17-22

Cholecystitis

Special considerations for the therapist are the same as for the client with cholelithiasis (see also the section on Obstructive Jaundice in this chapter). It is possible for a person to develop acholelithiasis cholecystitis, or inflammation of the gallbladder without gallstones. The therapist may see a clinical picture typical of gallbladder disease, including mid-upper back or scapular pain (below or between the scapulae) or right shoulder pain associated with right upper quadrant abdominal pain. Close questioning may reveal accompanying associated GI signs and symptoms.

Continued.

The person may have been evaluated for gallbladder disease, but ultrasonography does not always show small stones. Unless further and more elaborate testing has been performed to examine gallbladder function, the individual may end up in therapy for treatment of the affected musculoskeletal areas. Lack of results from therapy and/or progression of symptoms corresponding to progression of disease requires further medical follow-up.

Primary Biliary Cirrhosis

See Primary Biliary Cirrhosis, earlier in this chapter, in the Liver section.

Primary Sclerosing Cholangitis

Sclerosing cholangitis is a chronic cholestatic disease of unknown etiologic origin characterized by progressive destruction of intrahepatic and extrahepatic bile ducts. It has been linked to altered immunity, toxins, ischemia, and infectious agents, in people who are genetically susceptible. Approximately two-thirds of cases occur in clients 20 to 40 years of age and the incidence is believed to be rising; it is seen more commonly in men than women (3:1 ratio). Eighty percent of clients with primary sclerosing cholangitis also have inflammatory bowel disease, most frequently ulcerative colitis; yet only 5% of people with ulcerative colitis develop primary sclerosing cholangitis (PSC).⁴⁹

The inflammatory process associated with this disease results in hepatitis, fibrosis, and thickening of the ductal walls. This fibrosing process narrows and eventually obstructs the intrahepatic and extrahepatic bile ducts; the basic mechanisms of disease pathogenesis in PSC remain unknown.

Over 40% of people are asymptomatic at the time of diagnosis. But with the progression of disease, symptomatic presentation usually includes pruritus and jaundice accompanied by abdominal pain, fatigue, anorexia, and weight loss. Complications associated with the disease include bacterial cholangitis, pigmented bile stones, steatorrhea, malabsorption, and metabolic bone disease; severe complications involve the development of cirrhosis and portal hypertension, and the risk of developing cholangiocarcinoma (10% to 30% lifetime risk), HCC, and colon cancer.¹³⁰

Diagnosis is made on the basis of clinical, laboratory, and radiologic findings. ALP is typically 3 to 5 times normal accompanied by a mild elevation in bilirubin. The diagnosis is confirmed by ERCP or MRCP, which demonstrate the characteristic "beads on a string" appearance of the bile ducts (strictures and dilatation of the ducts). Liver biopsy is performed for staging rather than diagnosis. Causes of secondary sclerosing cholangitis (such as chronic bacterial cholangitis, biliary neoplasms, and drug-induced bile duct injury) should also be excluded.

Medical therapy is based on managing symptoms, correcting dominant strictures, and treating bacterial cholangitis when it occurs. Pruritus can be treated with bile-acid binding resins and dominant duct strictures can be endoscopically treated (by dilation or placement of stents). Clients should receive vitamin D and calcium supplements, although select people may require bisphosphonates.

UDCA improves biliary secretion and laboratory parameters but has not been shown to significantly improve survival. Currently, liver transplantation is the only therapeutic option for people with end-stage liver disease resulting from this disorder.^{53,144} Many clinical trials of medical therapy have been conducted, but none have demonstrated significant efficacy compared to liver transplant. The results of transplantation for PSC are excellent, with 1-year survival rates of 90% to 97% and 5-year survival rates of 80% to 86%.⁵⁰ Optimal timing for liver transplantation is still not well defined, but the goal of therapy is to treat people as early as possible to prevent progression to the advanced stages of this disease or the development of cancer. Recurrence of PSC after liver transplantation occurs in about 4% of clients per year but appears to have little effect on survival.⁵¹ Clients who develop cholangiocarcinoma and undergo liver transplant have a poor prognosis.⁴⁸

SPECIAL IMPLICATIONS FOR THE THERAPIST

17-23

Primary Sclerosing Cholangitis

Special considerations for the therapist are the same as for the client with cholelithiasis (see also the section on Obstructive Jaundice in this chapter).

Neoplasms of the Gallbladder and Biliary Tract

Benign Neoplasms

Biliary neoplasms, whether benign or malignant, are rare. Most nonmalignant tumors of the gallbladder and biliary tree are polyps. These polyps can be adenomas, pseudotumors, or hyperplastic inflammatory lesions and most are found incidentally by ultrasonography or during cholecystectomy (for gallstone symptoms). Adenomas may be premalignant and have been associated with carcinoma in situ and invasive adenocarcinomas. Because polyps that are 1 cm or larger have a greater potential to be malignant, treatment consists of cholecystectomy.

Malignant Neoplasms

Cancers of the biliary tract are divided into gallbladder cancer, cholangiocarcinoma, and adenocarcinoma of the ampulla of Vater. *Gallbladder cancer* is the sixth most common gastrointestinal cancer, causing about 2800 deaths per year, and is the most common cancer of the biliary tree.^{57a}

Risk factors for gallbladder cancer include age (the elderly are most often affected), female gender (women are three times more likely to develop gallbladder cancer), and gallstones (80% to 90% of people with gallbladder cancer have gallstones). Other factors include obesity, gallbladder wall calcification (porcelain gallbladder), chronic typhoid carriers, and gallbladder polyps. In elderly adults, gallbladder polyps greater than 10 mm are more likely to be malignant while smaller polyps can be followed. However, despite these known risk factors, many cases of gallbladder cancer occur in people without obvious risk factors.³⁰

Adenocarcinoma of the gallbladder is the most common type of gallbladder cancer (over 80% of cases), with squamous cell and small cell carcinoma accounting for the remaining cases. Clinical presentation of malignant gallbladder diseases depends on the stage of disease and the location and extent of the lesion, but it is often insidious. By the time the tumor becomes symptomatic, it is often incurable.

Symptoms most often mimic gallstone disease (acute and chronic cholecystitis). Right upper quadrant pain radiating to the upper back is the most common symptom (80% of cases), with weight loss, progressive (obstructive) jaundice (30% of cases), anorexia, fatty food intolerance, and right upper quadrant mass (in advanced disease).

Pruritus and skin excoriations are commonly associated with the presence of jaundice. Gallbladder cancer is usually found either as an incidental finding at surgery, as a suspected tumor (because of symptoms) with the prospect of resectability, or as advanced unresectable disease.

Ultrasonography is the most common initial test for diagnosis, although CT and MRI can detect the extent of disease. CT scans and cholangiography are used preoperatively to determine resectability of the tumor. Disease can be metastatic to lungs and bones and usually involves the liver. Simple cholecystectomy is appropriate only for stages 0 and 1; the remainder require extended or radical cholecystectomy (with removal of lymph nodes, adjacent hepatic tissue, and/or portions of the extrahepatic biliary tree).³⁴

For clients with unresectable disease and jaundice, a biliary bypass (hepaticojjunostomy) can be performed to relieve obstruction. Overall prognosis is poor with a 5-year survival rate of 5% to 10%. Cures are only obtained when all detectable tumor is surgically removed in the early stages of the disease. Stage I tumors have an overall survival rate of 100% and nearly 50% for node-negative stage II and stage III disease. Chemotherapy and radiation provide little benefit.

Cholangiocarcinoma, or cancer of the bile ducts, is a rare tumor. Historically the term cholangiocarcinoma referred only to tumors of intrahepatic bile ducts, although more recently it encompasses intrahepatic, perihilar, and distal extrahepatic tumors of the bile ducts.³⁰ Cholangiocarcinoma occurs more frequently in people between 50 and 70 years of age; other risk factors include primary sclerosing cholangitis, ulcerative colitis, recurrent bacterial cholangitis, bile duct adenomas and

papillomas, intraductal gallstones, certain infectious diseases (such as the liver fluke *Clonorchis sinensis*), and exposure in the past to the radiologic contrast agent thorium dioxide (Thorotrast).

Most tumors are located near the porta hepatis (60% to 80%), although 20% are in the distal bile duct and less than 5% are intrahepatic. Affected persons most often present with jaundice secondary to obstruction of the bile duct (90% of cases) with associated acholic stool (light colored) and pruritus. Other symptoms include weight loss, anorexia, and fatigue.

On physical examination, hepatomegaly or a palpable gallbladder (Courvoisier's sign) may be present with advanced disease. Laboratory values are consistent with biliary obstruction with an elevated bilirubin and ALP. CA 19-9 and carcinoembryonic antigen are elevated but nonspecific. CT scans or MRCP can detect the disease, and ERCP with brushings or biopsy may be diagnostic and relieve obstruction (a presurgical histologic diagnosis is often difficult to obtain).

Resectability is determined by a lack of metastatic disease, local invasion of the vascular structures around the liver, or the ability to completely resect the tumor. Laparoscopic surgery may be done initially to determine if metastatic disease is present (metastatic disease is found in 25% of cases that were felt to be resectable by imaging studies). A pancreaticoduodenectomy is performed for tumors in the distal portion of the biliary tree. However, since most cholangiocarcinomas are near the liver and large vessels, surgery must be tailored to the location of the tumor, with 35% actually resectable.

Radiation therapy may be of some survival benefit. Endoscopic or percutaneous stent placement for biliary decompression often relieves symptoms for clients with nonresectable disease. Cure is obtained by complete surgical resection of tumor. Survival rates are determined by extent of disease and involvement with large vessels and structures around the liver. In one study, 56% of the perihilar tumors were resectable, and the overall 5-year survival rate was 11%.¹⁰⁹ Improved survival rates of 21% to 56% have been associated with aggressive hepatic resection in order to remove all tumor with negative resection margins.^{20,103} Distal bile duct tumor has a 5-year survival of 28% after successful surgical treatment.

Adenocarcinoma of the ampulla of Vater is a rare, distal bile duct tumor. The ampulla of Vater is a small area (about 1 cm. in diameter) located at the common opening of the pancreatic and bile ducts into the duodenum (see Fig. 17-7). This cancer has an incidence of 2.9 cases per million people in the United States.

Risk factors include people with Peutz-Jeghers syndrome and familial adenomatous polyposis syndrome. Because of its location, this tumor causes obstructive jaundice early in the disease process (80% of cases). Abdominal pain (50%), weight loss (75%), and occult GI bleeding (30%) are other common symptoms.

Diagnosis is made by EUS, CT scan, and ERCP. Surgical resection, typically a pancreaticoduodenectomy, is the treatment of choice, with no clear benefit to chemoradiation. Resection is feasible in over 85% of cases with a 5-year survival of up to 45%.^{29,132}

SPECIAL IMPLICATIONS FOR THE THERAPIST 17-24***Gallbladder and Biliary Tract Neoplasm***

Special considerations for the therapist are the same as for the client with cholelithiasis. See also the section on Obstructive Jaundice in this chapter and Special Implications for the Therapist: Oncology in Chapter 9.

References

To enhance this text and add value for the reader, all references are included on the companion Evolve site that accompanies this textbook. The reader can view the reference source and access it on-line whenever possible. There are a total of 171 cited references and other general references for this chapter.

CHAPTER 18

The Renal and Urologic Systems

CATHERINE C. GOODMAN • CELESTE PETERSON

The structures associated with the excretion of urine are (1) the kidneys and ureters, comprising the *upper urinary tract*, and (2) the bladder and urethra of the *lower urinary tract* (Fig. 18-1). The kidneys serve as both an endocrine organ and a target of endocrine action, with the aim of controlling mineral and water balance. The kidneys' main function is to filter waste products and remove excess fluid from the blood. Every day the kidneys filter 200 qt of fluid; about 2 qt leave the body in the form of urine, and the remainder is retained in the body.

These filtration and storage functions associated with excretion expose the kidney and bladder to carcinogens for extended periods, increasing the risk of cancer's developing in these organs compared with the other urinary tract structures. In addition, the urethra of females lies close to the vaginal and rectal openings, allowing for relative ease of bacterial transport and increased risk of infection. The shorter urethra in females also contributes to the increased incidence of urinary tract infections (UTIs) in females.

Therapists have an important role on the medical team for primary intervention for a number of renal/urinary tract disorders such as urinary incontinence (UI) and for those on dialysis or having a renal transplant. UI afflicts a significant percentage of the geriatric population, and UTIs rank second only to upper respiratory tract infections in incidence of bacterial infections. Therapists encounter these two disorders often as common comorbidities in the clinical arena.

The presence of a UTI increases the risk of infections developing elsewhere. This could occur while the therapist is treating someone for a knee injury or after cerebral vascular accident. Recognizing clinical signs and symptoms of renal/urologic problems (Box 18-1) will facilitate medical referral. Understanding how these diseases and the prescribed medical treatment can influence rehabilitative efforts is essential to help ensure a positive functional outcome.

AGING AND THE RENAL AND UROLOGIC SYSTEMS

Aging is accompanied by a gradual reduction of blood flow to the kidneys, coupled with a reduction in

nephrons (the units that extract wastes from the blood and concentrate them in the urine; see Fig. 18-6). As a result the kidneys become less efficient at removing waste from the blood, and the volume of urine increases somewhat with age. A tendency toward greater renal vasoconstriction in the older adult is evident, as compared with young individuals. This occurs as a result of mental stress, in physiologic circumstances such as physical exercise, or in disease manifestations such as the effective circulatory volume depletion that develops in heart failure.¹⁹¹

Renal system changes that occur with aging cause alterations in the functional balance of fluid and electrolytes so that sodium regulation is not as effective. Older people are at greater risk for developing hyponatremia (reduced sodium in the blood), affecting the musculoskeletal system. Changes typical of the aging kidney are also accelerated when hypertension overlaps the physiologic renal process, because both aging and hypertension affect the same structure (i.e., the glomeruli).

A reduction in bladder capacity increases the number of times an individual urinates in a day, and the urinary timetable also changes. Although the kidneys produce most of the urine during the day in young people, a shift to night production over time makes one or two nocturnal trips to the bathroom commonplace after age 60.

Although specific age-related anatomic changes have not been associated with urinary tract disease, certain age groups (e.g., older adults) are at significant risk of developing a variety of disorders. Hormonal changes in women, combined with the aging properties of the connective tissues, fascia, or collagen fibers, contribute to pelvic floor disorders. Transient ischemic attacks (TIAs) and strokes may result in mild to severe deficits or fluctuations in muscle tone affecting the pelvic floor muscles.

The effect of multiple medications, conditions such as benign prostatic hyperplasia and pelvic floor disorders, and the incidence of pelvic surgeries and catheterization in the older population all increase the risk of developing urinary tract disease. A large number of adults over age 60 are incontinent, and many older adults require dependent living situations because of this disorder. Considering the percentage of the rehabilitation population made up by the older adult, therapists will continue to be involved in the treatment of renal/urologic disorders.

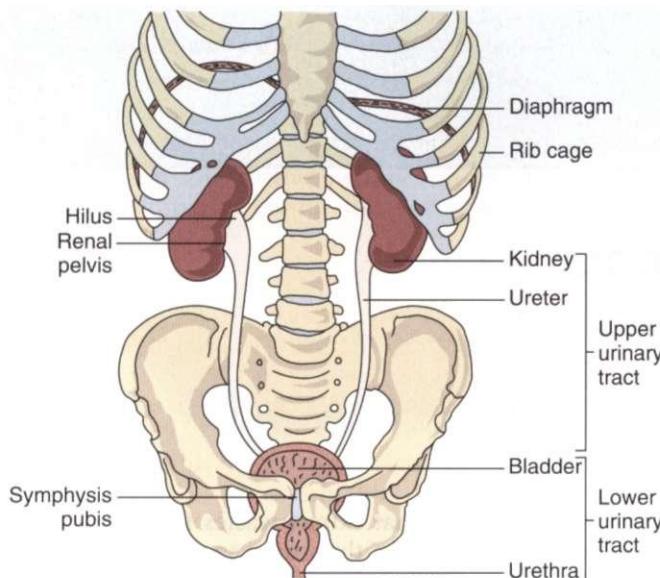


Figure 18-1

Structure and function of the renal and urologic systems. The kidneys are located in the posterior upper abdominal cavity in the retroperitoneal space (behind the peritoneum) at the vertebral level of T12 to L2. The upper portion of the kidney is in contact with the diaphragm and moves with respiration. The lower urinary tract consists of the bladder and urethra. The bladder, a membranous, muscular sac, is located directly behind the symphysis pubis and is used for storage and excretion of urine. From the renal pelvis, urine is moved by peristalsis to the ureters and into the bladder. The urethra serves as a channel through which urine is passed from the bladder to the outside of the body. (From Goodman CC, Snyder TE: *Differential diagnosis in physical therapy*, ed 3, Philadelphia, 2000, Saunders.)

INFECTIONS

Urinary Tract Infections

UTIs are very common, affecting men, women, and children. Any portion of the urinary tract can become infected, although the bladder (cystitis) and urethra (urethritis) are usually involved. Bacteria may also spread to the upper portion of the urinary tract and involve the kidneys, causing a more serious infection referred to as *pyelonephritis*.

UTIs can be defined as either uncomplicated or complicated, and relapsed or recurrent. Complicated infections develop in persons with factors that can make diagnosis and treatment difficult—including diabetes, history of stroke, pregnancy, immunosuppression, structural abnormalities, or functional abnormalities of the urinary tract. The presence of such complications often requires longer treatment and further testing.¹⁸³

Generally, UTIs in men, pregnant women, children, and clients who are hospitalized or in a long-term care setting can be considered complicated. Uncomplicated UTIs lack these factors and are more easily diagnosed and treated. UTIs may relapse or, more commonly, reoccur. Relapsed infections are infections that persist with the original organism without completely clearing. Reoccurrence of UTIs is considered a different infection that occurs after successful treatment of the initial infection,

Box 18-1

MOST COMMON SIGNS AND SYMPTOMS OF URINARY TRACT PROBLEMS

- Urinary frequency
- Urinary urgency
- Nocturia
- Pain (shoulder, back, flank, pelvis, lower abdomen)
- Costovertebral tenderness
- Fever and chills
- Hyperesthesia of dermatomes
- Dysuria
- Hematuria
- Pyuria
- Dyspareunia

although it may be with the same organism due to repeated contamination.¹⁸³

Incidence and Prevalence

UTIs frequently occur in the general population, although women and older adults comprise the majority of cases. UTIs affect over 11.3 million women per year,¹⁹ or up to 5% of all females. Five percent to thirty percent of the older adult population is also affected.⁶⁰ By age 24, one third of women will have had at least one physician-diagnosed UTI that is treated with prescription medication.

For those living in skilled nursing facilities, assisted living arrangements, or extended care facilities, the prevalence of infection is even higher: 25% for women and 20% for men.⁷ UTIs affect children, involving approximately 7% of girls and 2% of boys before the age of 6 years.¹²⁵ Recurrent UTIs can be problematic for many people, occurring in 3% to 5% of women⁸⁷ and 80% of children who previously experienced an uncomplicated infection. The cost is substantial at over \$1.6 billion per year (diagnosis, treatment, and management cost). UTIs also result in restrictions in daily activities and lost days of work.

Etiologic and Risk Factors

Most UTIs occur in adult women. The urethra in females is shorter, compared to that in males, and also close to the entrances to the vagina and rectum. The bacteria that result in most UTIs are acquired from the large bowel (fecal flora). The urethral meatus is close to the fecal reservoir and rectum.

Young, sexually active women are at higher risk of developing UTIs because it is thought that sexual intercourse can influence the movement of bacteria in the direction of the bladder. This again is due to the proximity of the urethral meatus and vagina. There are numerous risk factors for UTIs (Box 18-2) that depend upon the characteristics of the person affected. For example, risk factors for an acute, uncomplicated UTI in a premenopausal woman may be different than those for a postmenopausal woman in a long-term care setting.

For young women, the most common risk factors include a history of a previous UTI, frequent or recent sexual activity, or the use of a spermicidal agent.^{53,61} UTIs

Box 18-2**RISK FACTORS FOR URINARY TRACT INFECTIONS**

- Age
- Immobility/inactivity (impaired bladder emptying)
- Instrumentation and urinary catheterization
- Frequently catheterized neurogenic bladder
- Atonic bladder (spinal cord injury; diabetic neuropathy)
- Increased sexual activity
- Spermicide use with diaphragm or condom
- Uncircumcised penis (first year of life)
- Obstruction
 - Renal calculi
 - Prostatic hyperplasia
 - Malformations or urinary tract abnormalities
- Constipation (see Table 16-2)
- Female gender (see explanation in text)
 - Anatomic variations
 - Surgical or natural menopause without hormone replacement therapy
 - Pregnancy
- Kidney transplantation
- Diabetes mellitus
- Partner of sildenafil (Viagra) user*
- Sexually transmitted disease (STD) (urethritis)

*This is most likely the result of increased frequency of intercourse in women over the age of 35 who are more likely also to experience vaginal dryness.

are also more common during pregnancy. The increased risk is due to dilation of the upper urinary system, reduction of the peristaltic activity of the ureters, and displacement of the urinary bladder, which moves to a more abdominal position, thus further affecting the ureteral position.

In older women who are in a long-term care setting, the most frequently noted risk factors are advancing age and debilitation associated with conditions that impair voiding or cause poor perineal hygiene, such as dementia or stroke.⁵² Healthy, community-dwelling postmenopausal women share risk factors seen in both young and older women. Sexual activity and a previous history of UTI are common risk factors for both young and postmenopausal women, while incontinence is an additional risk factor in these older women.⁵³ The effects of estrogen decline (dry mucosa and vaginitis) may contribute to increased risk of infection because of the change in vaginal flora, but study findings remain unclear.

People with diabetes receiving treatment are also more prone to UTIs due to immunologic impairments; the presence of glycosuria, which provides a fertile medium for bacterial growth; and voiding difficulties resulting from diabetic neuropathy (detrusor paresis).⁵⁴⁻⁵⁷

Another significant and common risk factor for UTI is catheterization. Placement of a urinary catheter is a leading cause of infection in the hospital setting, accounting for 40% of nosocomial infections. The reasons are clearly related to the introduction of a foreign body that provides a direct pathway for bacteria to travel from the perineum to the bladder. Less commonly, a client may display a structural or functional abnormality that leads

to a UTI. Contributing structural problems may be kidney stones, cystocele, or prostatic hyperplasia. Examples of functional problems include reflux of urine from the bladder to the kidney and neurogenic bladder from diabetes, spinal cord injury, or multiple sclerosis.

Pathogenesis

The bacteria most often responsible for UTI are fecal-associated gram-negative organisms, with *Escherichia coli* accounting for about 80% of urinary tract pathogens. *Staphylococcus saprophyticus* causes 5% to 15% of UTIs, while *Enterococci*, *Klebsiella*, and *Proteus* make up the remaining common organisms.

Hospitalized clients are more likely to become infected with *Enterobacter*, *Klebsiella*, *Proteus*, *Pseudomonas*, *enterococci*, and *staphylococci* bacteria than outpatients with UTI. *Candida* species can be seen in persons who have undergone invasive instrumental investigations or catheterizations and in children with urogenital abnormalities.

These common urinary tract pathogens are able to adhere to the urinary tract mucosa, colonize, and cause infection. Several subtypes of bacteria contain genes that allow for greater virulence and ability to colonize urothelium than other organisms, making them uropathogenic. The most common route of entry of bacteria into the urinary tract is ascending up the urethra into the bladder. Although infrequent in occurrence, infections may be bloodborne (bacteria in the bloodstream) or acquired via the lymphatic system.

Clinical Manifestations

Classic features of UTIs are evident in older children and adults and include frequency, urgency, dysuria, nocturia, and, in children, enuresis. Fever, chills, and malaise may also be present. The individual may notice cloudy, bloody, or foul-smelling urine and a burning or painful sensation during urination or intercourse. Pain may be noted in the suprapubic, lower abdominal, groin, or flank areas, depending on the location of the infection.

In the case of kidney involvement, the diaphragm may become irritated, resulting in ipsilateral shoulder or lumbar back pain. The clinical manifestations in frail, older adults can be varied, often with malaise, anorexia, and mental status changes (especially confusion or increased confusion) as the most prominent features. Flank pain, fever, and chills often indicate an upper UTI or pyelonephritis.

MEDICAL MANAGEMENT

PREVENTION. UTIs can be prevented in some cases by drinking at least eight 8-oz glasses of water each day; urinating soon after sexual intercourse; for females, wiping from the front to back after urination so that bacteria from the anal area are not pushed into the urethra; changing sanitary pads often during menstruation; and washing the genital area with warm water before sexual activity to minimize the chance that bacteria can be introduced. The use of spermicidal agents with a diaphragm has been associated with an increased risk for UTIs. The use of another form of birth control may be warranted if repeated UTIs become problematic.

Certain foods may also be preventative. Berry juices and products containing fermented milk may be helpful in reducing the occurrence of UTIs, although further studies are needed to verify this relationship.¹⁰⁹ The use of cranberry juice in the prevention and treatment of UTIs has been controversial, with different studies showing positive and negative effects of cranberry juice as a preventive or therapeutic agent.^{6,31} More studies are needed to determine efficacy, dose, and appropriate candidates for this dietary treatment. The use of probiotics to increase normal vaginal flora may be of benefit. Preliminary studies are encouraging, although only certain types of *Lactobacillus* have had promising results.⁴⁹

There has also been debate as to whether hormone therapy can prevent UTIs in postmenopausal women. Recent studies indicate that oral as well as vaginal hormone therapy is not preventative and may be detrimental to heart health.^{17,195,158}

Instrumentation and particularly placement of urinary catheters frequently lead to UTI. However, if a catheter is needed, a condom catheter may have a reduced risk of causing UTI compared to indwelling catheters.¹⁶³ Preliminary studies also suggest that use of catheters coated with an antimicrobial agent may reduce the risk, but further investigations are needed.⁹⁸

DIAGNOSIS AND TREATMENT. The diagnosis of a UTI is typically made based on history and urinalysis results. A bacterial count of greater than 100,000 organisms per milliliter of urine is a commonly accepted criterion for diagnosis. Besides the bacterial count, the urine leukocyte count (more than 10 leukocytes per cubic millimeter of urine collected midstream), and presence of leukocyte esterase, nitrates, and protein are also helpful.

Many people demonstrate pyuria (leukocytes in the urine) without infection, and corroborating clinical and laboratory information must be evident to diagnose an infection. In clients who are healthy and without complicating features, empiric treatment with antibiotics is effective and urine cultures are not required.

Acute UTIs in healthy, nonpregnant clients are typically treated with antibiotics, particularly trimethoprim-sulfamethoxazole (TMP/SMX) or a fluoroquinolone, as recommended by the Infectious Diseases Society of America guidelines.¹⁹⁸ Yet over the past decade there has been a significant rise in resistance to TMP/SMX, with rates varying regionally. Initial treatment must take into account local resistance patterns as well as the health of the client. For individuals with complicating features, treatment failure could lead to severe morbidity and mortality, and in areas where TMP/SMX resistance is common, a fluoroquinolone may be more appropriate initial treatment until culture results are available.

Women who experience recurrent infections have several options for treatment depending upon the clinical situation and compliance of the client. They may take antibiotics prophylactically (typically as a daily dose), they may self-treat as they recognize typical symptoms,⁷⁵ or in the case of sexual intercourse as a precipitating factor, women may be advised to take antibiotics just after sex. Increased fluid intake may also help relieve symptoms and signs and is often used as an adjunct to

pharmacologic treatment. *Lactobacillus acidophilus*, a probiotic supplement of live, active organisms, may be recommended for anyone taking antibiotics to replace the naturally occurring bacteria in the intestines and to prevent candidiasis (yeast growth). A vaccine to prevent recurrent urinary infections of the bladder has proved successful in mice and is currently being tested in clinical trials.

For the minority of clients who develop UTIs as a result of structural or functional problems, further testing is needed to correct the abnormality. Ultrasound, radiographs, computed tomographic (CT) scans, and renal scans may be used to identify contributing factors such as obstruction. Postvoid residual and more complex tests such as voiding cystourethrography (VCUG) (upper urinary system) and urodynamic testing with and without fluoroscopy determination may be recommended for anyone at risk for urinary retention. Whenever possible, ultrasound assessment, rather than urinary catheterization, is recommended for measuring the postvoid residual.

SPECIAL IMPLICATIONS FOR THE THERAPIST 18-1

Urinary Tract Infections

PREFERRED PRACTICE PATTERNS

5B: Impaired Posture

5D: Impaired Joint Mobility, Motor Function, Muscle Performance, and Range of Motion Associated with Connective Tissue Dysfunction

Depending on the severity of the infection, the person with a UTI may not be able to participate fully in a rehabilitation program until the disease is brought under control. If the client begins to complain of nausea or vomiting, or has a fever greater than 102° F (39° C), or the therapist notes a change in mental status (most often confusion), immediate contact with the client's physician is warranted. These may be indications for hospital admission.

Awareness of the symptoms and signs associated with this disease may allow the therapist to recognize the onset of infection in its early stages. The initial symptoms may be subtle enough that the client is not alarmed to the point that he or she visits a physician. Early detection and treatment of this disorder are important to prevent possible permanent structural damage. In the case of insidious onset of back or shoulder pain, especially with a recent history of any infection, a medical screening examination may be warranted.

UTIs also increase the risk of development of infection elsewhere in the body, including osteomyelitis, pleurisy, and pericarditis. Therapists should also always be aware of their role in infection prevention and minimize their involvement as a risk factor (see Boxes 8-5 to 8-6).

In the case of the individual with recurrent, chronic infections such as inflammatory interstitial cystitis, intervention by a physical therapist will address any deficits in the musculoskeletal system as noted by the

evaluation, postural dysfunction, increased or decreased range of motion, and decreased strength. A crucial aspect to evaluation and intervention is the condition of the soft tissue, especially in the lower quadrant.

Restrictions are commonly found in people with interstitial cystitis involving the muscles that attach to the pelvis (e.g., adductors, gluteals, obturator internus and externus, piriformis, abdominals, and iliopsoas). A trigger point evaluation is essential in determining the presence of somatovisceral responses contributing to frequency and urgency. Specific passive and active stretching exercises and muscle reeducation activities are progressed according to the individual's response to the soft tissue interventions. Modalities such as biofeedback, ultrasound, and electrical stimulation along with behavioral techniques (e.g., for reducing frequency and urgency) may be employed.¹¹⁰ More specific intervention guidelines are available.^{91,92,185,203}

Pyelonephritis

Overview and Incidence

Pyelonephritis can be either an infectious process involving the kidneys (acute pyelonephritis) or a chronic inflammatory disease involving the kidney parenchyma and renal pelvis (chronic pyelonephritis). Acute pyelonephritis occurs in over 250,000 people per year, causing over 100,000 hospitalizations. The direct and indirect costs are estimated at \$2.14 billion.²⁰ It typically results from bacteria ascending from the bladder to infect the kidneys.⁸⁸ Similar to UTIs, acute pyelonephritis occurs more frequently in women than men, although men have a higher complication rate.⁶²

Chronic pyelonephritis is a tubulointerstitial disorder characterized by specific changes in the kidney (cortical scarring and deformation of the calices). These alterations can be a result of several diseases that can lead to renal insufficiency. Chronic pyelonephritis may be responsible for up to 25% of the population with end-stage renal disease (ESRD).

Etiologic and Risk Factors

The majority of acute pyelonephritis cases are associated with ascending UTIs (see Box 18-2) and are caused most commonly by *E. coli* (up to 85%).¹⁷³ A smaller proportion are caused by other gram-negative organisms such as *Proteus*, *Klebsiella*, *Enterobacter*, and *Pseudomonas* species.

Risk factors associated with increased risk for pyelonephritis in healthy, nonpregnant women include frequent sexual activity, recent UTI, recent spermicide use, diabetes, and recent incontinence.¹⁷³ In other cases, pyelonephritis can stem from bloodborne pathogens associated with infection elsewhere. People with bacterial endocarditis and miliary tuberculosis are susceptible to kidney involvement. In addition, immunocompromised people are at risk for bacterial and fungal seeding of the kidney with subsequent abscess formation.

Chronic pyelonephritis is the term that describes specific, abnormal renal findings. Several diseases or processes can lead to chronic pyelonephritis, such as vesicoureteral

reflux (urine is forced from the urinary bladder into the ureters and kidneys), urinary obstruction, analgesic nephropathy, or bacterial infection superimposed on a structural/functional abnormality. The most common cause of chronic pyelonephritis is vesicoureteral reflux, although the renal insufficiency associated with this is most often referred to as *reflux nephropathy*.

Pathogenesis

Although urine is typically sterile, the distal end of the urethra is commonly colonized by bacterial flora. As described under Etiologic and Risk Factors, bacteria can be transported to the urinary bladder in many ways. After urination, the subsequent passage of sterile urine from the kidneys to the bladder dilutes any bacteria that may have entered the bladder. If the residual urine volume is increased, as with an atonic bladder, an accumulation of insufficiently diluted bacteria can occur. Bacteria in the bladder urine typically do not gain access to the ureters for a variety of anatomic reasons. However, people with an abnormally short passage of the ureter within the bladder muscle wall and an angle of ureter insertion into the bladder wall that is more perpendicular are at risk for reflux of urine into the ureter itself. This reflux can be of sufficient force to carry the urine and the accompanying bacteria into the renal pelvis and calices.

Chronic pyelonephritis is defined by scarring with deformity of the calices. Processes that continually cause inflammation in the kidney can lead to chronic changes. Only a few processes can cause these changes, and they can be divided into three main groups: reflux, obstruction, and idiopathic.

Clinical Manifestations

The onset of symptoms and signs associated with acute pyelonephritis is usually abrupt. The complaints may include fever, chills, malaise, headache, and flank pain. The person may also complain of tenderness over the costovertebral angle (Murphy's sign). Symptoms of bladder irritation may be present (including dysuria, urinary frequency, and urgency) but are not required for the diagnosis.

Symptoms associated with chronic pyelonephritis vary depending upon the causative process; however, symptoms may not be present. The diagnosis is made more often by laboratory detection of kidney function changes.

MEDICAL MANAGEMENT

DIAGNOSIS AND TREATMENT. The presence of suggestive symptoms for acute pyelonephritis warrants laboratory testing and treatment. Urinalysis typically reveals pyuria, bacteriuria, and varying degrees of hematuria. A urine culture should always be obtained and often will result in the growth of the offending bacteria or fungus. In addition, the blood count usually demonstrates leukocytosis.

If the infection is severe enough or if complicating factors are present, hospital admission may be required for intravenous antibiotics and hydration. Typically, however, the condition is treated with an appropriate antibiotic medication. Symptoms typically begin

disappearing within several days. If the person does not show improvement within 48 to 72 hours, contact with the physician is warranted.

If the process associated with chronic pyelonephritis continues to progress, creating worsening scarring, the result may be ESRD requiring dialysis or transplantation.

RENAL DISORDERS

Cancer

Renal Cell Carcinoma

Overview and Incidence. Adult kidney neoplasms account for approximately 3% to 4% of all cancers.⁹⁶ During the past two decades, the incidence of these cancers has increased by approximately 2% each year.¹⁶¹

Renal cell carcinoma (RCC) is the most common adult renal neoplasm, accounting for more than 90% of renal tumors, and its incidence is rising (although the death rate is not). RCC occurs more frequently in males than females (about a 1.6:1 ratio), with a peak incidence between 60 and 70 years.

RCC is a heterogeneous group of cancers that are separated into four main types according to the cell type of origin: clear cell, papillary, chromophobe, and collecting duct RCC. Clear cell constitutes the majority of cases (80%), papillary is the next most common at 10% to 15% of RCCs, while chromophobe RCC and collecting duct RCC account for only 4% and 1%, respectively.

Etiologic and Risk Factors. RCC is linked to several hereditary diseases, including von Hippel-Lindau disease (a rare autosomal dominant familial cancer syndrome related to clear cell RCC), hereditary papillary renal carcinoma (an autosomal dominant disorder related to papillary RCC), and the Birt-Hogg-Dube syndrome (a rare autosomal dominant disorder related to chromophobe RCCs or mixed chromophobe RCCs-oncocytomas). These hereditary disorders are rare and only account for a small percentage of RCCs. Risk factors that can lead to the development of sporadic RCC include tobacco smoking, obesity, hypertension (diuretics), occupational exposure to substances such as organic solvents and asbestos, and acquired cystic kidney disease associated with ESRD.^{28,170}

Pathogenesis. As for other cancers, genetic mechanisms are now being discovered for RCC, which better explain the causes and aid in the treatment. Because RCC is seen in a few hereditary diseases, scientists have been able to locate specific genetic abnormalities. Von Hippel-Lindau disease has several characteristic abnormalities, including the development of RCC (clear cell type). The von Hippel-Lindau tumor suppressor gene (VHL) is located on chromosome 3.

Of interest, this same abnormality has been detected in 60% to 80% of people with sporadic clear cell RCC. The product of the VHL gene normally suppresses genes that, in the presence of hypoxia, cause endothelial growth, cell growth, and glucose uptake, and affect acid-base balance.³² When this gene is altered, cell proliferation occurs unchecked, despite the absence of hypoxia. Factors

other than VHL mutations are involved in this process and most likely account for the remaining percentage of sporadic clear cell RCC occurrences.

Another gene linked to RCC is the MET proto-oncogene. This abnormal gene, located on chromosome 7, is duplicated in approximately 75% of sporadic papillary RCC cases. If the FH gene (which encodes for the Krebs cycle enzyme fumarate hydratase) is inactivated, the result is another hereditary disorder known as hereditary leiomyomatosis and renal cell cancer syndrome. Chromophobe RCC may develop in clients with mutations to the BHD gene, whose product is suspected to suppress tumors.³²

Clinical Manifestations. The classic triad of symptoms related to RCC is flank pain, hematuria, and a palpable abdominal mass. Yet about half of all cases are discovered incidentally on a radiographic examination, such as a CT scan.³² Kidney cancers are generally silent, particularly in the early stages, although nonspecific symptoms may develop such as malaise, anemia, or unexplained weight loss. Hematuria is the single most common presenting finding, occurring in up to 50% of cases, yet it is frequently intermittent and microscopic.

Symptoms associated with metastasis can be the initial manifestation; about 25% to 30% of clients have metastatic disease at the time of diagnosis.¹¹⁶ Metastases most often occur in the lungs (75%), regional lymph nodes (65%), bones (40%), and liver (40%).²¹⁰ The client may develop a cough or bone pain secondary to metastasis to the lungs or bone, respectively.

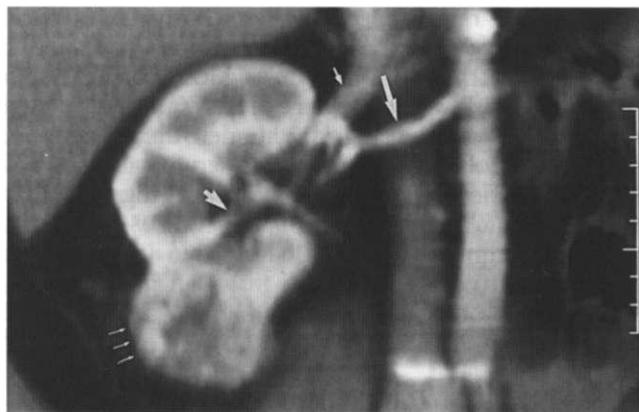
Potentially confusing the clinical presentation of this condition is the fact that RCCs are associated with ectopic hormone production and paraneoplastic symptoms, including fever, hypertension, hepatic dysfunction, and hypercalcemia. Hormones produced by the tumors include parathyroid-like hormone, gonadotropins, renin, erythropoietin, glucagon, and insulin.

As discussed earlier, several hereditary syndromes predispose to the development of RCC. Each of these disorders has its own unique clinical manifestations other than RCC. For example, von Hippel-Lindau disease is associated with retinal angiomas, hemangioblastomas of the central nervous system, pheochromocytomas, and clear cell RCCs. These distinguishing features lead to the diagnosis and allow regular monitoring and surveillance for RCC.

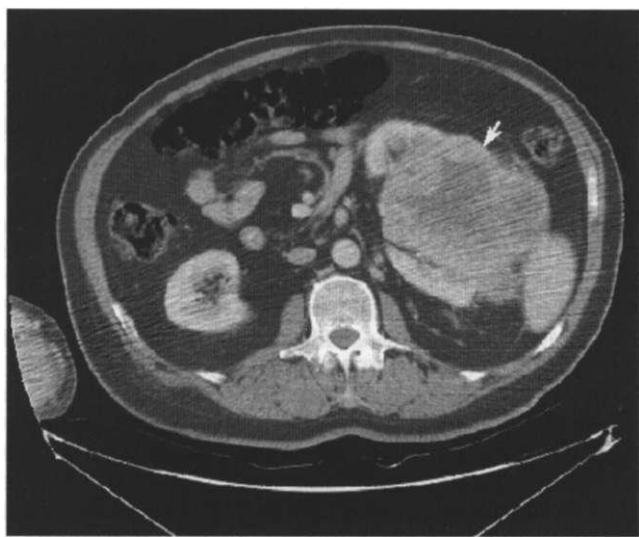
MEDICAL MANAGEMENT

DIAGNOSIS. The primary feature of RCC is the renal parenchymal mass, which can be detected by a variety of imaging modalities (Fig. 18-2). The widespread availability of abdominal ultrasound (Fig. 18-3), magnetic resonance imaging (MRI), and CT scanning has increased the diagnosis of incidental renal tumors.

Determining whether the mass is benign or malignant can be difficult, often requiring surgical removal before a definitive diagnosis can be made. If hematuria is present, intravenous pyelography (IVP) may be the initial procedure to identify renal abnormalities. IVP is a radiographic test that allows for evaluation of the kidneys, ureters, and bladder. A dye injected into the bloodstream is filtered and secreted by the renal tubules. The IVP provides infor-

**Figure 18-2**

Renal cell carcinoma on computed tomographic scan. A reconstructed image in the coronal plane of section shows vascular anatomy by demonstration of the renal artery (large arrow), renal vein (small arrow), excretion into the pelvicaliceal system, which is not obstructed (arrowhead); and renal cell carcinoma arising from the lower pole of the right kidney (thin arrows). The cancer is confined to the cortex; therefore, partial nephrectomy can be performed. (From Brenner BM: *Brenner and Rector's The kidney*, ed 7, Philadelphia, 2004, Saunders.)

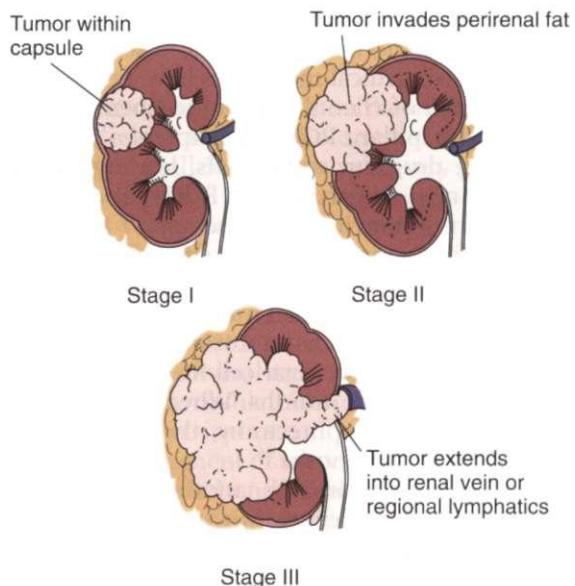
**Figure 18-3**

Computed tomographic scan of abdomen demonstrating a large left renal mass (arrow) consistent with renal cell carcinoma. (From Townsend CM: *Sabiston textbook of surgery*, ed 17, Philadelphia, 2004, Saunders.)

mation including renal size, function, position, the presence of calculi, masses, and congenital variants.

Ultrasonography can be used to further evaluate the renal parenchyma and detect small tumors (less than 1 cm). The advantage of the CT scan is that the greatest renal anatomic detail is obtained and details of neighboring organs such as the liver, colon, spleen, and lymphatics will also be available.

STAGING. The American Joint Committee on Cancer (AJCC) and the University of California, Los Angeles (UCLA) Integrated Staging Systems are currently used to stage this disease. The AJCC utilizes the TNM (tumor,

**Figure 18-4**

Renal cell carcinoma stages. Not shown: stage IV, distant metastases.

node, metastasis) system defining stages I through IV (Fig. 18-4). The UCLA Integrated Staging System employs the Eastern Cooperative Oncology Group (ECOG) performance status scale and the Fuhrman nuclear grade not only to determine stage but also prognosis. Clients are classified into low-, intermediate-, and high-risk groups. This staging system also provides risk categories for those with metastatic disease.

TREATMENT. Surgery is the principal treatment for RCC. Traditionally, a radical nephrectomy (removal of the kidney; Gerota's fascia, a fibroareolar tissue surrounding the kidney and perirenal fat; the adrenal gland; and regional lymph nodes) has been preferred, although less aggressive methods are being investigated. Nephrectomy may also be beneficial for clients with metastatic disease, since combined surgical and medical therapy has slightly improved survival. Metastatic lesions may be removed at the time of surgery; however, this has not been shown to improve survival.

A partial nephrectomy may be appropriate for clients with a small mass (less than 4 cm), a solitary kidney, masses in both kidneys, renal insufficiency, or the presence of a hereditary disorder related to RCC. This approach, however, carries a 3% to 6% risk of tumor recurrence.¹³⁸ Laparoscopic nephrectomy has gained acceptance as a method for reducing hospital stay and postoperative pain, and providing a faster recovery. Partial nephrectomy is challenging and often requires an open procedure.

Newer, less invasive methods for treating RCC include percutaneous thermal ablation using radiofrequency heat ablation or cryoablation. These types of procedures are best for small tumors (less than 3 cm) and in clients with comorbidities that can increase surgical risk. Further investigations are required, although the complication rates appear to be low.¹³²

Medical treatment, adjuvant to surgery, is offered for more locally advanced or metastatic disease. Response rates to standard medical modalities have not been good. Only 4% to 6% of clients respond to chemotherapy²⁰⁷; clear cell and papillary RCC may express a protein that transports the drug out of the cells, leading to chemotherapy resistance. Collecting duct RCC may demonstrate a higher response rate to chemotherapy.

Other chemotherapy agents are currently being tested to determine if they provide a better response rate. Immunomodulatory agents have been used with some success. Interferon-alfa has provided a 14% response rate alone in clients with metastatic clear cell RCC, which is apparent for an average of 6 months. When this drug is used in conjunction with nephrectomy, the survival rate has increased by 3 to 10 months.²⁰⁸

High-dose interleukin-2 is another agent that has shown some benefit in clients with metastatic disease; it is currently the only Food and Drug Administration (FDA)-approved agent for advanced RCC. High-dose interleukin-2 has demonstrated a 21% response rate, but the side effects (including capillary leak syndrome) are often too severe to continue treatment. For those persons able to tolerate the high dose, response rates are reported to be 54 months and perhaps longer.²⁰⁹

Research has shown that allogeneic stem cell transplantation following a nonmyeloablative regimen can successfully create a graft-versus-tumor effect, which in initial studies demonstrated a 44% response (although continued studies have been less successful).²¹⁰ Two difficulties encountered with transplantation include the life-threatening problem of graft-versus-host disease and the requirement of a matched sibling donor.

Other areas of ongoing research include tumor vaccines and tumor-specific targeting agents (i.e., targeting specific pathways with an antibody or blocking blood vessel formation). One angiogenic agent, sunitinib, a tyrosine kinase inhibitor, is able to block the receptors of vascular endothelial growth factor and platelet-derived growth factor, decreasing the blood supply to the tumor.²¹¹ Preliminary studies are encouraging, and other targeted agents are in trials.

PROGNOSIS. The prognosis of RCC depends upon the type and staging. Sporadic papillary RCC has a 5-year survival rate of almost 90% and is known to have a lower incidence of metastasis compared to clear cell RCC. However, individuals with metastatic papillary RCC have a lower survival rate than those with metastatic clear cell RCC.

Most chromophobe RCCs will have a favorable post-surgical course providing the tumor size is small and the grade low. Collecting duct RCC is an aggressive tumor with a poorer prognosis. The survival rates according to the AJCC system of tumor size demonstrate a 5- and 10-year survival of 95% and 91%, respectively, for T1-stage tumors; of 80% and 70% for T2 tumors; and of 66% and 53% for T3a tumors.

Utilizing the UCLA Integrated Staging System, the 5-year survival rate for the low-risk group is 91%, while the intermediate- and high-risk groups have an 80% and

55% survival rate, respectively. Unfortunately, 40% of locally removed renal cell tumors return.¹⁴⁶

Factors that portend a poor prognosis for metastatic RCC include a low performance score (Karnofsky performance status score), a high lactate dehydrogenase level, a low hemoglobin level, and a high serum calcium level. Metastatic disease has a much worse prognosis than localized tumor, with a 5-year survival of 0% to 7% for clients with multiple metastatic lesions.²¹²

SPECIAL IMPLICATIONS FOR THE THERAPIST 18-2

Renal Cell Carcinoma

Therapists working primarily with the geriatric population need to be aware of the symptoms and signs of this disease. Questions in the history related to hematuria, unexplained weight loss, fatigue, fever, and malaise are important, regardless of the reason for the physical therapy care.

Awareness of new onset of unexplained abdominal, flank, or back pain; cough; or other signs of pulmonary involvement should raise concern on the therapist's part and warrants communication with a physician. In addition, RCC is the most common metastatic tumor to the sternum. An onset of sternal pain or a mass in someone with a history of RCC should be brought to the physician's attention.

The extensive abdominal and thoracic surgical sites may produce scarring that affects the client's posture and ability to move, increasing mechanical stress on the musculoskeletal system. Myofascial and soft tissue mobilization of the abdominal and thoracic regions may be of benefit to these people. If a history of abnormal renal function in addition to the cancer is evident, additional precautions may need to be taken by the therapist. See the section on chronic renal failure later in this chapter.

Wilms' Tumor

Overview, Incidence, and Risk Factors. Wilms' tumor, or nephroblastoma, is the most common malignant kidney neoplasm in children. Approximately 500 new cases are reported annually in the United States. Age is the primary risk factor. The disease most commonly occurs during the first 6 years of life, with approximately 75% of cases occurring in children under the age of 5. The peak incidence is between the ages of 3 and 4, and the tumor occurs slightly more often in African Americans and girls. Wilms' tumors occur bilaterally in 5% of cases.

There are several hereditary syndromes that can predispose children to the development of Wilms' tumor. The three most common include the WAGR syndrome (Wilms, aniridia, genitourinary malformation, mental retardation), the Beckwith-Wiedemann syndrome, and the Denys-Drash syndrome.

Etiologic Factors and Pathogenesis. Although the majority of cases are sporadic, about 1% to 3% have a

family history of Wilms' tumor, and up to 10% are seen in hereditary syndromes. Molecular genetics plays an important role in the cause of Wilms' tumor. The biologic signaling pathways determining the origin of Wilms' tumor are complex, and several genes at several loci may be involved.

The most well-known and studied gene of Wilms' tumor is the WT1 suppressor gene, a complex protein that is an essential regulator of kidney development; mutations in this gene result in the formation of tumors in about 10% of Wilms' tumor cases.¹²¹ These genes have also been implicated in the formation of many other cancers.

Other genetic alterations such as WT2 and familial genetic alterations termed FWT1 and FWT2 have also been located. Significant investigations are ongoing to determine how these genes and their products interact in order to understand the mechanisms in the development of Wilms' tumor and provide improved therapy.

Clinical Manifestations. Wilms' tumors can be difficult to discover early because the tumor can grow to a large size before causing symptoms. Fortunately, despite large tumor size, most Wilms' tumors do not metastasize. An abdominal mass, most often detected by the parents, is the most common presenting sign. Up to 30% of children may complain of abdominal pain, malaise, loss of appetite, or nausea/vomiting. Hematuria may occur in up to 30% of cases and hypertension in up to 25% of affected children. Congenital abnormalities may be present, particularly those associated with hereditary syndromes with a predilection for Wilms' tumor (13% to 28%).

MEDICAL MANAGEMENT

STAGING AND DIAGNOSIS. Staging is performed according to the National Wilms Tumor Study Group (NWTSG) staging system. Tumors are staged into five groups (stages I to V), depending on tumor size and growth into surrounding structures. Histologic features are also important. Histologically, tumors can be classified as having favorable histology or unfavorable histology (anaplastic features). About 40% of tumors are discovered while in stage 1, while only 5% of cases are at stage V.

Abdominal ultrasonography helps define the cystic or solid nature of the mass and helps determine whether the renal vein or vena cava is involved. CT scan of the abdomen is helpful in determining the extent of the tumor but can be difficult to perform with small children. A chest radiograph and CT of the chest are used to determine the presence of metastases to the lung. MRI may also be beneficial in determining the extent of the disease.

TREATMENT. Surgical resection of the tumor is the primary treatment regardless of the stage of the disease. A radical nephrectomy is the most common procedure, although a nephron-sparing procedure may be performed in clients who have lesions in both kidneys. Regional lymphadenectomy may be carried out, as lymph node involvement strongly affects the prognosis. Chemotherapy is also used for all stages of the disease, sometimes preoperatively, with radiation therapy being added to the treatment regimen for stage III and IV disease and tumors with unfavorable histologic findings. (See Chapter 9 for the

side effects associated with chemotherapy and radiation therapy.)

PROGNOSIS. Prognosis depends on the histologic appearance of the lesion, stage of the disease, and age of the child. But the overall 5-year survival is very good at 92%. Individuals with stage I tumors with favorable histology have a 92% 4-year event-free survival rate and an overall survival rate of 98%. Those with stage I tumors with unfavorable histology have only a 70% 4-year event-free survival rate and an overall survival rate of 83%.⁴² Even those with stage V tumors with favorable histology have a 4-year event-free survival rate of 81%. Those with stage V tumors with unfavorable histology exhibit only a 17% 4-year event-free survival rate.

With the development of successful treatment, emphasis is now being placed on limiting significant long-term side effects while maintaining the high cure rate in tumors with favorable histology.⁹⁹ Further treatment options are needed for advanced tumors with unfavorable histology. More than 80% of people with Wilms' tumor can be cured using multimodal therapy.³⁴ Wilms' tumor may recur years after the initial diagnosis.

Renal Cystic Disease

Overview

A renal cyst is a cavity filled with fluid or renal tubular elements making up a semisolid material. The presence of these cysts can lead to degeneration of renal tissue and obstruction of tubular flow. Renal cysts vary considerably in size, ranging from microscopic to several centimeters in diameter, and can be single or multiple, unilateral or bilateral.

Cysts in the kidney are rather common and can be classified into six categories of cystic diseases: (1) polycystic kidney disease (PKD), (2) cystic diseases of the renal medulla, (3) acquired cystic disease, (4) single cysts, (5) cystic renal dysplasia, and (6) miscellaneous renal cystic disorders.

The formation of simple cysts is the most common cystic disorder of the kidney. Simple cysts are usually less than 1 cm in diameter and do not often produce symptoms or compromise renal function. Acquired cysts may develop secondary to dialysis, diabetes mellitus, or glomerulonephritis. PKD is a leading cause of ESRD, frequently requiring dialysis and renal transplantation. Because of the seriousness and fairly common occurrence of PKD, this section will principally discuss PKD. The remaining disorders constitute less common causes of renal cysts.

Incidence

PKD is manifested as either an autosomal dominant (ADPKD) or autosomal recessive (ARPKD) disorder. Although PKD can occur spontaneously, most cases are hereditary. ADPKD is one of the most common hereditary disorders in the United States, affecting more than 600,000 Americans (about 1 in every 500 to 1 in every 1000 persons). ARPKD is rare.

Persons with ADPKD may not manifest symptoms until the third or fourth decade of life, while ARPKD is

evident at birth and can cause death early in life. ADPKD affects people from all races and ethnic groups. Most people with ADPKD will exhibit evidence of the disease by the age of 80, but only half progress to ESRD. ADPKD is the fourth leading cause of ESRD and accounts for 10% of all cases of ESRD.

Risk Factors

While there is currently no way of determining which people with ADPKD will develop ESRD, there are a few risk factors that have been linked to a more rapid progression. These factors include hypertension, multiple pregnancies, male gender, and the expression of the genetic mutation PKD1.

Etiology and Pathogenesis

Most renal cysts form from the epithelium of a preexisting renal tubule. These epithelial cells typically exhibit a reabsorptive function, but have secretory capabilities. In the case of cyst formation, epithelial cells with genetic mutations begin to secrete fluid into the tubule once stimulated by endocrine, paracrine, and autocrine regulating proteins. Such proteins may also play a role in the size and rate of growth of the cyst.

As a cyst grows, it detaches from the nephron (about 75% detach completely). The epithelial cells then continue to proliferate and fibrosis develops. With time, the pressure created by the expanding, multiple cysts interrupts the function of neighboring nephrons, leading to apoptosis of noncystic nephrons. Although normal nephrons enlarge in an attempt to compensate for the loss of nephrons, this is unsuccessful in half of people with PKD.

In ADPKD, there have been several genes linked to the development of cysts. These abnormalities are located on chromosomes 16 and 4 and are called PKD1 and PKD2. Other genes are likely involved as well. These genes code for proteins that function in transferring signals from the extracellular matrix into the cell to promote cellular proliferation and differentiation. Both genes need to be affected before there is the resultant development of disease.

About 85% of persons with ADPKD express a mutation in PKD1, while only 15% demonstrate a mutation in PKD2. A small percentage has a mutation in another gene. Although clinical manifestations are similar for people with PKD1 and PKD2, clients who exhibit the PKE2 mutation progress to end-stage renal failure about 10 years later than those with the PKD1 mutation.

Mutations to the gene coding for a large protein called fibrocystin on chromosome 6 lead to ARPKD. Further studies are needed in order to clearly define the role of these genes and their products in the formation of PKD.

Clinical Manifestations

Although PKD is a hereditary disorder, only 60% of people are able to give a familial history of PKD, suggesting that spontaneous mutations occur frequently. For those families with a history of PKD, individuals can be monitored. In people who lack a familial history, cysts often are asymptomatic and found incidentally on routine urographic examination.

Symptoms associated with autosomal dominant disease may include pain, hematuria, fever, and hypertension. Abdominal or flank pain is the most common symptom in ADPKD. It can be associated with bleeding, growth of cysts, stones, infection, or, rarely, tumor. Most of these clients will have significantly enlarged kidneys that are palpable abdominally.

Associated hematuria may be gross or microscopic. Rupture of a cyst usually accounts for incidents of gross hematuria. Fever can be related to an infected cyst secondary to pyelonephritis. Hypertension is hypothesized to occur as a result of sodium and water retention because of damage to the tubules.^{118,157} Hypertension also hastens the development of fibrosis and is linked with accelerated progression to ESRD.

Liver cysts are also common in clients with ADPKD; about half have liver cysts at diagnosis. Unlike the kidney cysts, liver cysts rarely lead to problems such as liver failure or portal hypertension. People with ADPKD may also be affected with other genetic abnormalities, such as thoracic and abdominal aortic aneurysms, cerebral aneurysms, mitral and aortic valve prolapse, colonic diverticular disease, and pancreatic cysts.

MEDICAL MANAGEMENT

DIAGNOSIS. Ultrasonography is used to screen for PKD. People less than 30 years of age should demonstrate at least two cysts in *one* kidney in order for PKD to be diagnosed. Persons between the ages of 30 and 59 should have at least two cysts in *each* kidney, while people older than 60 years should demonstrate four cysts per kidney. Genetic tests can be performed to corroborate radiographic information. Simple cysts are uncommon in clients with PKD; the simultaneous presence of both large and small cysts is the norm.

CT is a useful radiographic test, distinguishing between solid and fluid-filled masses and displaying the presence of cysts of varied sizes. CT can also reveal the presence of hepatic cysts, making the diagnosis of PKD more likely. Prognostic information can also be obtained from the contrast-enhancing portion of a CT. Only the normal renal tubules will have contrast in them, revealing the degree of functioning nephrons.

MRI is often a better choice, especially for children or persons with renal dysfunction, or in the early stages of the disease. Urinalysis may detect hematuria and proteinuria, or the clinical examination may reveal enlarged, palpable kidneys. As appropriate, other causes of renal cysts should be addressed. Occasionally, tissue biopsy or surgical exploration is necessary to make the definitive diagnosis.

TREATMENT. Because hypertension is a known risk factor for progression to ESRD, blood pressure should be monitored and controlled, particularly if a family history is present and the disease is diagnosed in young adults. Stimulation of the renin-angiotensin system was thought to be the cause of hypertension in ADPKD, but this has been questioned and other causes postulated. For this reason, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have not been more successful than other blood pressure medications.

in preventing the progression of ADPKD.¹²⁶ Studies have suggested that by keeping blood pressure at a normotensive level there is a slowing of progression to ESRD.¹⁷⁴

Pain can be controlled through analgesics or treatment of the underlying cause (i.e., treating infections with antibiotics). Percutaneous aspiration of cystic fluid followed by injection of a sclerosing agent has helped some clients with pain from expanding cysts. Surgery and laparoscopic surgery can be performed to remove or unroof large cysts for pain relief. Infections can be difficult to treat, since the infection may be isolated in the cyst or an abscess may form. Possible associated findings, such as cerebral aneurysms, should be screened for and monitored.

SPECIAL IMPLICATIONS FOR THE THERAPIST 18-3

Renal Cystic Disease

When treating a client with a history of renal cystic disease, therapists should be aware of symptoms and signs suggesting that the condition is worsening. The presence of any of these clinical findings warrants referral to a physician. An awareness that this population is at risk for hypertension and UTI and at increased risk of developing cerebral and aortic aneurysms and mitral valve problems is also necessary. The presentation of any symptoms or signs suggestive of the presence of these conditions again warrants referral to a physician. Lastly, the fact the kidneys may be enlarged can account for atypical findings on palpation.

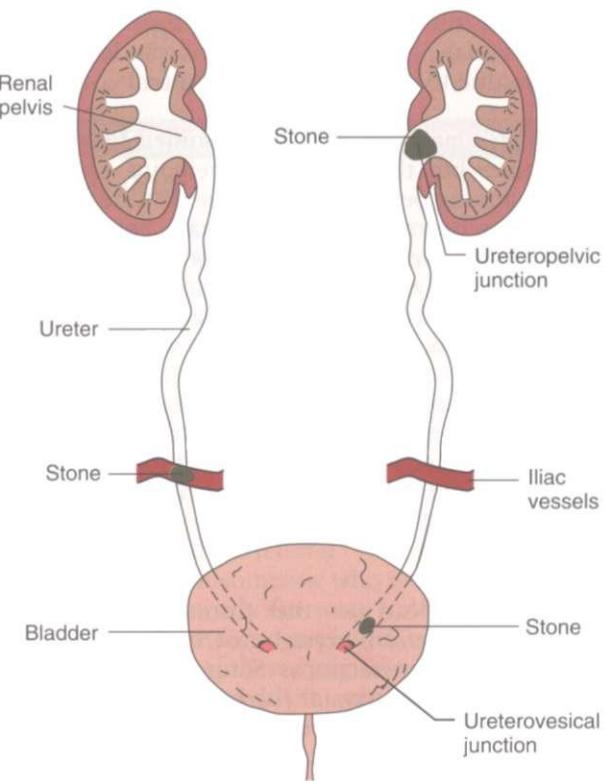


Figure 18-5

The three most common sites of urinary obstruction secondary to renal calculi.

Renal Calculi

Overview

Urinary stone disease, or nephrolithiasis, is the third most common urinary tract disorder, exceeded only by infections and prostate disease. A majority of the stones develop in the kidneys. Once the stones move out of the kidney into the ureter, they are referred to as ureteral stones (bladder stones are considered a separate disorder).

The stones, or calculi, are crystalline, ranging from popcorn kernel shapes to jagged starbursts, and can cause urinary obstruction and severe pain. Urinary obstruction typically occurs at one of the following three sites: (1) the ureteropelvic junction, (2) where the ureter crosses over the iliac vessels, and (3) at the ureterovesical junction (Fig. 18-5). The four basic types of stones are calcium (oxalate and phosphate), struvite, uric acid, and cystine.

Calcium stones are by far the most common (70% to 85%). Struvite stones are related to recurrent bacterial UTIs with organisms that produce urease. Uric acid stones (5% to 10% of nephrolithiasis cases) occur due to an increased level of urate in the blood and uric acid crystals in the urine, which is common in persons with gout. Cystine stones are uncommon (accounting for about 1% of all cases of nephrolithiasis) and caused by a hereditary disorder, cystinuria. Affected persons are unable to absorb cystine, and large amounts are excreted in the urine.

Incidence

Nephrolithiasis occurs in about 5% of adults, with men being affected more frequently than women (6% versus 4%, respectively).¹⁸² Because of the severe and debilitating pain associated with kidney stones, cost is significant, including doctor visits, hospitalizations, and lost work. In the year 2000, over 2 million doctor visits and 177,496 hospital stays resulted from kidney stones, costing \$2.07 billion.¹⁸¹ The primary age span for the initial presentation of the disease is 30 to 60 years of age for men, and 20 to 30 years for women. A higher incidence of renal calculi occurs in industrialized countries and areas noted for high temperatures and humidity. The incidence of this disease is highest in the hot summer months.

Etiologic and Risk Factors

With an understanding of the factors and mechanisms that lead to stone formation, risk factors are more evident and modifiable. Disorders that lead to an overexcretion and supersaturation of calcium or oxalate can lead to stone formation. These include illnesses such as idiopathic hypercalciuria, renal tubular acidosis (RTA), primary hyperparathyroidism, and hyperoxaluria.

It is also known that low quantities of citrate (which typically binds calcium, thereby acting as an inhibitor to stone formation) can lead to nephrolithiasis. Uric acid crystals are sensitive to urine pH, coming out of solution in an acidic pH; thus an acidic urine pH can lead to uric acid stones.¹⁸⁰ Gout is a disorder in which excess urate is

excreted into the urine, leading to a supersaturation of uric acid crystals. Chronic dehydration can lead to stone formation due to a decreased fluid content compared to crystals.

Other risk factors have been identified by epidemiologic studies but the mechanism remains unclear. For example, among persons with recurrent stone formation, it is often on one side only (unilateral). Some investigators have hypothesized that sleep posture (i.e., consistently sleeping on one side) may promote stone formation on the one side.¹⁷⁹ Obesity is associated with an increased incidence of urinary stone episodes in women but not in men.¹⁵⁴

Excess intake of supplemental calcium, sodium, sucrose, and animal protein have been dietary risk factors implicated in stone formation. A lack of sufficient calcium and potassium in the diet can also increase a person's risk for kidney stones.³⁶

Pathogenesis

Several factors lead to the formation of stones—saturation, nucleation, crystal growth and aggregation, and cell/crystal interactions. Saturation refers to the amount of dissolved crystal (such as calcium oxalate or calcium phosphate) in the urine compared to volume.

Crystals are able to stay dissolved in the urine until it becomes oversaturated. Factors such as the amount of calcium, oxalate, and water excretion determine saturation. With oversaturation, crystals come out of solution (or out of the urine) into a solid and begin to grow around a particle, or nucleus. It is uncommon for urine to become so oversaturated that a new nucleus of calcium oxalate or calcium phosphate is formed. Most often, a small particle, bacteria (small nanobacteria), or other crystal already present in the urine acts as a nucleus for the crystals to grow around (i.e., stones may have a nucleus of one crystal type, but surrounded by another crystal type).

Crystals then grow at a rate depending on the saturation of the urine. The more supersaturated, the more quickly larger stones form. These stones also require enough time to enlarge, since normal flow is often sufficient to move small stones through the urinary tract. It is proposed that the growing crystal aggregate becomes attached to the urinary tract epithelium and transported into the cell membrane. Here, the cell membrane may also act as a nucleus. Investigations are ongoing to determine the significance of cell/crystal interactions.

Clinical Manifestations

Clinical symptoms are the same for the various types of stones. The classic presentation of a kidney stone is acute "colicky" flank pain radiating to the groin or perineal areas (including the scrotum in males and labia in females) with hematuria. The pain is severe; most people are unable to find a comfortable position.

The location of the pain may vary depending on where the stone is lodged in the ureter. Abdominal pain with radiation to the groin may be more pronounced if the stone is higher in the abdomen, while a stone at the ureterovesical junction may give rise to lower quadrant abdominal pain radiating to the tip of the urethra.

Symptoms consistent with a UTI such as urinary urgency and frequency and dysuria are often present. Hematuria is present in over 90% of cases (although the absence of hematuria does not mean nephrolithiasis is not the diagnosis).¹⁴ Nausea and vomiting may also be manifested.

MEDICAL MANAGEMENT

PREVENTION. Recurrence of calculi is common in up to 50% of people within 5 years if preventive steps are not taken. A metabolic evaluation should be performed in clients who are willing to comply with tests and prophylactic methods (only 36% to 70% of people with recurrent stones comply long term with recommended measures).^{148,193} Tests and appropriate preventive measures vary depending on the type of stone passed. Common tests include 24-hour urine collection for calcium, oxalate, uric acid, phosphate, citrate, pH, potassium, and creatinine; serum calcium; serum blood urea and creatinine; and parathyroid hormone (PTH). If a specific disorder, such as hyperparathyroidism, is identified, treatment reduces the risk for further stones.

Adequate fluid intake is essential to the prevention of stones and recurrences by reducing the saturation of stone-forming crystals. Clients should be encouraged to drink enough fluid to maintain clear-colored urine. Other dietary modifications are made according to stone type. Urinary uric acid can be reduced by decreasing the amount of protein ingested. Urine citrate can be increased by consuming more fruits and vegetables and decreasing the amount of acid-producing food (such as animal protein).³⁶ A restriction of calcium is not recommended and may be harmful.^{13,38}

Medications can be helpful in certain situations if dietary means alone are not sufficient in preventing stone formation. Thiazide diuretics (which increase calcium excretion); alkali, such as potassium citrate (beneficial in increasing urine citrate excretion); and allopurinol (prevents the precipitation of uric acid crystals) may be useful. Further research is needed to determine the efficacy of specific dietary changes and the best means to prevent kidney stones.

DIAGNOSIS. A variety of tests are used to diagnose this disease. Noncontrast helical CT scanning is the first-line imaging test for renal colic. Once a stone has been visualized on CT, a plain radiograph can help determine the type of stone. Approximately 90% of calculi are radiopaque, making them visible on an abdominal radiograph. These types of stones are composed of calcium or other minerals, while uric acid stones are not visible on a plain radiograph. Other traditional imaging tests (e.g., ultrasonography and IVP) can also help in the management of stone disease. Hematuria, infection, the presence of stone-forming crystals, and urine pH can be determined on urinalysis.

TREATMENT. The mainstay of treatment for acute nephrolithiasis includes intravenous fluids and medications to relieve nausea/vomiting and pain (narcotics or nonsteroidal antiinflammatory drugs [NSAIDs]). The α -blockers and calcium channel blockers are commonly used to treat

hypertension, but both drugs also appear to flush out kidney stones by relaxing the ureter and increasing liquid pressure. Some physicians prefer *a*-blockers because they have fewer side effects. Most clients can be watched; however, some require immediate intervention to remove the stone.

Characteristics requiring urgent care include the presence of high-grade obstruction, anuria (no passage of urine), obstruction plus infection proximal to the stone, impending renal function deterioration, unresponsive pain or vomiting, or a solitary or transplanted kidney.¹⁸⁷ In these situations, percutaneous nephrostomy or ureteral stenting can be performed. Intravenous antibiotics are given for infection; *E. coli* is the most common organism.

A majority of stones less than 5 mm in diameter (a little smaller than the width of a pencil eraser) will pass spontaneously; two thirds that do pass on their own do so within 4 weeks. The urine should be strained in order to retrieve any stones; these can be analyzed for crystal content.

Persons waiting for stones to pass should continue drinking fluid (enough to produce about 2 L/day of urine or keep the urine clear-colored instead of yellow). Fluids with sodium should be avoided; lemonade may be helpful since it increases urinary citrate and decreases calcium oxalate supersaturation.¹⁷⁷ A follow-up CT 3 to 4 weeks after the initial episode will verify the passage of the stone or the need for intervention if the stone is unmoved.

Clients who have kidney stones of less than 1 cm in the proximal ureter can receive shock-wave lithotripsy. Shock-wave lithotripsy uses the transmission of shock waves (a type of sound wave) to break the calculi into fragments. Since the soft tissues of the body have similar densities, the shock waves pass through these structures with low attenuation. When the shock wave encounters a boundary between substances of differing acoustic density (i.e., a calculus in the ureter), high compressive forces are generated, causing a breakdown of the stone. The goal is to reduce the diameter to the point where spontaneous passage of the stone occurs.

Stones greater than 1 cm (and in the proximal ureter) benefit from ureteroscopy. Ureteroscopy involves passing a scope through the urethra and bladder into the ureter until the stone is reached. Then a laser (holmium:yttrium-aluminum-garnet [YAG]) is passed through the scope, the tip of the laser is placed on the stone, and the laser is discharged, producing photothermal lithotripsy.¹⁹⁵

Stones located in the distal portion of the ureter can be treated with either method. Ureteroscopy is less expensive than shock-wave lithotripsy but requires greater technical expertise.¹²² Some studies show that clients slightly prefer shock-wave lithotripsy to ureteroscopy.¹¹³ Both methods produce excellent results.¹¹² Guidelines from the Ureteral Stones Clinical Guidelines Panel are available.¹⁷⁶

Uric acid stones are unique in their treatment. Since these stones dissolve in acid, the urine of affected clients can be acidified with potassium citrate or sodium citrate to increase the urine pH to at least 6.5. Stones are fre-

quently not composed purely of uric acid, and further intervention may be required.

SPECIAL IMPLICATIONS FOR THE THERAPIST

18-4

Renal Calculi

If the classic symptoms are present, the renal colic associated with the calculi will not be confused with muscular or joint pain. The condition, however, may be manifested by symptoms that are intermittent and not severe. Depending on where the urinary collecting system is obstructed, the condition may be manifested solely by unilateral back pain, ranging from the thoracolumbar junction to the iliac crest. The therapist needs to be vigilant for complaints of urinary dysfunction and risk factors associated with this disease. Murphy's percussion test can be performed to determine the need for medical referral.

If working with someone who is concurrently being treated conservatively for renal calculi, the therapist must be vigilant for complaints of fever, chills, or sweats. An onset of these symptoms warrants immediate communication with the physician.

Chronic Kidney Disease

Overview

Chronic kidney disease (CKD) is defined as the alteration of kidney function or structure for greater than or equal to 3 months' duration.⁴⁶ CKD can be attributed to a variety of conditions that lead to a loss of kidney function. The three most common causes are diabetes (44%), hypertension (27%), and glomerulonephritis (8%). Cystic kidney disease and other urologic diseases account for about 5%, while other conditions (such as excessive aspirin or acetaminophen use) account for the remaining few percent.

ESRD is the final stage of CKD, with the loss of kidney function accompanied by symptoms requiring either dialysis or kidney transplant. The loss of kidney function is devastating, resulting in significant systemic effects, reduced quality of life, increased morbidity and mortality, and costing over \$23 billion per year.¹⁵⁹

Incidence

The incidence of CKD continues to increase in the United States, with more than 20 million people currently affected. The number of persons with ESRD also continues to rise, with a prevalence of over 400,000. Recent data show a significant leap in the number of people with ESRD requiring treatment (dialysis or transplant) from 1994 to 2004. In 1994, the number of people who started dialysis or received a renal transplant was 68,757; in 2004 this number had increased to 102,356.⁷⁰ Much of this increase was reported in persons with diabetes, with 26,848 cases reported in 1994 and 44,953 cases in 2004.

The incidence of ESRD from diabetes, hypertension, and glomerulonephritis is higher in African Americans

compared to the general population. The rate of ESRD caused by hypertension was three times higher in African Americans compared to the general population. Encouraging data from 2004, however, showed that the incidence of CKD decreased in the Native American population, although prevalence has tripled among Hispanic Americans.¹³⁷

ESRD carries a high mortality rate, particularly in the older population. In 2004, people over the age of 65 who received dialysis had a mortality rate seven times that of equivalent-aged people not on dialysis.⁷⁰ People over the age of 60 who start dialysis have a life expectancy of only 5 years, while a 60-year-old without ESRD can expect to live 20 more years.

Etiologic and Risk Factors

The presence of a number of diseases can account for destruction of nephrons, but diabetes mellitus (principally type 2 causes diabetic nephropathy), high blood pressure, and glomerulonephritis are the leading causes of CKD. Other disorders contributing to the development of kidney failure include PKD, urinary tract obstruction, repeated infection, hereditary defects of the kidneys, toxicities, and systemic lupus erythematosus.

An increased risk of renal damage and ESRD is also associated with excessive over-the-counter (OTC) analgesic drug use, called *analgesic nephropathy*. This association was first noted with phenacetin-containing analgesics,⁷⁶ but is also noted with the drugs acetaminophen, aspirin, and combination analgesics (i.e., combining analgesics with codeine or caffeine).^{58,84}

Heavy average intake or high cumulative intake of analgesics may increase the likelihood of developing ESRD, particularly in older people with a disorder already affecting the kidneys.⁷⁴ NSAIDs, both selective and non-selective, have significant short-term effects on the kidney, yet data have been inconsistent with regard to the risk for ESRD from NSAID use.^{37,175} More research is needed to answer this question, but it may be that moderate use of NSAIDS in healthy individuals does not put them at significant increased risk for ESRD.¹⁶⁰

Pathogenesis

The basic functioning unit of the kidney is the nephron. It is composed of the glomerulus, the renal tubules, and the collecting duct (Fig. 18-6). The glomerulus is a small bundle of capillaries, surrounded by a capsule, that allows fluid and electrolytes to pass through the membrane and into the tubules. The renal tubules transport electrolytes or create a gradient for fluid and electrolytes to become balanced, while the collecting tubule is responsible for the final regulation of electrolytes and water under the influence of the hormone aldosterone.

As discussed earlier, many disease processes can result in CKD. Diabetes, for example, induces kidney damage through hyperglycemia. Angiotensin II is also released, which causes vasoconstriction of the arterioles and arteries (both in the glomerulus and systemically) in an attempt to keep the pressure adequate for filtration.

Angiotensin II release also leads to the attraction of inflammatory cells, which release cytokines and growth factors (which change the structure of the glomerulus).

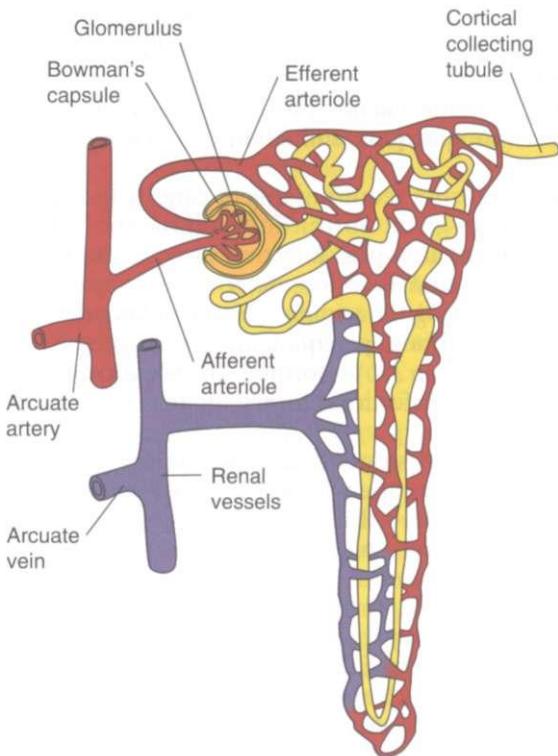


Figure 18-6

Components of the nephron. The afferent arteriole carries blood to the glomerulus for filtration through Bowman's capsule and the renal tubular system.

These changes result in mesangial expansion (a layer of cells around the glomerular capillaries), enlargement of the glomerulus, and ultimately interstitial fibrosis and glomerular sclerosis.

These processes slowly reduce the amount of surface area available for filtration to occur, thereby reducing the glomerular filtration rate (GFR). With the gradual loss of nephron function, the kidneys are unable to adequately regulate fluid, electrolytes, and pH balance or remove metabolic waste products from the blood.

The rate of nephron destruction can vary considerably, depending on the disease process. Typically, five stages mark the progression of chronic renal failure; each stage is defined by the level of the GFR (measured in milliliters per minute): (1) kidney damage with normal or increased GFR (90 ml/min or more), (2) kidney damage with mildly decreased GFR (60 to 89 ml/min), (3) moderately decreased GFR (between 30 and 59 ml/min), (4) severely decreased GFR (15 to 29 ml/min), and (5) kidney failure (ESRD; GFR of less than 30 ml/min). Systemic complications typically develop once stage 4 CKD is reached, when the GFR is less than 30 ml/min.

Clinical Manifestations

In stage 1 of CKD, the GFR is normal or increased (hyperfiltration). No overt symptoms of impaired renal function are typically evident. Depending on the health of the person, the kidneys have tremendous adaptive and compensatory capabilities, accounting for the delay in symptoms. The unaffected nephrons undergo structural and

physiologic hypertrophy in an attempt to make up for those nephrons that are no longer functioning. Results of blood tests such as blood urea nitrogen (BUN) and creatinine, which are indicative of kidney function, are typically normal.

The onset of symptoms is usually very gradual and subtle with the continued loss of nephrons and reduction in GFR, often resulting in a delay in diagnosis. Early clinical manifestations include hypertension and anemia. Abnormalities in laboratory values include an increase in BUN and creatinine, or protein detected in the urine. Stage 1 is reversible for some people (e.g., those with diabetes who benefit from early detection and proper glycemic control). Some individuals remain in stage 1 indefinitely, while others progress.

During stage 2, the damaged capillaries allow small amounts of albumin to be excreted in the urine. Individuals may remain in this stage for several years with proper control of hypertension and blood glucose levels. Stage 3 is more noticeable as albumin levels increase in the urine and decrease in the blood, resulting in noticeable edema. During this stage levels of creatinine and BUN increase, resulting in an accumulation of waste products in the blood called *azotemia*.⁴⁸

In the final stages of CKD (stages 4 and 5, with stage 5 being ESRD), the kidney is unable to function and a multitude of complications appear with accompanying symptoms and signs. Proteinuria is the hallmark of this stage; the kidneys are no longer able to excrete toxins, so there is a progressive increase in BUN and creatinine levels. Most people in this stage are hypertensive because of an increased production of renin. Hypertension accelerates the progression to stage 5 (ESRD) when the kidneys fail to function.

Stage 5 or ESRD is heralded by a cluster of symptoms referred to as *uremia*. The kidneys cannot excrete toxins; maintain fluid, pH, and electrolyte balances; or secrete important hormones (e.g., renin, vitamin D, erythropoietin). Uremia develops when poorly identified toxins are not removed from the blood. Uremia is characterized by nausea, vomiting, anorexia, lethargy, pruritus (itching), sensory and motor neuropathy, pericarditis, impaired heart function, asterixis, and seizures. Asterixis is an intermittent inability to sustain a posture, often noted when holding up the hand with the wrist flexed, creating a small "flapping-like" motion.

Dialysis or kidney transplant improves these symptoms. Hematologic, cardiovascular, gastrointestinal, musculoskeletal, and neurologic complications become more common in stages 4 and 5. Table 18-1 summarizes the systemic effects associated with CKD and ESRD.

Hematologic. Anemia is a significant hematologic problem associated with CKD. The hormone erythropoietin, primarily produced by the interstitial cells of the kidneys, has the principal function of controlling the production of red blood cells in the bone marrow. CKD leads to decreased erythropoietin production, reduced red blood cell lifespan, and reduced iron absorption, resulting in a subsequent decrease in red blood cells and anemia.

Anemia associated with CKD occurs most frequently in clients with a GFR of less than 60 ml/min and in

persons 75 years of age or older.³ However, a lack of erythropoietin is not the only factor causing anemia in clients with CKD. Other causes such as gastrointestinal bleeding, iron or folate deficiency, or hemolysis may play a role and should be evaluated.

Anemia in CKD can cause significant fatigue and reduced quality of life. Another important result of anemia is the stress it places on the heart. Anemia is an independent risk factor for cardiovascular disease. Because of this, anemia should be aggressively treated (see Chapter 14 for additional information regarding anemia).¹⁹⁰ ESRD also leads to white blood cell dysfunction and bleeding problems due to impaired platelet function.

Cardiovascular. Cardiovascular diseases often occur in people with CKD and are the leading cause of death in persons with ESRD. As the GFR decreases, the risk for cardiovascular disease increases in a graded fashion.⁷¹ Many of the risk factors that cause CKD, such as diabetes and hypertension, also contribute to cardiovascular disease. Diseases common in clients with CKD include coronary artery disease, left ventricular hypertrophy, and congestive heart failure. Persons with CKD often have hyperlipidemia, another risk factor for coronary artery disease.

Symptoms may include chest pain (although many often have atypical or no pain), nausea, shortness of breath, and sweating. Excess fluid volume, sodium retention, and anemia associated with ESRD lead to left ventricular hypertrophy, a thickening of the left ventricle of the heart, which predisposes to congestive heart failure.

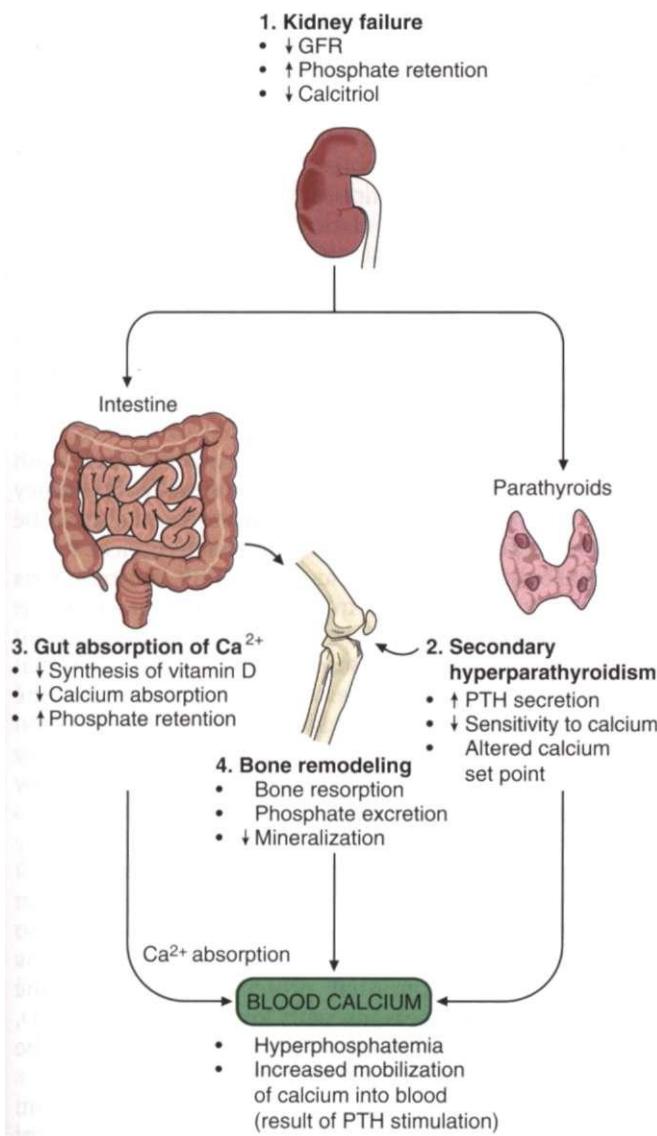
Associated clinical features include lower extremity edema and shortness of breath. Hypertension often appears early in the course of this disease because of increased angiotensin II production. Clients in stage 3 of CKD often need two or more medications to control blood pressure. Clients with CKD also have a higher incidence of stroke, peripheral vascular disease, arrhythmias, pericarditis, and heart valve abnormalities.

Gastrointestinal. Gastrointestinal system complaints occur often once the later stages of ESRD are reached. Azotemia (high levels of urea and other toxins in the blood) causes nausea, vomiting, and anorexia. The resultant depressed appetite contributes to malnutrition, fatigue, weakness, and malaise. Malnutrition has a high prevalence in those with advanced kidney disease, partly as a result of the therapeutic restriction on calories and proteins but also because of the metabolic reactions typical with this disease. Other clinical manifestations include gastritis, duodenitis, pancreatitis, hiccups (often difficult to control), and ascites.

Musculoskeletal. The skeletal changes associated with CKD are common and can occur early in the disease secondary to abnormalities in calcium, phosphate, and vitamin D metabolism. With the impairment of GFR, the body is unable to excrete phosphate or synthesize 1,25-dihydroxyvitamin D (a vitamin D derivative called *calcitriol*). Higher blood levels of phosphate lead to low ionized calcium levels. Calcitriol normally regulates calcium absorption from the gut and inhibits the parathyroid gland. But with low levels of calcitriol, hypocalcemia and increased PTH secretion result. A drop in serum calcium signals a cascade of events starting with

Table 18-1 Systemic Manifestations of Kidney Failure

Systemic Symptoms	Probable Causes
Urinary System	
Decreased urinary output	Damaged renal tissue
Abnormal urinary constituents (blood cells, protein, casts)	
Abnormal blood serum level, such as elevated blood urea nitrogen (BUN) and creatinine	
Cardiopulmonary System	
Coronary artery disease	Calcification of the arteries, other risk factors
Hypertension	
Congestive heart failure	Fluid overload
Pulmonary edema	
Dyspnea	
Pericarditis	Irritation of pericardial sac by uremic toxins
Gastrointestinal Tract	
Bleeding	Platelet changes
Nausea and vomiting	
Uremic breath	Change in saliva due to uremic toxins
Anorexia	
Nervous System	
<i>Central (CNS)</i>	
Headache	
Irritability	Effect of electrolyte and fluid changes on brain cells (usually resolves with dialysis treatment)
Impaired judgment	
Inability to concentrate	
Seizures	
Lethargy/coma	
Sleep disturbances	
<i>Peripheral (PNS)</i>	
Loss of vibratory sense and deep tendon reflexes	Effect of uremic toxins on peripheral nerves
Impairment of motor nerve conduction velocity	
Burning, tingling, paresthesias	
Tremors	
Muscle cramps, muscle twitching	Electrolyte imbalances (calcium, sodium, potassium)
Foot drop	
Weakness	
Integumentary System (Skin)	
Pruritus (itching)/excoriation (scratching)	
Hyperpigmentation	Skin calcifications related to calcium/phosphorus imbalances
Pallor	Retained uremic pigments
Bruising	Anemia
Eyes	
Band keratopathy	Platelet dysfunction
Visual blurring	
Dry eyes	Corneal calcifications related to calcium/phosphorus imbalance
Red eyes	Conjunctival calcifications related to calcium/phosphorus imbalance
Endocrine System	
Fertility impairment and sexual dysfunction	Effect of uremic toxins on menstrual cycles, ovulation, and sperm production
Hyperparathyroidism	Result of calcium/phosphorus imbalance
Hematopoietic System	
Anemia	Decreased production of erythropoietin by kidney; destruction of red blood cells by dialysis
Platelet dysfunction	Uremic toxins interference with platelet aggregation
Skeletal System	
Renal osteodystrophy (demineralization of bones)	Related to decreased calcium absorption and resultant calcium/phosphorus imbalance
Joint pain	Joint calcifications

**Figure 18-7**

Mechanisms of altered bone turnover. (1) Renal osteodystrophy can be viewed as the result of a vicious cycle that begins with moderate to severe renal failure. As the glomerular filtration rate (GFR) decreases, phosphate excretion decreases, and calcium elimination increases. (2) The body attempts to compensate for the loss of calcitriol and reduced calcium absorption by increasing parathyroid hormone (PTH) secretion. PTH mobilizes calcium from the bones (bone reabsorption) and facilitates phosphate excretion. This release of calcium and phosphate into the blood results in hyperphosphatemia and hypercalcemia. (3) As kidney failure progresses, the damaged kidneys can no longer convert vitamin D to its active form and without active vitamin D, calcium absorption in the intestines is decreased and paradoxically facilitates phosphate retention. (4) Thus the normal process of bone mineralization with calcium and phosphate is impaired. Demineralization of the bone frees more calcium and phosphorus into the blood. As the disease progresses even more, the parathyroid gland may become unresponsive to the normal feedback system and continue to produce PTH, causing acceleration of renal osteodystrophy.

the release of PTH, which signals the body to increase calcium resorption from bone to make up for the perceived loss (Fig. 18-7).

Several skeletal abnormalities result from varying types of bone turnover, collectively referred to as renal osteo-

dystrophy. Renal osteodystrophy is a type of rickets formerly called renal rickets and sometimes referred to as azotemic osteodystrophy. Although uncommon at one time, the incidence has risen with increased survival of people with renal disease on dialysis.

Renal osteodystrophy is characterized by varying degrees of osteomalacia, osteitis fibrosa, and adynamic bone disease. Osteomalacia occurs secondary to low bone turnover due to aluminum deposition in the bones with resultant increased nonmineralized bone matrix formation. Osteitis fibrosa results in inflammation and fibrosis of bone because of high bone turnover, while adynamic bone disease is a low bone turnover state, which may be related to excessive PTH suppression from therapy.⁴⁷

Clients with renal osteodystrophy may present with bone pain, especially in the spine, hips, knees, or lower extremities, and fractures.⁴⁷ The pain is worse with exercise and other weight-bearing activities; the fractures occur most often in the vertebrae and long bones.⁴⁸ Increased secretion of PTH and a decreased secretion of calcitriol appear to be the cause. Metabolic acidosis may also play a role, either by increasing osteoclastic activity or by increasing the effects of PTH.²⁰⁰

Osteopenia and pseudofractures are seen most frequently in people with osteomalacia. Osteitis fibrosa is evident on radiographic films, particularly in the phalanges, skull, and distal clavicles, where there is subperiosteal bone resorption.

In addition to bone demineralization, calcification of vessels and soft tissues occurs. This calcification may be related to bone turnover and occurs during both high and low bone turnover. It is postulated that deposition of minerals may occur in extraskeletal sites because the bone is unable to incorporate them. If bone turnover is high, minerals are removed from bone and are deposited in extraskeletal sites. If bone turnover is low, minerals are also deposited in extraskeletal sites because the bone is forming abnormally or at a slow rate.

The most common sites for extraskeletal calcification include the coronary arteries, lungs, skin, peripheral arteries, joints, and cornea. Calcifications of the coronary arteries are common and may be the reason for the high death rate in CKD clients. Intraarterial calcifications can occlude vessels, leading to ischemia and gangrene.

Deposition of minerals in the skin can lead to intense pruritus (itching), and occlusion of an arteriole can cause necrosis of skin, termed *calciphylaxis*. This occurs most commonly in the lower extremities, trunk, or buttocks. Articular cartilage and joints can become calcified, causing pseudogout and arthritis symptoms.

Calcification of a tendon may lead to spontaneous rupture with minimal stress. The quadriceps tendon may rupture simply by walking, tripping, or going down stairs. Tendon ruptures can lead to pain, deformity, and disability. Other areas of commonly observed ruptures in this population include the triceps and extensor tendons of the fingers.⁴⁸ Hyperparathyroidism and metabolic acidosis are responsible for the abnormal collagen that results in weak tendons.^{29,200}

Calcifications are frequently found on the cornea and conjunctiva but are typically asymptomatic. Clients who

have kidney disease characterized by a slow decline in function may have more severe cases of both renal osteodystrophy and calcification of vessels and soft tissue. (Although cardiovascular manifestations have already been discussed earlier in this section, in view of the information here on calcification, it should be noted that vascular calcification of the arteries resulting in vascular insufficiency has been observed in nearly all individuals with ESRD by age 50 years. In fact, most people with CKD actually die mainly from cardiovascular disease, rather than progress to the final stages of ESRD.^{100,158})

Myopathy can occur with proximal muscle weakness affecting the muscles of the shoulder and pelvic girdles, leading to functional disabilities. The gluteus medius, hamstring, and psoas muscles are affected first and most severely, resulting in gait impairments and difficulty rising from low seats or accomplishing functional activities such as getting in and out of a bathtub. As the condition progresses, activities of daily living (ADLs) such as combing the hair, brushing the teeth, or household tasks become more difficult to manage independently.

Neurologic. Alteration of central nervous system and peripheral nervous system function often occurs in association with ESRD. Early central nervous system changes include sleeping disturbances (both getting to sleep and staying asleep) followed by daytime sleepiness and personality changes.

Uremic encephalopathy occurs when the GFR is less than 10 ml/min and is manifested by recent memory loss, inability to concentrate, perceptual errors, confusion, asterixis, and decreased alertness. These symptoms abate once dialysis is instituted. Without treatment, seizures, lethargy, obtundation, and coma develop.

The peripheral neuropathy associated with uremic toxins is characterized by a dying back of the axons of both sensory and motor nerves. These neurologic changes are typically symmetrical (stocking-glove distribution) and similar to those of any other polyneuropathy with a stocking-glove distribution. Clients can also exhibit restless leg syndrome, which occurs in up to 40% of uremic clients.⁷⁸ Like central nervous system manifestations of uremia, peripheral nervous system symptoms improve with dialysis.

MEDICAL MANAGEMENT

PREVENTION. Everyone should be screened for hypertension and diabetes with early intervention when present. The ultimate goal and mission of the National Kidney Foundation is the eradication of diseases of the kidney. Toward that end, *Healthy People 2010* has identified several goals related to kidney failure, including (1) reduce kidney failure due to diabetes; (2) increase the proportion of people with chronic kidney failure who receive a transplant within 3 years of registration on the waiting list; (3) increase the proportion of people with chronic kidney failure who receive counseling on nutrition, treatment choices, and cardiovascular care 12 months before the start of renal replacement therapy; (4) reduce deaths from cardiovascular disease in persons with chronic kidney failure; and (5) reduce the rate of new cases of ESRD.

Since diabetic nephropathy is the leading cause of kidney failure in the United States, prevention strategies and risk factor modification related to improving glycemic control, preventing hypertension, preventing coronary artery disease, increasing physical activity, and reducing or eliminating tobacco-related behaviors (e.g., smoking) are a large part of the prevention of renal disease. In the future, pancreas transplantation may become a part of diabetes prevention and therefore ESRD prevention.

DIAGNOSIS. As discussed earlier, the early stages of CKD are often without symptoms. Because of the significant morbidity and mortality associated with CKD, early detection is emphasized, with the goal of slowing progression or reversing the disease if possible. People with diabetes, hypertension, or a family history of kidney disease are at high risk for kidney disease and should be monitored for early indications of kidney disease.

Because there are many causes for CKD, multiple tests may be required to determine the cause and severity. Several laboratory tests are helpful in detecting and following progression of CKD and ESRD. Persons with diabetes should routinely be tested for microprotein in the urine (an indication of early kidney disease). GFR, BUN, and creatinine are blood tests that can indicate kidney dysfunction (GFR is actually calculated using laboratory results).

In the presence of CKD, GFR will be the first laboratory indicator of renal damage, followed by increases in BUN and creatinine with continued kidney damage. GFR not only characterizes the stage of kidney disease but also demonstrates disease progression. Urine tests may show protein or casts (abnormal protein "castings" of the tubules). For those persons with known CKD or ESRD, intact PTH (or N-terminal PTH molecule) levels should be monitored in an attempt to avoid renal osteodystrophy.

Imaging modalities may demonstrate obstruction, masses, or bilateral small kidneys (which is consistent with ESRD from a chronic disease). A kidney biopsy may be needed to confirm specific kidney pathology (such as a glomerulonephritis).

TREATMENT. Following the diagnosis of CKD, a referral to a nephrologist should be made. Although best outcomes occur when a referral is made early in the course of CKD, up to 40% are not referred until 3 months prior to initiating dialysis.¹⁹² Delayed referrals lead to an increase in morbidity and mortality.

The goals of treating CKD include treating the underlying disease, modifying risk factors for cardiovascular disease, and preventing further loss of kidney function. For some diseases, treating the principal disease may involve immunosuppressive agents, such as with the treatment of membranous nephropathy. Renal artery stenosis may require angioplasty with stenting. Diabetes requires tight glycemic control.

Cardiovascular complications are common and require risk factor modification and treatment. Clients with CKD should lose weight, exercise, eliminate smoking, and modify their diet. Dyslipidemia treatment involves lifestyle modifications, and medication may be needed.

Blood pressure should be strictly controlled in order to reduce cardiovascular risk and prevent further loss of renal function (although the exact range is disputed, a systolic blood pressure between 120 mm Hg and 130 mm Hg should be the goal).¹²⁰

Measures that help prevent further loss of kidney function include avoidance of nephrotoxic drugs and radiocontrast agents; treatment of anemia; strict blood pressure control; and the use of ACE inhibitors or ARBs.¹²⁰

For the predialysis stage, data are lacking to establish the optimal hemoglobin level to begin erythropoietin therapy. But a current recommendation suggests initiation of subcutaneous erythropoietin when the hemoglobin drops below 10 g/dl, after verification of adequate iron stores and exclusion of other causes of anemia. Studies have demonstrated that the use of an ACE inhibitor or ARB is renoprotective beyond the ability of just lowering blood pressure.

The treatment of clients who develop ESRD continues with many of the same measures used to treat the other stages of CKD, such as blood pressure control and anemia treatment. Dietary modifications are necessary, including low-potassium, low-sodium, and low-protein diets. Excess protein can increase urea levels, and clients should not consume more than 1 g/kg/day of protein. Dietitian referrals are important, since malnutrition may occur with strict dietary regulation. Fluid intake is restricted, and diuretics are needed to maintain fluid balance.

Prevention of renal osteodystrophy necessitates monitoring of calcium/phosphate balance and PTH levels. The goal is to maintain calcium at less than 9.5 mg/dl and phosphate at less than 5.5 mg/dl. This has typically been accomplished using calcium-binding agents and vitamin D sterols.

New questions have been raised, however, concerning calcification of vessels (principally the coronary arteries) and calcium/phosphate metabolism. The traditional methods of lowering calcium and phosphate may still leave levels too high to reduce calcification of the coronary arteries. A new calcimimetic agent, recently approved by the FDA, called cinacalcet, appears to treat secondary hyperparathyroidism and maintain normal calcium and phosphate levels. Further use of this drug in a larger population will determine efficacy in preventing renal osteodystrophy and cardiovascular complications.

Renal replacement therapy (dialysis or transplantation) is the treatment of choice for ESRD. The decision is based on the client's age, general health, donor availability, and personal preference. Dialysis can take the form of hemodialysis (HD) or peritoneal dialysis (PD) (also referred to as *continuous ambulatory peritoneal dialysis [CAPD]* and *continuous cycling peritoneal dialysis [CCPD]*). The main difference between these methods of dialysis is in their exchange schedules (daytime versus nighttime, length of time required).

HD typically requires three sessions per week for 3 to 4 hours per session. The blood flows from an artery through the dialysis machine chambers and then back to the body's venous system, with the waste products and excess fluid and electrolytes diffusing into the dialyzing solution. HD can be done at home, although this requires specialized training, or the client can travel to a renal

center. During the procedure, the person remains relatively immobile throughout the session. Only 1% of dialysis clients receive home HD, while 85% receive in-center treatment.

Approximately 10% of dialysis clients use PD. PD relies on the same principles as HD but can be done independently at home. A catheter is implanted in the peritoneal cavity, and sterile dialyzing solution is instilled and then drained over a specific period. This process is completed four times daily. With CAPD/CCPD, fewer dietary restrictions and fewer of the dramatic symptom swings associated with HD occur. Potential complications of PD include infection, catheter malfunction, dehydration, hyperglycemia, and hernia. Peritonitis occurs about once every 3 years in those undergoing PD and is the most serious potential complication. The majority of affected people are successfully treated with intraperitoneal antibiotics.

The steady improvement in the outcome of renal allografts has made kidney transplantation the treatment of choice for many people with ESRD. Transplantation is less expensive than long-term dialysis, but donor availability limits the number of transplants performed. The current contraindications for transplant include active substance abuse or noncompliance, metastatic cancer, severe arterial disease involving the iliac arteries, active infection, active ischemic cardiac and cerebrovascular disease, advanced dementia, and debility.

In adults, the renal graft is placed extraperitoneally in the iliac fossa through an oblique lower abdominal incision. In small children, the graft is located retroperitoneally with a midline abdominal incision. Complications of the procedures include renal artery thrombosis, urinary leak, and lymphocele.

PROGNOSIS. Despite significant advances in technologic and pharmacologic interventions, the current annual mortality rate of people with ESRD in the United States is about 24%. Cardiovascular diseases remain the number one cause of death in those with all categories of renal disease, including persons with CKD, those with ESRD on dialysis, and renal transplant recipients. This is most likely due to the presence of multiple cardiovascular risk factors (e.g., hypertension, abnormal lipids, smoking, dietary factors).¹²³ Individuals with diabetes and ESRD have higher morbidity and mortality rates than individuals with ESRD only.¹³⁶

SPECIAL IMPLICATIONS FOR THE THERAPIST

18-5

Chronic Kidney Disease

PREFERRED PRACTICE PATTERNS

4A: Primary Prevention/Risk Reduction for Skeletal Demineralization (osteodystrophy)

4C: Impaired Muscle Performance

4D: Impaired Joint Mobility, Motor Function, Muscle Performance, and Range of Motion Associated with Connective Tissue Dysfunction (tendon rupture)

5A: Primary Prevention/Risk Reduction for Loss of Balance and Falling (myopathy)

Continued.

5D: Impaired Motor Function and Sensory Integrity Associated with Nonprogressive Disorders of the Central Nervous System—Acquired in Adolescence or Adulthood (*uremic encephalopathy*)

5G: Impaired Motor Function and Sensory Integrity Associated with Acute or Chronic Polyneuropathies

6B: Impaired Aerobic Capacity/Endurance Associated with Deconditioning

Other practice patterns may apply depending on developing associated conditions such as congestive heart failure, anemia, edema, and so on.

Therapists must be aware that several specific renal syndromes may be induced by the interaction of NSAIDs and other analgesics (see Table 5-1) on renal function. Although the nephrotoxicity is relatively low, the increased availability of these medications as OTC products and the concentration of people taking NSAIDs/analgesics in a rehabilitation setting are factors contributing to the fact that a larger percentage of these people come into contact with a therapist.

Older adults are especially susceptible and more likely to use these agents. Additionally, NSAID-related renal involvement is probably underrecognized, and with the FDA approval of OTC sale of NSAIDs (e.g., naproxen sodium, ketoprofen, ibuprofen), incidence may increase in the coming years. Any time a client reports a history of prolonged and regular NSAID/analgesic use and renal symptoms, medical evaluation is required.

Physical therapy care of people with CKD has increased significantly in the past 20 years. Treating people with a diagnosis of CKD can be extremely challenging because of malnutrition, side effects of medications, complications from dialysis, and the number of body systems involved. The decreased alertness, inability to concentrate, and short-term memory deficits interfere with following instructions, including transfers, exercises, body mechanics, and so on.

Musculoskeletal changes occur due to abnormalities in calcium, phosphate, and vitamin D metabolism, resulting in osteomalacia, osteoporosis, and soft tissue calcification. Neuromuscular effects of CKD include both central and peripheral nervous system disorders. Kasinskas and Piazza (2004) offer consideration for a clinical pathway for clients with CKD using the *Guide to Physical Therapist Practice* that is worth reviewing for any therapist working with this population group.^{2,102}

Adverse effects of some of the medications used for renovascular hypertension may include angioedema (i.e., swelling around the face, mouth, or throat), requiring immediate medical attention. Clients should be taught to rise slowly, dangling the legs and feet before standing, and to report any unusual swelling.

Reliance on the assistance of family and other health care providers is often necessary. The fatigue and general weakness may dictate that the therapist provide rest periods during a rehabilitation session. The potential osteodystrophy requires modification of evaluation and intervention techniques, including osteoporosis education and prevention (see Special

Implications for the Therapist: Osteoporosis in Chapter 24).

A number of potential renal transplantation complications that the therapist should be aware of are hypertension, lipid disorders, hepatitis, cancer, tendinopathies, and osteopenia (see the section on Transplantation in Chapter 21). Lastly, corticosteroids appear to be the primary factor in the impaired bone formation found in graft recipients (see Chapter 5).

Dialysis^{93,149}

Complications of dialysis are multiple and varied. Fluid shifts during dialysis can contribute to adverse neuromuscular and hemodynamic consequences that must be reported so that adjustments can be made in the dialysis fluid (dialysate). Symptoms of increased thirst and weight gain are common, and the weight gain and abdominal distention, especially with CAPD/CCPD, may cause extreme distress in the individual.

Depression among people on dialysis may be more common than is currently recognized, often masquerading as functional impairment, anorexia, or noncompliance. Impaired libido, impotence, infertility, dysfunctional uterine bleeding, amenorrhea, and anovulation are very common. Altered platelet function results in bleeding tendencies in anyone with uremia, and the therapist is advised to follow the precautions listed in Tables 40-8 and 40-9.

People on dialysis have increased susceptibility to infection by various pathogens because they are immunosuppressed, and the dialysis process requires vascular access for prolonged periods of time. Infection of the vascular access site is a major concern, because signs and symptoms of local infection are often absent early on. Careful monitoring for infection or inflammation is warranted, with early medical referral. Standard precautions are essential for the individual in a dialysis unit, for those individuals dialyzing and handling the equipment at home, and for the treating therapist.

Contact transmission can be prevented by hand hygiene (i.e., handwashing or use of a waterless hand rub), glove use, and disinfection of environmental surfaces. Of these, hand hygiene is the most important. In addition, nonsterile disposable gloves provide a protective barrier for workers' hands, preventing them from becoming soiled or contaminated, and reduce the likelihood that microorganisms present on the hands of personnel will be transmitted to clients. However, even with glove use, handwashing is needed, because pathogens deposited on the outer surface of gloves can be detected on hands after glove removal, possibly because of holes or defects in the gloves, leakage at the wrist, or contamination of hands during glove removal.²⁵

During progressive renal failure, catabolism and anorexia lead to loss of lean body mass, but concurrent fluid retention and weight gain can mask the loss of body mass. Malnutrition, anemia, and this loss of body mass can result in significant losses in muscle strength, requiring careful assessment and rehabilita-

tion. The mixed sensory and motor peripheral neuropathy common in people with uremia often improves symptomatically with adequate dialysis. Muscle mass will also improve with consistently good dialysis and nutrition.

Fluid retention also results in hypertension at the beginning of dialysis; alternatively, dialysis can result in hypotension. The therapist should ask the client about the dialysis schedule and encourage the individual not to miss any treatment. Younger clients and those who have recently started dialysis are more likely to miss treatments. This may be reflected in rising blood pressure and elevated pulse rate. Monitoring vital signs and laboratory values is essential throughout the rehabilitative process.

Chest and back pain can occur during the early days of dialysis, referred to as *first-use syndrome*. Delayed hypersensitivity reactions with mild itching and urticaria may be reported to (or observed by) the therapist. Maintaining the dialysis access site is critical but is often difficult secondary to recurrent thromboses. Extreme caution must be given to the access site during any rehabilitation or exercise intervention. Ischemia of the arm (or leg, depending on the location of the fistula) may be the first indication of thrombosis and subsequent stenosis. Any of these signs and symptoms should be reported to the renal staff.

Exercise and Chronic Kidney Disease

For the individual with CKD, myopathies, neuropathies, and reduced muscle mass, carrying and lifting the bag of dialysate can be difficult. Strength training, balance, and mobility are key components of a home exercise program for the person using CAPD/CCPD.

Gains in strength and mobility are possible but may require a mildly to moderately intense rehabilitation program of longer duration than expected.^{108,128,153} What may seem like a short-term goal for the average, healthy adult can be a long-term goal for someone with CKD, especially the client with end-stage kidney disease.

Exercise can be performed before, during, or after renal dialysis or PD. Finding the best schedule may take a period of trial and error. For some people, functional tolerance may be lowest the day before the first and second dialysis sessions of the week. Establishing a plan of care that takes into account day-to-day differences in energy, function, and motivation may have a chance for better outcomes.¹⁸⁸

Compliance can be a big issue if the therapist is unable to convey to the client the importance of exercise and how an exercise program can really benefit that individual. Focusing on greater function and independence in day-to-day activities and gaining an increased sense of well-being or quality of life may be more important to the client than riding a bicycle 10 minutes twice each day.

Living with CKD usually involves management of other chronic conditions such as diabetes or hypertension. The changes required in lifestyle can create a profound sense of loss, depression, and emotional fatigue for some individuals.¹⁸⁹ They often

report memory loss and a decreased ability to stay on task.

When exercise is performed after dialysis, blood chemistry levels will be at their optimum, although fatigue may be a factor. Exercise during dialysis may be an option for some and usually improves the efficiency of dialysis because of better mobilization of dependent fluids, but most people do not choose this option.

The limited research available has shown that impaired oxygen transport plays a role in limiting exercise in anyone with CKD, especially once dialysis begins.¹⁶⁵ Adults with CKD have low cardiorespiratory capacity with maximum oxygen consumption (VO_{max}) at one third to one half normal rates for age-matched sedentary but healthy adults without kidney disease. They often show signs and symptoms of anemia, fatigue, wasting, and reduced work capacity with concomitant findings of reduced cardiac performance and muscle mass.^{97,204}

Functional capacity in people on dialysis is typically more than two standard deviations below the age- and gender-predicted norm and is often far lower, sometimes barely enough to carry out ADLs. A prescriptive program of regular activity and exercise can improve physical functioning, exercise tolerance, and health-related quality of life.^{132,146,147} Fatigue severity does respond with low-level exercise during dialysis, but the exercise must continue in order to maintain the effect.²⁰⁴

Exercise Prescription

Low- to moderate-intensity exercise can increase exercise capacity and possibly improve blood pressure for individuals with CKD.¹⁴⁵ Individuals with CKD benefit from stationary bicycle exercise protocols requiring exercise three times a week at intensities of 40% to 70% target heart rate.

Exercise can be done on dialysis days as well as on nondialysis days. Some people may find it more difficult to exercise on dialysis days or even during dialysis due to decrease in blood pressure and muscle cramping. Both are common side effects of dialysis.²⁰⁵

Clients who exercise both during dialysis and on nondialysis days have greater improvements in exercise tolerance and peak VO_{max} compared to individuals who exercise only on dialysis days or only on nondialysis days.¹⁰⁸

Exercise protocols consisting of gentle stretching and warm-up followed by an aerobic phase beginning at intensities of 50% to 60% of the target heart rate, followed by a low-intensity cool-down and relaxation phase can increase exercise tolerance.¹⁸¹

The beneficial effects of regular aquatic exercise on cardiorespiratory function, renal lipids, and oxidative stress have been studied in a group of individuals with mild to moderate renal failure. Low-intensity aerobic exercises in the pool for 30 minutes twice a week over a period of 12 weeks led to improvement in cardiorespiratory function, improved resting blood pressure, and enhanced GFR.¹⁵²

Continued.

Exercise Considerations for Individuals with End-Stage Renal Disease

ESRD is characterized by compromised autonomic function associated with cardiac mortality; this is particularly prevalent in people with diabetes. Autonomic dysfunction may limit maximal age-predicted heart rates by as much as 20 to 40 beats/min. Therefore, when prescribing exercise intensity, the perceived exertion rating may be a better choice for monitoring exercise.¹¹⁹

Exercise has been identified as a factor associated with improved autonomic cardiac function in ESRD.²⁴ Exercise prescription for anyone with chronic disease and/or disability must take these factors into consideration. For anyone with CKD and diabetes, glucose levels must also be taken into consideration when planning, monitoring, and, when possible, progressing an exercise program.

A timely and effective rehabilitation program can improve quality of life, endurance, and functional abilities toward greater independence. For the individual on dialysis, the most important independent quality-of-life predictor is the usual level of exercise activity. The person's perception of physical functioning as it relates to quality of life is important, because these variables can be the focus for intervention strategies to prevent early deterioration in dialysis.¹¹⁴

The individual's clinical condition (and response to exercise) provides the greatest guidance in determining exercise or physical activity mode, intensity, frequency, and duration. With numerous medical problems associated with ESRD, a major concern before initiating an exercise program is physiologic stability.

Exercise testing before starting an exercise program is usually not recommended for this population group. Muscle fatigue limits testing procedures, and the results do not really offer any new information. General exercise guidelines for individuals with ESRD are for exercise four to six times each week; low exercise capacity may direct the therapist toward establishing an interval training program to start. The goal is to exercise for longer periods of time with 30 minutes as the final desired outcome. Intensity is kept low, especially on days the individual undergoes dialysis. The Rate of Perceived Exertion (RPE) scale can be used to monitor intensity.⁴⁸

Many of the risks of exercise are related more to exacerbation of comorbid conditions (e.g., arthritis, diabetes, hypertension) than to the kidney disease itself. Exercise might cause a potassium efflux from exercising muscles and may elevate blood levels, although the possibility of exercise-induced hyperkalemia and resultant cardiac arrhythmias is small. Serum potassium levels must be controlled before exercise and should not be greater than 5 mEq/L. Individuals with uncontrolled blood chemistries should avoid weight training.

Some sources recommend exercise during dialysis^{144,145} and the day after dialysis, since the chance of instability is greater before renal dialysis (PD is usually done daily and is easiest with an empty abdomen for

mechanical reasons). People on dialysis may have a low exercise capacity, with approximately half that of healthy individuals matched to age and gender. This corresponds to approximately 3 to 5 metabolic equivalents of the task (METs; 1 MET is equal to energy expenditure at rest; ADLs require 1.5 to 5 METs). Reviews of specific prescription principles, including weight-training guidelines, for individuals with chronic disease and specifically renal disease are available.^{8,45,119,132}

Exercise may help control blood pressure, especially in those individuals who are hypertensive. Blood pressure should be monitored in the arm opposite the arteriovenous shunt before exercise. If blood pressure is greater than 200/100 mm Hg, the individual should not exercise. Exercise can also improve lipid levels and glucose metabolism, and increase hematocrit and hemoglobin levels. Psychosocial effects such as improved mood and quality of life are also possible.^{142,143}

Anyone with diabetes should be monitored for hypoglycemia or sudden drops in blood glucose levels. In addition, the kidney is essential in the production of vitamin D, which is necessary for calcium absorption. Exercise training ameliorates the enhanced muscle protein degradation associated with chronic renal failure.

Anyone undergoing dialysis will be monitored for bone disease; strengthening exercises can help bone density, and bone density studies can provide outcome-based evidence of the value of exercise in these clients. In the case of PKD, moderate exercise in animal models was considered safe but did not alter bone mineral density. Additional research in this area is needed, since other benefits may be derived from exercise in this and other kidney-diseased populations.⁴⁰

Laboratory Values

Renal failure causes metabolic waste products to accumulate in the blood, which can be measured to assess renal function. The two most commonly measured waste products are serum creatinine and BUN. Changes in creatinine and BUN levels do not usually contraindicate physical or occupational therapy intervention, but other test measures are important. Depressed serum albumin levels reflect poor nutritional status and these laboratory values should be monitored whenever available (see the section on Renal Function Tests in Chapter 40 and Table 40-2).

People with ESRD often have low levels of hemoglobin associated with anemia and poor exercise tolerance due to excessive fatigue. Dyspnea at rest or on exertion, increased fatigue, and chest pain with exertion may be signs of low hematocrit levels. Exercise guidelines based on laboratory values provided in Chapter 40 can be used with clients who have ESRD. Keep in mind that hemoglobin and hematocrit levels are usually lower for people with ESRD; potassium, creatinine, and BUN levels will be higher than normal.

Glomerular Diseases

Overview

Glomerular diseases are a group of conditions that damage the kidney's filtering units (glomeruli). Glomerulonephritis is also a group of diseases that affect the glomeruli but specifically manifest with hematuria. Glomerulonephritis is a glomerular disease, but not all glomerular diseases are termed *glomerulonephritis*. Glomerular diseases are the most common cause of ESRD worldwide, while glomerulonephritis is the third leading cause of end-stage kidney disease in the United States.

The glomeruli are tufts of capillaries connecting the afferent and efferent arterioles of the nephron (see Fig. 18-6). The capillaries are supported by a stalk made up of mesangial cells and a basement membrane and are arranged in lobules. The circulating blood is filtered in the glomeruli, with the urine filtrate being an end-product. Glomerular damage produces two types of syndromes: the nephrotic syndrome and the nephritic syndrome.

Nephrotic syndrome is not a specific kidney disease but rather occurs as a result of any disease that causes damage to the kidney-filtering units. Nephrotic syndrome is principally associated with proteinuria, which occurs with such diseases as diabetes, amyloidosis, and membranous glomerulopathy. *Nephritic syndrome* is correlated with hematuria. Glomerular diseases that result in a nephritic syndrome include lupus nephritis, immunoglobulin A (IgA) nephropathy, and acute diffuse proliferative glomerulonephritis. Overlap of the two syndromes is common, and a precise diagnosis often requires a kidney biopsy.

Etiologic Factors

Most cases of nephritic syndrome and some cases of nephrotic syndrome have an immune origin and are part of a systemic process, such as lupus nephritis or membranoproliferative glomerulonephritis. Two different mechanisms have been proposed to account for the pathologic changes seen in glomerular diseases. The first is due to the deposition of a circulating antigen/antibody complex into some portion of the glomerulus (the glomerular basement membrane or GBM, mesangium), followed by an inflammatory response and damage. Injury is caused via the second mechanism when an antigen is deposited into the glomerulus with subsequent antibody interaction with the antigen, followed by an inflammatory response. Antigens may be exogenous, as seen in poststreptococcal glomerulonephritis, or endogenous, as noted with lupus nephritis.

Risk Factors

The presence of a variety of disorders can increase the risk of glomerular damage. Diabetes, principally type 2 diabetes, is a significant risk factor for CKD and the development of nephrotic syndrome. Age is another factor in the development of some diseases associated with nephrotic syndrome. For example, minimal change glomerulopathy is seen in children under the age of 10 and accounts for more than 80% of cases of nephrotic syndrome in children. Race is also a factor in the development of glomerular disease. Focal segmental glomerulosclerosis

(FSGS) is the most common cause of nephrotic syndrome in African Americans, while membranous nephropathy is seen more commonly in Caucasians. FSGS is also seen more often in persons who are obese.

Pathogenesis

Damage to the glomerular epithelial cells or the GBM allows larger molecules, such as protein, to escape out of the circulation and into the urine, causing nephrotic syndrome. Rupture of a capillary wall or proliferation of mesangial cells leads to hematuria and nephritic syndrome. The processes that cause this damage vary depending on the underlying glomerular disease.

Nephritic syndromes are caused by antibody/antigen complexes. Damage and clinical manifestations depend on where these complexes are deposited in the glomerulus. IgA nephropathy results when circulating antibodies (IgA antibodies) complex with an antigen (currently not defined) but are not able to be filtered through the glomerulus. These complexes stimulate an inflammatory response, accompanied by the release of cytokines and growth factors. Mesangial cell proliferation and glomerular scarring result.

Poststreptococcal glomerulonephritis occurs when antigen (streptococcal) is deposited between the glomerular epithelial cells and the GBM, resulting in an antibody response and damage to the GBM. This disruption of the GBM results in proteinuria as well as nephritis. Lupus nephritis can result from either antigen deposition followed by antibody reaction or the deposition of antibody/antigen complexes. These depositions can also occur in several locations. Those found in the mesangium result in proliferation of mesangial cells. Complexes placed in the GBM cause proteinuria, while deposition in the subepithelial space leads to nephrosis-range proteinuria. If the antigen is chronically produced, the recurrent inflammatory reactions lead to chronic glomerulonephritis. These changes adversely affect the glomerular filtration mechanism and alter capillary permeability.

While the nephritic syndrome results most often from depositions of immune complexes, causes of nephrotic syndrome vary, with many not well understood. For example, minimal change disease shows very few abnormalities on microscopic or electron microscopic inspection. This disease may result from damage created by a lymphocyte product. Causes of other diseases, such as membranous nephropathy, are better understood. Antigen is initially deposited in the GBM with subsequent antibody interaction and inflammatory response. These immune complexes also trigger the complement system, causing further damage to the GBM and allowing large amounts of protein to escape from the plasma.

Clinical Manifestations

Glomerular disease causing a nephrotic syndrome produces proteinuria (greater than 3 g in 24 hours), hypoalbuminemia, hyperlipidemia, lipiduria, and edema. The significant loss of protein from the kidney accounts for the hypoalbuminemia, which in turn reduces the plasma oncotic pressure in the vessels. Fluid flows to areas of greater protein concentration, which in this instance is outside the blood vessel, causing edema. The kidney

perceives a loss in volume and retains both fluid and sodium, thus increasing the edema. Edema is the principal symptom that brings affected people to the physician's office. The edema can be severe enough to be disabling.

The loss of protein also stimulates the liver to produce cholesterol, leading to hypercholesterolemia (cholesterol can be as high as 300 to 400 mg/dl). High cholesterol not only increases atherosclerosis of the coronary arteries but also worsens existing kidney disease. Other clinical manifestations include coagulation abnormalities from the loss of coagulation proteins, resulting in a venous thrombotic event (i.e., pulmonary embolism, deep venous thrombosis, or renal vein thrombosis). Hypothyroidism may occur secondary to the loss of thyroxine, and anemia may develop because of the loss of transferrin and erythropoietin.

The nephritic syndrome is characterized by hematuria, but oliguria, hypertension, and renal insufficiency often accompany this syndrome. The urine typically contains abnormally shaped erythrocytes (sometimes called "Mickey Mouse cells"), which distinguishes the hematuria of nephritic syndromes from that of urinary or bladder sources (normally shaped erythrocytes).

Proteinuria may be present, depending on which part of the glomerulus is affected. Hematuria may be asymptomatic, as with IgA nephropathy, or clinically apparent, as with anti-GBM antibody disease. Proliferation of mesangial cells may occur. If less than 50% of the glomeruli are affected, the disease may be asymptomatic. If greater than 50% of glomeruli are involved, hematuria and proteinuria are more profound. Renal insufficiency may be mild or may lead to a rapid loss in function. This depends on the percentage of kidney involved and the severity of the disease. Epithelial crescents form when the disease involves Bowman's space. Crescent formation or extracapillary proliferation is caused by the accumulations of macrophages, fibroblasts, proliferating epithelial cells, and fibrin within Bowman's space. *Crescentic glomerulonephritis* defines a disease process that results when more than 50% of the glomeruli have crescents. Progressive disease can result in ESRD.

MEDICAL MANAGEMENT

DIAGNOSIS. The diagnosis of glomerular disease requires analysis of urine, looking for protein, casts (protein, erythrocyte, or lymphocyte "castings" of the tubules), and erythrocytes. The erythrocytes are often misshaped, demonstrating the damage acquired while going through the glomerulus. A 24-hour urine collection may be required to assess the amount of proteinuria. Blood pressure is often elevated, and anemia may develop. A kidney biopsy is frequently needed to make the precise diagnosis.

TREATMENT. Treatment depends on the specific cause of the glomerular disease, but there are several features that may be shared and the treatment may be similar. Diseases causing nephrotic syndrome are treated with an ACE inhibitor or ARB to control blood pressure and to reduce proteinuria.

Hypercholesterolemia is usually treated with a hydroxymethylglutaryl-coenzyme A reductase inhibitor (statin).

Erythropoietin can be employed if anemia is symptomatic, and vitamin D sterols may be needed to prevent a deficiency in vitamin D. Fluid is restricted, and diuretics are often used to reduce edema. Diseases with immune-associated injury often require treatment with prednisone, cyclosporine, or cytotoxic agents. Others, such as membranoproliferative glomerulonephritis, improve with treatment of the underlying disorder (i.e., treating hepatitis C-induced disease with interferon-alfa-2 with ribavirin). Some diseases progress and require dialysis or transplantation.

SPECIAL IMPLICATIONS FOR THE THERAPIST 18-6

Glomerular Diseases

Therapists working with clients with a diagnosis of diabetes, systemic lupus erythematosus, vasculitis, and hypertension need to be aware of the association of glomerulonephritis with these disorders. Being vigilant for the clinical manifestations of glomerulonephritis (e.g., edema, hypertension, hematuria, oliguria) is important, and their presence warrants referral of the client to a physician.

An awareness of the side effects associated with diuretics is also important. Potential side effects include muscle weakness, fatigue, muscle cramps, headaches, and depression, all of which can interfere with the rehabilitation program. (See Chapter 5 for additional information regarding diuretics; see also Table 12-5.) The onset of any of these complaints also warrants communication with a physician. Finally, many clients with glomerulonephritis progress to chronic renal failure.

DISORDERS OF THE BLADDER AND URETHRA

Bladder Cancer

Overview and Incidence

The bladder is lined with transitional cells and in some places, such as at the trigone, epithelial cells. Transitional cell carcinoma is the most common type of bladder cancer, accounting for 90% of all cases. Transitional cell bladder cancer is a heterogeneous group of cancers with a wide spectrum of aggressiveness and clinical manifestations. Squamous cell carcinoma of the bladder is unusual, accounting for 8% of all cases, typically resulting from chronic inflammation. A more rare form, adenocarcinoma, accounts for the remaining 2% of cases and is thought to arise from remnants of the embryologic urachus (ligaments).

There are approximately 50,000 cases (21 per 100,000 people) of bladder cancer each year in the United States. As the fourth leading cause of cancer in men and eighth leading cause of cancer death in the United States, bladder cancer is more common than is generally appreciated.* Overall, the incidence of bladder cancer is increasing in industrialized countries, although the survival rate is improving.