SURGERY IN THE PATIENT WITH LIVER DISEASE

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ABSTRACT

Surgery is performed in patients with liver disease more frequently now than in the past, in part because of the long-term survival of patients with cirrhosis. Recent work has focused on estimating perioperative risk in patients with liver disease. Hemodynamic instability in the perioperative period can worsen liver function in patients with liver disease. Operative risk correlates with the severity of the underlying liver disease and the nature of the surgical procedure. Thorough preoperative evaluation is necessary prior to elective surgery. Surgery is contraindicated in patients with certain conditions, such as acute hepatitis, acute liver failure, and alcoholic hepatitis. Estimation of perioperative mortality is inexact because of the retrospective nature of and biased patient selection in available clinical studies. The Child-Pugh classification (Child-Turcotte-Pugh score) and particulary the Model for End-Stage Liver Disease (MELD) score provide reasonable estimations of perioperative mortality but do not replace the need for careful preoperative preparation and postoperative monitoring, as early detection of complications is essential for improving outcomes. Medical therapy for specific manifestations of hepatic disease, including ascites, encephalopathy, and renal dysfunction, should be optimized preoperatively or, if necessary, administered in the postoperative period.

Most surgical procedures, whether performed under general, spinal or epidural anesthesia, are followed by minor elevations in serum liver biochemical test levels (1, 2). Minor postoperative elevations of serum aminotransferase, alkaline phosphatase or bilirubin levels in patients without underlying liver disease are not clinically significant. However, in patients with underlying liver disease, and especially those with compromised hepatic synthetic function, surgery can precipitate hepatic decompensation. Operative risk correlates with the severity of

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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 have been demonstrated to correlate with preoperative risk.

REDUCED HEPATIC BLOOD FLOW, HYPOXEMIA, AND ALTERED DRUG METABOLISM

Cirrhosis causes 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 30–50%, and agents such as isoflurane, desflurane, sevoflurane and propofol, which cause less perturbation in hepatic arterial blood flow than other inhaled anesthetic agents, are 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 abdominal viscera may cause reflex dilatation of splanchnic veins and thereby lower hepatic blood flow.

Risk factors for acute intraoperative hypoxemia in patients with cirrhosis include ascites, hepatic hydrothorax, hepatopulmonary syndrome (the triad of liver disease, an increased alveolar-arterial gradient and intrapulmonary shunting), which is found in 5–32% of cirrhotic patients followed at transplant centers, and portopulmonary hypertension, which is found in up to 6% of patients with advanced liver disease and which increases postoperative mortality after noncardiac surgery (5). In general, ascites and hepatic hydrothorax should be treated preoperatively, and elective surgery should be avoided in patients with either hepatopulmonary syndrome or portopulmonary hypertension.

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 considered the preferred muscle relaxants in patients with liver disease because neither the liver nor the kidney is required for their elimination. Doxacurium is the preferred muscle relaxant in longer procedures such as liver transplantation, even though it is metabolized by the kidney. Sedatives, narcotics and intravenous induction agents are generally tolerated in patients with compensated liver disease but must be used with caution in patients with hepatic dysfunction, because they may cause a prolonged depression of consciousness and precipitate hepatic encephalopathy. In general, narcotics and benzodiazepines should be avoided in these patients; however, when necessary, remifentanil and oxazepam are the preferred narcotic and sedative, respectively, because metabolism of these agents is unaffected by liver disease (1).

OPERATIVE RISK IN PATIENTS WITH LIVER DISEASE

In a patient with liver disease, surgical risk depends on the severity of liver disease, nature of the surgical procedure and presence of comorbid conditions. There are a number of liver-related contraindications to elective surgery (Table 1). When these contraindications are absent, patients should undergo a thorough preoperative evaluation, and their conditions should be optimized prior to elective surgery. Patients found to have advanced liver disease may benefit from alternative nonsurgical therapies when available and appropriate.

Once liver disease is identified in a patient in need of surgery, an assessment of the severity of liver disease should be undertaken, as should an evaluation for other known risk factors for perioperative mortality (Table 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, or Child-Pugh, class) and MELD score (see later). The majority of published studies describing

TABLE 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)

TABLE 2
Risk Factors in Patients With Cirrhosis Who Undergo Surgery

Patient Characteristics	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
Type of Surgery	Cardiac surgery
	Emergency surgery
	Hepatic resection
	Open abdominal surgery

MELD, Model for End-Stage Liver Disease.

operative risk in patients with liver disease derive from single-center, retrospective cohorts and involve 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 patients with liver disease have been remarkably consistent. As one might expect, operative morbidity and mortality increase with increasing severity of liver disease, whether measured by 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.

CONDITIONS FOR WHICH ELECTIVE SURGERY IS GENERALLY CONTRAINDICATED

Acute Hepatitis

Patients with acute hepatitis of any cause are thought to have an increased operative risk (1, 2). This conclusion is based on data from older studies, in which operative mortality rates of 10–13% were reported among patients who underwent laparotomy to distinguish intrahepatic from extrahepatic causes of jaundice (6, 7). Although diagnostic and surgical techniques have improved since these studies were published, elective surgery is still considered 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 emergent surgery. Laparotomy performed in a patient with alcoholic hepatitis may have serious consequences (8). 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 one death in the former group was secondary to intra-abdominal hemorrhage, open abdominal surgery, rather than liver biopsy, is likely to have been responsible for the high mortality rate.

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 and without preexisting liver disease) are critically ill. All surgery other than liver transplantation is contraindicated in these patients.

OPERATIVE RISK ASSESSMENT IN PATIENTS WITH CIRRHOSIS

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

Stratification by Child's Class

Since the 1970s, the standard for assessing perioperative morbidity and mortality in patients with cirrhosis has been the CTP scoring system, which is 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 76–82% for those with Child class C cirrhosis (Table 3) (9, 10). In addition to predicting perioperative mortality, the Child class correlates with the frequency

TABLE 3

Mortality Rates Associated With Specific Types of Surgery in Patients With Cirrhosis

Type of Surgery	Mortality				
	Overall	Child Class			MELD Score
		A	B	C	
Appendectomy	9%	NA	NA	NA	NA
Cardiac	16–17%	0–3%	42–50%	100%	NA
Cholecystectomy	1–3%	0.5%	3%	NA	$<8 = 0\%$ $\geq 8 = 6\%$
Colorectal cancer surgery	12.5%	6%	13%	27%	NA
Esophagectomy	17%	NA	NA	NA	NA
Hepatic resection	9%	9%	NA*	NA	$<9 = 0\%$ $\geq 9 = 29\%$
Major abdominal surgery	26–30%	10%	30–31%	76–82%	NA
Total knee arthroplasty	0%	0%	NA	NA	NA
Treatment of hepatic hydrothorax with talc	39%	NA	NA	NA	NA

NA, not available.

* The exact number of Child class B patients was not available for this study; however, the overwhelming majority of patients had Child class A cirrhosis.

Data from references 9, 10, 20, 23, 27, 28, 31–33, and the following:

Gervaz P, Pak-art R, Nivatvongs S, et al. Colorectal adenocarcinoma in cirrhotic patients. J Am Coll Surg 2003; 196:874–9.

Milanez de Campos JR, Filho LO, de Campos Werebe E, et al. Thoracoscopy and talc poudrage in the management of hepatic hydrothorax. Chest 2000; 118:13–7.

Poulsen TL, Thulstrup AM, Sorensen HT, et al. Appendicectomy and perioperative mortality in patients with liver cirrhosis. Br J Surg 2000; 87:1664–5.

Shih LY, Cheng CY, Chang CH, et al. Total knee arthroplasty in patients with liver cirrhosis. J Bone Joint Surg Am 2004; 86-A:335–41.

Tachibana M, Kotoh T, Kinugasa S, et al. Esophageal cancer with cirrhosis of the liver: results of esophagectomy in 18 consecutive patients. Ann Surg Oncol 2000; 7:758–63.

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, and possibly in patients with Child class B and C cirrhosis, may be reduced by preoperative placement of a transjugular intrahepatic portosystemic shunt (TIPS) (11–13).

Several other factors can increase the perioperative risk above and beyond the Child class. Emergency surgery is associated with a higher mortality rate than non-emergent 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 (10). 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 (14).

A 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), and contraindicated in patients with Child class C cirrhosis (15).

Stratification by MELD Score

The MELD score was created to predict mortality after TIPS, then implemented to risk stratify patients awaiting liver transplantation, and more recently utilized to predict perioperative mortality. (16) The MELD score is a linear regression model based on a patient's serum bilirubin and creatinine levels and international normalized ratio (INR). The MELD score has several distinct advantages over the Child classification: it is objective, weights the variables, and does not rely on arbitrary cutoff values. Each one-point increase in the MELD score makes an incremental contribution to risk, thereby suggesting that the MELD score increases precision in predicting postoperative mortality (17).

A number of studies have examined the MELD score as a predictor of surgical mortality in patients with cirrhosis (see Table 3). In a retrospective study of 140 patients with cirrhosis who underwent surgery, a 1% increase in mortality for each one-point increase in the MELD score from 5 to 20 and a 2% increase in mortality for each one-point increase in the MELD score above 20 was observed (18). The largest retrospective study of the MELD score as a predictor of perioperative mortality, by Teh and colleagues (19), evaluated 772 patients with cirrhosis who underwent abdominal (other than laparoscopic cholecystectomy), orthopedic, and cardiovascular surgery. 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 60,000mm^3/L and an INR less than 1.5. In this selected cohort, patients with a MELD score of 7 or less had a mortality 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 12–15 had a mortality rate of 25.4%

(Figure 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) classification (on a scale of 1 to 5) and the patient's age were shown by Teh, et al. to contribute to postoperative mortality

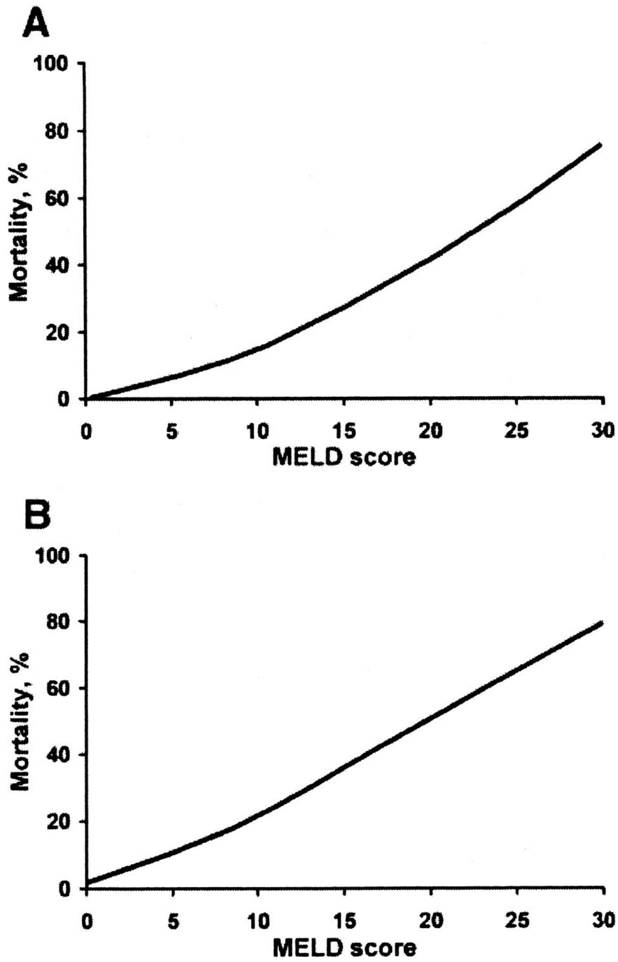

FIG. 1. Relationship between operative mortality and MELD score in 772 patients with cirrhosis who underwent surgery in 1980–1990 and 1994–2004. *Panel A*: shows 30-day mortality; *Panel B*: shows 90-day mortality. For patients with a MELD score >8, each one-point increase in the MELD score was associated with a 14% increase in both 30-day and 90-day mortality rates. (From Teh SH, Nagorney DM, Stevens SR, et al. Gastroenterology 2007;132:1261–9, with permission.) MELD, Model for End-Stage Liver Disease.

risk (19). 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 (19), no patient under age 30 died, and an age greater than 70 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 considered, because patients who underwent emergency surgery had higher MELD scores.

Based on the study of Teh, et al. (19), 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.

OPERATIVE RISK ASSOCIATED WITH SPECIFIC TYPES OF SURGERY

Biliary Tract Surgery

Patients with cirrhosis are at increased risk of gallstone formation and associated complications when compared with non-cirrhotic persons. In a case-control study of patients who underwent cholecystectomy, a MELD score $\geq$8 had a sensitivity of 91% and specificity of 77% for predicting 90-day postoperative morbidity (20). In general, laparoscopic cholecystectomy is permissible for patients with Child class A cirrhosis and selected patients with Child class B cirrhosis without portal hypertension (21–23). In contrast, in patients with Child class C cirrhosis, cholecystostomy, rather than cholecystectomy, is recommended; when surgery is deemed the only option, an open rather than laparoscopic approach is recommended.

In patients with benign etiologies of obstructive jaundice or malignant causes that are not amenable to curative surgery, non-surgical approaches to decompression via endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography are preferred. Before ERCP was widely used, a study of patients with obstructive jaundice indentified 3 predictors of mortality: a hematocrit value less than 30%, an initial serum bilirubin level greater than 11 mg/dL (200 μmol/L), and a malignant cause of obstruction (24). When all three factors were present, the mortality rate approached 60%; when none was present, the mortality rate 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 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 appear to reduce subsequent operative mortality.

Endoscopic or percutaneous biliary drainage is always preferable to surgery for benign conditions, when possible. Although endoscopic sphincterotomy is associated with an increased risk of bleeding in patients with cirrhosis, morbidity and mortality rates for this procedure are low even in patients with Child class C cirrhosis (25). 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 (26).

Cardiac Surgery

Cardiac surgery and other procedures that require use of 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 use of cardiac bypass, total time on bypass, use of nonpulsatile as opposed to pulsatile bypass flow, and need for perioperative vasopressor support. In two retrospective series of patients who underwent surgery requiring cardiopulmonary bypass, relatively 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 (27, 28). 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 low (29); however, elevated right-sided cardiac pressures from cardiac dysfunction and pulmonary hypertension are absolute contraindications to TIPS placement.

Hepatic Resection

Mortality rates as high as 25% are reported following hepatic resection (i.e., partial resection of the liver) in patients with cirrhosis (30). 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 $\geq$9 but 0% in those with a MELD score $\leq$8 (31). 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 (6.5) was low, which likely limited the ability of the MELD score to discriminate between risk groups (32). In addition to predicting mortality, the MELD score can predict morbidity after liver resection. In one study (33), the frequency of post-liver resection liver failure was 0%, 3.6%, and 37.5% in patients with MELD scores of less than 9, 9–10, and greater than 10, respectively. The extent of hepatectomy is also a predictor of mortality, as is a low serum sodium concentration (34).

Post-resectional liver failure has been defined as a prothrombin-time index of less than 50% (INR $>$1.7) and serum bilirubin greater than 50 μmol/L (2.9 mg/dL), the so-called "50-50" criteria. When these criteria are met, the postoperative mortality rate is 59%, compared with 1.2% in patients not meeting these criteria (35).

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. When any of these indicators is found, supportive therapy should be initiated immediately. The prothrombin time is the single best indicator of hepatic synthetic function. An elevated serum bilirubin can indicate worsening hepatic function but can be elevated for other reasons, including blood transfusions, resorption of extravasated blood or infection. Renal function must be monitored closely. When renal dysfunction is found, the cause should be established 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 when 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 under-perfusion. 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.

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DISCUSSION

Mushlin, New York: I enjoyed your comments, and again, as we heard yesterday. I think it is really refreshing to see more and more work being done on predictive models and trying to predict clinical phenomena. I have one sort of technical question about the way you presented your data, and it has to do with whether or not you are able or have thought about calculating not only percent adverse outcomes but also sensitivity and specificity at each level and perhaps to present ROC curves along with the sensitivity and specificity. I ask that question because I think it's more useful to clinicians sometimes to know the actual accuracy of the prediction that's facilitated through the development of predictive models. So, I wonder if you've thought about that and if you know of any data on the actual accuracy of those indices?

Friedman, Newton: I think that's a terrific idea, and it needs to be done. The model that I showed you is a first attempt, and my understanding is that the investigators will go back and refine it. It hasn't yet been confirmed independently. This comes from a single institution so it has to be considered preliminary, and I think the take-home message is that there is still no substitute for clinical judgment, rather than blind allegiance to a preliminary predictive model.

Ende, Philadelphia: Larry, I enjoyed the talk greatly. Do we have any information on surgical risks in that large group of patients with hepatitis C about whom we know that the liver function tests might not be a real reliable barometer of what's going on in the liver? If you put them up on the MELD score they would look great. Do they do great, or are there concerns about hepatitis C?

Friedman, Newton: In many of the large studies involving patients with cirrhosis there were patients with hepatitis C, although there haven't been any studies specifically about surgical risk in those patients. As best as we can tell, they do fine if they don't have advanced cirrhosis. Having hepatitis C, per se, does not increase surgical risk. The issue really is liver function, and that correlates with either the Child class or the MELD score. So, surgical risk really relates to patients with cirrhosis or decompensated liver disease. Analogous to that, patients with autoimmune hepatitis have been looked at, retrospectively, and those with preserved liver function also do fine. Those with deranged liver function manifested by an elevation of the bilirubin and a prolongation of the prothrombin time have correspondingly increased surgical morbidity and mortality. Most patients with hepatitis C are perfectly compensated. So, I think they would fall in the same risk category as the patients with compensated autoimmune hepatitis.

Boyer, New Haven: Thank you, Larry, for this very nice review. I wondered whether you could comment a little further on the role of bariatric surgery and the risk of this type of surgery in patients with liver disease. Many of these patients, of course, come with fatty liver, and some have cirrhosis, which currently, I guess, surgeons may consider a contraindication to that procedure even though their-Child class may be very good. Could you comment further on this?

Friedman, Newton: There is little in the literature on bariatric surgical risk in cirrhotic patients. If you perform bariatric surgery, you will find cirrhosis unexpectedly up to 6% of the time, and all patients have some degree of fatty liver. It is not clear if the perioperative mortality rate is increased in those with cirrhosis Probably, based on limited data, mortality is slightly increased but not prohibitive to preclude going ahead with the surgery, which may turn out to be therapeutic and lead to reversal of fatty liver and possibly cirrhosis.