

Surgery in the Patient with Liver Disease

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- Child class • Liver disease

Administration of anesthesia reduces blood flow to the liver during all surgical procedures. In patients with normal liver function, the reduction in blood flow can result in asymptomatic elevation in the results of serum liver biochemical tests postoperatively; in patients with compromised liver function preoperatively, hepatic decompensation can occur intra- and postoperatively, leading to morbidity and mortality. Because liver disease is common and patients with liver disease are frequently asymptomatic, the preoperative assessment of all patients undergoing surgery must include a careful history and physical examination to uncover risk factors for and evidence of liver dysfunction. If liver disease is present, elective surgery should be deferred until the patient has been evaluated or recovered. Operative risk correlates with the severity of the underlying liver disease and the nature of the surgical procedure. In patients with cirrhosis, the Child class and Model for End-Stage liver Disease (MELD) score should be calculated to assist in preoperative risk assessment. When patients with decompensated liver disease must undergo surgery, their clinical condition should be optimized perioperatively to improve the chances of a favorable outcome.

EFFECTS OF ANESTHESIA AND SURGERY ON THE LIVER

Changes in Liver Biochemical Test Levels

Most surgical procedures, whether performed under general or conduction (spinal or epidural) anesthesia, are followed by minor elevations in the results of serum liver

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biochemical tests.^{1,2} Minor postoperative elevations of serum aminotransferase, alkaline phosphatase, or bilirubin levels in patients without underlying cirrhosis are not clinically significant. However, in patients with underlying liver disease, and especially those with compromised hepatic synthetic function, surgery can precipitate frank hepatic decompensation.

Hemodynamic Effects

Cirrhosis is associated with a hyperdynamic circulation with increased cardiac output and decreased systemic vascular resistance. At baseline, hepatic arterial and venous perfusion of the cirrhotic liver may be decreased: portal blood flow is reduced as a result of portal hypertension, and arterial blood flow can be decreased because of impaired autoregulation. Moreover, patients with cirrhosis may have alterations in the systemic circulation due to arteriovenous shunting and reduced splanchnic inflow. The decreased hepatic perfusion at baseline makes the cirrhotic liver more susceptible to hypoxemia and hypotension in the operating room. Anesthetic agents may reduce hepatic blood flow by 30% to 50% following induction.² Animal data suggest, however, that isoflurane (along with desflurane and sevoflurane, which are believed to be similar) causes less perturbation in hepatic arterial blood flow than other inhaled anesthetic agents and therefore is preferred for patients with liver disease.³

Additional factors that may contribute to decreased hepatic blood flow intraoperatively include hypotension, hemorrhage, and vasoactive drugs. Intermittent positive-pressure ventilation and pneumoperitoneum during laparoscopic surgery mechanically decrease hepatic blood flow.⁴ In addition, traction on the abdominal viscera may cause reflex dilatation of splanchnic capacitance vessels and thereby lower hepatic blood flow.

Hypoxemia

Risk factors for acute intraoperative hypoxemia in patients with cirrhosis include ascites and hepatic hydrothorax. Postoperatively, ascites, encephalopathy, and anesthetic agents increase the risk of pulmonary aspiration in patients with cirrhosis. Hepatopulmonary syndrome (HPS)—the triad of liver disease, an increased alveolar-arterial gradient, and intrapulmonary shunting—is found in 5% to 32% of cirrhotic patients followed at transplant centers.⁵ Clues to the presence of HPS include platypnea (increased dyspnea in an upright posture) and orthodeoxia (oxygen desaturation in an upright posture). Portopulmonary hypertension—pulmonary hypertension associated with cirrhosis—is found in up to 6% of patients with advanced liver disease.⁶ Although published data regarding surgery in patients with portopulmonary hypertension are limited, pulmonary hypertension regardless of the cause has been shown to increase postoperative mortality after noncardiac surgery.⁷

The severity of HPS and portopulmonary hypertension does not correlate with the severity of associated liver disease. These pulmonary processes must be suspected in any patient with hypoxia and cirrhosis regardless of hepatic synthetic function. In addition, both conditions significantly increase the risk of perioperative mortality. Therefore, elective surgery should be avoided in patients with either HPS or portopulmonary hypertension.

Hepatic Metabolism of Anesthetic Agents and Perioperative Medications

Acute hepatitis associated with the administration of halothane, now rarely used, is believed to be caused by immune sensitization to trifluoroacetylated liver proteins formed by oxidative metabolism of halothane by cytochrome P450 2E1 in genetically predisposed persons.⁸ With this notable exception, few data suggest that either the

choice of anesthetic agent or mode of administration (inhaled or spinal) influences surgical outcome in patients with liver disease.⁹

In many patients with cirrhosis the volume of distribution of drugs is increased. In addition, the action of anesthetic agents may be prolonged in patients with liver disease because of impaired metabolism and hypoalbuminemia (resulting in decreased drug binding and impaired biliary clearance). Propofol is an excellent anesthetic choice in patients with liver disease, because it retains a short half-life even in patients with decompensated cirrhosis.¹⁰ Unlike halothane, hepatitis caused by isoflurane, desflurane, and sevoflurane, which undergo little hepatic metabolism, is rare. These anesthetic agents are also good choices in patients with liver disease.

The volume of distribution of nondepolarizing muscle relaxants is increased in patients with liver disease, and therefore larger doses may be required to achieve adequate neuromuscular blockade. Atracurium and cisatracurium are the preferred muscle relaxants in patients with liver disease because neither the liver nor the kidney are required for their elimination. Doxacurium is the preferred muscle relaxant in longer procedures such as liver transplantation, as it is metabolized by the kidney.

Sedatives, narcotics, and intravenous induction agents are generally well tolerated in patients with compensated liver disease but must be used with caution in patients with hepatic dysfunction, because they may cause prolonged depression of consciousness and precipitate hepatic encephalopathy. Blood levels of narcotics that undergo high first-pass extraction by the liver increase as hepatic blood flow decreases. Elimination of benzodiazepines that undergo glucuronidation (eg, oxazepam, lorazepam) is unaffected by liver disease, whereas the elimination of those that do not undergo glucuronidation (eg, diazepam, chlordiazepoxide) is prolonged in liver disease. In general, narcotics and benzodiazepines should be avoided in these patients; however, when necessary, remifentanyl is the preferred narcotic and oxazepam is the preferred sedative, because the metabolism of these agents is unaffected by liver disease.

OPERATIVE RISK IN PATIENTS WITH LIVER DISEASE

Challenges in Estimating Operative Risk

In a patient with liver disease, surgical risk depends on the degree of hepatic dysfunction, the nature of the surgical procedure, and the presence of comorbid conditions. There are several liver-related contraindications to elective surgery (**Box 1**). When these contraindications are absent, patients with liver disease should undergo a thorough preoperative evaluation, and care of their liver disease should be optimized before elective surgery. Patients found to have advanced liver disease may be best managed with nonsurgical interventions if appropriate.

Once liver disease is identified in a patient who requires surgery, an assessment of the severity of liver disease should be undertaken, as should an evaluation for other nonhepatic risk factors for perioperative mortality (**Box 2**). Data from studies of patients with cirrhosis suggest that the severity of liver disease can best be assessed by the Child–Turcotte–Pugh (CTP) score (Child class) and MELD score (see section on [Stratification by MELD score](#)). Additional comorbid conditions increase the morbidity and mortality of surgery in patients with liver disease, although their effects are difficult to quantitate.

Most published studies describing operative risk in patients with liver disease are based on single-center, retrospective cohorts in patients with cirrhosis. These data have limitations, including small cohort size, selection bias, and lack of external validation. Despite these limitations, the results of studies describing operative risk in

Box 1
Contraindications to elective surgery in patients with liver disease
Acute liver failure
Acute renal failure
Acute viral hepatitis
Alcoholic hepatitis
Cardiomyopathy
Hypoxemia
Severe coagulopathy (despite treatment)

patients with liver disease have been remarkably consistent. As one might expect, operative morbidity and mortality increase with increasing severity of liver disease, as reflected in the Child class or MELD score. In general, patients with compensated cirrhosis who have normal synthetic function have a low overall risk, and the risk increases for patients with decompensated cirrhosis.

Preoperative Screening

Whether healthy, asymptomatic patients should undergo routine preoperative liver biochemical testing is debatable. The prevalence of elevated serum aminotransferases in serum in the adult population in the United States is 9.8%.¹¹ Not only is the

Box 2
Risk factors for surgery in patients with cirrhosis
<i>Patient characteristics</i>
Anemia
Ascites
Child class (Child–Turcotte–Pugh score)
Encephalopathy
Hypoalbuminemia
Hypoxemia
Infection
Malnutrition
MELD score
Portal hypertension
Prolonged prothrombin time (>2.5 seconds) that does not correct with vitamin K
<i>Type of surgery</i>
Cardiac surgery
Emergency surgery
Hepatic resection
Open abdominal surgery
<i>Abbreviation:</i> MELD, Model for End-Stage Liver Disease.

presence of an elevated aminotransferase level associated with liver disease but also patients with an elevated serum alanine aminotransferase level in the absence of viral hepatitis or excessive alcohol use may be at increased long-term risk of coronary heart disease and mortality, probably because the alanine aminotransferase level correlates with the presence of metabolic syndrome and its individual components, including obesity and diabetes mellitus.¹²

Reliance on routine liver biochemical tests alone may be misleading, because patients with cirrhosis may have normal results. Therefore, laboratory testing can never replace thorough history taking and physical examination. Obtaining liver biochemical tests preoperatively for screening purposes in asymptomatic persons without risk factors or physical findings indicating liver disease is not routinely recommended preoperatively.

The evaluation should include careful history taking to identify risk factors for liver disease, including prior blood transfusion, illicit drug use, sexual promiscuity, a family history of jaundice or liver disease, a personal history of jaundice, excessive alcohol use, and use of potentially hepatotoxic medications, including over-the-counter and herbal preparations. In some cases, cirrhosis may be suspected after evaluation for characteristic symptoms such as pruritus or fatigue, or on the basis of findings on physical examination such as palmar erythema, spider telangiectasias, abnormal hepatic contour or size, splenomegaly, hepatic encephalopathy, ascites, testicular atrophy, or gynecomastia.

When liver disease is suspected on the basis of physical examination findings or persistent liver biochemical test abnormalities, elective surgery should be deferred so that additional investigations can be undertaken, including biochemical and serologic testing for viral hepatitis, autoimmune liver disease, and metabolic disorders. Abdominal ultrasonography or magnetic resonance cholangiopancreatography may be considered when biliary obstruction is suspected. Abdominal computed tomography or magnetic resonance imaging may reveal a liver size and contour suggestive of cirrhosis or may detect intraabdominal varices and splenomegaly compatible with portal hypertension, but cannot reliably identify hepatic fibrosis or cirrhosis. Although noninvasive serologic and radiologic testing is often adequate for diagnosis and surgical risk assessment, liver biopsy remains the gold standard for the diagnosis and staging of liver disease.

Conditions for which Elective Surgery is Generally Contraindicated

Acute hepatitis

Acute hepatitis may be caused by viruses, drugs, and toxins (including those contained in over-the-counter medications, herbal preparations, and alcohol), autoimmune diseases, and genetic disorders. In addition, hypoperfusion, vascular congestion, and hepatic clotting disorders can lead to acute liver injury without significant inflammation. The cause of acute hepatitis can be determined in most instances noninvasively by history taking, physical examination, imaging, and serologic testing. A liver biopsy is sometimes needed for diagnosis and staging.

Patients with acute hepatitis of any cause are regarded as having an increased operative risk.² This conclusion is based on data from older studies, in which operative mortality rates of 10% to 13% were reported among patients who underwent laparotomy to distinguish intrahepatic from extrahepatic causes of jaundice.^{13,14}

Although diagnostic and surgical techniques have improved since these studies were published, elective surgery is still contraindicated in patients with acute hepatitis. In most cases, acute hepatitis is either self-limited or treatable, and elective surgery can be undertaken after the patient improves clinically and biochemically.

Alcoholic hepatitis

Alcoholic hepatitis is a contraindication to elective surgery and greatly increases perioperative mortality after urgent or emergency surgery. Fever, right upper quadrant tenderness, and leukocytosis can occur in patients with alcoholic hepatitis, which must be distinguished from acute cholecystitis and ascending cholangitis.¹⁵ Gallbladder wall edema, caused by hypoalbuminemia, can result from alcoholic hepatitis. In addition, hyperbilirubinemia, more often associated with alcoholic hepatitis, greatly impairs the diagnostic accuracy of cholescintigraphy (eg, a hydroxy iminodiacetic acid scan).

Laparotomy performed in a patient with alcoholic hepatitis may have serious consequences.¹⁶ In a retrospective series of patients with alcoholic hepatitis, the mortality rate was 58% among the 12 patients who underwent open liver biopsy, compared with 10% among the 39 who underwent percutaneous liver biopsy. Because only 1 death in the former group was secondary to intraabdominal hemorrhage, open abdominal surgery, rather than liver biopsy, is likely to have been responsible for the high mortality rate.

Abstinence from alcohol for at least 12 weeks generally results in dramatic improvement in hepatic inflammation and hyperbilirubinemia. After more than 12 weeks of abstinence from alcohol, the patient should undergo a thorough reassessment of hepatic function before elective surgery is considered.

Acute liver failure

Patients with acute liver failure (defined as the development of jaundice, coagulopathy, and hepatic encephalopathy within 26 weeks in a patient with acute liver injury in the absence of preexisting liver disease) are critically ill. All surgery other than liver transplantation is contraindicated in these patients.

Operative Risk Assessment

Chronic hepatitis

Chronic hepatitis is characterized by persistent liver inflammation for greater than 6 months duration. A variety of viral, genetic, autoimmune, metabolic, and drug-induced causes of chronic hepatitis have been identified. Regardless of the cause, the histopathologic findings are classified by the grade of necroinflammatory activity and stage of fibrosis. If a patient is found preoperatively to have chronic hepatitis, treatment of the underlying disease can often reduce necroinflammatory activity and may even reverse fibrosis.

Surgical risk in patients with chronic hepatitis and without cirrhosis correlates with the clinical, biochemical, and histologic severity of the disease. A patient's perioperative risk may be linked to the grade of inflammation, although little is known about the predictive value of hepatic inflammation alone. The few published studies of the risk of surgery in patients with mild to moderate chronic hepatitis without cirrhosis suggest that such patients are at no additional surgical risk.^{17,18} Patients with biochemically and histologically severe chronic hepatitis have an increased surgical risk, particularly when hepatic synthetic or excretory function is impaired, portal hypertension is present, or bridging or multilobular necrosis are found on a liver biopsy specimen.

Cirrhosis

Cirrhosis is characterized by parenchymal necrosis, fibrosis, nodular regeneration, and vasculature distortion leading to portal hypertension. Decompensated cirrhosis is defined as the presence of ascites, hepatic encephalopathy, varices, hepatorenal syndrome, or synthetic dysfunction (such as hypoalbuminemia or prolongation of

the prothrombin time). Surgical risk is increased in patients with cirrhosis. The magnitude of perioperative risk correlates with the degree of hepatic decompensation.

Stratification by Child class Although the optimal measure of hepatic decompensation in patients with cirrhosis remains unclear, since the 1970s the standard for assessing perioperative morbidity and mortality in patients with cirrhosis has been the CTP scoring system based on the patient's serum bilirubin and albumin levels, prothrombin time, and severity of encephalopathy and ascites.¹ The studies that led to this standard have all been retrospective and limited to a small number of highly selected patients, but the results have been remarkably consistent. Two of the most important studies, separated by 13 years, reported nearly identical results: mortality rates for patients undergoing surgery were 10% for those with Child class A, 30% for those with Child class B, and 76% to 82% for those with Child class C cirrhosis (**Table 1**).^{19,20} In addition to predicting perioperative mortality, the Child class correlates with the frequency of postoperative complications, which include liver failure, worsening encephalopathy, bleeding, infection, renal failure, hypoxia, and intractable ascites.

Even in patients with Child class A cirrhosis, the risk of perioperative morbidity is increased when there is associated portal hypertension. Postoperative morbidity in such patients may be reduced by preoperative placement of a transjugular intrahepatic portosystemic shunt (TIPSS).^{21,22}

Several factors other than the Child class can increase the perioperative risk. Emergency surgery is associated with a higher mortality rate than elective surgery: 22% versus 10% for patients in Child class A; 38% versus 30% for those in Child class B; and 100% versus 82% for those in Child class C.²⁰ A diagnosis of chronic obstructive lung disease and surgery on the respiratory tract are also independent risk factors for perioperative mortality in patients with cirrhosis.²³

The general consensus is that elective surgery is well tolerated in patients with Child class A cirrhosis, permissible with preoperative preparation in patients with Child class B cirrhosis (except those undergoing extensive hepatic resection or cardiac surgery, see later discussion), and contraindicated in patients with Child class C cirrhosis.²⁴

Stratification by MELD score The MELD score was created to predict mortality after TIPSS, then extended to risk stratify patients awaiting liver transplantation, and more recently to predict perioperative mortality.²⁵ The MELD score is a linear regression model based on serum bilirubin, creatinine levels, and international normalized ratio (INR). It has several distinct advantages over the Child classification: it is objective, weights the variables, and does not rely on arbitrary cutoff values. One study showed that each 1 point increase in the MELD score makes an incremental contribution to risk, thereby suggesting that the MELD score increases precision in predicting postoperative mortality.²⁶

Several studies have examined the MELD score as a predictor of surgical mortality in patients with cirrhosis (see **Table 1**). In a retrospective study of 140 patients with cirrhosis who underwent surgery, a 1% increase in mortality for each 1 point increase in the MELD score from 5 to 20 and a 2% increase in mortality for each 1 point increase in the MELD score greater than 20 was seen.²⁷ The largest retrospective study of the MELD score as a predictor of perioperative mortality, by Teh and colleagues,²⁸ evaluated 772 patients with cirrhosis who underwent abdominal (other than laparoscopic cholecystectomy), orthopedic, and cardiovascular surgery. The patients' median preoperative MELD score was 8, and few had a MELD score greater than 15. In addition, most patients had a platelet count greater than 60,000/ μ L and an INR less than 1.5. In this selected cohort, patients with a MELD score of 7 or less had a mortality

Table 1
Mortality rates associated with specific types of surgery in patients with cirrhosis

Type of Surgery and References	Number of Patients in Study(ies)	Mortality, %				
		Overall	Child Class			MELD Score
			A	B	C	
Appendectomy ⁸⁸	69	9	NA	NA	NA	NA
Cardiac ^{58,59}	44, 18	16–17	0–3	42–50	100	NA
Cholecystectomy ^{45,48}	226, 33	1–3	0.5	3	NA	<8 = 0% ≥ 8 = 6%
Colorectal cancer surgery ⁸⁹	72	12.5	6	13	27	NA
Esophagectomy ⁹⁰	18	17	NA	NA	NA	NA
Hepatic resection ^{66–68}	587, 154, 82	9	9 ^a	NA	NA	<9 = 0% ≥ 9 = 29%
Major abdominal surgery ^{19,20}	100, 92	26–30	10	30–31	76–82	NA
Total knee arthroplasty ⁹¹	51	0	0	NA	NA	NA
Treatment of hepatic hydrothorax with talc ⁹²	18	39	NA	NA	NA	NA

Abbreviation: NA, not available.

^a The exact number of Child class B patients was not available for the largest study; however, almost all patients had Child class A cirrhosis.

rate of 5.7%; patients with a MELD score of 8 to 11 had a mortality rate of 10.3%; and patients with a MELD score of 12 to 15 had a mortality rate of 25.4% (**Fig. 1**). The increase in relative risk of death was almost linear for MELD scores greater than 8.

In addition to the MELD score, the American Society of Anesthesiologists (ASA) class (**Table 2**) and the patient's age were shown by Teh and colleagues²⁸ to contribute to postoperative mortality risk. An ASA class of IV added the equivalent of 5.5 MELD points to the mortality rate, whereas an ASA class of V was associated with a 100% mortality rate. The influence of the ASA class was greatest in the first 7 days after surgery, after which the MELD score became the principal determinant of risk. In this study,²⁸ no patient younger than 30 years died, and an age older than 70 years added the equivalent of 3 MELD points to the mortality rate. Unlike studies that evaluated the ability of the Child class to predict surgical mortality, emergency surgery was not an independent predictor of mortality when the MELD score was used, because patients who underwent emergency surgery had higher MELD scores.

Based on the study of Teh and colleagues,²⁸ a Web site (<http://www.mayoclinic.org/meld/mayomodel9.html>) can be used to calculate 7-day, 30-day, 90-day, 1-year, and 5-year surgical mortality risk based on a patient's age, ASA class, INR, and serum bilirubin and creatinine levels (the last 3 items constitute the MELD score). Use of the MELD score and Child class are not mutually exclusive and may complement one another, but the MELD score is probably the most precise single predictor of perioperative mortality.

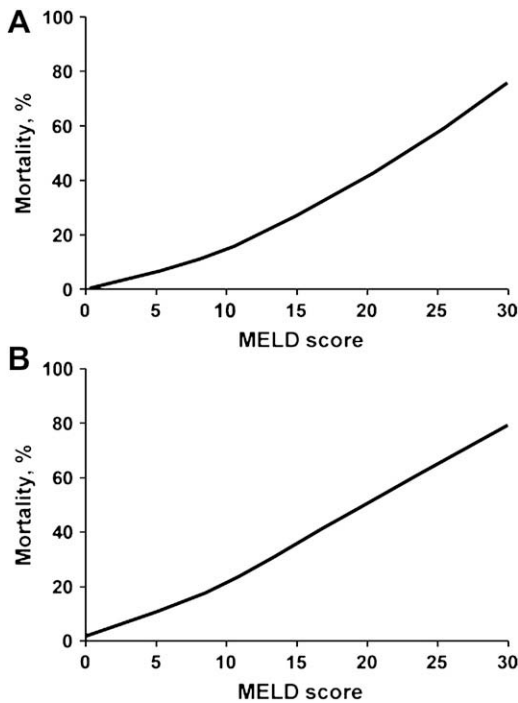


Fig. 1. Relationship between operative mortality and MELD score in 772 patients with cirrhosis who underwent surgery in 1980 to 1990 and 1994 to 2004. (A) Thirty-day mortality; (B) 90-day mortality. For patients with a MELD score greater than 8, each 1 point increase in the MELD score was associated with a 14% increase in both 30-day and 90-day mortality rates. (From Teh SH, Nagorney DM, Stevens SR, et al. Risk factors for mortality after surgery in patients with cirrhosis. *Gastroenterology* 2007;132(4):1261–9; with permission.)

Table 2 American Society of Anesthesiologists (ASA) classification	
Class	
I	Healthy patient
II	Patient with mild systemic disease without functional limitation
III	Patient with severe systemic disease with functional limitation
IV	Patient with severe systemic disease that is a constant threat to life
V	Moribund patient not expected to survive >24 h with or without surgery
E	Emergent nature of surgery (added to classification I–V above)

Specific causes of liver disease

Chronic hepatitis B and C More than 350 million people worldwide and 1.25 million people in the United States are chronically infected with hepatitis B virus (HBV).^{29,30} Inactive carriers of HBV, who have normal serum aminotransferase levels and no hepatic inflammation, are not at increased risk for postoperative complications, but patients with chronic hepatitis B, with or without cirrhosis, may be at increased risk of operative morbidity if they have significant hepatic inflammation or dysfunction. In patients treated with nucleoside or nucleotide analogues, therapy for chronic HBV should not be interrupted in the perioperative period; hepatitis flares can occur following cessation of therapy, and interruption of treatment may allow viral resistance to develop.

An estimated 170 million people worldwide and 1.6% of the United States population are chronically infected with hepatitis C virus (HCV).^{31,32} Patients with chronic HCV infection typically have elevated serum aminotransferase levels ranging from 1.3 to 3 times the upper limit of normal, although levels may be within normal limits. The impact of the presence of antibodies to HCV on surgical outcome has been studied retrospectively in United States veterans, and in the absence of cirrhosis, HCV infection does not increase the morbidity or mortality of surgery.¹⁸ Patients undergoing therapy for HCV infection may experience myelosuppression due to peginterferon and hemolytic anemia due to ribavirin; leukopenia, when present, may contribute to functional immunosuppression. Treatment-induced thrombocytopenia, if severe, may contribute to operative bleeding. In general, however, peginterferon and ribavirin therapy should not be discontinued without consulting the patient's treating physician.

Nonalcoholic fatty liver disease Nonalcoholic fatty liver disease (NAFLD) encompasses a spectrum from bland steatosis, to nonalcoholic steatohepatitis (NASH), to cirrhosis. Given the current epidemic of obesity, an increasing number of patients with NAFLD are undergoing surgery. More than 90% of morbidly obese patients who undergo bariatric surgery have histologic evidence of hepatic steatosis, and up to 6% are found intraoperatively to have cirrhosis.^{33,34} Patients with NAFLD but without cirrhosis do not seem to have increased mortality following elective surgery. Patients with compensated cirrhosis caused by NASH may be considered candidates for bariatric surgery, because weight loss improves hepatic inflammation and in some cases fibrosis.^{35–37} Even though patients with NAFLD do not have an increased risk of perioperative mortality from their liver disease, this population is at higher risk for diabetes, hypertension, hypertriglyceridemia, and coronary heart disease.^{38,39} As a result, preoperative cardiac risk stratification is essential.

A trend toward increased mortality following hepatic resection has been observed in patients with moderate to severe hepatic steatosis (greater than 30% of hepatocytes containing fat) despite the absence of cirrhosis, probably because steatosis inhibits hepatic regeneration.⁴⁰

Other causes Surgery in patients with Wilson disease can precipitate or aggravate neuropsychiatric symptoms. Treatment with D-penicillamine, a copper chelator, interferes with the cross-linking of collagen and may impair wound healing.⁴¹ As a result, the dose of D-penicillamine should be decreased before planned surgery and during the first several postoperative weeks.

Patients with hemochromatosis should be evaluated preoperatively for additional complications of iron overload, especially diabetes and cardiomyopathy. Although original reports suggested lower survival rates for liver transplantation in patients with hemochromatosis, compared with patients who had other causes of cirrhosis, subsequent reports have noted survival outcomes similar to those for other indications.⁴²

Autoimmune hepatitis in remission is not a contraindication to elective surgery in patients with compensated hepatic function. Patients receiving chronic glucocorticoid therapy should be given appropriate stress doses during the perioperative period.

Patients with α -1 antitrypsin deficiency are at risk for liver and lung disease. Therefore, careful evaluation of the patient's pulmonary status should be undertaken before surgery, and pulmonary function testing should be performed when pulmonary dysfunction is suspected.

OPERATIVE RISK ASSOCIATED WITH SPECIFIC TYPES OF SURGERY

Biliary Tract Surgery

Biliary tract surgery of any kind, including cholecystectomy, presents unique challenges in patients with cirrhosis because of the combination of portal hypertension and coagulopathy. An increased risk of bleeding should be anticipated in patients with advanced cirrhosis as demonstrated by a prolonged prothrombin time or thrombocytopenia, although the actual risk of bleeding does not correlate with the degree of coagulopathy.^{43,44}

Patients with cirrhosis are at increased risk of gallstone formation and associated complications when compared with noncirrhotic persons. In a case-control study of patients who underwent cholecystectomy, a MELD score of 8 or more had a sensitivity of 91% and specificity of 77% for predicting 90-day postoperative morbidity.⁴⁵ In general, laparoscopic cholecystectomy is permissible for patients with Child class A cirrhosis and selected patients with Child class B cirrhosis without portal hypertension.⁴⁶⁻⁴⁸ In contrast, in patients with Child class C cirrhosis, cholecystostomy, rather than cholecystectomy, is recommended; however, when surgery is deemed the only option, an open rather than laparoscopic approach is recommended.

In addition to jaundice reflecting hepatocellular dysfunction, cirrhotic patients can present with jaundice due to biliary obstruction. In a patient with a benign cause for obstructive jaundice or a malignant cause not amenable to curative surgery, nonsurgical approaches to decompression using endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography should be explored. Before ERCP was widely used, a study of patients with obstructive jaundice identified 3 key predictors of mortality: a hematocrit value less than 30%, an initial serum bilirubin level greater than 11 mg/dL (200 μ mol/L), and a malignant cause of obstruction.⁴⁹ When all 3 factors were present, the mortality rate approached 60%; when none was present, it was only 5%. Not surprisingly, malignant biliary obstruction carried a dramatically higher operative mortality rate (26.1%) than benign biliary obstruction (3.7%). In addition, patients with obstructive jaundice are at increased risk of bacterial infections, disseminated intravascular coagulation, gastrointestinal bleeding, delayed wound healing, wound dehiscence, incisional hernias, and renal

failure. Routine preoperative decompression of an obstructed biliary tree does not seem to reduce subsequent operative mortality.

Intestinal barrier integrity may be compromised in patients with obstructive jaundice and cirrhosis, leading to increased permeability to microorganisms.^{50,51} Furthermore, patients with cirrhosis are immunosuppressed due to reticuloendothelial cell and neutrophil dysfunction.⁵² Bacterial translocation because of Kupffer cell dysfunction can lead to bacteremia and endotoxemia. The paucity of bile salts in the gastrointestinal tract resulting in obstructive jaundice enhances intestinal absorption of endotoxin. Limited evidence suggests that administration of lactulose to patients with obstructive jaundice may prevent endotoxemia,^{53,54} but it is not clear that any additional clinical benefit occurs when lactulose is added to the administration of antibiotics and careful attention is paid to the patient's intraoperative hemodynamic and volume status.⁵⁵

Endoscopic or percutaneous biliary drainage is preferable to surgery for benign conditions in cirrhotic patients. Although endoscopic sphincterotomy is associated with an increased risk of bleeding in these patients, morbidity and mortality rates are low even in patients with Child class C cirrhosis.⁵⁶ In patients with coagulopathy or thrombocytopenia, endoscopic papillary balloon dilation is associated with a lower risk of bleeding than standard sphincterotomy and is preferred despite a possibly higher risk of pancreatitis.⁵⁷

Cardiac Surgery

Cardiac surgery and other procedures requiring cardiopulmonary bypass are associated with greater mortality in patients with cirrhosis than are most other surgical procedures. Risk factors for hepatic decompensation following cardiac surgery include the total time on bypass, use of pulsatile as opposed to nonpulsatile bypass flow, and need for perioperative vasopressor support. Cardiopulmonary bypass can exacerbate underlying coagulopathy by inducing platelet dysfunction, fibrinolysis, and hypocalcemia.

In 2 retrospective series of patients who underwent surgery requiring cardiopulmonary bypass, low mortality rates were observed in those with Child class A cirrhosis (0% [0/10] and 3% [1/31]) but rates were markedly increased in those with Child class B (42%–50%) and C (100%, $n = 2$) cirrhosis. In addition, more than 75% of Child class B and C patients experienced hepatic decompensation.^{58,59} Increased mortality is also predicted by an increased MELD score. A MELD score greater than 13 predicted a poor prognosis, although no safe cutoff score could be established. Therefore, a CTP score of 7 or less (Child class A) or a low MELD score suggests that cardiopulmonary bypass can be accomplished safely in patients with cirrhosis.

In addition to an elevated CTP or MELD score, clinically significant portal hypertension is a contraindication to cardiothoracic surgery. Portal decompression with TIPS placement may make the risk acceptable if the CTP and MELD scores remain low⁶⁰; however, elevated right-sided cardiac pressures from cardiac dysfunction and pulmonary hypertension are absolute contraindications to TIPSS placement.

In general, the least invasive option—angioplasty with or without stent placement—should be considered whenever feasible in a patient with advanced cirrhosis who requires coronary artery revascularization. The type of stent used is important as coated stents require longer use of aspirin and clopidogrel than do uncoated stents. In addition, the patient's likelihood of requiring surgery after coronary artery intervention and risk of bleeding due to coagulopathy or thrombocytopenia should be taken into consideration.

Hepatic Resection

Hepatocellular carcinoma (HCC) occurs in patients with cirrhosis at a rate of approximately 1% to 4% per year.^{61–63} As a result, screening of patients with cirrhosis is recommended,⁶⁴ and many HCCs are now detected that may be amenable to resection. Patients with cirrhosis who undergo hepatic resection for HCC or other benign or malignant tumors are at increased risk of hepatic decompensation and mortality compared with cirrhotic patients who undergo other types of surgery. These patients lose functional hepatocellular mass in the setting of an already compromised hepatic reserve. In addition, underlying NAFLD, if present, inhibits hepatic regeneration post-operatively, further increasing the risk of hepatic decompensation.⁴⁰

Mortality rates as high as 25% are reported following hepatic resection in patients with cirrhosis.⁶⁵ Risk stratification based on the Child class and MELD score have allowed more appropriate selection of patients, thus leading to lower mortality rates. In an analysis of 82 cirrhotic patients who underwent hepatic resection, the perioperative mortality rate was 29% in patients with a MELD score of 9 or more but 0% in those with a MELD score of 8 or less.⁶⁶ Another study identified Child class and ASA class, but not MELD score, as significant predictors of outcome following liver resection. In this study, the mean MELD score was low (6.5), which likely limited the ability of the MELD score to discriminate between risk groups.⁶⁷

In addition to predicting mortality, the MELD score can predict morbidity after liver resection. In one study,⁶⁸ the frequency of liver failure post-resection was 0%, 3.6%, and 37.5% in patients with MELD scores of less than 9, 9 to 10, and greater than 10, respectively.

The effect of chronic viral hepatitis on surgical outcome in patients with cirrhosis and compensated hepatic function is uncertain. In a series of 172 patients with HCV-related HCC who underwent hepatic resection, the outcome was best predicted by tumor-related factors, including the serum α -fetoprotein level and tumor vascular invasion.⁶⁹ In contrast, another study suggested that the risk of recurrent HCC may be higher and overall long-term survival poorer following hepatectomy for patients with HCC and chronic viral hepatitis compared with patients who have HCC without viral hepatitis.⁷⁰

Despite better outcomes in recent years, likely resulting from better patient selection, 5-year HCC recurrence rates are as high as 100%, and 5-year survival rates are no higher than 55%.^{24,71,72} The high recurrence and mortality rates reflect the underlying liver disease, which leads either to the development of a new or recurrent liver cancer or worsening hepatic synthetic dysfunction. As a result, liver transplantation is often advised in acceptable candidates, even in patients with Child class A cirrhosis, in regions where timely transplantation can be accomplished.^{71–73}

Nonsurgical options for treating HCC include radiofrequency ablation, microwave ablation, ethanol injection, transarterial chemoembolization, and intrahepatic yttrium-90 microsphere radioembolization. These options are currently applied in patients awaiting liver transplantation and in those who are not surgical candidates.⁷³ Although only surgical options are considered potentially curative, combinations of nonsurgical methods have improved long-term survival over single-modality therapy.⁷⁴

Endoscopic Procedures

Patients with cirrhosis should be screened for esophageal varices by upper gastrointestinal endoscopy. Moderate (conscious) sedation does not increase mortality in patients with cirrhosis who do not have clinically overt hepatic encephalopathy. Coagulopathy and thrombocytopenia do not increase the risk associated with variceal

band ligation but may influence the approach to endoscopic tissue acquisition and the treatment of bleeding from lesions other than varices.

Gastrostomy tube placement generally should be avoided in patients with cirrhosis and is contraindicated in patients with ascites, because of a high risk of leakage and infection. In addition, enlarged intraabdominal veins may be inadvertently punctured during blind percutaneous trocar placement in patients with portal hypertension.

PERIOPERATIVE CARE

Coagulopathy

In patients with liver disease, impaired hemostasis reflects decreased production of clotting factors because of hepatic synthetic dysfunction and, in some cirrhotics, depletion of vitamin K stores due to malnutrition or decreased intestinal absorption. Increased fibrinolytic activity with laboratory features of mild disseminated intravascular coagulation are also frequent in patients with cirrhosis. Thrombocytopenia due to portal hypertension-induced splenic sequestration and alcohol-induced bone marrow suppression is common.

Subcutaneous administration of vitamin K, 10 mg/d for 1 to 3 days, will correct coagulopathy due to nutritional or bile salt deficiency but not due to hepatic synthetic dysfunction. Transfusion of fresh frozen plasma and platelets may be necessary perioperatively in patients with marked coagulopathy or thrombocytopenia, respectively, to permit safe surgery. The risk of surgery in patients with severe coagulopathy and thrombocytopenia (defined as an INR >1.5 and platelets $<50,000/\text{mm}^3$, respectively) has not been studied and is uncertain. Cryoprecipitate, which contains large quantities of von Willebrand multimers and is rich in fibrinogen, should be considered when hemorrhage cannot be controlled. A prolonged bleeding time also can be treated with diamino-8-D-arginine vasopressin.

Recombinant factor VIIa has been introduced as an additional option for the treatment of bleeding due to coagulopathy in cirrhotic patients undergoing surgery. In a randomized, controlled trial of cirrhotic patients undergoing liver transplantation, patients randomized to perioperative recombinant factor VIIa were less likely to require packed red blood cell transfusions than patients randomized to placebo.⁷⁵ Because of the high cost, transient effect, absence of data showing improved outcomes, and theoretical concern about an increased risk of thromboembolic events, recombinant factor VIIa should only be used when bleeding cannot be controlled by other means. Optimal surgical technique and maintenance of a low central venous pressure may reduce blood loss.⁷⁶

Ascites

Ascites with or without hepatic hydrothorax can compromise respiration. Following abdominal surgery, ascites increases the risk of wound dehiscence and abdominal wall herniation. Although ascites can be drained at the time of abdominal surgery, it typically reaccumulates within days. Therefore, preoperative control of ascites with diuretics or TIPS placement is advisable. Medical therapy for ascites includes salt restriction to 2 g/d with the combination of spironolactone and furosemide, beginning at daily doses of 100 mg and 40 mg, respectively.

An umbilical hernia is a frequent complication of ascites and can be at risk of incarceration or spontaneous rupture. Elective surgical umbilical hernia repair, either with or without mesh prosthesis, may be considered only in carefully selected patients with decompensated cirrhosis.⁷⁷ TIPSS placement should be considered in patients with difficult to control ascites and those with rupture of an umbilical hernia.⁷⁸

Renal Dysfunction

Renal dysfunction is a dreaded complication in patients with cirrhosis. Advanced liver disease is associated with increased levels of endogenous vasodilators, which lead to peripheral vasodilatation, a chronic hyperdynamic circulation, and low blood pressure. Among the clinical consequences of a hyperdynamic circulation is activation of the sympathetic nervous system and renin-angiotensin-aldosterone axis. Elevated levels of renal vasodilatory prostaglandins attempt to compensate for the vasoconstrictive influence of angiotensin, and when this fails, hepatorenal syndrome develops. The impact of hepatorenal syndrome on mortality is well established and accounts for inclusion of the serum creatinine level in the MELD score. In patients with cirrhosis, however, the serum creatinine level often overestimates the actual glomerular filtration rate because of muscle wasting and decreased urea synthesis.

Perioperative renal dysfunction in a patient with cirrhosis may be the result of intravascular volume depletion, nephrotoxicity, acute tubular necrosis, or hepatorenal syndrome. It is imperative to differentiate among these possibilities. Cirrhotic patients may be intravascularly volume depleted but total body volume overloaded, and this possibility should always be considered first in patients with cirrhosis in whom renal dysfunction develops. Diuretics and a fluid challenge should be initiated, and potential nephrotoxins (aminoglycoside antibiotics, nonsteroidal anti-inflammatory agents, intravenous contrast agents) should be discontinued or avoided.

In an attempt to avoid acute tubular necrosis and hepatorenal syndrome perioperatively, the patient's volume status, urine output, and systemic perfusion should be monitored assiduously. Intravenous infusions of salt-poor albumin or blood are widely used in lieu of crystalloid fluid replacement in patients with liver disease, despite a lack of data supporting an advantage to this approach.

Treatment of hepatorenal syndrome can be attempted with the combination of the oral α -agonist midodrine, subcutaneous octreotide, and intravenous salt-poor albumin.⁷⁹ Another strategy includes intravenous norepinephrine (titrated to increase mean arterial blood pressure by 10 mm Hg) plus intravenous salt-poor albumin.⁸⁰ In patients who fail to respond to medical therapy, TIPSS can be attempted if the MELD score remains low.⁸¹

Hepatorenal syndrome is a terminal event unless patients are treated successfully or transplanted. Therefore, surgery other than liver transplantation is unlikely to change a patient's prognosis in this setting.

Encephalopathy

Hepatic encephalopathy is a state of disordered central nervous system function characterized by disturbances in consciousness, behavior, and personality.⁸² The diagnosis of hepatic encephalopathy should be made clinically by evaluating the patient for personality changes, sleep disturbances, tremor, hyperreflexia, and asterixis. Later stages of encephalopathy are associated with frank confusion, stupor, and coma. An elevated serum arterial or venous ammonia level is present in patients with encephalopathy but is not specific. The serum ammonia level may be useful, however, in patients in whom the diagnosis of encephalopathy is unclear, such as those with concomitant psychiatric or neurologic disorders or sedated patients.

Elective surgery should be deferred until hepatic encephalopathy has been controlled, because precipitating factors are inevitable in the postoperative period. Precipitants include volume contraction, hypokalemia, infection, bleeding, and use of sedative or psychoactive medications. Even for patients without overt hepatic decompensation, some degree of encephalopathy may be encountered following

surgery. Despite the high frequency of subclinical encephalopathy in patients with cirrhosis, no compelling data support a role for prophylactic therapy to prevent encephalopathy in patients undergoing surgery. Risk factors should be minimized by ensuring adequate volume resuscitation, repleting potassium, controlling infection and bleeding, and minimizing the use of narcotics and other sedating medications.

Oral or rectal (as retention enemas) lactulose is often used to treat hepatic encephalopathy. Lactulose should be titrated to 2 to 3 soft stools daily, and electrolyte abnormalities and volume depletion should be avoided. Oral antibiotics such as rifaximin, neomycin, or metronidazole may also be used, and rifaximin is increasingly preferred as a first-line antibiotic agent.⁸³

Gastroesophageal Varices

Whether surgery per se is a risk factor for variceal bleeding is uncertain. For patients with known large varices, elective cardiothoracic and probably major abdominal surgery should only be considered after TIPSS placement. For patients with known varices who undergo minor surgery, primary prophylaxis with either a nonselective oral β -adrenergic antagonist (eg, propranolol, nadolol) or endoscopic band ligation should be instituted.⁸⁴ Patients with prior variceal bleeding who undergo minor surgery should be treated, if necessary, with band ligation and β -blockade or TIPSS placement.

Nutrition

All patients with chronic liver disease are at high risk for protein-energy malnutrition. Patients with cholestatic liver disease are also at risk for fat-soluble vitamin malabsorption. Persons with alcohol-induced liver disease are often deficient in thiamine and folate and have depleted levels of total body potassium and magnesium. Nutritional deficiencies among these patients are often underdiagnosed. Clinical clues to nutritional deficiencies include muscle wasting, ascites, and hypoalbuminemia, which may not be solely attributable to hepatic synthetic dysfunction.⁸⁵

Poor nutritional status impacts the prognosis adversely in patients with cirrhosis in general.⁸⁶ In addition, mortality is increased after general surgical procedures or liver transplantation in malnourished patients.⁸⁷ Whenever possible, a patient's nutritional status should be addressed before elective surgery. Enteral nutritional supplementation seems to improve immunocompetence and short-term prognosis in patients with cirrhosis and is the preferred approach. Percutaneous gastrostomy, as discussed earlier, is contraindicated in patients with ascites or suspected abdominal wall varices. Central venous catheterization for parenteral nutrition carries a risk of infectious and bleeding complications and should be avoided whenever possible.

Postoperative Monitoring

Postoperatively, patients with cirrhosis need to be monitored for the development of signs of hepatic decompensation, including encephalopathy, coagulopathy, ascites, worsening jaundice, and renal dysfunction. If any of these indicators are found, supportive therapy should be initiated immediately. The prothrombin time is the single best indicator of hepatic synthetic function. An elevated serum bilirubin level can indicate worsening hepatic function but can occur for other reasons, including blood transfusion, resorption of extravasated blood, or infection. Renal function must be monitored closely. If renal dysfunction is found, the course should be pursued aggressively and treatment initiated.

Hypoglycemia may occur in patients with decompensated cirrhosis or acute liver failure as a result of depleted hepatic glycogen stores and impaired gluconeogenesis.

Serum glucose levels should be monitored closely if postoperative liver failure is suspected.

Careful attention should be paid to the assessment of intravascular volume, which is often difficult to assess in the setting of extravascular volume overload. Intravascular volume maintenance minimizes the risk of hepatic and renal underperfusion. On the other hand, infusion of too much crystalloid may lead to acute hepatic congestion, increased venous oozing, and pulmonary edema and to postoperative ascites, peripheral edema, and wound dehiscence.

SUMMARY

Surgery is performed more frequently now than in the past in patients with cirrhosis, in part because of the long-term survival of patients with advanced liver disease. Estimation of perioperative mortality is limited by the retrospective nature of and biased patient selection in the available clinical studies. Use of the Child classification and MELD score provides a reasonably precise estimation of perioperative mortality but does not replace the need for careful preoperative preparation and postoperative monitoring, as early detection of complications is essential to improve outcomes.

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