CHAPTER 33

Anesthesia for Patients with Liver Disease

Michael Ramsay, MD, FRCA

KEY CONCEPTS

1. Because of the increased risk of perioperative morbidity and mortality, patients with acute hepatitis should have any elective surgery postponed until the acute hepatitis has resolved, as indicated by the normalization of liver tests.
2. Isoflurane and sevoflurane are the volatile agents of choice because they preserve hepatic blood flow and oxygen delivery. Factors known to reduce hepatic blood flow, such as hypotension, excessive sympathetic activation, and high mean airway pressures during controlled ventilation, should be avoided.
3. In evaluating patients for chronic hepatitis, laboratory test results may show only a mild elevation in serum aminotransferase activity and often correlate poorly with disease severity.
4. Approximately 10% of patients with cirrhosis also develop at least one episode of spontaneous bacterial peritonitis, and some patients may eventually develop hepatocellular carcinoma.
5. Massive bleeding from gastroesophageal varices is a major cause of morbidity and mortality, and, in addition to the cardiovascular effects of acute blood loss, the absorbed nitrogen load from the breakdown of blood in the intestinal tract can precipitate hepatic encephalopathy.
6. The cardiovascular changes observed in the patient with hepatic cirrhosis are usually that of a hyperdynamic circulation, although clinically significant cirrhotic cardiomyopathy is often present and not recognized.
7. The effects of hepatic cirrhosis on pulmonary vascular resistance vessels may result in chronic hypoxemia.
8. Hepatorenal syndrome is a functional renal defect in patients with cirrhosis that usually follows gastrointestinal bleeding, aggressive diuresis, sepsis, or major surgery. It is characterized by progressive oliguria with avid sodium retention, azotemia, intractable ascites, and a very high mortality rate.
9. Factors known to precipitate hepatic encephalopathy in patients with cirrhosis include gastrointestinal bleeding, increased dietary protein intake, hypokalemic alkalosis from vomiting or diuresis, infections, and worsening liver function.
10. Following the removal of large amounts of ascitic fluid, aggressive intravenous fluid replacement is often necessary to prevent profound hypotension and kidney failure.

The prevalence of liver disease is increasing in the United States. Cirrhosis, the terminal pathology in the majority of liver diseases, has a general population incidence as high as 5% in some autopsy series. It is a major cause of death in men in their fourth and fifth decades of life, and mortality rates are increasing. Ten percent of the patients with liver disease undergo operative procedures during the final 2 years of their lives. The liver has remarkable functional reserve, and thus overt clinical manifestations of hepatic disease are often absent until extensive damage has occurred. When patients with little hepatic reserve come to the operating room, effects from anesthesia and the surgical procedure can precipitate further hepatic decompensation, leading to frank hepatic failure.

COAGULATION IN LIVER DISEASE

In stable chronic liver disease, the causes of excessive bleeding primarily involve severe thrombocytopenia, endothelial dysfunction, portal hypertension, renal failure, and sepsis (see Chapters 32 and 51). However, the hemostatic changes that occur with liver disease may cause hypercoagulation and thrombosis, as well as an increased risk of bleeding. Clot breakdown may be enhanced by an imbalance of the fibrinolytic system.

Chronic liver disease is characterized by the impaired synthesis of coagulation factors, resulting in prolongation of the prothrombin time (PT) and international normalized ratio (INR) (Table 33–1). However, the anticoagulant factors (protein C, antithrombin, and tissue factor pathway inhibitor) are also reduced and may balance out any effect of a prolonged PT. This may be confirmed by assessing thrombin generation in the presence of endothelial-produced thrombomodulin. Adequate thrombin production requires an adequate number of functioning platelets. If the platelet count is >60,000/μL, coagulation may well be normal in a patient with severe cirrhosis.

The patient with cirrhosis will typically have hyperfibrinolysis. However, there is a delicate balance between the activators and inactivators that regulate the conversion of plasminogen to plasmin, and, therefore, individual laboratory tests may not give a true picture of the state of fibrinolysis. The thromboelastography (TEG®), rotational thromboelastometry (ROTEM®), and Sonoclot® technologies are the optimal methods of demonstrating the global state of the coagulation system at a specific moment in time in any patient with liver disease (see Chapter 51).

TABLE 33–1 Coagulation test abnormalities.[1]

	PT	PTT	TT	Fibrinogen
Advanced liver disease	↑	↑	N or ↑	N or ↓
DIC	↑	↑	↑	↓
Vitamin K deficiency	↑↑	↑	N	N
Warfarin therapy	↑↑	↑	N	N
Heparin therapy	↑	↑↑	↑	N
Hemophilia				
Factor VIII deficiency	N	↑	N	N
Factor IX deficiency	N	↑	N	N
Factor VII deficiency	↑	N	N	N
Factor XIII deficiency	N	N	N	N

[1]PT, prothrombin time; PTT, partial thromboplastin time; TT, thrombin time; N, normal; DIC, disseminated intravascular coagulation.

Hepatitis

ACUTE HEPATITIS

Acute hepatitis is usually the result of a viral infection, drug reaction, or exposure to a hepatotoxin. The illness represents acute hepatocellular injury with a variable degree of cellular necrosis. Clinical manifestations depend both on the severity of the inflammatory reaction, and, more importantly, on the degree of necrosis. Mild inflammatory reactions may present merely as asymptomatic elevations in the serum transaminases, whereas massive hepatic necrosis presents as acute fulminant hepatic failure.

Viral Hepatitis

Viral hepatitis is most commonly due to hepatitis A, hepatitis B, or hepatitis C viral infection. At least two other hepatitis viruses have also been identified: hepatitis D (delta virus) and hepatitis E (enteric non-A, non-B). Hepatitis types A and E are transmitted by the fecal-oral route, whereas hepatitis types B and C are transmitted primarily percutaneously and by contact with body fluids. Hepatitis D is unique in that it may be transmitted by either route and requires the presence of hepatitis B virus in the host to be infective. Other viruses may also cause hepatitis, including Epstein–Barr, herpes simplex, cytomegalovirus, and coxsackieviruses.

Patients with viral hepatitis often have a 1- to 2-week mild prodromal illness (fatigue, malaise, low-grade fever, or nausea and vomiting) that may or may not be followed by jaundice. The jaundice typically lasts 2–12 weeks, but complete recovery, as evidenced by serum transaminase measurements, usually takes 4 months. Because clinical manifestations overlap, serological testing is necessary to determine the causative viral agent. The clinical course tends to be more complicated and prolonged with hepatitis B and C viruses relative to other types of viral hepatitis. Cholestasis (see below) may be a major manifestation. Rarely, fulminant hepatic failure (massive hepatic necrosis) can develop.

The incidence of chronic active hepatitis (see below) is 3% to 10% following infection with hepatitis B virus and at least 50% following infection with hepatitis C virus. A small percentage of patients (mainly immunosuppressed patients and those on long-term hemodialysis regimens) become asymptomatic infectious carriers following infection with hepatitis B virus, and up to 30% of these patients remain infectious with the hepatitis B surface antigen (HBsAg) persisting in their blood. Most patients with chronic hepatitis C infection seem to have very low, intermittent, or absent circulating viral particles and are therefore not highly infective. Approximately 0.5% to 1% of patients with hepatitis C infection become asymptomatic infectious carriers, and infectivity correlates with the detection of hepatitis C viral RNA in peripheral blood. Such infectious carriers pose a major health hazard to operating room personnel.

In addition to "universal precautions" for avoiding direct contact with blood and secretions (gloves, mask, protective eyewear, and not recapping needles), immunization of healthcare personnel is highly effective against hepatitis B infection. A vaccine for hepatitis C is not available; moreover, unlike hepatitis B infection, hepatitis C infection does not seem to confer immunity to subsequent exposure. Postexposure prophylaxis with hyperimmune globulin is effective for hepatitis B, but not hepatitis C.

Drug-induced Hepatitis

Drug-induced hepatitis (Table 33–2) can result from direct, dose-dependent toxicity of a drug or drug metabolite, an idiosyncratic drug reaction, or a combination of these two causes. The clinical course often resembles viral hepatitis, making diagnosis difficult. Alcoholic hepatitis is probably the most common form of drug-induced hepatitis, but the etiology may not be obvious from the history. Chronic alcohol ingestion can also result in hepatomegaly from fatty infiltration of the liver, which reflects impaired fatty acid oxidation, increased uptake and esterification of fatty acids, and diminished lipoprotein synthesis and secretion. Acetaminophen ingestion of 25 g or more usually results in fatal fulminant hepatotoxicity. A few drugs, such as chlorpromazine and oral contraceptives, may cause cholestatic-type reactions (see below). Ingestion of potent hepatotoxins, such as carbon tetrachloride and certain species of

TABLE 33–2 Drugs and substances associated with hepatitis.

Toxic
Alcohol
Acetaminophen
Salicylates
Tetracyclines
Trichloroethylene
Vinyl chloride
Carbon tetrachloride
Yellow phosphorus
Poisonous mushrooms (*Amanita, Galerina*)
Idiosyncratic
Volatile anesthetics (halothane)
Phenytoin
Sulfonamides
Rifampin
Indomethacin
Toxic and idiosyncratic
Methyldopa
Isoniazid
Sodium valproate
Amiodarone
Primarily cholestatic
Chlorpromazine
Cyclosporine
Oral contraceptives
Anabolic steroids
Erythromycin estolate
Methimazole

mushrooms (*Amanita, Galerina*), also may result in fatal hepatotoxicity.

1 Because of the increased risk of perioperative morbidity and mortality, patients with acute hepatitis should have elective surgery postponed until the illness has resolved, as indicated by the normalization of liver tests. In addition, acute alcohol toxicity greatly complicates anesthetic management, and acute alcohol withdrawal during the perioperative period may be associated with a mortality rate as high as 50%. Only emergent surgery should be considered for patients presenting in acute alcohol withdrawal. Patients with hepatitis are at risk of deterioration of hepatic function and the development of complications from hepatic failure, such as encephalopathy, coagulopathy, or hepatorenal syndrome.

Laboratory evaluation of the patient with hepatitis should include blood urea nitrogen, serum electrolytes, creatinine, glucose, transaminases, bilirubin, alkaline phosphatase, and albumin, platelet count, and PT. Serum should also be checked for HBsAg whenever possible. A blood alcohol level is useful if the history or physical examination is compatible with ethanol intoxication. Hypokalemia and metabolic alkalosis are not uncommon and are usually due to vomiting. Concomitant hypomagnesemia may be present in chronic alcoholics and predisposes to cardiac arrhythmias. The elevation in serum transaminases does not necessarily correlate with the amount of hepatic necrosis. The serum alanine aminotransferase (ALT) is generally higher than the serum aspartate aminotransferase (AST), except in alcoholic hepatitis, where the reverse occurs. Bilirubin and alkaline phosphatase are usually only moderately elevated, except with the cholestatic variant of hepatitis. The PT is the best indicator of hepatic synthetic function. Persistent prolongation of longer than 3 sec (INR > 1.5) following administration of vitamin K is indicative of severe hepatic dysfunction. Hypoglycemia is not uncommon. Hypoalbuminemia is usually not present except in protracted cases, with severe malnutrition, or when chronic liver disease is present.

If a patient with acute hepatitis must undergo an emergent operation, the preanesthetic evaluation should focus on determining the cause and the degree of hepatic impairment. Information should be obtained regarding recent drug exposures, including alcohol intake, intravenous drug use, recent transfusions, and prior anesthetics. The presence of nausea or vomiting should be noted, and, if present, dehydration and electrolyte abnormalities should be anticipated and corrected. Changes in mental status may indicate severe hepatic impairment. Inappropriate behavior or obtundation in alcoholic patients may be signs of acute intoxication, whereas tremulousness and irritability usually reflect withdrawal. Hypertension and tachycardia are often also prominent with the latter. Fresh frozen plasma may be necessary to correct a coagulopathy. Premedication is generally not given, in an effort to minimize drug exposure and not confound hepatic encephalopathy in patients with advanced

liver disease. However, benzodiazepines and thiamine are indicated in alcoholic patients with, or at risk for, acute withdrawal.

Intraoperative Considerations

The goal of intraoperative management is to preserve existing hepatic function and avoid factors that may be detrimental to the liver. Drug selection and dosage should be individualized. Some patients with viral hepatitis may exhibit increased central nervous system sensitivity to anesthetics, whereas alcoholic patients will often display cross-tolerance to both intravenous and volatile anesthetics. Alcoholic patients also require close cardiovascular monitoring, because the cardiac depressant effects of alcohol are additive to those of anesthetics; moreover, alcoholic cardiomyopathy is present in many alcoholic patients.

Inhalation anesthetics are generally preferable to intravenous agents because most of the latter are dependent on the liver for metabolism or elimination. Standard induction doses of intravenous induction agents can generally be used because their action is terminated by redistribution rather than metabolism or excretion. A prolonged duration of action, however, may be encountered with large or repeated doses of intravenous agents, particularly opioids. Isoflurane and sevoflurane are the volatile agents of choice because they preserve hepatic blood flow and oxygen delivery. Factors known to reduce hepatic blood flow, such as hypotension, excessive sympathetic activation, and high mean airway pressures during controlled ventilation, should be avoided. Regional anesthesia, including major conduction blockade, may be employed in the absence of coagulopathy, provided hypotension is avoided.

CHRONIC HEPATITIS

Chronic hepatitis is defined as persistent hepatic inflammation for longer than 6 months, as evidenced by elevated serum aminotransferases. Patients can usually be classified as having one of three distinct syndromes based on a liver biopsy: chronic persistent hepatitis, chronic lobular hepatitis, or chronic active hepatitis. Patients with chronic active hepatitis have chronic hepatic inflammation with destruction of normal cellular architecture (piecemeal necrosis) on the biopsy. Evidence of cirrhosis is either present initially or eventually develops in 20% to 50% of patients. Although chronic active hepatitis seems to have many causes, it occurs most commonly as a sequela of hepatitis B or hepatitis C. Other causes include drugs (methyldopa, isoniazid, and nitrofurantoin) and autoimmune disorders. Both immunological factors and a genetic predisposition may be responsible in most cases. Patients usually present with a history of fatigue and recurrent jaundice; extrahepatic manifestations, such as arthritis and serositis, are not uncommon. Manifestations of cirrhosis eventually predominate in patients with progressive disease.

In evaluating patients for chronic hepatitis, laboratory test results may show only a mild elevation in serum aminotransferase activity and often correlate poorly with disease severity. Patients without chronic hepatitis B or C infection usually have a favorable response to immunosuppressants and are treated with long-term corticosteroid therapy with or without azathioprine.

Anesthetic Management

Patients with chronic persistent or chronic lobular hepatitis should be treated similarly to those with acute hepatitis. In contrast, those with chronic active hepatitis should be assumed to already have cirrhosis and should be treated accordingly (see below). Patients with autoimmune chronic active hepatitis may also present with problems related to other autoimmune manifestations (such as diabetes or thyroiditis) or long-term corticosteroid therapy that they have likely received.

Cirrhosis

Cirrhosis is a serious and progressive disease that eventually results in hepatic failure, and the most common cause of cirrhosis in the United States is chronic alcohol abuse. Other causes include chronic active hepatitis (postnecrotic cirrhosis), chronic biliary inflammation or obstruction (primary biliary cirrhosis, sclerosing cholangitis), chronic right-sided congestive heart failure (cardiac cirrhosis),

autoimmune hepatitis, hemochromatosis, Wilson's disease, α_1-antitrypsin deficiency, nonalcoholic steatohepatitis, and cryptogenic cirrhosis. Regardless of the cause, hepatocyte necrosis is followed by fibrosis and nodular regeneration. Distortion of the liver's normal cellular and vascular architecture obstructs portal venous flow and leads to portal hypertension, whereas impairment of the liver's normal synthetic and other diverse metabolic functions results in multisystem disease. Clinically, signs and symptoms often do not correlate with disease severity. Manifestations are typically absent initially, but jaundice and ascites eventually develop in most patients. Other signs include spider angiomas, palmar erythema, gynecomastia, and splenomegaly. Moreover, cirrhosis is generally associated with the development of three major complications: (1) variceal hemorrhage from portal hypertension, (2) intractable fluid retention in the form of ascites and the hepatorenal syndrome, and (3) hepatic encephalopathy or coma. Approximately 10% of patients with cirrhosis also develop at least one episode of spontaneous bacterial peritonitis, and some patients eventually develop hepatocellular carcinoma.

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A few diseases can produce hepatic fibrosis without hepatocellular necrosis or nodular regeneration, resulting in portal hypertension and its associated complications with hepatocellular function often preserved. These disorders include schistosomiasis, idiopathic portal fibrosis (Banti's syndrome), and congenital hepatic fibrosis. Obstruction of the hepatic veins or inferior vena cava (Budd–Chiari syndrome) can also cause portal hypertension. The latter may be the result of venous thrombosis (hypercoagulable state), a tumor thrombus (eg, renal carcinoma), or occlusive disease of the sublobular hepatic veins.

Preoperative Considerations

The detrimental effects of anesthesia and surgery on hepatic blood flow are discussed below. Patients with cirrhosis are at increased risk of deterioration of liver function because of their limited functional reserves. Successful anesthetic management of these patients is dependent on recognizing the multisystem nature of cirrhosis (Table 33–3) and controlling or preventing its complications.

TABLE 33–3 Manifestations of cirrhosis.

Gastrointestinal
Portal hypertension
Ascites
Esophageal varices
Hemorrhoids
Gastrointestinal bleeding
Circulatory
Hyperdynamic state (high cardiac output)
Systemic arteriovenous shunts
Low systemic vascular resistance
Cirrhotic cardiomyopathy; pulmonary hypertension
Pulmonary
Increased intrapulmonary shunting; hepatopulmonary syndrome
Decreased functional residual capacity
Pleural effusions
Restrictive ventilatory defect
Respiratory alkalosis
Renal
Increased proximal reabsorption of sodium
Increased distal reabsorption of sodium
Impaired free water clearance
Decreased renal perfusion
Hepatorenal syndrome
Hematological
Anemia
Coagulopathy
Hypersplenism
Thrombocytopenia
Leukopenia
Infectious
Spontaneous bacterial peritonitis
Metabolic
Hyponatremia and hypernatremia
Hypokalemia and hypocalcemia
Hypomagnesemia
Hypoalbuminemia
Hypoglycemia
Neurological
Encephalopathy

A. Gastrointestinal Manifestations

Portal hypertension leads to the development of extensive portosystemic venous collateral channels.

TABLE 33–4 Child's classification for evaluating hepatic reserve.[1]

Risk Group	A	B	C
Bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	3.0–3.5	<3.0
Ascites	None	Controlled	Poorly controlled
Encephalopathy	Absent	Minimal	Coma
Nutrition	Excellent	Good	Poor
Mortality rate (%)	2–5	10	50

[1]Adapted and reproduced, with permission, from Child CG: *The Liver and Portal Hypertension*. W.B. Saunders, 1964.

Four major collateral sites are generally recognized: gastroesophageal, hemorrhoidal, periumbilical, and retroperitoneal. Portal hypertension is often apparent preoperatively, as evidenced by dilated abdominal wall veins (*caput medusae)*. Massive bleeding from gastroesophageal varices is a major cause of morbidity and mortality, and, in addition to the effects of acute blood loss, the absorbed nitrogen load from the breakdown of blood in the intestinal tract can precipitate hepatic encephalopathy.

The treatment of variceal bleeding is primarily supportive, but frequently involves endoscopic procedures for identification of the bleeding site(s) and therapeutic maneuvers, such as injection sclerosis of varices, monopolar and bipolar electrocoagulation, or application of hemoclips or bands. In addition to the risks posed by a patient who is physiologically fragile and acutely hypovolemic and hypotensive, anesthesia for such endoscopic procedures frequently involves the additional challenges of an encephalopathic and uncooperative patient and a stomach full of food and blood. Endoscopic unipolar electrocautery may adversely affect implanted cardiac pacing and defibrillator devices.

Blood loss should be replaced with intravenous fluids and blood products. Nonsurgical treatment includes vasopressin, somatostatin, propranolol, and balloon tamponade with a Sengstaken–Blakemore tube. Vasopressin, somatostatin, and propranolol reduce the rate of blood loss. High doses of vasopressin can result in congestive heart failure or myocardial ischemia; concomitant infusion of intravenous nitroglycerin may reduce the likelihood of these complications and bleeding. Placement of a percutaneous transjugular intrahepatic portosystemic shunt (TIPS) can reduce portal hypertension and subsequent bleeding, but may increase the incidence of encephalopathy. When the bleeding fails to stop or recurs, emergency surgery may be indicated. Surgical risk has been shown to correlate with the degree of hepatic impairment, based on clinical and laboratory findings. Child's classification for evaluating hepatic reserve is shown in Table 33–4. Shunting procedures are generally performed on low-risk patients, whereas ablative surgery, esophageal transection, and gastric devascularization are reserved for high-risk patients.

B. Hematologic Manifestations

Anemia, thrombocytopenia, and, less commonly, leukopenia, may be present. The cause of the anemia is usually multifactorial and includes blood loss, increased red blood cell destruction, bone marrow suppression, and nutritional deficiencies. Congestive splenomegaly secondary to portal hypertension is largely responsible for the thrombocytopenia and leukopenia. Coagulation factor deficiencies arise as a result of decreased hepatic synthesis. Enhanced fibrinolysis secondary to decreased clearance of activators of the fibrinolytic system may also contribute to the coagulopathy.

The need for preoperative blood transfusions should be balanced against the obligatory increase in nitrogen load. Protein breakdown from excessive blood transfusions can precipitate encephalopathy.

However, coagulopathy should be corrected before surgery. Clotting factors should be replaced with appropriate blood products, such as fresh frozen plasma and cryoprecipitate. Platelet transfusions should be considered immediately prior to surgery for counts less than 75,000/μL.

C. Circulatory Manifestations

End-stage liver disease, and, in particular, cirrhosis of the liver, may be associated with disorders of all major organ systems (Tables 33–3 and 33–5). The cardiovascular changes observed in the patient with hepatic cirrhosis are usually that of a hyperdynamic circulation, although clinically significant cirrhotic cardiomyopathy is often present and not recognized (Table 33–6). There may be a reduced cardiac contractile response to stress, altered diastolic relaxation, downregulation of β-adrenergic receptors, and electrophysiological changes as a result of cirrhotic cardiomyopathy.

Echocardiographic examination of cardiac function may initially be interpreted as normal because of significant afterload reduction caused by low systemic vascular resistance. However, both systolic and diastolic dysfunction are often found. Noninvasive stress imaging is frequently used to assess coronary artery disease in patients older than age 50 years and those with risk factors.

TABLE 33–6 Hemodynamic and pathological changes in the typical cirrhotic patient.

- Increased cardiac output
- Increased heart rate
- Decreased systemic vascular resistance
- Increased circulating volume
- Coronary artery disease
- Cirrhotic cardiomyopathy (often unrecognized)
- Low systemic vascular resistance conceals poor left ventricular function
- Reduced responsiveness to β-agonists

Hepatopulmonary Syndrome

The effects of hepatic cirrhosis on the pulmonary vascular resistance (PVR) vessels may result in chronic hypoxemia. *Hepatopulmonary syndrome* (Table 33–7) is found in approximately 30% of liver transplant candidates and is characterized

TABLE 33–5 Differential diagnosis of cardiopulmonary dysfunction in chronic liver disease and portal hypertension.

Primary cardiopulmonary disorders
• Chronic obstructive pulmonary disease
• Congestive heart failure
• Asthma
• Restrictive lung disease
• Pneumonia
Complications of cirrhosis
• Ascites
• Pleural effusions
• Muscle wasting
Cardiopulmonary/liver disease
• Alcoholic liver disease with alcoholic cardiomyopathy
• Hemochromatosis with iron overload cardiomyopathy
• A-1 antitrypsin deficiency with panacinar emphesema
• Primary biliary cirrhosis with fibrosing alveolitis
Pulmonary vascular disorders
• Hepatopulmonary syndrome
• Portopulmonary hypertension

TABLE 33–7 Hepatopulmonary syndrome.

Clinical features
• Cyanosis
• Digital clubbing
• Cutaneous telangiectasia
• Orthodeoxia – oxygen desaturation on sitting or standing
• Platypnea – breathing easier lying flat
• Dyspnea
Diagnostic criteria
• Presence of liver disease, usually with portal hypertension and cirrhosis
• An alveolar to arterial oxygen gradient of >15 mm Hg
• Pulmonary arteriovenous connections demonstrated by:
▪ A delayed contrast-enhanced (agitated saline) echocardiogram showing contrast in the left heart chambers 4 to 6 heartbeats after contrast appears in the right heart chambers
▪ Brain uptake >6% following technetium-99m macroaggregated albumin lung perfusion scan
Indications
• Liver transplantation is the only therapy that will cure hepatopulmonary syndrome

by pulmonary arteriolar endothelial dysfunction. The resultant intrapulmonary vascular dilatation causes intrapulmonary right-to-left shunting and an increase in the alveolar to arterial oxygen gradient.

Portopulmonary Hypertension

Pulmonary vascular remodeling may occur in association with chronic liver disease, involving vascular smooth muscle proliferation, vasoconstriction, intimal proliferation, and eventual fibrosis, all presenting as an obstructive pathology that causes an increased resistance to flow. This may result in pulmonary hypertension; if associated with portal hypertension, it is termed *portopulmonary hypertension* (POPH; Table 33–8).

The diagnostic criteria for POPH include a mean pulmonary artery pressure (mPAP) >25 mm Hg at rest, and a PVR > 240 dyn.s.cm^{-5}. The transpulmonary gradient of >12 mm Hg (mPAP – pulmonary arteriolar occlusion pressure [PAOP]) reflects the obstruction to flow and distinguishes the contribution of volume and resistance to the increase in mPAP.

POPH may be classified as mild (mPAP 25–35 mm Hg), moderate (mPAP > 35 and <45 mm Hg), and severe (mPAP > 45 mm Hg). Mild POPH is not associated with increased mortality at liver transplantation, although the immediate recovery period may be challenging if there is a significant increase in cardiac output after reperfusion of the new graft. Moderate and severe POPH are associated with significant mortality at transplantation. However, the key factor is not mPAP, but rather right ventricular (RV) function.

TABLE 33–8 Clinical features of portopulmonary hypertension.

- Increased pulmonary vascular resistance: vasoconstriction, structural vascular remodeling, and eventual fibrosis.
- Mean pulmonary artery pressure >25 mm Hg with normal pulmonary capillary wedge pressure
- Right ventricular overload
- Right heart failure
- Hepatic congestion
- Increased liver transplantation mortality risk, especially if mean pulmonary artery pressure is >35 mm Hg

The success of liver transplantation will depend on the right ventricle maintaining good function during and after the transplant procedure despite increases in cardiac output, volume, and PVR. If RV dysfunction or failure occurs, graft congestion with possible failure and serious morbidity, including mortality, may ensue. Assessment of the right ventricle using transesophageal echocardiography (TEE) is often helpful.

The role of liver transplantation in the management of POPH is not well defined. In some patients, pulmonary hypertension will reverse quickly after transplant; however, other patients may require months or years of ongoing vasodilator therapy. Other patients may continue to progress and eventually develop RV failure. Some patients will develop pulmonary hypertension after liver transplantation. Liver transplantation offers the best outcome in patients with POPH that is responsive to vasodilator therapy.

D. Respiratory Manifestations

Disturbances in pulmonary gas exchange and ventilatory mechanics are often present. Hyperventilation is common and results in a primary respiratory alkalosis. As noted above, hypoxemia is frequently present and is due to right-to-left shunting of up to 40% of cardiac output. Shunting is due to an increase in both pulmonary arteriovenous communications (absolute) and ventilation/perfusion mismatching (relative). Elevation of the diaphragm from ascites decreases lung volume, particularly functional residual capacity, and predisposes to atelectasis. Moreover, large amounts of ascites produce a restrictive ventilatory defect that increases the work of breathing.

Review of the chest radiograph and arterial blood gas measurements is useful preoperatively because atelectasis and hypoxemia are usually not evident on clinical examination. Paracentesis should be considered in patients with massive ascites and pulmonary compromise, but should be performed with caution because excessive fluid removal can lead to circulatory collapse.

E. Renal Manifestations and Fluid Balance

Derangements of fluid and electrolyte balance may manifest as ascites, edema, electrolyte disturbances,

and hepatorenal syndrome. Important mechanisms responsible for ascites include (1) portal hypertension, which increases hydrostatic pressure and favors transudation of fluid across the intestine into the peritoneal cavity; (2) hypoalbuminemia, which decreases plasma oncotic pressure and favors fluid transudation; (3) seepage of protein-rich lymphatic fluid from the serosal surface of the liver secondary to distortion and obstruction of lymphatic channels in the liver; and (4) avid renal sodium and water retention.

Patients with cirrhosis and ascites have decreased renal perfusion, altered intrarenal hemodynamics, enhanced proximal and distal sodium reabsorption, and often an impairment of free water clearance. Hyponatremia and hypokalemia are common. The former is dilutional, whereas the latter is due to excessive urinary potassium losses (from secondary hyperaldosteronism or diuretics). The most severe expression of these abnormalities is seen with the development of hepatorenal syndrome. Patients with ascites have elevated levels of circulating catecholamines, probably due to enhanced sympathetic outflow. In addition to increased renin and angiotensin II, these patients are insensitive to circulating atrial natriuretic peptide.

8 **Hepatorenal syndrome** is a functional renal defect in patients with cirrhosis that usually follows gastrointestinal bleeding, aggressive diuresis, sepsis, or major surgery. It is characterized by progressive oliguria with avid sodium retention, azotemia, intractable ascites, and a very high mortality rate. Treatment is supportive and often unsuccessful unless liver transplantation is undertaken.

Judicious perioperative fluid management in patients with advanced liver disease is critical. The importance of preserving kidney function perioperatively cannot be overemphasized. Overzealous preoperative diuresis should be avoided, and acute intravascular fluid deficits should be corrected with colloid infusions. Diuresis of ascites and edema fluid should be accomplished over several days. Loop diuretics are administered only after measures such as bed rest, sodium restriction (<2 g NaCl/d), and spironolactone are deemed ineffective. Daily body weight measurements are useful in preventing intravascular volume depletion during diuresis. In patients with both ascites and peripheral edema, no more than 1 kg/day should be lost during diuresis; in those with ascites alone, no more than 0.5 kg/day should be lost. Hyponatremia (serum $[Na^+]$ < 130 mEq/L) also requires water restriction (<1.5 L/d), and potassium deficits should be replaced preoperatively.

F. Central Nervous System Manifestations

Hepatic encephalopathy is characterized by alterations in mental status with fluctuating neurological signs (asterixis, hyperreflexia, and/or inverted plantar reflex) and characteristic electroencephalographic changes (symmetric high-voltage, slow-wave activity). Some patients also have elevated intracranial pressure. Metabolic encephalopathy seems to be related to both the amount of hepatocellular damage present and the degree of shunting of portal blood away from the liver and directly into the systemic circulation. The accumulation of substances originating in the gastrointestinal tract (but normally metabolized by the liver) has been implicated.

9 Factors known to precipitate hepatic encephalopathy include gastrointestinal bleeding, increased dietary protein intake, hypokalemic alkalosis from vomiting or diuresis, infections, and worsening liver function.

Hepatic encephalopathy should be aggressively treated preoperatively. Precipitating causes should be corrected. Oral lactulose 30–50 mL every 8 hr or neomycin 500 mg every 6 hr is useful in reducing intestinal ammonia absorption. Lactulose acts as an osmotic laxative, and, like neomycin, likely inhibits ammonia production by intestinal bacteria. Sedatives should be avoided.

Intraoperative Considerations

Patients with postnecrotic cirrhosis due to hepatitis B or hepatitis C who are carriers of the virus may be infectious. Universal precautions are always indicated in preventing contact with blood and body fluids from all patients.

A. Drug Responses

The response to anesthetic agents is unpredictable in patients with cirrhosis. Changes in central nervous system sensitivity, volumes of distribution, protein

binding, drug metabolism, and drug elimination are common. An increase in the volume of distribution for highly ionized drugs, such as neuromuscular blockers (NMBs), is due to the expanded extracellular fluid compartment; an apparent resistance may be observed, requiring larger than normal loading doses. However, smaller than normal maintenance doses of NMBs dependent on hepatic elimination (pancuronium, rocuronium, and vecuronium) are needed. The duration of action of succinylcholine may be prolonged because of reduced levels of pseudocholinesterase, but this is rarely of clinical consequence.

B. Anesthetic Technique

The cirrhotic liver is very dependent on hepatic arterial perfusion because of reduced portal venous blood flow. Preservation of hepatic arterial blood flow and avoidance of agents with potentially adverse effects on hepatic function are critical. Regional anesthesia may be used in patients without thrombocytopenia or coagulopathy, but hypotension must be avoided. A propofol induction followed by isoflurane or sevoflurane in oxygen or an oxygen–air mixture is commonly employed for general anesthesia. Opioid supplementation reduces the dose of the volatile agent required, but the half-lives of opioids are often significantly prolonged, which may cause prolonged postoperative respiratory depression. Cisatracurium may be the NMB of choice because of its nonhepatic metabolism.

Preoperative nausea, vomiting, upper gastrointestinal bleeding, and abdominal distention due to massive ascites require a well-planned anesthetic induction. Preoxygenation and a rapid-sequence induction with cricoid pressure are often performed. In unstable patients and those with active bleeding, either an awake intubation or a rapid-sequence induction using ketamine or etomidate and succinylcholine is suggested.

C. Monitoring

Pulse oximetry should be supplemented with arterial blood gas measurements to monitor acid–base status. Patients with large right-to-left intrapulmonary shunts may not tolerate the addition of nitrous oxide and may require positive end-expiratory pressure (PEEP) to treat ventilation/perfusion inequalities and subsequent hypoxemia. Patients receiving vasopressin infusions should be monitored for myocardial ischemia from coronary vasoconstriction.

Continuous intraarterial pressure monitoring is often used because hemodynamic instability frequently occurs as a result of excessive bleeding and surgical manipulations. Intravascular volume status is often difficult to optimize, and goal-directed hemodynamic and fluid therapy utilizing esophageal Doppler, arterial waveform analysis, or echocardiography should be considered. Such approaches may be helpful in preventing the hepatorenal syndrome. Urinary output must be followed closely; mannitol may be considered for persistently low urinary outputs despite adequate intravascular fluid replacement.

D. Fluid Replacement

Most patients are sodium-restricted preoperatively, but preservation of intravascular volume and urinary output takes priority intraoperatively. The use of predominantly colloid intravenous fluids (albumin) may be preferable to avoid sodium overload and to increase oncotic pressure. Intravenous fluid replacement should take into account the excessive bleeding and fluid shifts that often occur in these patients during abdominal procedures. Venous engorgement from portal hypertension, lysis of adhesions from previous surgery, and coagulopathy lead to excessive bleeding during surgical procedures, whereas evacuation of ascites and prolonged surgical procedures result in large fluid shifts. Following the removal of large amounts of ascitic fluid, aggressive intravenous fluid replacement is often necessary to prevent profound hypotension and kidney failure.

Most preoperative patients are anemic and coagulopathic, and perioperative red blood cell transfusion may lead to hypocalcemia (citrate toxicity) because of elevated plasma citrate levels resulting from impaired citrate metabolism in the cirrhotic liver. Citrate, the anticoagulant in stored red blood cell preparations, binds with plasma calcium, producing hypocalcemia. Intravenous calcium is often necessary to reverse the negative inotropic effects of decreased blood ionized calcium concentration (see Chapter 51).

Hepatic Surgery

Common hepatic procedures include repair of lacerations, drainage of abscesses, and resection of primary or metastatic neoplasms, and up to 80% to 85% of the liver can be resected in many patients. In addition, liver transplantation is performed in many centers. The perioperative care of patients undergoing hepatic surgery is often challenging because of coexisting medical problems and debilitation found in many patients with intrinsic liver disease, and because of the potential for significant operative blood loss. Hepatitis and cirrhosis greatly complicate anesthetic management and increase perioperative mortality. Multiple large-bore intravenous catheters and fluid blood warmers are necessary; rapid infusion devices facilitate management when massive blood transfusion is anticipated. Continuous intraarterial pressure monitoring is typically utilized.

Hemodynamic optimization is often complicated by the conflict between the need to maintain sufficient intravascular volume to ensure adequate hepatic perfusion and the need to keep central venous pressure low to minimize liver engorgement and surgical bleeding." Central venous pressure measurement is not an accurate monitor of volume status, and, when this determination is important, the appropriate alternative modality is goal-directed therapy utilizing esophageal Doppler, arterial waveform analysis, or TEE. Care should be taken in placing an esophageal Doppler or TEE probe in a patient with esophageal variceal disease.

Some clinicians avoid hypotensive anesthesia because of its potentially deleterious effects on liver tissue, whereas others believe that it can reduce blood loss when used judiciously. Administration of antifibrinolytics, such as ε-aminocaproic acid or tranexamic acid, may reduce operative blood loss. Hypoglycemia, coagulopathy, and sepsis may occur following large liver resections. Drainage of an abscess or cyst may be complicated by peritoneal contamination. In the case of a hydatid cyst, spillage can cause anaphylaxis due to the release of *Echinococcus* antigens.

Postoperative complications include hepatic dysfunction, sepsis, and blood loss secondary to coagulopathy or surgical bleeding. Severe postoperative pain from the often extensive surgical incision may hinder postoperative mobilization and convalescence, but perioperative coagulopathy may limit the use of epidural analgesia. Infusion of local anesthetic into the surgical wound can reduce the need for opioids. Postoperative mechanical ventilation may be necessary in patients undergoing extensive resections.

Liver Transplantation

When a center opens a liver transplantation program, a credentialed director should be appointed to the anesthesia component. This individual should be an anesthesiologist with experience and training in liver transplantation anesthesia. A dedicated team of anesthesiologists should be assembled to manage the perioperative course of all liver transplantation patients. This team should have a thorough understanding of the indications for, and contraindications to, liver transplantation (Tables 33–9 and 33–10), as well as associated comorbidities (eg, coronary artery disease, cirrhotic cardiomyopathy, portopulmonary hypertension, hepatopulmonary syndrome, hepatorenal syndrome and hepatic encephalopathy and cerebral edema). It has been demonstrated that such an approach improves outcomes, as measured by

TABLE 33–9 Indications for liver transplantation.

Pediatric	Adult
Congenital hepatic fibrosis	Primary biliary cirrhosis
Alagille's disease	Primary sclerosing cholangitis
Biliary atresia	Autoimmune hepatitis
α_1-antitrypsin deficiency	Cryptogenic cirrhosis
Byler's disease	Viral hepatitis with cirrhosis
Metabolic disorders	Alcoholic cirrhosis
Wilson's disease	Primary hepatocellular malignancies
Tyrosinemia	Nonalcoholic steatohepatitis
Glycogen storage diseases	Fulminant hepatitis
Crigler–Najjar disease	Hepatic vein thrombosis
Hemophilia	Familial amyloid polyneuropathy
Lysosmal storage diseases	Chronic viral hepatitis
Protoporpyria	
Familial hypercholesterolemia	
Primary hyperoxaluria	

TABLE 33–10 Contraindications to liver transplantation.

Absolute	Relative
Active sepsis	Severe obesity
Active substance or alcohol abuse	Severe pulmonary hypertension
Advanced cardiac disease	Severe cardiomyopathy
Extrahepatic malignancy	High viral load HIV
Metastatic malignancy	
Cholangiocarcinoma	

reduced blood transfusions, the need for postoperative mechanical ventilation, and the duration of stay in the intensive care unit.

Preoperative Considerations

The **Model for End-stage Liver Disease (MELD)** score is used by the United Network for Organ Sharing (UNOS) to prioritize patients on the waiting list for a liver transplant. The score is based on the patient's serum bilirubin, serum creatinine, and INR, and is a predictor of survival time if the patient does not get a liver transplant. A score of 20 predicts a 19.6% risk of mortality at 3 months, whereas a score of 40 predicts a 71.3% risk of mortality at 3 months (Figure 33–1).

$$\begin{aligned}\text{The MELD score} &= 0.957 \times \log_e[\text{serum creatinine (mg/dL)}] \\ &\quad + 0.378 \times \log_e[\text{total serum bilirubin (mg/dL)}] \\ &\quad + 1.120 \times \log_e[\text{INR}]\end{aligned}$$

Multiply the resulting value by 10, and round to nearest whole number. The minimum for all values is 1.0; the maximum value for creatinine is 4.0.

Most liver transplant candidates have high MELD scores and present with jaundice, renal failure, and coagulopathy. They may also be emaciated and have massive ascites, and some may have encephalopathy, hepatopulmonary syndrome, cirrhotic cardiomyopathy, and POPH. The typical hemodynamic finding is a high cardiac index and low systemic vascular resistance.

Significant blood loss may be anticipated, and large-bore intravenous catheters should be placed for access. A rapid infusion pump should be available. Routine hemodynamic monitoring should include intraarterial pressure monitoring and a central venous catheter. TEE is routinely utilized

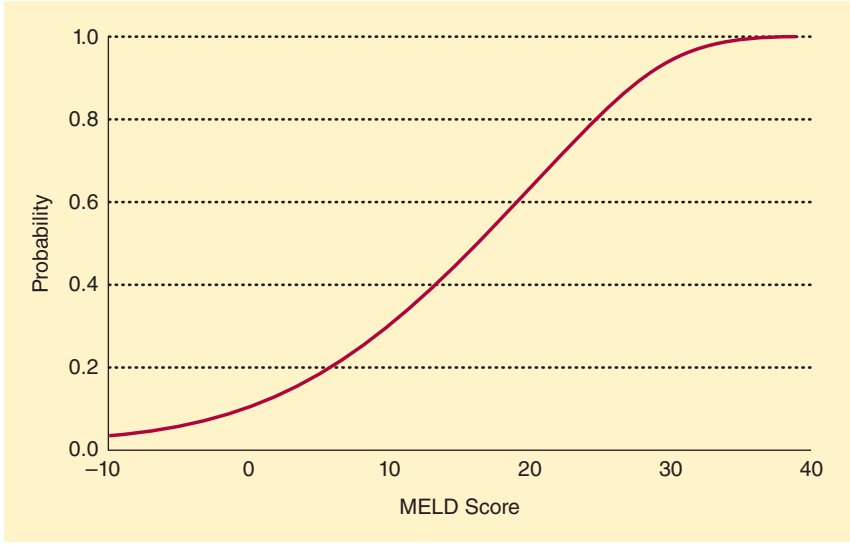

FIGURE 33–1 Relationship between Model for End-stage Liver Disease (MELD) score and 3-month mortality in patients with cirrhotic liver disease. (Reproduced, with permission, from Wiesner RH, McDiarmid SV, Kamath PS, et al: MELD and PELD: application of survival models to liver allocation. Liver Transpl 2001;7:567.)

in many centers. Pulmonary artery catheterization, once routine, has now been abandoned for liver transplant patients at many centers.

The immediate availability of intraoperative continuous venovenous hemodialysis (CVVHD) may be very helpful for volume management in the patient with marginal or no renal function. In patients with significant electrolyte abnormalities, serum sodium and potassium can be closely managed by adjusting the CVVHD dialysate solution.

Intraoperative Management

As noted above, hepatic disease causes endothelial dysfunction that impairs all organs of the body. The heart develops cirrhotic cardiomyopathy; the brain, encephalopathy and eventual cerebral edema; the kidneys, hepatorenal syndrome and eventual acute tubular necrosis; and the lungs, hepatopulmonary syndrome and/or portopulmonary hypertension. Therefore, each organ must be carefully managed throughout the operative procedure and the postoperative period.

Maintenance of cerebral perfusion pressure is particularly important in patients with cerebral edema, and many centers will temporarily correct the coagulopathy in order to place an intracranial transducer for monitoring intracranial pressure. Additional cerebral protective measures include head elevation of 20°, mild hypothermia, and mild hypocarbia with vasopressor support to maintain mean arterial pressure. When the patient's head is elevated, the arterial pressure transducer should be zeroed at the level of the external auditory meatus for accurate determination of cerebral perfusion pressure.

The coagulopathy is managed with the aid of a point-of-care viscoelastic coagulation assay device (TEG®, ROTEM®, or Sonoclot®) or frequent assessment of conventional tests of coagulation. Blood loss may be significant, and transfusions are targeted to maintain the hemoglobin level >7 g/dL.

Transfusions must be tempered to keep the central venous pressure (CVP) low during the liver dissection to reduce blood loss and minimize liver congestion, and at reperfusion and during the remainder of the procedure to prevent graft congestion and hepatic dysfunction. Most coagulopathies will correct with the new liver if its function is good. Fibrinolysis, a low ionized calcium level, and hypothermia must be corrected, as these may promote bleeding. However, coagulation defects usually do not need to be treated preoperatively or intraoperatively unless bleeding is a problem. Intraoperative transfusion of platelets and fresh frozen plasma is associated with decreased long-term patient survival.

The liver transplantation surgical procedure is divided into three stages: dissection (preanhepatic), anhepatic, and neohepatic periods.

The dissection (preanhepatic) phase is highlighted by the management of hemodynamic changes related to blood loss and surgical compression of major vessels. Hyponatremia should be carefully managed without rapid serum sodium correction, because this may promote the development of central pontine myelinolysis. Hyperkalemia may require aggressive intervention with diuresis, transfusion of only washed packed red blood cells, or CVVHD. Citrate toxicity (hypocalcemia) will occur rapidly if blood is transfused; therefore, ionized calcium should be closely monitored, and calcium chloride administered as necessary. A low CVP is helpful to minimize blood loss while systemic arterial pressure is maintained.

The anhepatic phase begins with the vascular occlusion of the inflow to the liver and ends with reperfusion. Some centers utilize venovenous bypass to prevent congestion of the visceral organs and improve venous return. It *may* protect kidney function.

In the neohepatic phase, two pathophysiological events may occur on opening the portal vein and allowing reperfusion of the graft. The first is a reperfusion syndrome caused by the cold, acidotic, hyperkalemic solution that may contain emboli and vasoactive substances being flushed from the graft directly into the right heart. This may cause hypotension, right heart dysfunction, arrhythmias, and even cardiac arrest, and may be preempted to some extent by the prophylactic administration of calcium chloride and sodium bicarbonate. The second syndrome that may occur is ischemia/reperfusion injury. This may result from impaired reperfusion due to severe endothelial dysfunction,

and, in rare cases, may lead to primary nonfunction of the graft.

Postoperative Management

Patients who undergo liver transplantation are often severely debilitated and malnourished and have multiorgan dysfunction; therefore, they will need careful support until they have recovered. Continuous monitoring of cardiovascular, pulmonary, renal, and neurological status is necessary. Early extubation is appropriate in selected patients if they are comfortable, cooperative, and not excessively coagulopathic. Immunosuppression must be precisely managed to minimize the risk of sepsis. A close watch on graft function must be maintained, with a low threshold for checking hepatic artery patency and flow. Postoperative bleeding, biliary leaks, and vascular thromboses may require surgical reexploration.

SPECIAL SITUATIONS

Patients with elevated intracranial pressure and those at risk of its development should have intracranial pressure (ICP) monitoring in place, if possible, to enable the appropriate management of cerebral perfusion pressure. The cerebral perfusion pressure should be maintained >50 mm Hg by adequate mean arterial pressure and a 20–25° head-up position. Mild hypothermia should be considered.

The management of patients who are at risk of or have elevated ICP should include the following:

- ICP < 20 mm Hg
- CPP > 50 mm Hg
- Mean arterial pressure >60 mm Hg
- Proper bed position (elevate the head of the bed by 20–25°)
- Controlled airway and ventilation
- Controlled sedation (eg, propofol)
- Vasopressor support (eg, vasopressin, norepinephrine) when necessary
- Controlled hypothermia (32–33°C)
- Glycemic control
- Aggressive treatment of metabolic acidosis and coagulopathy
- CVVHD

Pediatric Liver Transplantation

Selected pediatric centers report survival rates of 90% at one year. The use of reduced-size and living donor grafts has increased the organ availability in this patient population.

Living Donor Transplantation

The use of living donors has increased the pool of organs available for transplantation. However, this procedure does expose healthy individuals to morbidity and mortality risks. Informed consent from the donor must be obtained with the understanding that there is often a great deal of emotional pressure on family members to donate, and that consent must be freely given without coercion.

In most donor anesthesia protocols, maintenance of a CVP <5 cm H_2O is utilized to reduce intraoperative blood loss. Good postoperative analgesia is required so that comfortable donor patients may be extubated at the end of the procedure. Complications of this surgery for the donor patient include transient hepatic dysfunction, wound infection, postoperative bleeding, portal vein thrombosis, and biliary leaks. An increased incidence of perioperative nerve injury to the brachial plexus has been reported in donor patients.

CASE DISCUSSION

Liver Transplantation

A 23-year-old woman develops fulminant hepatic failure after ingesting wild mushrooms. She is not expected to survive without a liver transplant.

What are the indications for liver transplantation?

Orthotopic liver transplantation is usually performed in patients with end-stage liver disease who

begin to experience life-threatening complications, especially when such complications become unresponsive to medical or nontransplant surgery. Transplantation is also carried out in patients with fulminant hepatic failure (from viral hepatitis or a hepatotoxin) when survival with medical management alone is judged unlikely. The Model for End-stage Liver Disease (MELD) score is used to assess urgency for transplantation.

The most common indications for liver transplantation in children, in order of decreasing frequency, are biliary atresia, inborn errors of metabolism (usually α_1-antitrypsin deficiency, Wilson's disease, tyrosinemia, and Crigler–Najjar type I syndrome), and postnecrotic cirrhosis.

The most common indications in adults are postnecrotic (nonalcoholic) cirrhosis, primary biliary cirrhosis, and sclerosing cholangitis, and, less commonly, primary malignant tumors in the liver.

What factors have contributed to the recent success of liver transplantation?

One-year survival rates for liver transplantations exceed 80% to 85% in some centers. Currently, 5-year survival rates are 50% to 60%. The success of this procedure owes much to the use of cyclosporine and tacrolimus for immunosuppressant therapy. These drugs selectively suppress the activities of helper T cells (CD4 lymphocytes) by inhibiting production of interleukin-2 (IL-2) and other cytokines. IL-2 is required for the generation and proliferation of cytotoxic T cells responsible for graft rejection and for activating B cells responsible for T cell-dependent humoral responses. Cyclosporine is usually initially combined with corticosteroids and other agents (eg, mycophenolate and azathioprine). Tacrolimus has proved effective in cyclosporine-resistant rejection and is the preferred alternative to cyclosporine as the primary immunosuppressant agent. The use of anti-OKT-3, a monoclonal antibody directed against lymphocytes, has been extremely useful in treating steroid-resistant acute rejection.

Additional factors influencing the improvement in liver transplantation outcome include a greater understanding and experience with transplantation, the safe use of venovenous bypass, and the introduction of rapid infusion devices that allow +transfusion of up to 2 L/min of warmed blood.

What are the three phases of the transplantation surgical procedure?

These procedures can be divided into three phases: A dissection (preanhepatic) phase, an anhepatic phase, and a neohepatic phase.

1. Dissection (preanhepatic) phase: Through a wide subcostal incision, the liver is dissected so that it remains attached only by the inferior vena cava, portal vein, hepatic artery, and common bile duct. Previous abdominal procedures greatly prolong the duration of, and increase the blood loss associated with, this phase.
2. Anhepatic phase: Once the liver is freed, the inferior vena cava is clamped above and below the liver, as are the hepatic artery, portal vein, and common bile duct. The liver is then completely excised. Venovenous bypass (see below) may or may not be employed during this phase. The donor liver is then anastomosed to the supra- and infrahepatic inferior venae cavae and the portal vein.
3. Revascularization and biliary reconstruction (neohepatic or postanhepatic) phase: Following completion of the venous anastomoses, venous clamps are removed and the circulation to the new liver is completed by anastomosing the hepatic artery. Lastly, the common bile duct of the donor liver is then usually connected to the recipient via a choledochocholedochostomy or Roux-en-Y choledochojejunostomy.

What major problems complicate anesthesia for liver transplantation?

Problems include the multisystem nature of cirrhosis, the often massive blood loss throughout the transplantation procedure, the hemodynamic consequences of clamping and unclamping the

inferior vena cava and portal vein, the metabolic consequences of the anhepatic phase, and the risks of air embolism and hyperkalemia when circulation to the new liver is fully established.

Preoperative coagulation defects, thrombocytopenia, and previous abdominal surgery greatly increase blood loss. Extensive venous collaterals between the portal and systemic venous circulations also contribute to increased bleeding from the abdominal wall. Potential complications of massive blood transfusion include hypothermia, coagulopathies, hyperkalemia, citrate intoxication (hypocalcemia), and the potential transmission of infectious agents. Blood salvaging techniques can be extremely useful in reducing donor red blood cell transfusion.

What is adequate venous access for these procedures?

Bleeding is a recurring problem during each phase of liver transplantation. Adequate venous access is paramount in anesthetic management. Several large-bore (14-gauge or larger) intravenous catheters should be placed above the diaphragm. Specialized 8.5F catheters can be placed in antecubital veins and used in conjunction with rapid infusion devices. Efforts to minimize the risk of hypothermia should include the use of fluid warming and forced-air surface warming devices.

What monitoring techniques are most useful during surgery?

All patients require direct intraarterial pressure monitoring. A central venous catheter should be used to deliver fluid replacement. Goal-directed hemodynamic and fluid management utilizing arterial pulse wave analysis, esophageal Doppler, or TEE is becoming common. Urinary output should be monitored carefully throughout surgery via an indwelling urinary catheter.

Laboratory measurements constitute an important part of intraoperative monitoring. Serial hematocrit measurements are mandatory to guide red blood cell replacement. Similarly, frequent measurements of arterial blood gases, serum electrolytes, serum ionized calcium, and serum glucose are necessary to detect and appropriately treat metabolic derangements. Coagulation can be monitored by measuring PT, activated partial thromboplastin time, fibrinogen level, platelet counts, and by point-of-care viscoelastic coagulation analysis—TEG®, ROTEM®, or Sonoclot® analysis. These latter modalities not only assess overall clotting and platelet function, but can also detect fibrinolysis.

What anesthetic technique may be used for liver transplantation?

Most patients should be considered as having a "full stomach," often because of marked abdominal distention or recent upper gastrointestinal bleeding. General anesthesia is usually induced via a rapid sequence induction with cricoid pressure. The semiupright position during induction prevents rapid oxygen desaturation and facilitates ventilation until the abdomen is open. Hyperventilation should be avoided unless there is increased intracranial pressure. Anesthesia is generally maintained with a volatile agent (usually isoflurane or sevoflurane), and an intravenous opioid (usually fentanyl or sufentanil). The concentration of the volatile agent should be limited to less than 1 minimum alveolar concentration in patients with severe encephalopathy. Nitrous oxide is usually avoided. Many patients are routinely transferred to the intensive care unit intubated and mechanically ventilated at the end of the operative procedure. Immediate postoperative extubation may be considered if the patient is comfortable, cooperative, physiologically stable, and not hemorrhaging significantly.

What physiological derangements are associated with the anhepatic phase?

When the liver is removed, the large citrate load from blood products is no longer metabolized and results in hypocalcemia and secondary myocardial depression. Periodic calcium chloride administration (200–500 mg) is necessary, but should be

guided by ionized calcium concentration measurements to avoid hypercalcemia. Progressive acidosis is also encountered because acid metabolites from the intestines and lower body are not cleared by the liver. Sodium bicarbonate therapy may be necessary and should similarly be guided by arterial blood gas analysis. Excessive administration of sodium bicarbonate results in hypernatremia, hyperosmolality, and accentuation of the metabolic alkalosis that typically follows massive blood transfusions. Tromethamine should be considered when large amounts of alkali therapy are necessary. Although hypoglycemia can occur during the anhepatic phase, hyperglycemia is a more common occurrence following reperfusion.

Pulmonary and systemic (paradoxic) air embolism can occur when the circulation is fully reestablished to the donor liver because air often enters hepatic sinusoids after harvesting. Systemic air embolism probably reflects the fact that many of these patients have extensive arteriovenous communications. The anhepatic phase ends when the three venous clamps are removed and the donor liver is perfused. Thromboembolic phenomena are also possible following reperfusion.

What problems may be anticipated during the revascularization phase?

Perfusion of the donor liver by the recipient's blood often results in transiently increased serum potassium concentration of up to 1–2 mEq/L and increased systemic acidosis. Reperfusion releases potassium from any remaining preservative solution (115–120 mEq/L of potassium) still within the liver, as well as potassium released from tissues distal to venous clamps. Unclamping may also release a large acid load from ischemic tissue in the lower body (particularly without venovenous bypass); preemptive administration of sodium bicarbonate is advocated by some.

When the circulation to the new liver is established, the sudden increase in blood volume, acidosis, and hyperkalemia can produce tachyarrhythmias, or, more commonly, bradyarrhythmias. In addition to calcium chloride and sodium bicarbonate, inotropic support is also often required. Hyperfibrinolysis is commonly present and seems to be due to a marked increase in tissue plasminogen activator and a decrease in plasminogen activator inhibitor and α_2-antiplasmin during the anhepatic phase. Fibrinolysis can be detected by point-of-care viscoelastic coagulation analysis. ε-Aminocaproic acid or tranexamic acid, which inhibit the formation of plasmin, may be indicated in those instances, but should not be used prophylactically.

What problems are encountered postoperatively?

Patients often have an uncomplicated postoperative course, and, after a sufficient period of observation in the postanesthesia care unit, may be transferred directly to the nursing unit designed for liver transplant patients. Problems to anticipate include persistent hemorrhage, fluid overload, metabolic abnormalities (particularly metabolic alkalosis and hypokalemia), respiratory failure, pleural effusions, acute kidney injury or failure, systemic infections, and surgical complications (eg, bile leaks or stricture, or thrombosis of the hepatic or portal vessels). The last two complications may be suspected during Doppler ultrasound and are confirmed by angiography. Neurological complications include seizures, intracranial hemorrhage, encephalopathy, central pontine myelinolysis from a sudden increase in serum sodium, and immunosuppressant-related neurotoxicity. Kidney dysfunction is often multifactorial in origin; contributory factors include periods of hypotension, impaired renal perfusion when the inferior vena cava is clamped (resulting in high pressures in the renal veins), and cyclosporine or antibiotic nephropathy. Measurement of immunosuppressant levels may be helpful in avoiding toxicity.

Prophylactic antibiotics and antifungal agents are routinely given in many centers because of a high incidence of infections.

Graft function is usually monitored by the PT, serum bilirubin, aminotransferase activity, and serum lactate measurements. Diagnosis requires liver biopsy.

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