Approach to the Patient with Abnormal Liver Chemistry Values

Differential Diagnosis

Evaluation of suspected liver disease requires an understanding of the diverse tests of liver function and serum markers of hepatobiliary disease. Abnormalities in liver chemistry values may result from cholestasis, hepatocellular injury, and infiltrative diseases of the liver (Table 16-1). The approach to the patient with jaundice is discussed in detail in Chapter 15. Hepatocellular disorders produce elevations in liver enzymes that are released by damaged hepatocytes. Infiltration resulting from malignancy, granulomas, amyloid, and other conditions results in elevations of enzymes that are localized to the bile canalicular membrane, usually without development of jaundice.

Cholestatic Disorders

Cholestasis may result from intrahepatic or extrahepatic processes. Intrahepatic causes of cholestasis include primary biliary cirrhosis (PBC), sepsis, medications, postoperative cholestasis, familial conditions (e.g., benign recurrent intrahepatic cholestasis and cholestasis of pregnancy), and congenital disorders (e.g., Rotor's syndrome, Dubin-Johnson syndrome, and Byler's disease). Extrahepatic biliary obstruction is caused by choledocholithiasis, benign and malignant strictures, extrinsic compression, and sclerosing cholangitis.

Disorders with Hepatocellular Injury

Hepatocellular injury may result from a diverse group of diseases. Acute viral hepatitis in the United States most commonly results from infection with hepatitis A and B, or, less commonly, C viruses. Hepatitis D complicates the course of infection in chronic hepatitis B carriers.

Hepatitis E occurs primarily in developing countries and can present with fulminant hepatic failure, particularly in pregnant women. Other viral causes of hepatitis include cytomegalovirus, herpes simplex virus, Epstein-Barr virus, and varicella-zoster virus. Chronic infection with either hepatitis B or C viruses may also produce chronic hepatitis or cirrhosis. Ethanol consumption produces a broad range of liver disease, including fatty liver, alcoholic hepatitis, and cirrhosis. Hereditary liver diseases that produce hepatocellular injury are Wilson's disease, hemochromatosis, and α_1-antitrypsin deficiency. Congestive and ischemic disease in the liver is caused by congestive heart failure, constrictive pericarditis, hypotension, portal vein thrombosis or hepatic vein (outflow) obstruction from Budd-Chiari syndrome, inferior vena cava occlusion, or veno-occlusive disease. Significant liver disease during pregnancy occurs in the third trimester including acute fatty liver of pregnancy and hepatocellular damage secondary to toxemia. Medication- and toxin-induced causes of injury are very common and require a high index of suspicion and careful questioning.

Infiltrative Diseases

Malignant diseases including primary tumors (e.g., hepatocellular carcinoma, cholangiocarcinoma), metastases, lymphoma, and leukemia, may produce infiltrative liver disease. Granulomatous liver infiltration may result from infections (e.g., tuberculosis and histoplasmosis), sarcoidosis, and numerous medications.

Workup

History

An accurate history is critical in assessing the patient whose laboratory studies provide evidence of liver disease. The presenting symptoms provide important diagnostic clues. Pruritus is often a presenting symptom in patients with cholestasis. Although classically associated with PBC and

primary sclerosing cholangitis (PSC), pruritus is also reported in extrahepatic biliary obstruction and hepatocellular disease. Many conditions that produce abnormal liver chemistry values are painless, but acute biliary obstruction from stones can produce intense right upper quadrant pain. Concurrent high fever raises concern for cholangitis. Acute hepatitis produces a less well-defined right upper quadrant discomfort with profound fatigue, whereas hepatic tumors may cause subcostal aching.

Family history is useful in diagnosing and evaluating hereditary hemolytic states, benign recurrent intrahepatic cholestasis, hemochromatosis, Wilson's disease, and α_1-antitrypsin deficiency. Exposure to ethanol, and industrial and environmental toxins should be identified. A detailed medication history is critical including over-the-counter and herbal remedies. In particular patients may not relate the use of episodic or intermittent medications, e.g. steroid tapers for asthma, antibiotics, without specific questioning. Alcoholic patients should be questioned about acetaminophen use, because hepatotoxicity can occur with therapeutic dosing due to induction of cytochrome P450 in alcoholics. Intravenous drug abuse, sexual contact, and blood transfusions suggest a risk of viral hepatitis B or C, whereas sudden worsening of liver chemistry values in a chronic hepatitis B carrier suggests possible hepatitis D superinfection. Waterborne outbreaks of viral hepatitis have been reported in Southeast Asia and India, underscoring the importance of obtaining a travel history. Risk factors for hepatitis A include recent ingestion of raw or undercooked oysters or clams, male homosexuality, or exposure through day care.

Other diseases associated with liver disorders should be ascertained. Right-sided congestive heart failure, hypotension, and shock are recognized causes of abnormal liver chemistry findings. Chronic pancreatitis may produce abnormal liver tests from stenosis of the

common bile duct. PSC is seen in 10% of patients with inflammatory bowel disease, in particular with ulcerative colitis. Obesity, hyperlipidemia, diabetes and corticosteroid are risk factors for non-alcoholic fatty liver disease (NAFLD). Hematologic disorders (e.g., polycythemia rubra vera, myeloproliferative disorders, and paroxysmal nocturnal hemoglobinuria) associated with hypercoagulable states predispose to hepatic vein thrombosis. Hemoglobinopathies (e.g., sickle cell anemia and thalassemia) lead to pigment stone formation. Rashes, arthritis, renal disease, and vasculitis may develop with viral hepatitis. The presence of hypogonadism, heart disease, and diabetes suggests possible hemochromatosis. Concurrent lung disease is found with α_1-antitrypsin deficiency, and central nervous system findings are associated with Wilson's disease. Patients with leptospirosis will present with hepatic and renal abnormalities. Renal cell carcinoma manifests as abnormal liver chemistry values in the absence of metastases. Recent surgery should be noted because anesthetic exposure, perioperative hypotension, and blood transfusions all may affect the liver. Recent biliary tract surgery raises concern for bile duct stricture. Cirrhosis is a late complication of jejunoileal bypass surgery, but not more recent gastric bypass operations, for morbid obesity.

Physical Examination

Physical findings are of discriminative value in a patient with abnormal liver chemistry findings. Fever is suggestive of an infectious cause or hepatitis. Jaundice is seen when the serum bilirubin concentration exceeds 2.5 to 3.0 mg per dl. Spider angiomas, palmar erythema, parotid enlargement, gynecomastia, Dupuytren's contracture, and testicular atrophy are stigmata of chronic liver disease, usually cirrhosis, though many of these signs have low specificity. Hyperpigmentation is seen with hemochromatosis and PBC. Ichthyosis and koilonychia are found with hemochromatosis. Xanthomas and xanthelasma appear in chronic cholestasis.

Kayser-Fleischer rings and sunflower cataracts suggest Wilson's disease. Conjunctival suffusion raises the possibility of leptospirosis. A liver span of >15 cm is suggestive of passive congestion or liver infiltration. Splenomegaly is found with portal hypertension or infiltrative processes. Abdominal tenderness suggests an inflammatory process (e.g., cholecystitis, cholangitis, pancreatitis, or hepatitis) whereas a palpable, nontender gallbladder (Courvoisier sign) raises the possibility of an obstructive malignancy. Murphy's sign (i.e., inspiratory arrest during deep, right upper quadrant palpation) is highly suggestive of acute cholecystitis. A pulsatile liver suggests tricuspid insufficiency, and hepatic bruits or rubs raise the possibility of hepatocellular carcinoma. Occult or gross fecal blood on rectal examination suggests possible inflammatory bowel disease or neoplasm.

Additional Testing

Hepatic Function Tests

Measurements of hepatic function evaluate the liver's ability to excrete substances and assess its synthetic and metabolic capacity.

Bilirubin. Serum bilirubin determination provides a measure of hepatic conjugation and organic anion excretion capabilities. Hyperbilirubinemia can occur from increases in the unconjugated or conjugated bilirubin fractions. Increased production of bilirubin because of hemolysis and defective conjugation produces unconjugated hyperbilirubinemia, whereas hepatocellular disorders and extrahepatic obstruction cause conjugated hyperbilirubinemia. A third form of bilirubin, seen with prolonged cholestasis, is covalently bound to albumin. The presence of this albumin-bound bilirubin explains the slow resolution of jaundice in convalescing patients with resolving liver disease. The urine bilirubin level is elevated in conjugated, not unconjugated, hyperbilirubinemia.

Albumin. Total serum albumin is a useful measure of hepatic synthetic function. With a half-life of 20 days, albumin is a better index of disease severity in chronic rather than acute liver injury. Hypoalbuminemia may result from increased catabolism of albumin, decreased synthesis, dilution with plasma volume expansion, and increased protein loss from the gut or urinary tract. Prealbumin has a shorter half-life (1.9 days) than albumin and therefore has been proposed as a useful measure of hepatic synthetic capacity after acute injury (e.g., acetaminophen overdose).

Clotting Factors. The prothrombin time detects activity of the vitamin K– dependent coagulation factors (II, VII, IX, and X). Synthesis of these factors requires adequate intestinal vitamin K absorption and intact hepatic synthesis. Therefore, prolonged prothrombin times result from hepatocellular disorders that impair synthetic functions and from cholestatic syndromes that interfere with lipid absorption. Parenteral vitamin K administration distinguishes these possibilities. Improvement in the prothrombin time by 30% within 24 hours of vitamin K administration indicates that synthetic function is intact and suggests vitamin K deficiency. A prolonged prothrombin time is a poor prognostic finding; it signifies severe hepatocellular necrosis in acute hepatitis and the loss of functional hepatocytes in chronic liver disease. Individual clotting proteins have been proposed as useful clinical guides in severe acute hepatitis. Factor VII is the best indicator of liver disease severity and prognosis.

Miscellaneous Tests of Hepatic Function. Serum bile acid determination has been advocated for the assessment of suspected liver disease, although poor diagnostic sensitivity in mild disease has prevented widespread application. However, the finding of normal levels of fasting bile acids in a patient with unconjugated hyperbilirubinemia supports a diagnosis of Gilbert's syndrome in questionable cases. Plasma clearance of sulfobromophthalein, an organic anion, may help distinguish between Dubin-Johnson syndrome and Rotor's syndrome. Serum globulin

determinations can also give useful diagnostic information. Levels in excess of 3 g per dl are primarily observed in autoimmune liver disease, whereas selective increases in levels of immunoglobulin A (IgA) and IgM are noted in alcoholic cirrhosis and PBC, respectively. Elevated serum ammonia levels may be noted with severe acute or chronic liver disease and can correlate roughly with hepatic encephalopathy. Acute viral and alcoholic hepatitis produce decreases in the alpha and pre-beta bands on serum protein electrophoresis because of reduced activity of lecithin-cholesterol acyltransferase, whereas the beta band may be broad because of altered triglyceride lipase activity resulting in elevated low-density lipoproteins. Breath tests of antipyrine clearance and aminopyrine demethylation measure impaired hepatic drug metabolism.

Serum Markers of Hepatobiliary Dysfunction/Necrosis

Aminotransferases. Aspartate aminotransferase (AST, SGOT) and alanine aminotransferase (ALT, SGPT) are markers of hepatocellular injury. Because AST is also found in muscle, kidney, heart, and brain, ALT elevations are more specific for liver processes. The highest elevations occur in viral, toxin-induced, and ischemic hepatitis, whereas smaller (<300 IU per ml) elevations are observed in alcoholic hepatitis and other hepatocellular disorders. An AST/ALT ratio of >2 is suggestive of alcoholic liver disease, whereas a ratio of <1 characterizes viral infection and biliary obstruction. When evaluating a patient with liver disease, decreases in AST and ALT levels usually suggest resolving injury, although decreasing aminotransferase levels may also be an ominous indicator of overwhelming hepatocyte death in fulminant liver failure, particularly when associated with progressive increases in prothrombin time.

Alkaline Phosphatase. Alkaline phosphatase originates in the bile canalicular membranes. Elevations of this enzyme are prominent in cholestasis and infiltrative liver disease; smaller increases are observed in other liver diseases. Alkaline phosphatase activity is also present in

bone, placenta, intestine, kidney, and some malignancies. Low levels of alkaline phosphatase may be observed in acute hemolysis complicating Wilson's disease as well as in hypothyroidism, pernicious anemia, and zinc deficiency.

Miscellaneous Markers of Hepatobiliary Dysfunction. Serum levels of γ-glutamyl- transferase (GGT), 5'-nucleotidase, and leucine aminopeptidase (LAP) are elevated in cholestatic syndromes and may help distinguish hepatobiliary from bony sources of alkaline phosphatase elevations. Levels of GGT are also elevated with pancreatic disease, myocardial infarction, uremia, lung disease, rheumatoid arthritis, NAFLD, and diabetes. Alcohol, anticonvulsants, and warfarin induce hepatic microsomal enzymes, producing striking GGT level increases. Levels of LAP may be elevated in normal pregnancy. The hepatic mitochondrial enzyme glutamate dehydrogenase is elevated in alcoholic patients and in patients with liver disease secondary to congestive heart failure. The lactate dehydrogenase concentration is frequently obtained as a "liver function test"; however, it has limited specificity for liver processes.

Disease-Specific Markers

Viral Serology. Hepatitis A IgM antibody (anti-HAV IgM) is initially detectable at the onset of clinical illness and persists for 120 days. Anti-HAV IgG is a convalescent marker that may persist for life. Hepatitis B surface antigen (HBsAg) precedes aminotransferase elevations and symptom development and persists for 1 to 2 months in self-limited infections. Antibody to core antigen (anti-HBc) is detected 2 weeks after the appearance of HBsAg, and initially is of the IgM class. Antibody to HBsAg (anti-HBs) appears sometime after the disappearance of HBsAg and may persist for life. During the window period between the disappearance of HBsAg and appearance of anti-HBs, anti-HBc IgM may be the only marker of recent hepatitis B infection. Hepatitis B e antigen and antibody, as well as PCR for Hepatitis B DNA levels in serum can be

used to quantify the degree of active viral replication in some patients with chronic hepatitis B infection. Enzyme-linked immunosorbent assays (ELISAs) are screening tests for detection of hepatitis C exposure. Recombinant immunoblot assays can be used as a supplement to ELISAs in cases where a false positive ELISA is suspected. Both tests may produce negative findings for up to 6 months after acute infection; therefore, if hepatitis C is a diagnostic possibility, Hepatitis C viremia should be determined by a polymerase chain reaction determination of hepatitis C RNA. Quantitative Hepatitis C RNA levels as well as genotype should also be determined prior to therapy and RNA levels followed serially during Hepatitis C therapy. Hepatitis D infection occurs only in patients with HBsAg positivity and can be measured by hepatitis D viral RNA and anti–hepatitis D antibodies, though these tests are not readily available. Persistence of anti-HDV IgM predicts progression to chronic hepatitis D infection. Acute Hepatitis E can be detected by ELISA foe anti-HEV. A subset of patients who test negative for the above viral markers will exhibit positive serologic findings for cytomegalovirus, herpes simplex, coxsackievirus, or Epstein-Barr virus.

Immunologic Tests. Markers that may be detected in autoimmune liver disease include antinuclear antibody (ANA, homogeneous pattern in a titer of $\geq$1:160) and the anti–smooth muscle antibodies (SMAs). SMAs are detected in 70% of patients with autoimmune chronic active hepatitis but may also be present in 50% of patients with PBC. The presence of anti-liver/kidney microsomal antibodies (anti-LKM$_1$) with reduced titers of anti-actin or ANAs identifies a subset of patients with autoimmune chronic active hepatitis that presents with an aggressive course in young women. Antimitochondrial antibodies (AMAs) are present in 90% of patients with PBC and 25% of patients with chronic active hepatitis or drug-induced liver

disease. Antibodies to the Ro antigen and to anticentromere antibodies are observed with PBC, especially in patients with sicca syndrome or scleroderma.

Copper Storage Variables. Ceruloplasmin is a copper transport protein in the plasma that circulates in low concentrations in Wilson disease; low levels (<20 mg per dl) are found in 90% of homozygotes and 10% of heterozygotes. Reductions may also be observed with severely depressed synthetic function caused by other end-stage liver diseases. Alternate diagnostic tests for Wilson disease include urinary copper, which exceeds 100 mg per 24 hours in nearly all patients, and free serum copper, which is markedly elevated. Urinary copper is also elevated in patients with cholestasis or cirrhosis. Though the gene for Wilson disease has been identified (ATP7B), the lack of a dominant mutation has prevented the development of genetic tests for the disease.

Iron Storage Variables. Serum iron level and total iron-binding capacity (transferrin) are useful measures in the diagnosis of hemochromatosis. Transferrin is normally 20% to 45% saturated. A transferrin saturation above 45% will identify over 98% of patients with hemochromatosis. Elevations in serum iron with normal transferrin saturation are observed in alcoholic liver disease. Serum ferritin more closely correlates with hepatic and total body iron stores, although ferritin may be elevated in inflammatory disease because it is an acute phase reactant. The identification of a single recessive mutation in the HFE gene (C282Y) responsible for the majority of hemochromatosis, liver biopsy is no longer required for diagnosis. Liver biopsy may be required in older patients with high ferritin levels for quantitative determination of tissue iron and to determine the extent of fibrosis which will guide the need for screening for hepatocellular carcinoma.

α_1-Antitrypsin. α_1-Antitrypsin is a hepatic glycoprotein that migrates in the α_1-globulin fraction on serum protein electrophoresis. Homozygotes for the Pi ZZ variant (normal is Pi MM) of this protein exhibit decreased serum α_1-antitrypsin activity, which predisposes to development of chronic liver and pulmonary disease. Hepatocytes that are unable to excrete the Z protein accumulate periodic acid–Schiff (PAS)-positive, diastase-resistant globules as seen in liver biopsy specimens. Phenotyping is more accurate for diagnosis than determination of serum levels of the protein, it is controversial whether heterozygotes (Pi MZ) can develop liver disease in the absence of other hepatic insults is controversial.

α-Fetoprotein. α-Fetoprotein (AFP) is present in the serum of 70% to 90% of patients with hepatocellular carcinoma (HCC), although small resectable tumors may not produce AFP. AFP levels are also elevated with germ cell tumors, other GI malignancies, PBC, and acute and chronic hepatitis. To reliably exclude these disorders, a level of >400 mg per ml is said to be specific for hepatocellular carcinoma, although this level excludes nearly one-third of patients with HCC. With improved imaging, all elevations of AFP should be investigated radiologically in patients with chronic liver disease.

Percutaneous Liver Biopsy

As a general rule, direct forms of liver injury tend to cause predominant centrizonal necrosis; immunologically mediated forms of hepatocyte injury are localized to the periportal region; and cholestatic injury is recognized by the accumulation of canalicular bile and feathery degeneration of hepatocytes in the absence of a significant inflammatory infiltrate. Clinical applications of liver biopsy include evaluation of persistently abnormal liver chemistry values, establishment of the diagnosis in unexplained hepatomegaly, and evaluation of suspected systemic diseases or carcinoma involving the liver. Contraindications to liver biopsy are an uncooperative or unstable

patient, ascites, right-sided empyema, and suspected hemangioma or echinococcal cyst. Impaired coagulation function is a relative contraindication. For patients with increased bleeding risk or ascites, a transjugular biopsy approach is an alternative.

Coordinated Diagnostic Approach

Liver disease is classified into three groups: cholestatic, hepatocellular, immunologic, and infiltrative. Screening the patient by determining levels of AST and ALT activity, serum alkaline phosphatase, serum total and direct bilirubin, serum protein and albumin, and prothrombin time can direct the subsequent evaluation into one of these four groups of liver disease (Fig. 16-1).

Cholestatic liver disease usually results in increased serum bilirubin and alkaline phosphatase levels with normal to mildly elevated aminotransferase levels, although in early biliary obstruction, transient profound aminotransferase elevations may occur. In extrahepatic cholestasis, the serum bilirubin level increases by 1.5 mg per dl per day, reaching a maximum of 35 mg per dl in the absence of renal dysfunction or hemolysis. In partial biliary obstruction, the bilirubin level may remain normal in the face of an elevated alkaline phosphatase concentration. The most direct approach to the evaluation of suspected cholestasis is to perform ultrasound to assess bile duct size. If malignancy or pancreatic disease is suspected, a computed tomography (CT) scan may provide better anatomic definition of the desired structures. If biliary dilation is detected, endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) can further define and potentially be used to treat the abnormality (see Chapter 15). In some cases of extrahepatic obstruction, bile duct size will be normal; in these cases, ERCP or PTC may still be indicated because of a high clinical suspicion. In questionable cases, percutaneous liver biopsy may provide a definitive diagnosis. However, intrahepatic

cholestasis cannot always be distinguished from extrahepatic cholestasis on liver biopsy specimens.

Hepatocellular injury is suggested by aminotransferase levels of >400 IU per ml; levels of >300 IU per ml are nonspecific and are observed with cholestasis as well as with hepatocellular disease. Alkaline phosphatase and bilirubin elevations are variable in hepatocellular disease, depending on the cause and severity of the clinical condition. Prolongation of the prothrombin time and decreases in serum albumin levels indicate significant hepatic synthetic dysfunction. In the setting of acute malaise, anorexia, nausea, jaundice, tender hepatomegaly, and elevated levels of aminotransferases, viral markers should be obtained to exclude hepatitis A, B, or C viruses, depending on the patient risk factors. With disease duration of >6 months, additional studies (e.g., serum protein electrophoresis, ferritin or iron studies, and ceruloplasmin) should be added to the viral serologic studies to exclude hereditary liver disease. Eosinophilia suggests possible drug hypersensitivity. For a patient with prominent systemic symptoms suggestive of autoimmune disease, the clinician should determine the sedimentation rate; serum protein electrophoresis; quantitative immunoglobulins; and the presence of ANA, AMA, and SMA. A hepatocellular pattern is observed with ischemic and congestive liver disease, but measures to improve hepatic blood flow in these conditions can produce brisk reductions in aminotransferases to near normal levels within 48-72 hours. With congestive liver disease, the prothrombin time may be prolonged out of proportion to other signs of liver disease. Hepatic vein thrombosis (Budd-Chiari syndrome) may be suggested by increased caudate lobe size on scanning and usually confirmed by ultrasound, CT or MRI showing hepatic vein outflow obstruction and IVC narrowing. Most acute elevations in aminotransferase levels do not require further evaluation unless they are severe or progressive. If aminotransferase levels remain high

for >6 months without an identifiable cause, however, a liver biopsy is indicated for diagnosis and to offer prognostic information about possible progression to cirrhosis. Many persons are obese or use ethanol, and the usual finding on liver biopsy is NAFLD in the absence of serologic diagnosis. However, the unexpected finding of chronic active hepatitis in a subset of these patients provides support for biopsy even in asymptomatic individuals.

Isolated elevation of alkaline phosphatase levels of hepatic origin (confirmed by LAP, 5'-nucleotidase, or GGT) suggests an infiltrative process. These patients should undergo diagnostic imaging as described above, however, to rule out extrahepatic cholestasis. A more than threefold increase in the alkaline phosphatase level in a patient with known cirrhosis raises concern for hepatocellular carcinoma. In these patients, levels of α-fetoprotein should be measured, and an ultrasonound or CT scan performed to exclude mass lesions. An elevated alkaline phosphatase level, detectable titers of AMA, and an elevated serum IgM level in a middle-aged woman are consistent with PBC. If imaging studies are nondiagnostic, liver biopsy is essential to exclude neoplasm, infection, cholestasis, or granuloma.

Patients who have undergone liver transplantation are frequently evaluated for abnormal liver function tests. Based on the time period following transplant, acute cellular rejection, hepatic artery thrombosis, opportunistic infection, drug-induced liver disease or recurrence of the primary liver disease all vary in likelihood. Liver biopsy and Doppler ultrasound of the liver are usually required to establish a diagnosis and guide management.

Principles of Management

The management of patients with abnormal liver chemistry values is dependent on obtaining an accurate diagnosis. For extrahepatic obstruction, the goal of treatment is to relieve or bypass the obstruction (see Chapter 15). In drug-induced intrahepatic cholestasis, removal of the offending

medication is indicated, although this does not always produce prompt normalization of liver chemistry values. Management of PBC depends on the stage of disease. The synthetic bile acids ursodiol is usually given in the early stages of the disease with modest success; advanced liver failure in PBC usually warrants liver transplantation. Cholestyramine, rifampicin, phenobarbital, or ondansetron are given for pruritus in the cholestatic disorders.

Specific therapies for many hepatocellular disorders have been well described. Hemochromatosis is managed with phlebotomy, or alternatively, desferrioxamine. Wilson's disease is initially treated with D-penicillamine; maintenance regimens may include oral zinc to reduce intestinal copper absorption. Patients with severe acute hepatitis may require hospitalization for supportive care. An encephalopathic patient may need mechanical ventilation, intracranial pressure monitoring, and possible emergency liver transplantation to avert a fatal outcome. Pegylated Interferon-α, usually with the oral agent ribavirin may eliminate the virus or slow disease progression in chronic active hepatitis C. Interferon-α and oral nucleosides and nucleotides are used to treat Hepatitis B. Autoimmune chronic active hepatitis is usually responsive to corticosteroids, although most patients require long-term immunosuppressives with a maintenance anti-metabolite immunosuppressive, like azathioprine. Congestive and ischemic hepatopathy improves with control of the underlying hemodynamic state. Anticoagulants agents may be used in the early stages of Budd-Chiari syndrome or veno-occlusive disease, although these do not prevent clinical deterioration in many patients, and many require portosystemic shunting (e.g., transjugular intrahepatic portosystemic shunt, TIPS). Drug-induced hepatocellular injury is managed by medication withdrawal, although some agents have the potential for fatal hepatic necrosis (e.g., acetaminophen). With recent acetaminophen ingestion, administration of *N*-acetylcysteine is indicated.

Many of the causes of infiltrative liver disease have no effective treatment. Hepatic tuberculosis and candidiasis are exceptions; they respond to appropriate antimicrobial therapy. Although advanced hepatocellular carcinoma usually has a poor prognosis, early stage (I-II) tumors may be cured with resection or transplantation. The fibrolamellar variant of hepatocellular carcinoma in young patients has a better prognosis. Multiple metastatic carcinomas are usually unresectable and have dismal prognoses, although prolonged survival has been reported after excision of the primary tumor and three or fewer solitary hepatic metastases.

Complications

Patients with chronic cholestasis or hepatocellular injury may progress to end-stage liver disease, depending on the cause. With hepatocyte loss, coagulopathy and hypoproteinemia develop, increasing the risks of hemorrhage, edema, ascites, and infection. Portal hypertension may lead to ascites, hydrothorax, and hemorrhage from esophageal or gastric varices or portal gastropathy. Other complications of end-stage liver failure include hepatic encephalopathy and hepatorenal syndrome. Infiltrative fungal infections of the liver may progress to abscess formation and death. Infiltrative malignancy usually is fatal.

Hepatitis B and C may be transmitted to contacts of the infected patient, usually by transfer of bodily fluids (e.g., blood), although sexual transmission of hepatitis B (and to a much lesser degree, hepatitis C) is possible. Patients who report body fluid contact with an HBsAg-positive patient should receive hepatitis B immune globulin, and, in most instances, they will benefit from a vaccination against hepatitis B. Immune serum globulin is recommended for individuals potentially exposed to hepatitis A. There is no established role of immune serum globulin in hepatitis C prophylaxis.