Preoperative preparation of patients with advanced liver disease

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Objective: To review the characteristic features of patients with advanced liver disease that may lead to increased perioperative morbidity and mortality rates.

Design: Literature review.

Results: Patients with end-stage liver disease are at high risk of major complications and death following surgery. The most common complications are secondary to acute liver failure and include severe coagulopathy, encephalopathy, adult respiratory distress syndrome, acute renal failure, and sepsis. The degree of malnutrition, control of ascites, level of encephalopathy, prothrombin time, concentration of serum albumin, and concentration of serum bilirubin predict the risk of complications and death following surgery. Other determinants of adverse outcome include emergency surgery, advanced age, and cardiovascular disease. Portal hypertension is a prominent feature of advanced liver disease, and it predisposes the patient to variceal hemorrhage, hepatic encephalopathy, ascites, and renal failure.

Conclusions: Optimal preparation, which addresses the common features of advanced liver disease, may decrease the risk of complications or death following surgery. Preparation should include correcting coagulopathy, minimizing preexisting encephalopathy, preventing sepsis, and optimizing renal function. (Crit Care Med 2004; 32[Suppl.]:S106–S115)

Key Words: cirrhosis; anesthesia; surgery; coagulopathy; encephalopathy; ascites; renal failure; respiratory failure; liver transplantation; acute liver failure

Patients with advanced liver disease continue to be at risk of excessive mortality and morbidity rates following surgery despite the advances in surgery, anesthesia, blood banking, and intensive care seen in the last 4 decades. The comorbid issues responsible for these excess morbidity and mortality rates are easily identified before surgery and, although it may be difficult to achieve complete resolution, targeted preoperative interventions may improve outcomes.

Advanced liver disease is usually manifested as cirrhosis of the liver, which can be staged according to the degree of fibronodular hyperplasia and bridging fibrosis. Fibronodular hyperplasia is an attempt of the liver to heal the hepatocellular injury that has occurred from whatever cause. Bridging fibrosis is characteristic of the final stages of hepatocellular destruction. Functionally, end-stage liver disease results in marginal synthetic hepatocellular function, cholestasis, and a variable degree of portal hypertension.

The causes of advanced liver disease are myriad, but the most common causes include viral infection, alcohol abuse, autoimmune disease, drug reaction, genetic metabolic aberrations, cholestasis, and inflammatory disease of the bile tracts.

The common features of advanced liver disease are the basis of the Child-Pugh staging and include three clinical findings and three laboratory findings (Table 1). The severity of each of these findings is graded, and a score can be summed from 0 to 18. As originally described, the Child's classification applied to patients undergoing portal-systemic shunting procedures for variceal hemorrhage (1). Subsequent studies have shown that the excess mortality and morbidity rates apply to patients undergoing other intra-abdominal procedures.

Decreased hepatocellular function leads to muscle wasting, decreased protein synthesis, and coagulation abnormalities and is scored by a clinical evaluation of nutrition, serum albumin concentration, and the prothrombin time or international normalized ratio. Hyperbilirubinemia and portal hypertension lead to ascites, which is scored in accord with the degree of control obtained with diuretics. Encephalopathy results from the inability of the liver to extract derivatives of protein metabolism, such as ammonia, and is scored according to a clinical evaluation of asterixis, orientation to person, place, and time, as well as the need for a low-protein diet and hospitalization for uncontrolled encephalopathy. Finally, excretory function is scored by the serum bilirubin. Scores assigned for hyperbilirubinemia need to be adjusted in patients with primary biliary cirrhosis in whom the degree of hyperbilirubinemia is excessively elevated out of proportion to the degree of cirrhosis.

The clinical and laboratory elements used in the Child-Pugh stratification of liver disease encompass the primary functions of the liver. Virtually every organ or organ system in the body is at risk of secondary manifestations of advanced liver disease. These include the heart and circulation, brain, lungs, kidneys, bone marrow, spleen, endocrine system, and immune system. The degree to which any or all of these are compromised by advanced liver disease plays an important role in determining outcome following surgery, and their involvement requires the same assessment and intervention as given to the primary manifestations of liver disease.

In this article, I will address each of the common features of advanced liver disease and develop strategies for improv-
ing the preoperative preparation of patients with cirrhosis for surgery. For the most part, the emphasis will be on preoperative preparation for abdominal surgery because both general anesthesia and intra-abdominal surgery appear to be able to impede marginal hepatocellular function and precipitate acute hepatic failure.

The History of the Assessment of Outcomes in Patients With Advanced Liver Disease. In 1964, Child and Turcotte (1) reviewed their experience with 128 patients undergoing surgery with portal decompression to control acute hemorrhage from esophageal varices. Patients with advanced cirrhosis had a mortality rate of 53%, whereas those with minimal mortality rate of only 4.3%. Their patients were high risk because of the indication for surgery, failed conservative management of esophageal hemorrhage. In that era, the general anesthetic technique continued to include the use of cyclopropane; blood replacement therapy consisted mainly of whole blood, packed red blood cells, and pooled plasma. Invasive monitoring, at best, consisted of an arterial catheter and perhaps a single-lumen central venous catheter inserted by way of an antecubital vein. Postoperative ventilator support was provided either by pressure-limited, volume-cycled ventilators (Bird and Bennett) or volume limited, time-cycled ventilators (Emerson and Engstrom).

Child and Turcotte analyzed the clinical variables common to those patients who did poorly and noted five consistent factors: poor nutrition with wasting, hepatic encephalopathy with coma, uncontrolled ascites, hypoalbuminemia, and hyperbilirubinemia. They established the Child-Turcotte classification, subsequently modified to the Child-Pugh classification (Table 1), based on these variables and ranked patients as having minimal (class A), moderate (class B), or advanced disease (class C).

Ten years later, Pugh and Murray-Lyon (2) reported the results of transthoracic ligation of esophageal varices to control variceal hemorrhage as a bridge to portal decompression by means of portacaval shunting. In their series of 38 patients, 11 patients died of continuing or recurrent hemorrhage and ten patients died of acute liver failure. Again their patients were easily divided into three groups based on the criteria described by Child and Turcotte. Of the 18 patients classified as grade 3, none survived for 1 yr. Pugh added the prothrombin time as an additional element and assigned numeric values so that a total score could be calculated. However, Pugh eliminated the nutritional assessment from his scoring system. As we will see, this may have been a mistake because malnutrition is a consistent feature of advanced cirrhosis. Pugh’s scoring system (1, 2, or 3 points for normal, moderately abnormal, or markedly abnormal indicators) allowed for inconsistencies in the presentation of the clinical manifestations of cirrhosis. In some patients, control of ascites may be more manifest than encephalopathy, and vice versa in other patients. Grade A patients (scores of 5 or 6) were considered good operative candidates; grade B patients (scores of 7–9) moderate risk; and grade C (scores of 10–15) high risk (Table 2).

The results reported in Pugh’s series of 38 patients were as disheartening as those reported by Child and Turcotte despite the improvements in technology that had occurred over the intervening 10 yrs. The operative mortality rate was 77% in patients with class C manifestations of cirrhosis (score ≥10 points), 38% in patients with class B, and 29% in patients with class A. Six-month overall mortality rate for all groups was 68%, pointing to the ongoing problems these patients endured even after variceal bleeding was controlled.

The Child-Pugh classification includes an assessment of six factors: nutrition, control of ascites, level of encephalopathy, elevation of serum bilirubin, prolonged prothrombin time, and decrease in serum albumin concentrations (Table 1).

In 1984, Garrison et al. (3) reviewed a series of 100 consecutive patients with cirrhosis of the liver who underwent abdominal surgery for a variety of procedures not directly related to their cirrhosis. The procedures included cholecystectomy, common duct exploration, gastrectomy, and intestinal resections, open liver biopsy, herniorrhaphy, splenectomy, pancreatectomy, vascular surgery, and exploratory laparotomy. The report includes several multivariate analyses of preoperative, intraoperative, and postoperative factors that led to postoperative morbidity and mortality. Garrison et al. observed that 10% of patients with advanced liver disease would undergo surgical procedures with high morbidity and mortality rates in the final 2 yrs of their lives.

The highest predictive value of variables in Garrison’s series were those seen in the combined Child-Pugh classification, again malnutrition, uncontrolled ascites, encephalopathy, elevated bilirubin, elevated prothrombin time, and decreased serum albumin concentrations. Emergency surgery was an important predictor of adverse events. It was present as an indicator in 80% of the nonsurvivors.

Table 1. Child-Pugh classification of liver disease

<table>
<thead>
<tr>
<th></th>
<th>Class A</th>
<th>Class B</th>
<th>Class C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrition</td>
<td>Normal nutrition</td>
<td>Moderate malnutrition</td>
<td>Severe malnutrition</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
<td>Moderately well controlled with diuretics</td>
<td>Poorly controlled with diuretics</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Grade 1</td>
<td>Grade 2 or 3</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>0–2 secs &gt; control</td>
<td>2–4 secs &gt; control</td>
<td>≥8 secs &gt; control</td>
</tr>
<tr>
<td>Bilirubin*</td>
<td>0–2 mg/dL</td>
<td>2–3 mg/dL</td>
<td>≥3 mg/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>&gt;3.5 g/dL</td>
<td>2.5–3.5 g/dL</td>
<td>&lt;2.5 g/dL</td>
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*The plasma concentration of bilirubin is adjusted higher in patients with primary biliary cirrhosis because the degree of hyperbilirubinemia is out of proportion to the extent of overall liver dysfunction.

Table 2. Pugh scoring system

<table>
<thead>
<tr>
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<th>Severity Points For Increasing</th>
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<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1–2 mg/dL</td>
</tr>
<tr>
<td>Albumin</td>
<td>≥3.5 g/dL</td>
</tr>
<tr>
<td>Prothrombin time beyond control</td>
<td>1–4 secs</td>
</tr>
</tbody>
</table>

Class A, 5–6 points; class B, 7–9 points; class C, 10–15 points. From Reference 2.
itors and 40% of the survivors who sustained serious complications. The average Child-Pugh class was 2.4 ± 0.1 in nonsurvivors, 1.6 ± 0.1 in survivors with complications, and 1.25 ± 0.1 in survivors without complications (class A scored as 1.0, class B scored as 2.0, class C scored as 3.0). Sepsis was equally important as an indicator of poor outcome. It was assessed as present with documentation of positive cultures and white blood cell counts >10,000-cells/mm³. Reoperative surgery was another important indicator and was often a surrogate for an ascitic leak following laparotomy.

Garrison et al. concluded that celiotomy in the cirrhotic patient is associated with very high morbidity and mortality rates and that preoperative assessment, using the variables they outlined, could predict survival with 89% accuracy and nonsurvival with 71% accuracy.

Mansour et al. (4) reported a current series of patients with cirrhosis undergoing nonportasystemic shunting surgical procedures. Ninety-two patients were reviewed retrospectively following laparotomy for elective as well as emergent procedures. Overall mortality rate for elective surgery was 26% (10% for Child-Pugh class A, 30% for Child-Pugh class B, 82% for Child-Pugh class C). Overall mortality rate was 50% for emergency procedures (22% for Child-Pugh class A, 38% for Child-Pugh class B, and 100% for Child-Pugh class C), again underscoring the importance of emergency procedures as a predictor of adverse outcome. Blood loss increased with the severity of disease but did not correlate with statistical significance. Postoperative renal and pulmonary dysfunction also correlated with severity of disease and adverse outcome in both Garrison et al.’s and Mansour et al.’s series. The most important correlation in all series continued to be coagulopathy, encephalopathy, uncontrolled ascites, and poor synthetic and excretory function.

In all series, sepsis ranks with coagulopathy and emergency surgery in the final common pathway toward mortality following intra-abdominal surgery. A common predicament is the need to surgically control fecal contamination in a patient with uncontrolled ascites. This combination leads to ongoing ascitic leaks and peritonitis. Experience suggests that avoiding open anastomoses, diverting colostomies, and using peritoneal drains when possible may lead to improved outcome. When sepsis is not the initiating event leading to mortality, encephalopathy is and results from acute liver failure usually seen in the first few days following surgery.

The Child-Pugh classification was not found to be predictive in one series of 40 consecutive patients with liver disease, 28 of whom had abdominal surgery (5). Eleven (28%) patients died within 30 days of surgery. Although neither the Child classification nor the Pugh score was predictive, an international normalized ratio >1.6 (ten-fold increased risk of mortality) and encephalopathy (35-fold increased risk of mortality) were highly predictive in a multivariate analysis of risk factors.

Additional Reports of Surgery in Patients With Cirrhosis. Cholecystitis and cholelithiasis are more common in patients with cirrhosis than in patients without liver disease. Open cholecystectomy was one of the procedures identified in both Garrison et al.’s and Mansour et al.’s series as a procedure with significantly increased morbidity and mortality rates. Fernandes et al. (6) reported a case-controlled retrospective review of laparoscopic cholecystectomy in 48 patients with class A and B cirrhosis. Nearly 80% of the patients were Child-Pugh class A and none were Child-Pugh class C. Four case control patients were matched to each patient with cirrhosis. The patients with cirrhosis had increased length of stay (p = .152), longer duration of surgery (p = .57), greater need for transfusion (p = .025), higher rate of conversion to open cholecystectomy (8 cases vs. 0 cases), and more frequent complications (p < .05). Although the authors concluded that laparoscopic cholecystectomy is reasonably safe and shows no increase in morbidity or mortality rates or worsening of outcome, there is selection bias toward patients with fairly well-compensated cirrhosis. Furthermore, although the comparisons to case controls often did not meet statistical significance, most of the patients were in the low-risk stage of their disease and the trend was adverse in each variable that was reported. Similar results have been reported in a small series of patients with cirrhosis undergoing laparoscopic cholecystectomy (7). Of 12 patients, only one required transfusion, postoperative complications were seen in four, and no patient developed postoperative acute liver failure. Again, however, most of the patients were Child class A (eight cases) and Child class B (four cases).

Pronovost et al. (8) reviewed all patients having abdominal aortic surgery in the state of Maryland between 1994 and 1996. This was a retrospective study using an administrative data set. End points included in-hospital mortality rate, length of stay, and intensive care unit (ICU) length of stay. Mild liver disease and chronic renal failure stood out as the two preexisting comorbid diseases associated with increased mortality rates or prolonged hospital and/or ICU stay. The odds ratio for risk associated with mild liver disease was 4.6 with confidence intervals of 2.0–10.9. Advanced age, emergency or emergency surgery, and ruptured aneurysm were associated with similar odds ratios/confidence limits. Interestingly, the authors found that admission to the hospital 1 or 2 days before surgery did not improve incomes, and they believed that this practice should be reevaluated. In fact, they showed that early admission was associated with prolonged hospital and ICU stay. Although both of these are true, it is difficult to suggest that they are related. The more likely case is that patients with mild liver disease and chronic renal failure needed additional preoperative preparation (dialysis, correction of coagulopathy, etc.), and it was the impact of the comorbid disease that led to prolonged hospital and ICU stay. Early admission to the hospital before surgery for optimal and appropriate management before surgery is supported by the approach recommended by Patel (9) at the Mayo Clinic.

Portal venous shunting to the systemic circulation can be accomplished by various surgical approaches including mesocaval, distal splenorenal, and portacaval shunting. It may be accomplished, as well, by percutaneous placement of a transjugular, portasystemic endovascular prosthesis (discussed subsequently). Portal venous decompression decreases the risk of variceal hemorrhage and improves the ability to control ascites. It is reasonable to ask whether there remains a role for portal shunting procedures in the era of liver transplantation. The results from Shaw’s group at the University of Nebraska indicate that shunting continues to be good procedure for at least two groups of patients, those with well-preserved hepatocellular function who needed a long-term bridge before transplantation and those for whom transplantation was contraindicated because of advanced age or uncontrolled alcoholism (10). Operative mortality rate was only
5-7%, which compared favorably to that associated with liver transplantation (19% in patients with advanced liver disease). The best results were seen in those patients for whom shunting represented a long-term bridge to transplantation.

van der Vliet et al. (11) noted that there is a changing pattern of portasystemic shunt surgery. They reviewed the results seen in 74 patients receiving portasystemic shunts during a 15-yr period. Fewer patients underwent early elective portasystemic shunting, whereas the number of emergency procedures remained constant. Early mortality rate was 3% in patients with Child class A disease, 7% in Child class B, and 56% in Child class C. Patients with alcoholic cirrhosis fared worse than those with other forms of liver disease. Postoperative encephalopathy was noted in 22% of patients, irrespective of the type of shunt. The authors recommended the use of a shunt that will lead to the least interference with subsequent liver transplantation.

Is there a final common denominator that explains the susceptibility of patients with advanced liver disease to acute liver failure and death following surgery? Friedman (12) emphasized the effect of hemodynamic changes that accompany surgery as the root of acute liver failure in patients with marginal liver function. Total hepatic blood flow, especially hepatic arterial blood flow, is reduced during general anesthesia and surgery. The impact of this reduction to hepatic oxygen delivery is critical and leads to a drastic loss of minimally remaining hepatocellular function. Of the inhaled anesthetics, halothane has been shown to produce the most dramatic reduction of hepatic arterial blood flow. It is well preserved with isoflurane especially if systemic blood pressure is not reduced >30% (13, 14). Although cirrhosis attenuates the responsiveness to a variety of vasopressors (15), α-adrenergic vasopressors, such as phenylephrine, should probably be avoided in patients with liver disease because of the potential to decrease hepatic arterial blood flow.

Manifestations of Advanced Liver Disease

Malnutrition. Malnutrition becomes manifest with advancing cirrhosis, and severe malnutrition is a prominent feature of Child’s class C cirrhosis. Skeletal muscle wasting, loss of adipose tissue, and poor skin turgor are a reflection of the decreased synthetic function that accompanies cirrhosis. Child’s class C patients are protein-depleted, overhydrated, and hypermetabolic. Total body protein may be reduced to 82% of estimated preillness total body protein. Plank et al. (16) showed that body composition and function did not return to normal for ≥12 months following orthotopic liver transplantation. However, recovery of respiratory muscle strength remained incomplete. Hypermetabolism occurred early in the neohepatic period and peaked at the tenth postoperative day.

Essential fatty acid deficiencies have been demonstrated in patients with chronic liver disease. Abnormalities are not corrected with short-term intravenous lipid supplementation. Although the significance of these deficiencies is unknown, Duerksen et al. (17) speculated that they may affect eicosanoid metabolism.

Severe malnutrition is associated with a greater requirement for packed red cells, fresh frozen plasma, and cryoprecipitate during liver transplantation and a longer length of stay postoperatively. Stephenson et al. (18) suggested that if nutritional repletion were possible before transplantation, patient outcomes could be improved.

Hepatic and muscle glycogen stores are depleted and the patient with advanced cirrhosis is at risk of perioperative hypoglycemia. On the other hand, patients with nonalcoholic steatohepatitis demonstrate insulin resistance and may be hyperglycemic (discussed subsequently).

There is consensus that patients with advanced liver disease should receive both enteral and parenteral nutrition in the perioperative period, and, when time permits, this should start in the preoperative period because of the energy expenditures expected in the postoperative period. Caloric balance should be carefully calculated and nutritional supplements should be prescribed in a manner that will not aggravate a preexisting tendency toward hepatic encephalopathy (high carbohydrate/lipid content and decreased amino acid content).

Wernicke’s encephalopathy in the patient with alcoholic cirrhosis may result from the vitamin deficiencies that accompany the malnutrition of advanced liver disease. Preoperatively, vitamin supplementation should include vitamin B1 (19). Neuropathology in the mammillary body and thalamus, characteristic of Wernicke’s encephalopathy, have been found in 23 of 36 patients who died while in hepatic coma (20). In addition, all patients had pathologic findings of mild to severe Alzheimer’s type II astrocytosis. Clinical manifestations of Wernicke’s encephalopathy had been present in only two of these patients during life. These findings underscore the need for careful neurologic evaluation and radiologic assessment both before and after surgery.

Dam et al. (21) showed regional cerebrovascular perfusion defects in patients with cirrhosis. These are diffuse in patients with alcoholic cirrhosis. Some of these may normalize following liver transplantation, but persistent frontal lobe defects persisted in patients with alcoholic cirrhosis.

Encephalopathy. Hepatic encephalopathy can be either an acute, life-threatening complication or a relapsing, chronic feature of advanced liver disease. Alternatively, it can be the primary pathologic feature of acute liver failure, such as that seen with acetaminophen overdose. Acute liver failure can also occur in the postoperative period in patients with stable liver disease probably as a result of the changes in hepatic arterial and portal venous blood flow secondary to anesthesia and intra-abdominal surgery. Postoperative acute liver failure may not be evident until the second or third postoperative day.

The etiology of hepatic encephalopathy is multifactorial, and precise mechanisms are not clear. Traditionally, it has been treated with lactulose, neomycin, and a low-protein diet (22). This strategy aims at lowering the potential for absorption of ammonia produced by gastrointestinal metabolism of proteins. Lactulose lowers the pH of the colon contents and helps convert ammonia to ammonium ions, which are not absorbed. Neomycin eliminates the bacteria, which produce ammonia. The low-protein diet unfortunately can further aggravate the malnutrition already present in these patients.

Hepatic encephalopathy can evolve without significant or progressive elevations of serum ammonia concentrations. Benzodiazepine-like substances are associated with hepatic encephalopathy, and benzodiazepine antagonists have been used to provide temporary improvement in patients with hepatic coma (23, 24). Ferenci et al. (25) reported on the successful long-term use of oral flumazenil in a patient with recurrent episodes of hepatic encephalopathy.

Branched chain amino acid therapy
has been reported in one case report to dramatically decrease hepatic encephalopathy in a patient who was refractory to conventional therapy (26).

Hepatic encephalopathy is aggravated by portosystemic shunting for portal hypertension whether it is by surgical shunts or by transjugular intrahepatic portosystemic shunt because of the diversion of toxic metabolites away from the residual but limited extraction capability of the liver (27).

Acute hepatic encephalopathy is a common feature of acute hepatic failure. The transition from grade 1 to grade 2 and grade 3 encephalopathy is insidious and can occur over a period of a few hours. Treatment needs to be aggressive and is aimed at controlling the life-threatening increase in intracranial pressure that leads to coma and brain death. Treatment strategies include head elevation, endotracheal intubation with hyperventilation, osmotic diuretics, plasma expansion and even exchange transfusion. The benzodiazepine antagonist flumazenil can produce brief improvement in cortical neurologic manifestations of encephalopathy but it is probably not of value for prolonged control and prevention of coma.

**Coagulopathy.** With the exception of von Willebrand factor, all the coagulation proteins and most inhibitors of coagulation are synthesized in the liver. Thus, it is not surprising that coagulopathy is one of the primary features of liver disease and one that becomes most apparent when patients are threatened by other manifestations of liver disease, such as variceal bleeding.

However, low blood concentrations of coagulation proteins are not the only cause of coagulopathy in advanced liver disease. Portal hypertension (discussed subsequently) leads to hypersplenism. The spleen can become large enough to place patients at risk of splenic rupture with abdominal trauma that would not be significant. Hypersplenism usually resolves following liver transplantation and can be controlled by splenectomy or embolization of the splenic blood supply (28).

Thrombocytopenia is often present in liver transplant candidates. Pooled platelets are a scarce resource and are a potential source of transmission of viral disease. At times it is difficult to decide whether to perform a splenectomy at the time of orthotopic liver transplantation. Platelet administration is necessary if surgical bleeding is evident and blood platelet counts are <70,000/mm³.

Preoperative preparation of the coagulopathic liver disease patient focuses on the administration of fresh frozen plasma and/or cryoprecipitate. The end point of treatment should be normalization of prothrombin time, plasma fibrinogen concentration, and, if available, factor analysis (factor VII, VIII). Synthetic factor VIIa is available but, especially considering its short half-life, is very expensive. The oncotic load associated with the administration of large volumes of fresh frozen plasma can cause fluid overload and pulmonary congestion. If coagulopathy is pronounced, central venous monitoring may be warranted before major surgery. Fisher and Mutimer (29) showed that the incidence of complications from central catheter insertion in patients with liver disease and coagulopathy is low and that the presence of an elevated prothrombin time should not be considered a contraindication.

Coagulopathy can be monitored in a global fashion by thrombelastography (Fig. 1). In liver disease patients with coagulopathy, the thrombelastogram will show a delayed onset of coagulation (R-time), a decreased angle between the base of the curve and the shoulder, and decreased maximum amplitude (30, 31). Often, with active bleeding, one will see accelerated fibrinolysis evidenced by narrowing of the tracing after achieving maximum amplitude. When using the thrombelastogram for diagnosis of coagulopathy or as an index of the effect of treatment, it is imperative to make sure that samples are free from any possible contamination with heparin. The error associated with heparin contamination can be avoided by assaying a parallel sample with the addition of heparinase (32, 33).

Blood loss during liver transplantation and increased fibrinolytic activity on thrombelastogram can be prevented and reversed with the administration of aprotinin and epsilon amino caproic acid (34–36). Transesmionic acid has been shown, as well, to be effective in treating the coagulopathy associated with liver disease (37).

**Portal Hypertension.** Portal hypertension is the result of fibronodular hyperplasia and fibrosis in the hepatic lobules. Sinusoidal ablation prevents effective portal venous blood flow. Increasing portal venous blood pressure causes engorgement of the splanchnic veins. The small bowel, colon, and spleen become congested. Splenomegaly caused by portal hypertension leads to platelet trapping and increased risk of splenic rupture with abdominal trauma. As portal hypertension continues, accessory venous drainage along the diaphragm, mediastinum, and esophagus leads to the development of esophageal varices and gastroptery. Vasculopathy in the colon also occurs and can be the cause of lower gastrointestinal bleeding and worsening of encephalopathy. Portal hypertension causes ascites and pleural effusion. The accessory venous drainage of the portal venous sys-

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**Figure 1.** Thrombelastogram (TEG) in a patient with severe coagulopathy secondary to advanced liver disease. The reaction time for initiation of the coagulation cascade is prolonged. The angle indicating the time required for clot consolidation is decreased. Maximum amplitude, an indicator of platelet function, is decreased. There is marked fibrinolytic activity indicated by early lysis of the clot.
system can be so intense that direct vascular connections can occur between the portal system and the pulmonary vasculature. This sets the stage for hepatopulmonary syndrome (discussed subsequently).

Varices are diagnosed on endoscopy and can be well controlled with endoscopic sclerotherapy (38). The size of esophageal varices can be decreased with long-term β-blocker therapy, usually propranolol (39). It is unclear whether this is an effect of propranolol on the β-2 receptors of the venous blood vessels, and it is equally unclear whether other β-blockers (metoprolol or atenolol) would have similar effects.

Shunts established between the portal venous system and the venous return via the inferior vena cava could control variceal bleeding secondary to portal hypertension and offer the best protection against rebleeding (40). These shunts can be placed surgically (mesocolic, splenorenal, portacaval) or percutaneously (transjugular intrahepatic portosystemic shunt, or TIPS). When TIPS was developed in the 1980s, it was hoped that the procedure would eliminate the need for surgical shunts with their risk of mortality and morbidity. However, although TIPS is performed percutaneously and does not require general anesthesia, it is not a benign procedure. TIPS has a high complication rate, and its mortality rate is not distinctly different from that reported by centers well experienced in shunt surgery. Complications include perforation of the liver capsule, injury to the vena cava, hepatic, and portal veins, and massive hemorrhage. As noted previously, worsening of encephalopathy occurs so commonly that preexisting encephalopathy is a relative contraindication to the procedure.

TIPS is most effective and safest when placed electively in patients with preserved hepatocellular function. Williams et al. (41) reported their results in placing TIPS successfully in 65 of 67 patients referred for control of variceal bleeding. Although they observed no procedural mortality, the 30-day mortality rate was 21%. Child-Pugh class C and advanced age were predictive of mortality. Cumulative rebleeding rate was 25% at 1 yr with shunt abnormalities being the leading cause. Only three of 25 deaths were due to rebleeding.

A strategy for controlling esophageal bleeding includes sequential sclerotherapy, TIPS, and liver transplantation (42). For many patients, this strategy should include operative shunting especially when there will be a long interval before transplantation. Transabdominal esophageogastic devascularization, with or without splenectomy, is an alternative for those patients who are refractory to sclerotherapy or have contraindications to shunting procedures (43). However, TIPS has a lower mortality rate than esophageogastic devascularization for emergency control of esophageal hemorrhage (44).

Octreotide, a somatostatin analog, has been used to control nonvariceal bleeding in patients with gastropathy and variceal bleeding in the colon and should be included in the strategy for emergency control of bleeding (45, 46).

Portal vein thrombosis is another complication of long-standing portal hypertension, and it results in sudden deterioration of remaining liver function. The incidence of portal vein thrombosis in liver transplant patients is reported to be 2.1–13.8% but was significantly higher (26%) in a report of U.S. veterans receiving liver transplants (47). Portal vein thrombosis is graded according to the degree of obstruction of the portal vein and the degree of thrombus extension into the superior mesenteric vein (Table 3). Grades 2, 3, and 4 portal vein thrombosis are associated with a higher incidence of primary nonfunction of the liver after transplantation, rethrombosis of the portal vein, and a lower 5-yr survival (48). Diagnosis can be established by microbubble color Doppler ultrasound in those patients for whom conventional portal venography is suboptimal (49). Portal vein thrombosis makes orthotopic liver transplantation much more difficult and increases both the risk of complications and mortality rate. Liatos et al. (50) reported the successful recannulation of the portal vein via TIPS in two patients awaiting liver transplantation. Continued patency required systemic anticoagulation, not often recommended in patients (51) at risk of coagulopathy secondary to liver disease.

It is important to consider portal vein thrombosis in patients with sudden deterioration of liver function, and diagnosis should be pursued with ultrasound or portal venography. Portal vein thrombosis may heighten the urgency for liver transplantation or may be judged as a contraindication.

Variceal Hemorrhage. The mainstays of treatment of esophageal varices, and the prevention of hemorrhage, include β-blocker therapy, endoscopic sclerosing, TIPS, and portal blood flow preserving shunt procedures. Somatostatin analogs (octreotide) can be added for the immediate therapy of bleeding. Varices may not be limited to the esophagus; they can be present also in the colon.

The mortality rate of acute variceal hemorrhage is high irrespective of the type of therapy, 42% for TIPS and 79% for esophageal transaction (51). Rebleeding occurred in 15.6% of patients with TIPS compared with 26.2% of patients who underwent esophageal transection. Infection was common after either procedure. Rebleeding is less common after portal blood flow preserving shunts (5%) compared with β-blocker therapy (68%) and sclerotherapy (71%) in a group of low-risk (Child-Pugh class A) patients (40).

Pulmonary Hypertension. The hepatoportal syndrome is a rare complication of end-stage liver disease but is one with a poor prognosis and may represent a contraindication to orthotopic liver transplantation. Hepatopulmonary syndrome includes marked pulmonary hypertension in the presence of systemic-to-pulmonary vascular shunts and intrapulmonary arteriovenous shunts, both of which result in systemic arterial desaturation (52). Orthodeoxia and platypnea (desaturation and shortness of breath when upright compared with supine) are clinical signs of hepatopulmonary syndrome.

One group has recommended a trial of

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Table 3. Grading of portal vein thrombosis

<table>
<thead>
<tr>
<th>Portal Vein Thrombosis</th>
<th>Portal Vein</th>
<th>Superior Mesenteric Vein</th>
<th>Incidence at Time of Orthotopic Liver Transplantation, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>&lt;50% occlusion</td>
<td>Minimal involvement</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>&gt;50% occlusion</td>
<td>Minimal involvement</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>Complete thrombosis</td>
<td>Proximal thrombosis</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>Complete thrombosis</td>
<td>Thrombosis entire length</td>
<td>16</td>
</tr>
</tbody>
</table>

From Reference 47.
vasodilators in patients with severe pulmonary hypertension before liver transplantation. Failure to respond to vasodilators is recommended as a criterion to preclude proceeding with transplantation (53).

Portal decompression with TIPS may improve arterial oxygenation and decrease calculated shunt fraction, both of which may improve the preoperative preparation of a patient before liver transplantation (54).

Patients with hepatopulmonary syndrome who have survived orthotopic liver transplantation are faced with prolonged recovery from pulmonary hypertension. In one case report, pulmonary hemodynamics did not normalize for >2 yrs after surgery (55).

**Hepatorenal Syndrome.** Hepatorenal syndrome (HRS) is a diagnosis of exclusion, and the cause is not known but may be related to undefined nephrotoxins not cleared by the liver; it appears to be related to alterations in renal blood flow secondary to increased intra-abdominal pressure in those patients with massive ascites. However, massive ascites is not a requirement for HRS. HRS is seen most often as oliguric deterioration in renal function that occurs in patients with exacerbated liver failure.

Although HRS may resolve immediately after liver transplantation (56), intraoperative and postoperative dialysis or hemofiltration may be necessary. In patients with severe hepatic and renal failure, combined liver and kidney transplantation may be necessary. Minor incompatibilities for the kidney are tolerated better when the kidney is transplanted along with the liver.

Dialysis or hemofiltration are the obvious methods of treatment of HRS. Renal function can be improved by large-volume paracentesis and supplementation of intravascular volume with fresh frozen plasma (57).

**Cardiovascular Disease.** The hemodynamic profile of patients with advanced liver disease is hyperdynamic with a resting cardiac index twice normal, a low peripheral vascular resistance, low to normal blood pressure, normal to increased stroke volume, and mildly elevated heart rate (58). Some causes of advanced liver disease are associated with cardiomyopathy (alcoholic liver disease, hemosiderosis). Beyond these, patients with advanced liver disease often have risk factors for coronary artery disease, such as cigarette smoking and hyperlipidemia.

A common dilemma in the care of patients with advanced liver disease and cardiac disease is whether they should undergo first, liver transplantation or cardiac surgery. Patients with Child-Pugh class A liver disease do well after either valve replacement or coronary artery bypass grafting. However, in two small series, the mortality rate for Child-Pugh class B and C was extremely high, 80–100% (59, 60). A large prospective cohort study of the effect of comorbid conditions on the in-hospital mortality rate of patients undergoing coronary artery bypass grafting failed to show liver disease as a predictor of death (61). Manas et al. (62) reported a case of sequential coronary artery bypass grafting and liver transplantation performed with cardiopulmonary bypass. The patient was alive and asymptomatic at 3 months after surgery.

Considering the stress of liver transplantation, a reasonable approach for a patient with inducible ischemia and advanced liver disease could include coronary revascularization first with the anticipation and hope of an available organ should the patient develop acute liver failure for a patient with Child-Pugh class A liver disease. This approach may not be feasible because of the issues of coagulopathy in patients with Child-Pugh class B and C disease. If coronary artery bypass grafting is contemplated, there may be a sound argument to perform the procedure without cardiopulmonary bypass.

**Spontaneous Bacterial Peritonitis.** Spontaneous bacterial peritonitis (SBP) is a serious complication of chronic liver disease. Although SBP is seen most frequently in patients who are hospitalized for other complications of their liver disease, it has been observed in 3.5% of asymptomatic outpatients with known cirrhosis (63). The organisms seen in this group were Gram-positive and the patient survival at 1 yr was 67%.

Hospitalized patients are at risk of more serious infection with SBP, usually with Gram-negative organisms and with a much higher mortality rate, 46% in the series reported by Lipka et al. (64). Predominant organisms were *Escherichia coli* and *Klebsiella pneumoniae*. Because of the high recurrence rate of SBP, prophylactic antibiotic therapy with a third-generation cephalosporin is recommended (65). Gram-negative infection in hospitalized patients may be spontaneous or it may be related to procedural interventions such as high-volume paracentesis. Usually patients with SBP will be Child-Pugh class C and will manifest other complications such as hepatorenal syndrome or hepatic encephalopathy.

In the absence of hepatocellular carcinoma, multiple-system organ failure, age >66 yrs, and a 60-day survival interval following diagnosis of SBP, liver transplantation may be recommended (66).

**Nonalcoholic Steatohepatitis.** Nonalcoholic steatohepatitis (NASH) is the consequence of the metabolic syndrome (syndrome X) characterized by obesity, type 2 diabetes, hypertriglyceridemia, and hepatic steatosis (67). Although NASH appears to be multifactorial, the fatty liver is vulnerable to oxidative hepatic cellular injury. It is a common complication of morbid obesity. It can progress to cirrhosis and liver failure. In a series of 75 patients undergoing Roux-en-Y gastric bypass surgery, 84% had steatosis, 20% had moderate to severe inflammation and fibrosis, and 8% had bridging fibrosis or cirrhosis (68). Aspartate aminotransferase, alanine aminotransferase, and body mass index correlated poorly with the presence of significant liver disease. Based on these findings, the authors recommend routine liver biopsy at the time of bariatric surgery. In a second series of 105 consecutive patients undergoing laparoscopic bariatric surgery, the incidence of NASH was lower, 25%; however, 42% of those patients had advanced fibrosis (69). Insulin resistance and systemic hypertension along with blood alanine aminotransferase concentrations were highly predictive for the presence of liver disease. A history of alcohol consumption appeared to be protective probably because of its effect in reducing insulin resistance. A third study showed the incidence of NASH to be 91%, but only 10% showed severe fibrosis (70).

Bariatric surgery is blossoming as an opportunity for a new program in surgery throughout the United States with estimates of tens of thousands of potential candidates for bypass procedures. Although acute hepatic failure has not been identified as a common postoperative problem, the high incidence of NASH warrants caution and a careful preoperative assessment of liver function. Certainly, liver biopsy at the time of surgery is recommended.

**Perspective on Liver Transplantation.** The purpose of this article is not to discuss preoperative preparation of patients for liver transplantation. This has been
well described in reviews and texts (71, 72). However, readers may be placed in the position of referring a patient for urgent transplantation as the only means of salvage following acute hepatic decompensation. A recent review (51) has suggested that severe cardiovascular disease, uncontrolled systemic infection, extrahepatic malignancy, severe psychiatric or neurologic disorders, and absence of a viable splanchnic venous inflow system are absolute contraindications to liver transplantation (73). In the absence of these contraindications, the optimal correction of the issues described in this review represents the optimal physiologic preparation of the patient needing urgent liver transplantation.

Central Pontine Myelinolysis. Central pontine myelinolysis is a demyelinating disorder whose cause is unknown but occurs frequently in patients with chronic alcoholism, severe malnutrition, and hyponatremia. The effect of correction of hyponatremia in the evolution of this syndrome is probably a result of osmotic endothelial injury in an area of the brain with a high admixture of gray and white matter (74).

Severe hyponatremia occurs in patients with advanced liver disease because of the fluid balance abnormalities associated with massive ascites, large volume paracentesis, and abnormal water reten tion associated with abnormal renal function. Severe hyponatremia leads to abnormal central nervous function including seizures. Correction of hyponatremia, if performed rapidly before or during the course of liver transplantation, can lead to fatal central pontine myelinolysis postoperatively (75). In the series of 379 orthotopic liver transplants performed at Baylor Medical Center (76), severe hyponatremia (serum sodium ≤127 mEq/L) was present in 3.5% of their patients (76). Three patients developed central pontine myelinolysis, and all three died within 3 months of transplantation. The increase in serum sodium concentration postoperatively was significantly higher in the patients with central pontine myelinolysis (20.7 ± 8.1 mEq/L) than it was in patients in whom it did not develop (7.0 ± 5.1 mEq/L). The authors recommend slow correction of severe hyponatremia when possible. Serum sodium concentrations should be monitored closely especially if sodium bicarbonate administration is planned for correction of metabolic acidosis.

Soupart and Decaux (77) recommended correction of chronic hyponatremia at <10 mEq/L per 24 hrs in patients with advanced liver disease and malnutrition. If the patient is asymptomatic, fluid restriction and the administration of urea may protect against evolving brain edema. If patients have neurologic symptoms, 3% sodium chloride may be administered intravenously. If correction needs to be stopped, desmopressin may be used to stop diuresis.

Primary Nonfunction. Primary nonfunction of a transplanted liver is a disastrous complication of liver transplantation that often requires retransplantation in the early postoperative period. Primary nonfunction is associated with severe fatty infiltration or hydropic degeneration on needle biopsy performed during procurement (78). Perioperative physicians may be charged with dealing with the physiologic abnormalities associated with this syndrome during the period of time when the patient is awaiting a second organ.

Although primary nonfunction is poorly understood, the appearance of the liver and the clinical sequelae are similar to hyperacute rejection. The liver appearance degrades immediately in the postperfusion period. In the extreme, it turns black and becomes mottled, obviously not viable. The patient becomes severely coagulopathic with continuous oozing from all areas of the surgical wound. Acute respiratory failure requiring high inspired concentrations of oxygen and positive end-expiratory pressure is common. Additionally, the patient will usually develop acute renal failure. Reversal of these features following retransplantation can be dramatic. If allograft hepatectomy is performed early in the course of primary nonfunction, cardiovascular and respiratory stability are improved while the patient awaits retransplantation (79).

Early reports of a beneficial effect of prostaglandin E1 on early graft survival have not been borne out in controlled studies (80). Prostaglandin E1 infusions improved early postoperative renal function but did not decrease the incidence of allograft primary nonfunction.

Tests for early graft function after liver transplantation have eluded us. One of the best tests is the assay of factor VII level, since factor VII has a short half-life (approximately 4 hrs) and it is synthesized exclusively in the liver (81, 82). Fibrinogen and albumin are also good markers of synthetic graft function, but their half-lives are quite long. The utility of factor VII is limited because fresh frozen plasma is a good source of factor VII and most patients for whom an accurate assessment of graft function is necessary are usually receiving fresh frozen plasma. Hyaluronic acid uptake, a natural function of hepatic endothelium, has been shown to correlate with early graft function (83). The first metabolite of lidocaine, monoethyl glycine xylidide, has been tested as a measure of residual hepatocellular function preoperatively and of graft function in the postoperative period (84, 85). However, issues of drug distribution have made the assay of this marker unreliable as an indicator of early graft function.

Group specific protein (Gc protein) is a serum protein synthesized in the liver and released into the bloodstream, and it is preserved in fresh frozen plasma. It plays a role in capping actin filaments that polymerize in the bloodstream following organ injury (86). A Gc protein assay that is immunonephelometric has been developed that is nonspecific, fully automated, and accurate (87). The assay is a good measure of synthetic hepatocellular function. Actin is an intracellular protein that normally is not present free in the circulation. However, with severe organ injury, as in primary nonfunction of a liver allograft, actin is released into the circulation where it can polymerize into actin filaments capable of obstructing small blood vessels. In patients with acute liver failure, the capping proteins Gc protein and gelsolin are diminished and actin monomers freely polymerize into actin filaments. Polymerized actin filaments may contribute to multiorgan failure (88).

CONCLUSIONS

Advanced liver disease is a systemic disease manifested by dysfunction of the
Acute Liver Failure: a Review
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Since publication of the first descriptions of acute liver failure (ALF) as a distinct clinical entity in the 1950s [1], the understanding of the pathophysiologic mechanisms involved and the management options have increased substantially. ALF still represents a major challenge for today’s hepatologists, because it can lead rapidly to multiorgan failure and death that may be preventable with appropriate intervention. This article summarizes the basic pathophysiology underlying ALF, compares epidemiologic trends in the United States, the United Kingdom, and the Far East, and reviews prognostic markers and treatment options for ALF.

Pathophysiology

ALF occurs when the rate of hepatocyte death exceeds the rate of hepatocyte regeneration as a result of various causes that lead to a combination of apoptosis or necrosis [2]. Apoptosis is associated with nuclear shrinkage but without cell membrane rupture. Therefore there is no release of intracellular content and no subsequent secondary inflammation [2]. Necrosis is associated with ATP exhaustion resulting in a swollen cell that eventually lyses with release of intracellular content and consequent secondary inflammation [1]. Most causes of ALF result in either apoptosis or necrosis; for example,
acetaminophen (paracetamol) toxicity predominantly results in apoptosis, and ischemia results in necrosis. The clinical result of the cellular damage is a catastrophic illness that can lead rapidly to coma and death caused by multiorgan failure [3].

Apoptosis follows activation of caspases (cysteine proteases) (eg, after oxidative mitochondrial damage). The caspase cascade is activated by various cytokines such as tumor necrosis factor-alpha and Fas ligand through receptors on the hepatocyte cell membrane [4]. Any insult that can induce apoptosis may also lead to cell death by necrosis, especially if the level of mitochondrial damage is such that ATP stores are depleted [2]. Processes resulting in marked oxidative stress tend to produce necrotic rather than apoptotic cell death, because of severe mitochondrial damage and also inhibition of the proapoptotic caspase cascade [2,5–7]. Other crucial factors regulating pathways of hepatocyte death include cellular nitric oxide, antioxidants such as glutathione, tyrosine kinases, transcription factors, and various pro- and anti-inflammatory cytokines including interferon, interleukin (IL)-10, IL-12, and natural killer cell–derived IL-5 [2].

Epidemiology and causes of acute liver failure in the United States

ALF affects approximately 2000 people per year in the United States [8]. Early studies were based on small case series; for example, in 1969 an analysis of 31 patients found that 74% of cases were secondary to viral hepatitis and 23% to drugs [9]. More recent studies have analyzed data from the multicenter Acute Liver Failure Study Group, formed in 1997 [10]. Their first prospective series, of 308 cases between 1998 and 2001, reported that 39% of ALF cases were caused by acetaminophen (paracetamol) poisoning, and only a minority were caused by viral hepatitis [11]. This study was the most detailed to date. Table 1 gives a breakdown of the demographics and causes of liver failure in this cohort. Most cases involved women; the median age was 38 years (range, 15–78 years). There were significant differences in survival rates and percentage of patients receiving transplantation depending on the cause of ALF. In the acetaminophen group there was 68% rate of spontaneous survival, and 6% received a liver transplant; in patients who had ALF secondary to idiosyncratic drug reactions, there was a 25% survival rate, and 53% of patients received transplantation.

Acetaminophen

Acetaminophen poisoning leading to ALF was virtually unknown in the United States before 1980 but has now become the commonest cause of ALF. A recent analysis from the ALF Study Group reviewed 275 cases of acetaminophen-induced ALF over a 6-year period from 22 tertiary centers in the United States [12]. The percentage of ALF cases secondary to acetaminophen rose during the study from 28% in 1998 to 51% in 2003. Unintentional
overdoses accounted for 48% of cases, intentional overdoses accounted for 44%, and in 8% the intent was unknown. Overall, 178 (65%) survived, 74 (27%) died without liver transplantation, and 23 (8%) underwent transplantation. The transplant-free survival rates and rates of transplantation were similar in the intentional- and unintentional-overdose groups [12].

Idiosyncratic drug reactions

Although accounting for only 13% of the 308 cases in the original ALF Study Group review and having a slower clinical evolution, idiosyncratic drug reactions were associated with a worse prognosis and higher rate of liver transplantation [11]. Examples of causative drugs include bromfenac and troglitazone, both of which were withdrawn from the market in the United States. Other reported causes included trimethoprim, propylthiouracil, phenytoin, disulfiram, and herbal medications (eg, chaparral and *Teucrium polium*).

Other causes

In the same study, 8% of ALF cases were secondary to hepatitis B (HBV) and 4% to hepatitis A. No patients had acute hepatitis C (HCV). Eight of the 308 cases were caused by Wilson’s disease, 17 were related to cardiogenic causes, 6 were pregnancy-related, and cancer was the underlying cause in 4. Autoimmune disease and Budd-Chiari syndrome were responsible in a few patients. Seventeen percent of cases were of indeterminate cause [11].

Outcome

Although a variety of causes lead to ALF, the final clinical scenario is similar. In addition to the hallmark coagulopathy and encephalopathy,
patients develop hypotension, renal impairment, sepsis, and eventually multiorgan failure including respiratory failure and cardiac arrhythmias [14]. In the pretransplantation era, overall survival was less than 20% [14]. Of the 308 patients enrolled in the original ALF Study Group analysis, 43% (n = 132) spontaneously survived, 29% (n = 89) received a liver transplant (of whom 75 survived), and 28% (n = 87) died before transplantation [11]. ALF secondary to idiosyncratic reactions and HBV had the poorest outcome (ie, less than 25% spontaneous survival). Acetaminophen-related ALF had the best transplant-free survival rate (68%). Age was not related to the overall survival rate.

Acute liver failure in the United Kingdom

ALF is relatively uncommon in the United Kingdom, causing fewer than 500 deaths and being responsible for less than 15% of liver transplantations per annum (less than 100 transplants per year) [13].

Acetaminophen

As in the United States, acetaminophen poisoning is the commonest cause of ALF in the United Kingdom, causing up to 70% of cases [14]. Unlike the United States however, most cases of acetaminophen overdose in the United Kingdom are a consequence of deliberate self-harm (DSH) rather than unintentional [15]. DSH secondary to self-poisoning leads to more than 60,000 hospital admissions per year in the United Kingdom, and most of these involve acetaminophen [16]. In fact, the United Kingdom has the highest rate of DSH by acetaminophen use in the world [17]. Up to 10% of cases of acetaminophen self-poisoning develop severe liver damage, and less than 2% go on to develop ALF, the worst outcomes being in patients with concurrent alcohol use [18].

Other causes

Over the past 30 years, as acetaminophen has increasingly become the dominant cause of ALF in the United Kingdom; other causes have correspondingly contributed fewer cases (Table 2). In an analysis of 999 cases

<table>
<thead>
<tr>
<th>Study period (reference)</th>
<th>n</th>
<th>Acetaminophen (%)</th>
<th>Non-acetaminophen (%)</th>
<th>Viral (%)</th>
<th>Seronegative (%)</th>
</tr>
</thead>
</table>
over a 7-year period at King’s College, 5% of cases were caused by non-acetaminophen drugs such as antituberculous therapy, anticonvulsants, steroids, nonsteroidal anti-inflammatory medications, herbal remedies, and recreational drugs (eg, ecstasy [3,4-methylenedioxy-methamphetamine] and cocaine) [14]. There has been a decrease in the incidence of hepatitis A– and HBV-induced ALF. Less than 0.05% of cases of acute hepatitis A and HBV lead to ALF, and these viruses contribute less than 5% of all ALF cases [19,21,22]. Seronegative (non-A–E) hepatitis, a diagnosis of exclusion, is the commonest presumed viral cause in the United Kingdom and other Western countries [23] but contributed less than 10% of all cases of ALF in the King’s College series. This percentage is decreasing, possibly because of improved diagnosis. Unusual viral causes include herpes simplex, Epstein-Barr, cytomegalovirus, and varicella-zoster. Small numbers of ALF cases resulted from miscellaneous causes such as pregnancy, Wilson’s disease, Budd-Chiari syndrome, autoimmune hepatitis, ischemic hepatitis, and malignant infiltration.

*Analgesic legislation in the United Kingdom*

The rise in acetaminophen as a cause of ALF in the United Kingdom paralleled increasing sales and availability of the drug [24]. In September 1998, the United Kingdom Medicines Control Agency introduced legislation to reduce over-the-counter availability of acetaminophen as well as aspirin. Under this legislation, pharmacies (previously unrestricted) were limited to selling a maximum of 32 tablets of paracetamol (total 16 g) per sale. The maximum allowable sale for other retailers was reduced from 24 to 16 tablets. Other strategies to combat increasing rates of acetaminophen-induced ALF included printing specific warnings about overdose in the packets, use of acetaminophen/methionine combination analgesics, and promotion of alternative analgesics [25].

In the 2 years immediately after the legislation (ie, between 1998 and 2000) total acetaminophen sales in the United Kingdom fell by 41%. This decrease was associated with a 173% increase in sales of ibuprofen [26]. Between 1995 and 2000 the number of acetaminophen overdoses decreased from 77 to 67 per 100,000, although the use of antidepressants and tranquilizers in DSH increased from 56 to 75 per 100,000 [16]. According to the United Kingdom National Transplant Database, between 1995 and 1998 there was an almost 80% increase in the number of patients who had acetaminophen-induced ALF listed for a liver transplant [13]. In 1997 and 1998, 30 patients underwent transplantation, representing 38% of all super-urgent listings. In 2001 and 2002, 17 patients received a transplant. During this period the percentage of emergency transplantations performed for acetaminophen-induced ALF decreased from 38% to 16% of all liver transplantations. In the same period, the number of patients listed for seronegative hepatitis rose by more than 60% [27].
Further beneficial effects of the acetaminophen legislation of 1998 were highlighted by a recent paper that examined data from the Office of National Statistics and six liver units around the United Kingdom [28]. Mean annual admissions for acetaminophen-poisoning fell from 349 in the 2 years before the legislation to 230 during the 4 years afterwards. Suicidal deaths from paracetamol fell by 29% in the year after the legislation. Although ibuprofen overdoses increased, this increase had no significant effect on mortality [28]. An estimated 118 deaths from acetaminophen hepatotoxicity have been avoided in the 3 years following the legislation [28].

In summary, since September 1998, when the legislation was introduced, there has been a reduction in acetaminophen sales, in the dose taken at DSH, and in acetaminophen-related hospital admissions and liver transplantations and an increase in the proportion of patients undergoing liver transplantation for non-acetaminophen causes [29]. The United Kingdom experience with acetaminophen may be relevant to other countries where acetaminophen sales are unrestricted.

Acute liver failure in the Far East

Although ALF accounts for fewer than 10% of all liver transplantations in the United States, it accounts for more than two thirds of transplantations in the Far East [30]. There is also significant worldwide variation in the cause of ALF. ALF is most commonly drug-induced in the West, but in the developing world and Far East ALF is most often caused by viral hepatitis. Particularly common causes are exacerbations of chronic HBV, which is endemic in many countries including Hong Kong, and hepatitis E in India (Table 3) [31]. Flares of chronic HBV may be spontaneous, represent a secondary response to increased levels of replicating wild-type or mutant virus, occur after immunosuppressive and cytotoxic therapy, or occur following superinfection with other hepatotropic viruses such as hepatitis D and HCV [32]. Particularly severe exacerbations have been reported in patients

<table>
<thead>
<tr>
<th>Cause (%)</th>
<th>Hong Kong</th>
<th>Japan</th>
<th>India</th>
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<tbody>
<tr>
<td>Hepatitis B</td>
<td>79</td>
<td>22</td>
<td>31</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>na</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Hepatitis E</td>
<td>na</td>
<td>na</td>
<td>38</td>
</tr>
<tr>
<td>Seronegative hepatitis</td>
<td>na</td>
<td>na</td>
<td>24</td>
</tr>
<tr>
<td>Drug reactions</td>
<td>na</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Unknown</td>
<td>na</td>
<td>62</td>
<td>na</td>
</tr>
</tbody>
</table>

Table 3
Causes of acute liver failure in Far Eastern countries

Abbreviation: na, not available.

who have pre-core mutant HBV infection [31,32]. Preemptive lamivudine has helped reduce the exacerbations of hepatitis in hepatitis B surface antigen–positive patients treated with immunosuppressants [31].

HCV infection in ALF may be higher in Asian countries, at least from early studies. In Western case series of non-A non-B fulminant hepatitis, less than 12% were positive for HCV-RNA [20,33,34]. In Taiwan and China, this figure was 50% and above 50%, respectively [35]. The reasons for this difference are unclear.

**Liver transplantation**

Although liver transplantation is not the focus of this article, a few developments warrant mentioning.

*Orthotopic liver transplantation*

Transplantation for ALF generally has a worse outcome than transplantation for chronic liver disease, mainly because of high postoperative mortality caused by sepsis and multiorgan failure [36,37]. Multiorgan failure can be particularly severe in acetaminophen-associated ALF, so that in some cases listing for transplantation is not an option, as seen in some United Kingdom series [38]. Other factors associated with poor outcome include small-size grafts and ABO incompatibility. Nevertheless, liver transplantation has significantly improved the prognosis of ALF in both the West and the Far East. Postoperative survival rates in the Far East are roughly equivalent to those in the West (60%–80%) [39,40], compared with 15% to 20% survival rates in patients who do not receive grafts [39,40].

*Living-donor liver transplantation*

The availability of cadaveric donors in the Far East, less than five per million population per year, is much less than in the West, partly because of cultural beliefs [31]. Therefore the use of living-donor liver transplantation (LDLT), already established in pediatric liver failure, is being increasingly used for adults in places such as Japan, Hong Kong, Taiwan, and Singapore [41–43]. The first reported series of Japanese patients undergoing LDLT showed a promising survival rate (19 of 34 patients, 56%) [41].

A major consideration in LDLT is graft size. LDLT grafts are smaller than cadaveric ones and are more prone to reperfusion injury. Required graft volume is at least 25% of the recipient’s standard liver volume [44]. Originally LDLTs were performed using one or more segments from the left lobe. A right hepatic lobe LDLT, to improve the donor-to-recipient ratio, was first described in Japan in 1994 [45]. In a more recent study from Hong Kong, 14 of 16 patients survived following right hepatic lobe LDLT [46]. Indeed, most successful reported cases of LDLT in ALF have involved right lobe grafts [31]. Complications are more common in those
donating a right than a left lobe [47], and this higher risk of complications in healthy donors clearly has ethical implications. In a recent review from Japan of 1841 living liver donors, although postoperative hospital stay was significantly longer in donors of the right lobe, there was no perioperative mortality [47].

**Auxiliary liver transplantation**

In auxiliary liver transplantation a partial liver graft is inserted while the native liver is left in situ. In theory, when the insult causing ALF resolves, the native liver subsequently regenerates, so use of immunosuppressive medications may be stopped, and the graft is allowed to atrophy or is removed [48]. It currently is difficult to predict which patients will regenerate the native liver. Favorable indicators include young age, cause of ALF (viral or acetaminophen-related), mode of presentation (hyperacute), and limited extrahepatic organ involvement [49]. In most centers, auxiliary liver transplantation is limited to patients who meet these criteria [50].

**Prognostic factors in acute liver failure**

Given that the only proven beneficial therapeutic intervention in advanced ALF is transplantation [22], the timing of transplantation and selection of patients are crucial [50]. A false-negative selection can result in a preventable death. On the other hand, unnecessary transplantation carries up to 30% 1-year mortality, commits the patient to lifelong immunosuppressants, is expensive, and wastes a precious graft [50].

Although scoring systems have been proposed, the variety of causes of ALF tends to limit their accuracy. Two main prognostic criteria are currently used, Clichy and King’s College. Validating selection criteria is difficult because of poor methodology in several reported series [22,50]. Furthermore, ALF is uncommon; hence, most case series involve small numbers. As a result, most series span long periods of time, during which important supportive medical therapies may have evolved that could affect survival [50].

**The Clichy criteria**

The Clichy criteria were the first to be described [51]. They were derived from a multivariate analysis of prognostically important variables in 115 patients who had fulminant HBV, managed medically in the pre–liver transplantation era between 1972 and 1981. According to Clichy, ALF patients should undergo transplantation if

1. There is grade 3 or 4 encephalopathy.
2. Factor V is less than 20%, and the patient is under 30 years.
3. Factor V is less than 20%, and the patient is over 30 years [52].
Although the Clichy criteria are widely used in Europe, they have several limitations. The cohort of patients all had ALF of the same cause, and the cause of ALF plays an important role in prognosis, particularly in relation to acetaminophen [53]. There is also limited availability for Factor V measurement. Furthermore, there is a lack of good prospective validation [54].

The King’s College criteria

The King’s College criteria (Table 4) are more widely used, one reason being that they take into account the cause of ALF. They were derived from a retrospective cohort of 588 patients medically managed between 1973 and 1985, with subsequent validation in 175 patients who had ALF treated between 1986 and 1987 [55]. A recent meta-analysis of prognostic criteria for acetaminophen-induced ALF found the King’s College criteria to have good specificity (ie, patients who fulfill the criteria and are likely to die without transplantation): 92%. Sensitivity was lower (69%), however, suggesting a proportion of patients will die without fulfilling the criteria [50,56]. In a comparison of both sets of criteria in acetaminophen-related ALF, the Clichy criteria performed less well, with lower positive predictive value (49% versus 92%) and predictive accuracy (56% versus 83%) [57].

There are fewer studies relating to non-acetaminophen criteria. Recent reviews of these studies [50,58] suggest acceptable specificity but a low negative predictive value (generally less than 0.6), reflected by the higher proportion of deaths in patients who do not fulfill the criteria. When both sets of criteria were applied to a non-acetaminophen study population, the King’s College criteria performed better than the Clichy criteria [59].

Additional prognostic models and indicators

Current prognostic indicators are limited. The time interval from fulfilling a set of criteria to becoming medically unsuitable for liver transplantation can be short, hence the need for more sensitive tests with greater negative predictive value without loss of specificity [50]. In particular, both the King’s College and the Clichy criteria have been found to have a low

<table>
<thead>
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<th>Table 4</th>
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<tbody>
<tr>
<td><strong>King’s College criteria for transplantation in acute liver failure</strong></td>
</tr>
<tr>
<td><strong>Non-acetaminophen cause</strong></td>
</tr>
<tr>
<td>INR &gt; 6.7</td>
</tr>
<tr>
<td>Or any three of</td>
</tr>
<tr>
<td>Unfavorable cause (eg, drug-induced)</td>
</tr>
<tr>
<td>Age &lt; 10 or &gt; 40 years</td>
</tr>
<tr>
<td>Acute/subacute presentation</td>
</tr>
<tr>
<td>Bilirubin level &gt; 300 µmol /L</td>
</tr>
<tr>
<td>INR &gt; 3.5</td>
</tr>
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*Abbreviation:* INR, international normalized ratio.
negative predictive value (less than 0.60) and thus may not identify a subgroup of patients who have a low risk of death. This low negative predictive value could lead in the inappropriate use of liver transplantation in patients who have ALF but who would recover without transplantation [60]. In a recent study, the London and Clichy criteria were compared with the Model for End-stage Liver Disease (MELD) score in patients presenting with fulminant hepatic failure of various causes, exclusive of acetaminophen. The study found that the MELD score seemed to be an excellent predictor of outcome in both adults and children who had fulminant hepatic failure, with a diagnostic accuracy of 95% and a C-statistic score of 0.96 [61]. Several markers have been proposed (Box 1). Most promising so far, at least in acetaminophen-related ALF, are blood lactate and hyperphosphatemia. When these markers are added to the King’s criteria, the result is improved sensitivity without significant reduction in specificity [62–64].

Management of acute liver failure

Death in ALF is predominantly related to sepsis, multiorgan failure, and intracranial hypertension [72]. The circulatory disturbances in ALF, which contribute to the often-associated renal failure, are characterized by a generalized vasodilatation that results in increased cardiac output and reduced systemic vascular resistance and mean arterial pressure [73,74]. Although emergency liver transplantation is the only therapeutic intervention of proven benefit, various supportive therapies should be initiated as soon as the patient presents, because rapid deterioration is likely.

General supportive measures

Close clinical monitoring is important, and patients who have ALF should be managed in an intensive care setting. Liberal volume expansion is likely to be required in most cases, usually with a mixture of crystalloids

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<th>Box 1. Additional prognostic indicators in acute liver failure</th>
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<tr>
<td>Lactate [63]</td>
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<td>Phosphate [64]</td>
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<td>Factor VIII and V ratios [65]</td>
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<td>Serum [Gc], vitamin D binding protein [66]</td>
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<td>Serial prothrombin times [67]</td>
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<td>Arterial ketone body ratio [68]</td>
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<td>Liver size on CT (&lt; 1 L) [69]</td>
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<td>Liver histology (necrosis) [70]</td>
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<td>Circulating [IL-6 and -8] [71]</td>
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and colloids. Correction of acid-base disturbances and hyperlactataemia is important because of their impact on circulatory function and increasing cerebral hyperemia [75]. Hyperthermia should be prevented, because it worsens intracranial hypertension [76]. Glucose levels must be monitored and adequately maintained to prevent the cerebral and systemic effects of hypoglycaemia while avoiding hyperglycaemia, which worsens cerebral edema [77]. Hyponatraemia is a negative prognostic sign and can worsen brain edema [78,79]. Sodium values less than 125 mmol/L are a contraindication for transplantation. Hypercapnia should be avoided, because it can lead to cerebral hyperemia and increases intracranial pressure (ICP) [80]. Careful management of the airway may necessitate early intubation if the patient’s neurologic status deteriorates.

Extracorporeal renal support will be required in up to 80% of cases of advanced ALF complicated by cerebral edema [81]. It has been suggested that continuous hemofiltration is safer than intermittent hemodialysis, because the former is associated with a lower rise in ICP, greater cardiovascular stability, and better cerebral perfusion [82]. Early liaison with a liver transplantation unit is clearly important, and any contraindications to transplantation should be identified with collateral histories through the family, friends, and the primary care physicians, if necessary.

**Prophylactic antibiotics**

Patients who have ALF are at high risk of sepsis, and there is increasing suspicion that the systemic inflammatory response is important in the pathogenesis of increased ICP in ALF [72,83,84]. Furthermore, the prophylactic use of parenteral and enteral antibiotics has been associated with lower rates of infection ($P < .005$) [85].

**N-acetylcysteine**

Several clinical trials support the use of $N$-acetylcysteine in ALF. In late-presenting acetaminophen overdose, mortality was 37% in patients who received $N$-acetylcysteine compared with 58% in the controls. Progression to grade III-IV hepatic encephalopathy also was slower in those receiving $N$-acetylcysteine (51% versus 75%) [86]. Another controlled trial in acetaminophen-related ALF found that survival was significantly higher in the group treated with $N$-acetylcysteine than in controls (48% versus 20%; $P < .04$) [87]. Certainly with respect to acetaminophen poisoning, irrespective of when the patient presents, administration of $N$-acetylcysteine is recommended because it may prevent the progression to full-blown ALF [72].

**Intracranial hypertension**

The underlying pathogenesis of intracranial hypertension in ALF is not clear, but several interrelated factors probably are responsible.
Ammonia-related brain edema is an early insult [88]. Autoregulation of cerebral blood flow is lost in ALF, resulting in cerebral hyperemia [89]. There also is increasing evidence that a systemic inflammatory response is important in the pathogenesis of increased ICP in ALF [75,83,84,90]. A lack of data from randomized, controlled trials prevents the use of robust evidence-based guidelines for specific therapies. Given that the management is aimed at controlling ICP, the use of ICP monitors seems logical, but routine monitoring needs to be balanced against the risk of bleeding. It may be possible to select patients for insertion of ICP monitors based on measurements using jugular bulb oxygen saturation [68]. In a retrospective study, the authors [68] recently observed that patients who had evidence of either high or low oxygen saturation (<65% or >80%) in reverse jugular catheter venous blood were more likely to have an ICP higher than 20 mm Hg. The complexity and risks of ICP monitoring and the emergence of new methods such as continuous EEG and microdialysis techniques suggest that such patients should be managed in specialist centers.

Reduction of ammonia

Although lactulose is often used to reduce ammonia, studies have not shown any benefit in ALF [72]. L-ornithine l-aspartate, a double amino acid mixture, reduces blood ammonia concentration by increasing ammonia detoxification in muscle. Controlled trials have shown that it reduces the severity of hepatic encephalopathy in cirrhosis [91]. Although data in humans who have ALF are lacking, studies in rat models of ALF suggest l-ornithine l-aspartate may inhibit brain edema [92].

Reduction of cerebral edema

The mainstay for treatment of increased ICP in ALF is mannitol, which increases the osmolality of capillaries in the brain. In patients who have ALF mannitol has been shown to reduce episodes of cerebral edema and increase survival significantly more than controls [93]. Reduction of blood volume with hemofiltration is also effective in reducing the ICP, although controlled studies are scarce [68].

In a small controlled clinical trial of 30 patients who had ALF, hypertonic saline (30%) significantly decreased ICP relative to baseline over the first 24 hours compared with controls [94]. Further studies are required to confirm its efficacy and safety, however, because hypertonic saline has several potential adverse effects, including multiple small hemorrhages, vein thromboses, brain shrinkage, pons demyelination, and aggravation of coagulopathy [95].

Indomethacin induces cerebral vasoconstriction through alterations in extracellular pH, inhibition of the endothelial cyclooxygenase pathway, and reduction in cerebral temperature [96]. In a study of 12 patients who had ALF and brain edema, intravenous indomethacin was associated with a reduction in ICP from a mean of 30 mm Hg (range, 7–53 mm Hg) to
12 mm Hg (range, 4–33 mm Hg; $P < .05$) [97]. Indomethacin may be toxic for the kidneys and the gut, however, and cannot be recommended for routine use in ALF without more data.

Moderate hypothermia (32°C–33°C) is known to reduce ICP in ALF [98]. It does so by affecting ammonia through its brain metabolism, cerebral blood flow, and autoregulation and by a reduction in the inflammatory response and its mediators such as nitric oxide, pro-inflammatory cytokines and products of oxidative stress [99]. The authors [99] recently reported successful bridging to orthotopic liver transplantation with a mean of 32 hours of cooling in 13 patients who had ALF and uncontrolled increase in ICP. During prolonged cooling, the ICP may rise in some patients, but most patients will respond to further doses of mannitol. Hypothermia also was associated with significant improvement in cardiovascular hemodynamics, manifested by increased mean arterial pressure and systemic vascular resistance and reduced inotrope requirements [99]. In theory, hypothermia can increase the risk of bleeding and infection, which must be carefully monitored and treated. The use of hypothermia in patients who have ALF and who have uncontrolled intracranial hypertension is promising, particularly as a bridge to orthotopic liver transplantation. Larger clinical trials are awaited.

Liver-support devices for acute liver failure

ALF has a high mortality while transplantation is awaited or if it is contraindicated. Liver-support devices may be used as a bridge to transplantation or to help recovery of the ailing liver. Two main categories of support devices exist, bioartificial and artificial [100]. Assessing their efficacy is difficult because such patients are uncommon, and there is a consequent lack of controlled data, with most studies being underpowered. Furthermore, when transplantation is indicated, it is likely to be done at different times in the clinical course of different patients. It is also difficult to standardize other therapies for studies in an intensive care setting.

Target toxins

ALF reduces the liver’s ability for synthesis and detoxification. This reduced ability results in declining albumin and clotting factor synthesis, urea cycle dysfunction (with subsequent increase in ammonia), and reduced metabolism of other protein breakdown products [100]. Toxins such as amino acids, bile acids, bilirubin, endogenous benzodiazepines, nitric oxide, and phenols accumulate and may contribute to multiorgan failure. These toxins are mostly bound to albumin in the plasma and therefore are not removable by hemofiltration or dialysis. These are the potential targets of liver-support devices.
Bioartificial livers

In bioartificial livers, hepatocytes are used to reproduce the synthetic, detoxifying, and excretory function of the failing liver. An estimated $10^{10}$ hepatocytes are necessary to provide the equivalent function of 10% to 30% of the normal liver mass [101]. The major problem is that human hepatocytes are difficult to grow in culture and are inherently unstable [100]. Hence devices in current use rely on animal, particularly porcine, hepatocytes that can be cryopreserved much more readily. An alternative is to use genetically engineered human hepatocytes designed to retain specific functional abilities [102].

The basic “bioreactor” mechanism is a column with hollow fiber capillaries through which the patient’s plasma flows, with hepatocytes in the extracapillary space. Free exchange of molecules occurs between hepatocytes and plasma across a membrane with a specific cut-off size (50–150 kD) allowing toxin and albumin migration but preventing passage of immunoglobulins, complements, and cells [100]. A prospective, multicenter, randomized controlled trial using the HepatAssist liver support system (Arbios Systems, Inc., Los Angeles, CA) was recently published [103]. In brief, 171 patients (86 controls and 85 patients who had bioartificial livers) were enrolled including patients who had fulminant/subfulminant hepatic failure and primary nonfunction after liver transplantation. Survival in patients who had fulminant/subfulminant hepatic failure was significantly higher in the bioartificial liver population than in the control group (risk ratio, 0.56; $P = .048$) [103].

Artificial, extracorporeal liver-support devices

Safety concerns regarding bioartificial livers include immune reactions to foreign antigens, xenozoonosis, and the escape of tumorigenic cells into the patient [100]. These concerns have led to a renewed interest in artificial extracorporeal devices. A major advance in artificial extracorporeal devices that has helped fuel this interest is the use of albumin dialysis with a membrane containing pores small enough to increase the selectivity of the detoxifying process. The system can be specific for albumin-bound substances, which include most of the toxins that accumulate in liver failure, whereas larger and more useful molecules (such as immunoglobulins) cannot cross over [100]. The most recently developed system is the Molecular Adsorbents Recirculating System (MARS, Teraklin AG, Rostock, Germany), which currently is undergoing clinical trials [104]. Risks of MARS include thrombocytopenia and disseminated intravascular coagulation.

Several studies have reported on the efficacy of MARS in ALF. A recent controlled, randomized multicenter study found MARS was associated with significant improvements in encephalopathy and reduction in ammonia, bilirubin, bile acids, aromatic amino acids, and creatinine [105]. In a Finnish review of 101 patients treated over 2.5 years [106], patients were stratified in three subgroups: ALF ($n = 56$), acute decompensation in chronic liver
failure (n = 35), and liver graft failure (n = 10). MARS was most promising for ALF, particularly if the underlying cause was toxic [106].

In addition, there have been reports of MARS success in relation to fulminant Wilson’s disease [107], following acute hypoxic liver injury after cardiogenic shock [108], and as a bridge to liver transplantation after *Amanita phalloides* (toxic mushroom) intoxication [109]. MARS may also have a role in treating the increase in ICP associated with ALF, according to early animal studies [110]. Controlled clinical trial data are lacking, however, making any recommendation about the use of MARS difficult.

**Future prospects**

Epidemiologic patterns and the causes of ALF are changing. These changes affect prognosis and service planning and therefore should be monitored worldwide. Many patients die waiting for a liver transplant, and there is a dire need for alternative therapies to regenerate a failing liver or as a bridge to transplantation. Effective liver-support devices may not be an immediate reality, and conclusive trials are awaited. Other possible modalities on the horizon include hepatocyte transplantation and the use of stem cells for bioartificial livers. Hepatocyte transplantation, in which human hepatocytes are infused into splenic or portal vascular beds, has shown early promise with reduction in encephalopathy, ammonia levels, and prothrombin times in small case series [111]. Further confirmatory trials are awaited but are hampered by the relatively small number of cases. Perhaps the most important steps for the future are the collaborative efforts of different groups with an interest in liver failure, around the world, to assess new interventions.

**References**


Adverse Effects of Biliary Obstruction: Implications for Treatment of Patients with Obstructive Jaundice

Robert V. Rege¹,²

The development of hypotensive complications, renal failure, and cholangitis in patients with jaundice [1-4] has particular implications for radiologists asked to perform diagnostic studies that require IV contrast material and for radiologists, gastroenterologists, and surgeons who do invasive procedures to relieve bile duct obstruction. Although systemic effects of obstruction eventually are eliminated by reestablishment of the free flow of bile, all invasive procedures are painful, require sedation or anesthesia, and can induce fluid shifts, electrolyte abnormalities, hemorrhage, bile peritonitis, and sepsis. A patient with jaundice is less able to respond to and easily decompensates after such stresses [4]. An awareness of the pathophysiologic effects of biliary obstruction is essential because proper preparation of patients with jaundice before invasive diagnostic and therapeutic procedures avoids complications and decreases morbidity and mortality [5-8]. An overview of the systemic effects of bile duct obstruction and their implications for patients who require invasive diagnostic and therapeutic procedures is provided in this article.

Background

The liver is a complex organ that performs a multitude of essential metabolic functions, including metabolism of carbohydrates, proteins, fats, and vitamins; synthesis of proteins involved in coagulation; secretion of bile; detoxification and excretion of potentially harmful substances; and protection against infection [1]. In addition to the normal function of hepatocytes and Kupffer’s cells, normal hepatic function requires patency of the biliary tree, ensuring free drainage of bile into the intestine. Obstruction of the biliary tree and the inability to excrete bile into the intestine cause all substances normally excreted into bile to accumulate in the vascular system. Many of these substances, including bile salts, have systemic toxic effects [1, 2, 9, 10]. In addition, lack of bile in the intestine causes malabsorption of fats and fat-soluble vitamins [1, 11]. Bile may become colonized with bacteria, predisposing patients to systemic and local infectious complications [12, 13]. Chronic or recurrent, intermittent episodes of biliary obstruction eventually lead to an inflammatory response and, later, to fibrosis in the portal triads of the liver [14]. Patients eventually can develop hepatic damage, biliary cirrhosis, and liver failure [14].

The effects of both acute and chronic biliary obstruction have important implications for physicians caring for patients with biliary obstruction. Such patients are at particular risk for hypotension and acute renal failure [2, 4, 15, 16], complications that are highly morbid and contribute to the high mortality observed after surgery to relieve the obstruction [4]. Radiologic diagnostic and therapeutic interventions are now an integral and essential part of the care of patients with jaundice; however, although the benefit of these procedures in defining the problem and relieving biliary obstruction is clear, such procedures are invasive and not without risk. Manipulation of the biliary tract may cause reflux of toxins and bacteria into the vascular system and sometimes can induce an episode of cholangitis. Also, contamination of previously sterile bile with bacteria [17, 18] and damage to bile ducts, leading to intro-

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genic biliary stricture, can occur after radiologic, endoscopic, or surgical manipulation of the biliary tree. Not surprisingly, iatrogenic causes of biliary obstruction and cholangitis are becoming increasingly important as the number and type of procedures performed on the biliary tract increase.

Causes and Pathophysiology of Biliary Obstruction

In the United States, choledocholithiasis is the leading cause of biliary obstruction, although bile duct strictures, malignant obstruction of the bile duct from cholangiocarcinoma, periampullary and pancreatic tumors, and benign stricture of the distal bile duct from chronic pancreatitis have become increasingly prevalent [19, 20]. Other, less common causes of bile duct obstruction include choledochal cysts [21], indwelling biliary catheters, blood clots in the bile ducts because of hemobilia [22], strictures that develop with Caroli’s disease [23], and extrinsic compression of the bile duct. In the Orient and much less frequently in the United States, the parasites Clonorchis sinensis and Ascaris lumbricoides fill and obstruct the common bile duct and cause biliary fibrosis, with subsequent bile duct stricture, as the parasites attach themselves to the walls of the bile duct to derive nutrition [24, 25].

Obstruction of the bile duct, whether partial or complete, may be an acute, transient event, as it often is with passage of a gallstone, or may develop slowly, as it does with growth of a malignant tumor or with development of a benign fibrotic stricture. The chronicity of the problem, the number of episodes of jaundice and cholangitis, the degree of obstruction, and the presence or absence of bacteria in bile determine the type and severity of abnormalities that ensue [1]. Regardless of cause, obstruction of the bile duct increases pressure in the proximal part of the bile duct from normal values of 7–15 cm of water to values ranging between 18 and 30 cm of water, because bile continues to be secreted into the canaliculus by hepatocytes [26]. Tight junctions between hepatocytes and bile duct cells are disrupted, increasing canicular and bile duct permeability. With a pressure of 25 cm of water, components of bile and bacteria, if present, reflux freely into the sinusoids of the liver and gain access to the vascular system. These substances and bacteria cause a marked inflammatory response in the portal triads and spill into the vascular system. In addition, hepatocytes cannot excrete effectively against high ductal pressure, and excretory products of the cell reflux directly into the vascular system, adding to systemic toxicity. Serum levels of bilirubin, bile salts, and the enzyme alkaline phosphatase, which is synthesized by biliary epithelium, rise significantly. Serum bilirubin concentrations correlate with the degree of biliary obstruction, although, when obstruction is complete, they usually plateau at 20–30 mg/dl, as the daily load of bilirubin is excreted by the kidneys [1]. Although serum concentrations of alkaline phosphatase increase, they do not correlate with either the degree or the cause of biliary obstruction [1]. When bacteria are present in bile, a patient with elevated ductal pressure is at risk for infectious complications, including acute cholangitis, hepatic abscess, and sepsis, as bacteria can readily gain access to the hepatic parenchyma and vascular system. Repeated reflux of bacteria and endotoxin into the vascular system eventually results in systemic signs and symptoms of sepsis.

Complications of Biliary Obstruction

Nutritional Effects of Biliary Obstruction

Although short-term obstruction of the bile duct rarely causes specific nutritional problems, prolonged obstruction, with exclusion of bile from the intestine, impairs absorption of fats and results in steatorrhea [1]. Fat-soluble vitamins are poorly absorbed, and night blindness attributable to vitamin A deficiency and hepatic osteopathy resulting from vitamin D deficiency occur with prolonged cholestasis [1]. Vitamin E deficiency does not seem to cause clinical problems in adults [1] but reportedly causes neuromuscular weakness in children [11]. Deficiency of vitamin K is of particular importance when invasive procedures are contemplated; lack of vitamin K prolongs prothrombin time because of the deficiency of vitamin K-dependent clotting factors [1]. If not recognized and corrected, the bleeding diathesis may result in unnecessary blood loss after any invasive procedure. Vitamin K deficiency is simple to diagnose; an elevated prothrombin time that is corrected by administration of vitamin K suffices.

Patients with obstructive jaundice also may have severe weight loss and malnutrition because of their primary disease, usually malignant tumor or chronic or intermittent bouts of infection. These deficits add to the problems directly caused by obstruction of the biliary tract. Nutritional deficits are difficult to correct in patients with obstructive jaundice because these patients have hepatocellular deficits in protein synthesis, gluconeogenesis, and ketogenesis [17] (Fig. 1). Heart failure.

Cardiovascular and Renal Effects of Obstructive Jaundice

Patients with obstructive jaundice are particularly prone to renal failure, especially after operative procedures [3, 4, 12, 16, 27]. Examination of kidneys from jaundiced patients with renal failure reveals pathologic findings of acute tubular necrosis indistinguishable from those observed in patients with hypotension and low renal blood flow from other causes [15, 28]. These pathologic lesions suggest that biliary obstruction causes systemic effects that decrease renal blood flow. Therefore, the kidneys are more susceptible to further injury. Studies with animals [3, 16, 29–32] have shown that bile duct obstruction initially induces profound diuresis, as bile salts and products of hepatic metabolism are excreted by the kidneys. The diuresis leads to significant depletion of both intravascular and extravascular volumes [16, 29, 31, 33, 34]. As with hypovolemia from any cause, renal blood flow decreases. Later, cardiovascular function is depressed [10, 31, 35–39], and responsiveness to the vasoactive substances angiotensin II and norepinephrine is blunted [35, 36]. The combination of hypovolemia and impaired cardiovascular function leads to systemic hypotension and further injury of the kidneys. The factors that mediate systemic alterations have not yet been fully identified, but evidence [9, 10, 40–42] indicates that increased plasma and tissue levels of bile salts contribute in part to abnormal renal as well as cardiovascular function (Fig. 1).
Evidence also implicates endotoxemia in the pathogenesis of renal failure in jaundiced patients [43]. In addition to the endotoxemia associated with overt sepsis, jaundiced patients without bacterial infection have elevated concentrations of endotoxin in their blood. Bile salts in the intestine normally prevent bacterial overgrowth and bind endotoxin in the intestinal lumen, preventing its absorption and subsequent portal endotoxemia. With obstructive jaundice, the absence of bile results in both increased growth of the intestinal flora and absorption of endotoxin; liver dysfunction allows increased spillover into the systemic circulation [43]. Endotoxin absorbed from the intestine and entering the systemic circulation then may cause low-grade intravascular coagulation and renal vasocostriction [44], both of which contribute to the development of renal failure.

It is important to recognize fluid and cardiovascular deficits in jaundiced patients (Fig. 1). Both affect a patient’s ability to respond to anesthetic and operative stresses, to blood loss, or to further shifts in fluid, especially when sepsis is present. Renal failure in patients with bile duct obstruction can be avoided in many instances because it is attributable primarily to a lack of renal blood flow and only partially to direct toxic effects of hepatic metabolites on the kidneys [5–8]. The deficits can be improved by correction of hypovolemia alone [5–8].

**Infectious Complications of Obstructive Jaundice**

The tendency of patients to have bacteria in their bile and to develop biliary tract infection is one of the most important effects of bile duct obstruction. The presence of bacteria in bile alone does not indicate that a patient has an infection. Colonization of bile with bacteria [45], termed bactilibia, is observed in 15% of patients undergoing elective cholecystectomy [13]. Patients who are older than 60 and who have a history of acute cholecystitis or jaundice as well as biliary-enteric anastomoses [19] are more frequently found to have bacteria in their bile, and as many as 90% of patients with obstructing stones in the bile duct [13] develop bactilibia. Therefore, obstruction of the bile duct predisposes patients to the development of bactilibia and, when bile duct pressure increases, to infectious complications.

Although the sphincter of Oddi presents a barrier to retrograde contamination of the biliary tract, it is believed that bacteria routinely ascend into the biliary tract from the intestine but are rapidly cleared from bile [45]. As bacteria can be cultured from bile from 64% of patients with partial biliary obstruction but only 10% of patients with complete biliary obstruction [45], retrograde contamination of bile may indeed be important. In addition, the prevalence of bactilibia increases in patients after sphincterotomy or biliary-enteric anastomosis and in patients treated with internal biliary drains and biliary stents, because the sphincter of Oddi is destroyed or bypassed. Alternatively, bacteria may enter bile proximally from the hepatic artery or the portal venous systems or possibly via biliary lymphatics [46, 47], explaining the colonization of bile in patients with complete biliary obstruction. Finally, bacteria now are commonly introduced into the biliary tract during invasive biliary tract procedures [5–7, 17, 18], iatrogenic colonization of the biliary tract is becoming increasingly more common as the number, type, and complexity of diagnostic and therapeutic procedures performed on the biliary system increase.

Once bacteria enter the biliary system, bile salts limit their proliferation [46], the reticuloendothelial system efficiently eliminates them from bile, and normal transit of bile through the biliary tract clears them from the ducts [13, 19, 45–48]. Bile becomes colonized with significant numbers of bacteria when defense mechanisms are compromised; acute cholangitis, or true infection in the biliary tract, develops only when bacteria invade periductal tissues and hepatic sinusoids. Bacteria in bile usually are of little consequence when bile is flowing freely through the ampulla of Vater or through an anastomosis, catheter, or stent, but cholangitis ensues rapidly when bile duct obstruction, anastomotic stricture, or catheter or stent occlusion occurs because of an increase in bile duct pressure (Fig. 1). Bacterial colonization of bile also contributes significantly to disease in patients with partial biliary stricture. Bacteria in bile deconjugate bilirubin and hydrolyze free fatty acids from phospholipids, causing the ductal sludge and stones found behind strictures [49, 50], and are largely responsible for catheter/stent malfunction [51–54].

Aerobic gram-negative organisms, usually *Escherichia coli* and *Klebsiella, Proteus*, and *Pseudomonas* species, and
gram-positive organisms, mainly *Streptococcus* and *Enterobacter* species, are isolated from bile in 90–100% of patients with acute cholangitis [55–57]; *Streptococcus faecalis* is present in up to one third of patients [56]. Two or more species are present in as many as 60% of patients [57]. Anaerobic organisms may contribute to the infection in 10–50% of patients [56–59]. In addition, in one study, bile from almost one fifth of patients also harbored a fungus of *Candida* species [56]. Fungi and *Klebsiella, Enterobacter, Streptococcus*, and *Pseudomonas* species are cultured more commonly from bile from patients with malignant bile duct obstruction and from patients who are immunosuppressed, who have diabetes, or who have undergone recent treatment with antibiotics [56, 60].

Acute cholangitis refers to bacterial and sometimes fungal or parasitic infections of the biliary system that are characterized by fever, chills, pain in the right upper region of the abdomen, and jaundice. Acute cholangitis has a wide range of manifestations, from a mild illness, often mistaken for a number of other upper abdominal maladies, to life-threatening sepsis. Signs and symptoms are unreliable for predicting outcome. All patients are in danger of dying if the disease progresses, and prompt diagnosis and treatment are critical for all patients if morbidity and mortality are to be minimized.

Pain in the right upper quadrant of the abdomen, jaundice, and fever, referred to as Charcot’s triad [61], are the classic signs and symptoms of acute cholangitis. However, the entire triad is present in fewer than 60% of patients with acute cholangitis [20, 33, 55, 62]. Reynolds and Dargan [63] observed that patients with acute cholangitis have confusion and hypotension when sepsis complicates the illness. Reynolds’ pentad [63] refers to the presence of Charcot’s triad plus confusion and hypotension. It is characteristic of toxic cholangitis. Although Charcot’s triad and Reynolds’ pentad are specific for acute cholangitis and toxic cholangitis, respectively, many patients do not exhibit all of the characteristic findings, and the diagnosis of acute cholangitis must be considered for any patient with one or more of the five signs or symptoms of cholangitis.

As expected with a bacterial illness, intermittent fever and chills are the most common signs of cholangitis. A history of fever and chills or an elevated temperature is a feature of presentation in as many as 90% of patients [20, 33, 55, 62]. Jaundice and abdominal pain, but not significant abdominal tenderness, are also important findings but are present in only one third to three quarters of patients [19, 20, 33]. The WBC count frequently is elevated, and the differential count shows increased numbers of immature forms, but it can be depressed in patients with sepsis. Results of liver function tests, including serum levels of bilirubin, are almost always abnormal, but one fifth of patients have bilirubin concentrations lower than 2 mg/dl [20, 33, 55]. Serum bilirubin concentrations lower than 4–5 mg/dl are more likely to be associated with a benign cause of cholangitis, whereas high serum bilirubin levels (and weight loss) suggest a malignant tumor. Damage to ductal cells and hepatocytes elevates the serum levels of alkaline phosphatase and transaminases in up to 90% of patients [20, 33]. Blood and bile cultures are essential because they can reliably identify the organism responsible for the infection.

**Adverse Effects of Obstructive Jaundice: Implications for Treatment of Patients**

Adequate preparation of patients with obstructive jaundice before invasive procedures is imperative. Patients should be evaluated for signs of hypovolemia; a complete blood count and a platelet count should be obtained; and serum electrolyte, blood urea nitrogen, and creatinine levels, prothrombin time, and partial prothrombin time should be measured. Intake and output should be monitored during every hospital shift, with special attention to urinary output. Invasive procedures should not be performed until fluid and electrolyte deficiencies and coagulopathies have been corrected. When coagulation defects are present, they should be corrected before invasive procedures are carried out. If time permits, coagulopathy can be corrected with intramuscular vitamin K (1–10 mg); urgent correction requires the IV administration of fresh frozen plasma. However, vitamin K cannot correct coagulopathy late in the course of biliary obstruction, when liver failure is present. When synthetic function is lost, deficiencies of other clotting factors not dependent on vitamin K, including fibrinogen, also are present. IV fresh frozen plasma and cryoprecipitate are required under these circumstances, but the effects will be transient unless liver function improves.

Patients with long-term obstruction may have significant vitamin deficiencies that can be avoided with proper long-term management. Fat malabsorption and steatorrhea are avoided in patients with chronic cholestasis by restriction of neutral fat intake to 40 g/day and administration of medium-chain fatty acids, which are well absorbed by the intestine in the absence of bile salts. Vitamin K deficiency can be avoided by giving 10 mg of vitamin K monthly [1]. Vitamin A (100,000 IU) and vitamin D (100,000 IU) are required monthly [1]. Patients also may require oral calcium supplementation with low-fat dairy products or oral calcium preparations.

Fortunately, correction of volume deficits in patients with bile duct obstruction corrects intravascular deficits, decreases the propensity for the development of hypotension, increases renal blood flow, maintains urine output for the excretion of hepatic metabolites, and decreases circulating concentrations of toxic substances [5–7, 18]. If sepsis is avoided and volume deficits are promptly corrected, then systemic effects of biliary obstruction are minimized. Results of preoperative correction of fluid and electrolyte deficits have been demonstrated in randomized, prospective studies [5–7]. When patients were prepared properly before invasive studies and surgery, routine percutaneous drainage of the bile duct to relieve obstruction in patients with serum levels of bilirubin lower than 20 mg/dl added no advantage [5, 6]. In one study, routine preoperative percutaneous drainage actually slightly increased mortality [7]. However, percutaneous drainage can effectively stabilize critically ill patients, allowing correction of fluid and electrolyte imbalances and coagulopathies [64, 65].

Patients with obstructive jaundice are at high risk for infectious complications after invasive procedures are performed on the biliary tract, because they often have bacteria in their bile. These bacteria gain access to perihepatic and periductal tissues during the procedure when bile duct pressure is increased or when biliary epithelium is damaged by
guidewires, catheters, stents, or surgical manipulation. Complications are minimized by use of prophylactic antibiotics [56, 66] and by normalization of bile duct pressure after the procedure.

The antibiotics useful for prophylaxis are the same as those used to treat cholangitis, but they must be given at least 30 min before the procedure. In the past, ampicillin and an aminoglycoside were the regimen of choice, but resistant strains of Klebsiella and Enterobacter species have been reported [13], and aminoglycosides are nephrotoxic [67]. The broad-spectrum cephalosporins are effective in treating biliary tract infections but are less active against staphylococci and S. faecalis [56]. Ampicillin is required to treat these organisms. Methicillin, a ureidopenicillin, is more effective than ampicillin and an aminoglycoside, but it is not effective against Pseudomonas species [66]. The spectrum of piperacillin is similar to that of methicillin, but piperacillin is effective against Pseudomonas aeruginosa. In a randomized study, piperacillin was as effective as ampicillin plus tobramycin but was less nephrotoxic [56], making it the currently preferred antibiotic for treating patients who have cholangitis and who do not have a penicillin allergy.

When percutaneous transhepatic and endoscopic retrograde cholangiography are done, it is important to limit the pressure used to inject the contrast material. Rapid, high-pressure injection can elevate bile duct pressure and damage biliary epithelium, predisposing the patient to cholangitis. In addition, even careful injection of contrast material into an obstructed duct can induce a bout of cholangitis by increasing already abnormal bile duct pressure. The prevalence of postprocedural cholangitis can be decreased by instituting external biliary drainage after the procedure, usually by establishing percutaneous transhepatic drainage after percutaneous cholangiography [64, 65, 68] or nasobiliary drainage after endoscopic cholangiography [33, 69–71].

Once a diagnosis is established, the underlying problem in the biliary tract should be promptly corrected and the free flow of bile should be established to avoid further consequences of biliary obstruction, including serious episodes of cholangitis. These goals usually are accomplished by removal of ductal stones or by creation of an anastomosis between the bile duct and the intestine to bypass benign or malignant strictures. When these options are not possible, drainage of the biliary system with external biliary catheters and internal stents is useful in ameliorating symptoms, but long-term indwelling catheters and stents in the biliary tract are prone to occlusion, with subsequent episodes of cholangitis [51–54]. Episodes of occlusion of indwelling catheters seem to be less frequent with the recently introduced expandable stents [51–54].

An understanding of the pathophysiology and adverse effects of biliary obstruction is most important for patients with cholangitis that does not improve with medical therapy or already is associated with septic shock. Decompression of the bile duct with a decrease in ductal pressure may be lifesaving. In the past, only a major surgical procedure was available for these critically ill, unstable patients, and morbidity and mortality were high [72]. Currently, emergent surgery usually is avoided because the biliary tract can be effectively and safely decompressed with other, less invasive procedures. Definitive surgical procedures, when indicated, now are most often performed later, under elective conditions.

Pessa et al. [65] established the effectiveness of percutaneous transhepatic drainage by showing that 39 of 42 patients with acute cholangitis improved. Two patients (5%) died, and complications of the procedure occurred in 7% of patients [65]. Likewise, Chen et al. [64] noted a good response in 82% of patients who had severe cholangitis and who were treated with percutaneous transhepatic drainage, but 21% had a complication from the procedure. Several complications, including hemobilia, intraabdominal hemorrhage, transient hypotension, bile leak, pneumothorax, and hemothorax, were significant and led to emergent laparotomy in four patients [64]. Moreover, percutaneous transhepatic drainage did not significantly decrease mortality and morbidity from subsequent surgical procedures [65]. Percutaneous transhepatic drainage is effective for stabilizing patients with toxic cholangitis [64, 65] and can be effective for patients who cannot be treated successfully with endoscopic methods.

On the other hand, elective endoscopic treatment of biliary obstruction is effective and safe when performed by experienced endoscopists. Leese et al. [73] compared endoscopic sphincterotomy done early in the course of acute cholangitis with medical therapy alone and with operative therapy. The mortality rate of 5% with early endoscopic sphincterotomy was considerably lower than the mortality rate of 36% for patients treated medically. Mortality ranged from 17% to 50% for patients treated surgically; the highest rate was observed for patients who had had a previous cholecystectomy. Endoscopic sphincterotomy, like percutaneous transhepatic drainage, had a high complication rate (28%), but the authors thought that this rate was acceptable in comparison with the 58% complication rate observed for patients treated surgically.

More recently, Lai et al. [33, 69, 74–76] and others [70, 71] have shown the safety and efficacy of nasobiliary drainage with a 7-French catheter and a small (<0.5-cm) papillotomy for the treatment of acute cholangitis. No attempt is made to extract stones. Eighty-two patients with severe acute cholangitis were randomized to surgical decompression of the duct or endoscopic nasobiliary drainage followed by later definitive treatment [33]. Endoscopically treated patients had fewer complications (34% vs 66%) and lower mortality (10% vs 32%) than did patients treated initially by surgery. Endoscopic management of acute cholangitis that does not respond to medical therapy now appears to be the method of choice and should reduce the high morbidity and mortality of this disease [33].

Emergent surgical decompression of the biliary tract is now reserved for patients who do not respond to other procedures, because urgent operation on patients with acute cholangitis is associated with mortality rates ranging from 21% to 40% [72, 77, 78]. For critically ill patients, the operation should be limited to a choledochotomy to decompress the tense duct, removal of obvious stones, gentle irrigation of the duct to clear it of pus, and placement of a T tube. Choledocholithotomy may be done for selected patients who have choledocholithiasis and whose condition is stabilized after the duct is opened.
In summary, patients with obstruction of the bile duct may develop nutritional deficits, impairment of cardiovascular and renal function, and infectious complications that have an impact on their outcomes. The best outcomes occur when bile duct obstruction and its cause are recognized and corrected early, before complications develop. However, problems such as coagulopathy, volume deficits, and bactibilia can be insidious and can lead to significant problems after the invasive procedures currently used to diagnose and treat bile duct obstruction. An appreciation of the pathophysiology of obstruction of the extrahepatic bile duct and appropriate preparation of the patient before invasive procedures are essential if morbidity and mortality are to be minimized in patients with obstructive jaundice.

REFERENCES


Anesthetic considerations during liver surgery

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Recent advances in surgical and anesthetic management have reduced the operative risk of major hepatectomies significantly. Although these advances have been multifactorial, anesthetic approaches derived from liver transplantation have had a major impact in our own practice and given us greater capacity to perform complex resections safely. We have been liberal in the use of vascular isolation techniques to prevent hemorrhage in our approach to liver surgery, a modification that mandates a high level of anesthetic expertise to manage complex liver cases [1].

Understanding the underlying pathological conditions of liver disease and the physiology of vascular exclusion and surgical resection has significantly contributed to goal-oriented anesthetic management. The recognition of the importance of expert anesthetic management for liver surgery has led to the formation of anesthesiology teams dedicated to liver surgery and transplantation in most major institutions.

Preoperative considerations

Our experience with hepatectomy over nearly 2 decades has spanned a broad range of clinical scenarios, ranging from the healthy living donor to the patient with advanced cirrhosis undergoing local excision of a malignancy. The preoperative assessment is tailored to accommodate the clinical
needs of the patient, estimating the need for invasive monitoring based on
the extent of resection and the general health of the patient. Otherwise
healthy individuals presenting for even extensive liver surgery need no
additional work-up other than routine preoperative laboratories, which
include a complete blood count, serum chemistries, and plasma coagulation
studies. Increasingly, patients with significant comorbidities are scheduled
for major liver resections. Assessing the functional status of these patients is
often a significant challenge, as very few tests are available to assess with
adequate predictive power the hemodynamic, respiratory, and hepatic
reserve in this population.

Cardiac evaluation

Routine liver resections without major vascular exclusion represent
a mild-to-moderate hemodynamic challenge, and should be well tolerated by
all but those with marginal or unstable cardiac status. Major vascular
exclusion is always a possibility when extensive liver resection is planned,
however, and the hemodynamic consequences can only be handled with
unrestricted cardiac function and pulmonary circulation. We prefer exercise
or pharmacologic stress echocardiography for the preoperative assessment
of the cardiac status of our patients. This test informs us about the
contractile reserve of the myocardium, the mechanics of flow through the
cardiac valves and chambers, and the status of the pulmonary circulation at
rest and under duress. When limitations in cardiac function or reserve are
found, adjustments in surgical approach and anesthetic management can be
planned before surgery. In these cases, it is extremely important that the
surgical and anesthetic teams discuss and agree on an intraoperative plan.

Pulmonary evaluation

Room air-oxygen saturation measured using pulse oximetry may give
early indication of impaired pulmonary gas exchange or inadequate
ventilatory reserve [2]. Using cutoff values of 97% and 94% identifies
patients with an arterial $pO_2$ below 70 mmHg and 60 mmHg, respectively.
Should an abnormal value be found during preoperative assessment,
detailed arterial blood gas analysis and pulmonary function tests may
become warranted. Approximately one third of patients with cirrhosis or
noncirrhotic portal hypertension present with varying degrees of hepatopulmonary syndrome. The mild hypoxemia in these patients is due to
ventilation/perfusion mismatching, characterized by an increase in pulmo-
mary perfusion secondary to capillary distension, impaired hypoxic
pulmonary vasoconstriction, and accelerated transpulmonary blood flow
with unchanged alveolar ventilation [3]. Increasing cardiac output with the
progression of cirrhosis worsens the diffusion impairment and hypoxia.
Although hypoxemia in hepatopulmonary syndrome is initially responsive
to supplemental oxygen, as the disease advances major intrapulmonary
shunting develops that is refractory to oxygen therapy. Clinical signs like platypnea (dyspnea induced by the upright position), finger clubbing, and spider nevi are characteristic, and strongly suggestive of the presence of hepatopulmonary syndrome. Contrast-enhanced echocardiography was found to be the most sensitive noninvasive diagnostic tool for demonstrating the presence of intrapulmonary vascular dilatations [4]; however, it does not quantify the extent of shunting, nor does it differentiate between vascular dilatations and direct arteriovenous anastomoses.

Hepatic reserve

Hepatic cirrhosis limits the ability of the liver to regenerate. Fortunately, it appears that all but the most advanced cirrhotic livers can tolerate even major resections, and the presence of cirrhosis should not preclude potentially curative or life-prolonging surgery [5]. These patients may be more vulnerable to perioperative insults secondary to ischemia and hypoperfusion, which is reflected in the increased perioperative morbidity and mortality of this population [6]. Patients presenting with obstructive jaundice or for emergency liver resection, whether traumatic or infectious in origin, have the highest perioperative morbidity and mortality [6].

Intraoperative management

Induction and monitoring

Liver resections are performed under general anesthesia with endotracheal intubation and controlled ventilation. Patients presenting with significant ascites or other risk factors for regurgitation of stomach contents undergo rapid sequence induction to secure the airway; otherwise the anesthetic induction is adapted to the general condition of the patient. Maintenance of anesthesia is achieved using a halogenated volatile agent (most commonly isoflurane, which is a potent peripheral vasodilator with relatively mild cardiodepressive effects) in an air-oxygen mixture, supplemented with an intravenous narcotic. At least two large-bore intravenous cannulas are inserted, usually following induction of anesthesia. Although rapid infusion devices are seldom needed, they are available and primed in the operating room area at all times. The large operative field exposure necessary for liver resections is associated with significant heat losses. Hypothermia inhibits the enzymes of the coagulation cascade [7] and contributes to intraoperative blood loss. To counteract these losses, anesthetic gases are passed through a large-capacity heat-moisture exchanger, all fluids administered to the patient are warmed, and forced warm-air devices are applied to the upper and lower parts of the body.

Intraoperative monitoring is adapted to the preoperative condition of the patient, the extent of the liver resection, and the anticipated amount of
blood loss. For healthy patients with expected blood loss below 1000 mL one can use routine monitoring only: EKG, pulse oximetry, noninvasive blood pressure, and capnometry. An arterial line is inserted when repeat blood sampling is anticipated, or as part of extended hemodynamic monitoring. A large-bore central venous line is used for prolonged procedures with the potential for significant blood loss. Pulmonary artery catheterization is reserved for patients with known preoperative left-ventricular dysfunction, anticipated prolonged major vascular exclusion (eg, vena cava resection and reconstruction), or preoperative sepsis. We use point-of-care blood gas, chemistry, and coagulation analysis to detect and correct intraoperative anemia, acid-base, electrolyte, and coagulation disturbances.

**Fluid management**

In our practice colloids—5% albumin and hetastarch in a balanced salt solution—are used as maintenance and replacement fluid, and intraoperative use of crystalloid solutions is limited to a minimum. The use of colloid rather than crystalloid as maintenance fluid reduces extravascular translocation of fluids, which results in less bowel edema, improved mesenteric perfusion, and more rapid restoration of postvascular function. Fresh-frozen plasma is used as maintenance fluid in patients who are coagulopathic and require correction of their coagulopathy. Red cells are not transfused unless the hematocrit falls below 25%, except in patients with known coronary or cerebrovascular disease. Adequate volume status almost always results in satisfactory systemic blood pressure. In some cirrhotic patients, however, the vasculature acts as a fluid sump, and vasodilation and reduced sympathetic drive secondary to general anesthesia may result in inadequate peripheral perfusion pressures. Judicious use of vasopressin (2-5 U/hour) or a combination of vasopressin and norepinephrine is used to restore peripheral vascular resistance and systemic blood pressure in these patients, always keeping in mind the primary importance of avoiding undesired hypovolemia.

**Blood transfusion and conservation**

Major liver resections may result in significant blood loss, necessitating transfusion of red blood cells in about 25% to 30% of patients [8]. For example, healthy donors undergoing right hepatectomies are expected to lose about 600 mL to 900 mL of blood on average [9]. In our own series of living donor hepatectomies, blood loss has ranged from $294 \pm 145$ mL for left lateral hepatectomy to $583 \pm 277$ mL for right hepatectomy [10]. The presence of a preoperative coagulopathy, malignancy, and the extent of resection were the only predictors consistently found to correlate with the need for intraoperative blood transfusion. Transfusion requirements for
liver resections are quite unpredictable, however, and when blood transfusion is required, the mean volume of packed red blood cells is relatively high [11]. This makes, at least in our opinion, preoperative autologous blood donation ineffective and costly. Chronically ill patients are often already anemic and are poor candidates for autologous blood donation, whereas healthier patients, who are good candidates for autologous blood donation, tolerate blood loss well. The use of intraoperative blood recovery systems further reduces the need for autologous blood donation. In liver resections for malignancy, blood recovery systems are usually avoided, due to the concern of hematogenous spread [12].

The use of antifibrinolytic agents has been promoted in operations with major blood loss. In a randomized, controlled trial “full-dose” aprotinin (2*10^6 KIU load followed by 5*10^5 KIU/hour infusion) was found to reduce intraoperative blood loss by about 25% and transfusion requirements by half, without any thrombotic or thromboembolic complications [13]; however, the average blood loss, even in the aprotinin group in this study, was two times the pretest estimate, based on average blood loss for the same operation in the same institution (1200 mL versus 600 mL). Aminocaproic acid and tranexamic acid have not been studied in the context of liver resection surgery. Limited experience with their use in liver transplantation has yielded equivocal results so far [14]. In our practice, we often use intraoperative “half-dose” aprotinin (10^6 KIU load followed by 2.5*10^5 KIU/hour infusion) during hepatic transplantation in patients who have a significant coagulopathy or portal hypertension, as well as in those who have had previous abdominal surgery.

Hemodynamic manipulation

Intraoperative hemodynamic management is dictated by the surgical approach. Keeping the central venous pressure (CVP) low, that is between 2 mmHg and 5 mmHg, limits the distention of hepatic veins and sinusoids and was shown repeatedly to reduce blood loss during liver surgery [15,16]. This approach necessitates the placement of a central venous line, and restricts fluid administration during induction of anesthesia and hepatic resection to a minimum. Intravenous nitroglycerine is used to reduce the CVP to the target range if fluid restriction alone is ineffective [17]. Once the resection is completed and hemostasis is achieved, euvolemia is restored by fluid expansion, using crystalloid or colloid. The low-CVP approach exposes the patient to the risks of intraoperative hypovolemia, with potentially inadequate organ perfusion, and insufficient volume reserves, should a sudden unexpected intraoperative hemorrhage occur. Although there is no prospective, randomized trial to date addressing the relative risks and benefits of low-CVP anesthesia during liver resection, the incidence of perioperative renal failure has not been found to increase significantly when compared with historical controls [15].
As we seldom monitor central venous pressure during routine liver resection at our institution, fluid therapy is adjusted to maintain urine output at 0.5-1cc/kg/hr and to the extent of blood loss. When the resection is planned without vascular occlusion or with occlusion of the vessels of the portal triad only, we limit intravenous fluid administration prior to and during the resection, while maintaining hemodynamic stability and adequate (> 0.5 mL/kg/hr) urine output. The use of nitroglycerine is limited to the resection phase, when distension of the liver or excessive oozing of the resection surface is observed. Using this approach, our blood loss and intraoperative blood transfusion rate is comparable to or less than those reported for low CVP anesthesia. In patients undergoing extensive liver resections, where there is a high likelihood of vascular exclusion, a large-bore CVP line is placed from which a CVP can be monitored. If the anesthesia/surgical team feels that the information gained by measuring the CVP is necessary to guide fluid management, one should be placed to aid in fluid and hemodynamic manipulation.

When a major hepatectomy using total vascular exclusion is planned, anesthetic management is adjusted to anticipate the reduction in venous return, sudden decrease in cardiac output, and increase in afterload associated with cross-clamping of the inferior vena cava and portal vein [1]. Although pulmonary artery pressure monitoring is perhaps not necessary for successful management of routine cases with major vascular occlusion, it is often performed for the benefit of a more detailed assessment of intravascular volume status and cardiovascular response to cross-clamping. Furthermore, should a catastrophic hemorrhage from injury to the inferior vena cava occur, a pulmonary artery catheter will allow administration of a vasopressor agent beyond the site of the injury, to maintain adequate organ perfusion until control over the site of the injury is achieved. Volume expansion to a CVP of at least 14 mmHg allows cross-clamping of the inferior vena cava in most patients, while maintaining adequate circulation and blood pressure. Should the patient not tolerate cross-clamping after volume loading alone, pressors (vasopressin or norepinephrine) are added. If hypotension persists, veno-venous bypass using axillary or right atrial cannulation can be established to improve hemodynamics, or, if possible, the surgical plan is modified to avoid total vascular occlusion. Augmentation of renal function with an infusion of furosemide, dopamine, or mannitol is decided on an individual basis and is not used routinely.

Vascular exclusion

Temporary occlusion of hilar vessels is commonly used to reduce blood loss. For more extended resections, intra- or extrahepatic control of hepatic veins may also be necessary. Cross-clamping of the hepatic artery and the portal vein results in hepatic ischemia. It is believed that a healthy human...
liver can tolerate ischemia for up to 90 minutes. This time is reduced to about 30 minutes when significant cirrhosis is present [18]. Our own experience indicates that carefully selected patients with cirrhosis can tolerate planned hepatic clamping to ensure safe hepatectomy [19].

Portal triad clamping increases systemic vascular resistance by up to 40% and reduces cardiac output by 10%. The net effect on mean arterial blood pressure is an increase of about 15% (Fig. 1) [20]. Plasma vasopressin, epinephrine, and norepinephrine levels are significantly increased, whereas plasma renin activity remains unchanged following portal triad clamping [20]. Afferent discharges of sympathetic nerve fibers originating in the hepatic pedicle are responsible for these changes, as these hemodynamic and neurohumoral responses are prevented by infiltration of the hepatic pedicle with local anesthetics before clamping [21]. Following the release of the clamp, systemic vascular resistance, cardiac index, and heart rate increase, whereas mean arterial pressure and central venous pressure remain unchanged [22]. Indocyanine green clearance, an indicator of hepatic metabolic function, decreases following portal triad clamping, but returns close to the preoperative value toward the end of surgery [23]. Hepatic vascular exclusion combines portal vessel clamping with occlusion of the supra- and infrahepatic inferior vena cava. This intervention produces more profound hemodynamic changes than portal clamping alone. Although systemic vascular resistance and heart rate increase, the cardiac index is

![Fig. 1. Characteristic changes in heart rate, mean arterial blood pressure, cardiac index, and systemic vascular resistance following portal triad clamping (PTC) or hepatic vascular exclusion (HVE).](image-url)
reduced by half secondary to a steep reduction in preload (see Fig. 1) [24]. In our experience, it is characteristic for the CVP and pulmonary artery diastolic pressure to decrease from the mid teens to low single-digit numbers. As with portal triad clamping, serum vasopressin, epinephrine, and norepinephrine levels increase after hepatic vascular exclusion, but serum renin activity remains unchanged [24]. The elevated blood hormonal concentrations rapidly return to baseline following unclamping. Unclamping is also followed by an increase in cardiac index, normalization of cardiac filling pressures, and a significant reduction in systemic vascular resistance.

In preparation for total vascular occlusion, we often volume load with 500 mL colloid; that is, 5% albumin, hetastarch, or fresh frozen plasmas (FFP) if indicated. Some patients require blood pressure support with pressors if volume loading alone is inadequate. Most patients tolerate hepatic vascular occlusion with a mild-to-moderate reduction in the mean arterial pressure. Should the mean arterial pressure drop precipitously following clamping and show no tendency of recovery with rapid fluid loading and pressor support, the clamps should be released, and an alternate mode of circulatory support such as veno-venous or veno-atrial bypass must be considered.

Renal preservation

Understanding renal physiology and alterations in renal blood flow and function caused by liver disease, general anesthesia, and major liver surgery are necessary to maintain adequate renal function throughout the perioperative period. Renal autoregulation effectively ceases below renal perfusion pressures of 70 mmHg to 75 mmHg, below which flow becomes pressure dependent. In cirrhotic patients, the concomitant sympathetic activation results in a rightward shift of the autoregulation curve; thus these patients have even less tolerance of reductions in renal perfusion pressure [25]. Anesthetic agents reduce cardiac output and often cause vasodilation, resulting in a further reduction of renal blood flow. Redistribution, sequestration, and loss of extracellular and intravascular fluids are commonly associated with major surgery. The anesthesiologist has to maintain both adequate renal perfusion pressure and flow throughout the entire case to prevent renal impairment. It is no easy task: 3% of patients experience permanent and 10% transient renal dysfunction following major liver surgery [15].

Postoperative care

Approximately 20% of otherwise healthy patients may experience postoperative complications after elective liver resections [6]. The most frequent of these are pulmonary infection and abdominal abscesses, both usually responsive to antibiotic therapy. Less frequent but more significant complications include postoperative hemorrhage necessitating
re-exploration, hepatic, and renal failure. Preoperative American Society of Anesthesiologists (ASA) classification, presence of steatosis, extent of resection, simultaneous extrahepatic resection [6], and perioperative blood transfusion [26] have been found to be independent predictors for the development of postoperative complications. In-hospital mortality following liver resection has been associated with perioperative myocardial infarction, sepsis with multiple organ failure, pulmonary embolism, and duodenal ulcer perforation [6,26]. Extravascular lung-water accumulation, indicating mild-to-moderate pulmonary edema following liver resection, has been reported; however, this does not appear to affect oxygenation significantly in the postoperative period [23]. Postoperative hepatic failure remains a significant challenge. Although low residual liver volume was found to be associated with postoperative liver failure, the regenerative ability of the liver is remarkable, and the residual, otherwise healthy liver is expected to double in size within the first week following the resection. A hyperdynamic state with increased cardiac index and augmented splanchnic blood flow persists for at least 3 days postoperatively [23]. This increased blood supply to the residual liver parenchyma ensures rapid growth. Increase in hepatic parenchymal mass does not necessarily result in full restoration of functional ability. Even when clinical parameters such as the coagulation profile return to normal, more sensitive tests such as indocyanine green clearance may remain below the baseline value 5 days after major hepatic resections [22]. Pre-existing cirrhosis or positive virus carrier status limits liver regeneration, and these patients are more susceptible to developing postoperative hepatic failure. The ability of the liver to regenerate is also reduced in diabetic patients, who have an increased incidence of postoperative hepatic failure following extensive resections [27].

Transient renal dysfunction is common in the postoperative period. Maintaining normovolemia and adequate renal perfusion pressure minimizes this risk. There is little, if any, benefit from routine use of low-dose dopamine and diuretic infusions to support renal function. Dopexamine, a dopamine-2 receptor agonist, is gaining popularity as a selective renal vasodilator; however, its renoprotective role remains to be proven. In cases of acute oliguric renal failure, continuous hemofiltration or intermittent hemodialysis may be necessary until renal function improves [25].

Postoperative pain following liver surgery is significant, and adequate analgesia remains a challenge for the caregivers. Neuraxial anesthesia has severe limitations in liver surgery. Many patients presenting for hepatic surgery have a coagulopathy or thrombocytopenia that makes them ineligible for an epidural or intrathecal therapy. Epidural catheter placement has been studied in a group of patients undergoing liver surgery, and the postoperative prolongation in prothrombin time delayed catheter removal in 9% of patients who had three or more segments resected [28]. Although we have no knowledge of any reports of spinal hematoma following epidural catheter placement in patients after liver surgery, the prolongation of prothrombin time potentially predisposes these patients to spinal hematoma.
formation and cord compression. Thus we use epidural catheters only in selected patients, undergoing limited resections with normal coagulation status and good hepatic function. Intrathecal morphine in doses of 0.5 mg to 0.7 mg is used as an alternative in almost all patients who have no underlying coagulopathy or thrombocytopenia. This significantly reduces systemic morphine requirements postoperatively, without increasing the risk of neurological complications. Patients who do not qualify for intrathecal morphine administration receive preoperative coaching in the use of a patient-controlled analgesia device.

Summary

This article demonstrates the broad range of considerations that affect the outcome of patients undergoing hepatectomy. The progressive improvements in survival, despite the increasing complexity of the surgery, are a testament to advances in both surgery and anesthesia. The key elements include careful patient selection, appropriate monitoring, and mechanical and pharmacologic protection of the liver and other vital organs.

References


Assessing liver function

Samir G. Sakka

Purpose of review
This is a review on the techniques for assessing liver function in critically ill patients.

Recent findings
Actually, there is no ideal real-time and bedside technique for assessing liver function in critically ill patients. Though not allowing to differentiate between liver blood flow and cell function, dynamic tests, that is indocyanine green plasma disappearance rate and lidocaine metabolism (monoethylglycinxylidide test), are superior, however, to static tests. Recently, the indocyanine green plasma disappearance rate, which nowadays can be measured reliably by a transcutaneous system in critically ill patients, was confirmed to correlate well with indocyanine green clearance. In general, the indocyanine green plasma disappearance rate is superior to bilirubin, which is still used as a marker of liver function, and comparable or even superior to complex intensive care scoring systems in terms of outcome prediction. Furthermore, indocyanine green plasma disappearance rate is more sensitive than serum enzyme tests for assessing liver dysfunction and early improvement in the indocyanine green plasma disappearance rate after onset of septic shock is associated with better outcome.

Summary
Since no ideal tool is currently available, dynamic tests such as indocyanine green plasma disappearance rate and monoethylglycinxylidide test may be recommended for assessing liver function in critically ill patients. The indocyanine green plasma disappearance rate has the advantage, however, of being measurable noninvasively at the bedside and providing results within a few minutes.

Keywords
critical care medicine, liver function, monitoring

Abbreviations
ALAT alanine aminotransferase
BSP bromosulfophthalein
CPB cardiopulmonary bypass
CYP cytochrome P450
GEC galactose elimination capacity
ICG indocyanine green
ICG-PDR indocyanine green plasma disappearance rate
MEGX monoethylglycinxylidide

Introduction
Acute liver failure is frequently encountered in critically ill patients and still associated with a high mortality. Thus appropriate and clinically practicable tests are required to adequately follow liver function. Unfortunately, on-line monitoring of liver function at the bedside is not available. This review will present and discuss tests for clinical assessment of liver function, with particular emphasis on application in the intensive care scenario. Finally, some practical considerations in terms of indications for liver function monitoring and aspects of therapeutic guidance will also be mentioned.

Static and dynamic tests
Traditionally, assessment of liver function and injury is based on static tests, such as serum activities of liver enzymes, protein synthesis of the liver (i.e. coagulation factors, albumin) and bilirubin. Dynamic assessment of complex liver functions, that is clearance of substances (e.g. indocyanine green; ICG) or formation of metabolites (e.g. lidocaine to monoethylglycinxylidide (MEGX) or 14C-aminopyrine), however, has been shown to reveal otherwise hidden hepatocellular dysfunction [1]. An overview on the different tests for assessing liver function as mentioned in this paper is provided in Fig. 1.

Static tests
Several tests have been named static since these tests merely allow a spot check and a very restricted description of liver function. These tests are limited by the fact that they do not enable tracking changes in liver function quickly, which may be required especially in critically ill patients.

Bilirubin
Physiologically, bilirubin is a haem product, which after hepatocellular uptake undergoes catalysis and conjugation with glucuronic acid (direct bilirubin) before being excreted into the bile. In general, hyperbilirubinaemia may be caused by prehepatic pathologies (e.g. haemolysis),
intra hepatic factors (e.g. hepatitis, liver cell injury) or posthepatic occlusion (e.g. cholestasis). The quantification of direct and indirect bilirubin in combination with liver enzyme tests may allow a differentiation between different types of jaundice. Despite its limitations, bilirubin is still widely used for clinical routine assessment of liver function and in intensive care scoring systems.

The serum activities of enzymes, which are located in hepatocytes, have been clinically used for the assessment of liver function or injury. Simplified, enzymes may reflect the extent of hepatocellular necrosis (e.g. transaminases) or cholestasis (e.g. alkaline phosphatase, or \( \gamma \)-glutamyl transferase). Alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) play an important role in amino acid metabolism by catalysing reversible transfer of the \( \alpha \)-amino group. Transaminases are expressed in varying concentrations in organs and physiologically detectable in the serum. While high activities of ALAT are present in the periportal region of the liver, ASAT is found in high concentrations in numerous other organs. In general, serum activities of transaminases are increased in various liver diseases, for example hepatitis, cirrhosis, infections, carcinoma, or alcohol abuse. Serum activities of aminotransferases, however, are only of limited prognostic value and do not reflect the extent of liver cell necrosis appropriately [2]. Further enzymes, such as glutamate dehydrogenase (GLDH), may be used for assessing hepatocellular injury. In particular, GLDH is a marker of liver cell injury in the peri-central region. Alkaline phosphatase is involved in the hydrolysis of organic phosphate esters and, though not exclusively expressed in the liver, used as a marker of cholestasis [3]. Serum activity of alkaline phosphatase is elevated in acute or chronic hepatitis, cirrhosis and intrahepatic or extrahepatic malignomas [2]. Gamma-glutamyl transferase, which is responsible for the transfer of a \( \gamma \)-glutamyl group between peptides or to an amino acid, is associated with microsomes or the cell membrane, but not only expressed in the liver. In principle, \( \gamma \)-glutamyl transferase serum activity may be increased in cholestasis, anticonvulsive therapy, and chronic alcohol abuse. In general, alkaline phosphatase and \( \gamma \)-glutamyl transferase may be useful for follow-up of liver diseases associated with cholestasis, that is, occlusive jaundice.

**Hepatocellular synthesis**

Hepatic protein synthesis may be assessed by parameters of plasmatic coagulation (prothrombin and thromboplastin time) or albumin concentration. These indicators characterize the extent of loss of functional liver cell mass, a reduced synthesis activity would result in low concentrations of coagulation factors and antithrombin. For instance, coagulation factors V (half-life 4 h) and VII (half-life 5 h) may be used. With progressive liver
insufficiency, serum activity of cholinesterase (half-life 10 days) and albumin (half-life 19–21 days) will also decrease.

Static tests are, however, inferior to dynamic tests for assessment of liver function [4–9,10*]. For instance, differentiation between histologically proven no rejection or moderate to severe rejection in transplanted livers was not possible by serum enzyme markers [4]. In contrast, ICG elimination correlated well with microscopically described liver damage after transplant [10*]. Furthermore, dynamic tests are significantly superior with respect to outcome prediction [11] and are more sensitive for assessment of liver dysfunction in critically ill patients [6].

**Dynamic tests**

In general, dynamic tests are related to the ability of the liver to metabolize or eliminate defined substances. Thus dynamic tests have the advantage of quantifying the functional status at the time point of assessment and in relatively short time intervals. All the following tests have a place in the assessment of liver function; they may, however, vary considerably with respect to different hepatic partial functions, their clinical practicability and time intensity.

**Indocyanine green clearance**

The dye ICG is an infra-red absorbing and fluorescent agent, now clinically used for more than 50 years. After intravenous injection, ICG is nearly exclusively eliminated by the bile into the bile and does not undergo enterohepatic recirculation [12]. Physiologically, ICG appears unconjugated in the bile about 8 min after injection. For determination of its elimination kinetics, 0.25–0.5 mg/kg of ICG (as sodium iodine) are injected intravenously [13]. ICG is a safe substance, as side effects are very rare (1:40,000). Since ICG contains iodine, however, it should not be used in patients with an iodine allergy or thyrotoxicosis.

In general, ICG removal from the blood depends on liver blood flow, parenchymal cellular function and biliary excretion. ICG elimination may be expressed as half-life time, blood clearance, or plasma disappearance rate (ICG-PDR). For ICG-PDR, initial concentration at time 0 is normalized to 100% and ICG-PDR is the percentage change over time (percent per minute). Today, ICG-PDR can be measured noninvasively at the bedside by a transcutaneous system [14] and results can be obtained within 6–8 min. Normal values for ICG clearance and ICG-PDR are considered to be over 700 ml/min/m² and over 18 %/min, respectively. Reproducibility of ICG-PDR measurements has been confirmed by Godje et al. [15] who reported coefficients of variation between 14.6 and 16.4%.

The prognostic value of ICG elimination kinetics in critically ill patients has been shown in several papers. In 336 patients, we [16] confirmed previous studies [17,18] that ICG-PDR is correlated with ICU survival. Survivors had a significantly higher ICG-PDR (16.5 versus 6.4%/min) as was found within different sub-populations (acute respiratory distress syndrome, sepsis, others) [16]. Mortality was extremely high for ICG-PDR under 8%/min, individuals with an ICG-PDR of 8–16%/min were in between and patients with ICG-PDR over 16%/min had no higher mortality than those with ICG-PDR over 24%/min. Noteworthy, ICG-PDR as a single parameter was of comparable or even higher prognostic value than complex scoring systems (APACHE II, SAPS II) [16]. Furthermore, ICG-PDR is superior to bilirubin in terms of outcome prediction and does indicate liver dysfunction earlier [19,20]. In patients with septic shock, failure to increase ICG-PDR within 120 h to over 5%/min was associated with poor outcome [6]. Noteworthy, ALAT and bilirubin were less sensitive for early detection of liver dysfunction. Most recently, in contrast to global haemodynamics, ICG-PDR did allow differentiation between survivors and nonsurvivors after initial resuscitation in septic patients [21]. Thus, ICG-PDR allows early and sensitive detection of liver dysfunction, which might be helpful in clinical management, for example guiding fluid therapy in patients with acute respiratory distress syndrome or pulmonary oedema (Fig. 2).

Furthermore, ICG elimination kinetics has been shown to be of particular value in the setting of liver surgery, since the extent of resection can be determined appropriately. ICG-PDR is proportional to hepatic parenchymal cellular volume as assessed by computed tomography [22]. Long-term survival after liver resection and poor prognosis was associated with high ICG retention rates [23]. Nonami et al. [7] determined several factors of liver failure, for example, serum enzyme tests, albumin, bilirubin, surgical and tumour specific factors, in patients undergoing liver resection. As a result, ICG clearance and intraoperative blood loss were the most reliable prognostic markers of liver failure that were independently correlated with survival. The ICG retention was described as the best discriminating preoperative test for evaluating hepatic functional reserve in patients with hepatocellular carcinoma before hepatectomy [24]. Ishikawa et al. [25] emphasized the value of the ICG retention rate as a significant indicator of postoperative complications and morbidity. Amongst a variety of standard liver parameters and function tests, no other preoperative test than ICG clearance was useful in determining the outcome of resection in cirrhotic patients [26]. In this study, the cut-off point for ICG clearance below which hepatic resection should not be attempted was 5.2 ml/min/kg. Recently, an ICG-PDR of under 9%/min
was described to reliably detect liver failure and as cut-off that surgery should not be performed [27].

Finally, ICG-PDR may be useful in liver transplantation. In pretransplant patients, ICG elimination and the MEGX-test (lidocaine metabolite) were of highest predictive value, independent of the underlying pathogenesis in adults and children [11]. Furthermore, poor graft function in the recipient was found in donors with low ICG-PDR [28] and an ICG-PDR under 15 %/min was associated with a higher rate of primary transplant dysfunction. ICG clearance may be helpful as an immediate and early test of graft function after liver transplantation [29–31]. Krenn et al. [30] reported a patient who developed liver failure after transplant due to complete loss in perfusion. While numerous laboratory tests remained unchanged only ICG-PDR dropped dramatically, thus enabling diagnosis rapidly. Recently, we reported a patient in whom ICG-PDR indicated a rise in liver blood flow after relief of an increased intra-abdominal pressure [32]. Finally, also extracorporeal assist by a molecular absorbing system may be guided by ICG-PDR which is an important prognostic factor for hepatic recovery and survival (>5 %/min) [33].

ICG-PDR, however, is not exclusively a marker of cell function but even more blood flow, and short-term changes in ICG-PDR probably reflect changes in blood flow rather than hepatocellular function [34]. Several studies showed that ICG-PDR responds within 1-h intervals to changes in pharmacological treatment [34–38] and prone positioning [39]. The meaning of ICG-PDR as a marker of liver cell function has been questioned recently [40]. In an animal experimental model of sepsis, liver dysfunction was found not to be reflected by ICG-PDR as hepatic blood flow and ICG-PDR remained unchanged while biliary ICG excretion dropped dramatically. ICG metabolism was not studied in detail, however, and besides other mechanisms, intracellular hepatic storage of ICG has been discussed. Independently, ICG blood clearance and ICG-PDR have been found to correlate well in critically ill patients [41]. In general, decrease in ICG-PDR may be caused by a reduction in liver blood flow or parenchymal function or by both.

In summary, ICG-PDR is currently widely regarded as a most valuable tool for bedside assessment of liver function in critically ill patients [42].

**Caffeine test**

Physiologically, caffeine is metabolized by the liver to metabolites paraxanthine, theobromine, and theophylline.
The metabolite/caffeine ratio calculated from blood samples after 4, 8, and 12 h after 300 mg caffeine orally has been suggested for evaluation of hepatic dysfunction [43]. Elimination of caffeine takes significantly longer in patients with cirrhosis than in healthy volunteers: clearance (0.035 versus 0.094 l/hour/kg) and half-life (11.4 versus 4.3 h). Furthermore, serum metabolite/caffeine ratios are lower in cirrhotic patients while caffeine clearance and metabolite/caffeine ratios are highly correlated. No data are available, however, in critically ill patients and this test requires complex laboratory equipment (high-performance liquid chromatography, HPLC). Several years ago, caffeine plasma clearance and exhalation of 14CO2 following intravenous injection of 2 μCi of 3-methyl-14C-caffeine together with 125 mg of the unlabeled compound had already been suggested [44]. Patients with cirrhosis were characterized by highly significant reduction in clearance (0.76 ± 0.40 versus 2.02 ± 0.68 ml/min/kg) and prolonged half-life time (13.7 ± 13.0 versus 3.8 ± 0.9 h) when compared to healthy volunteers. Due to a good correlation between cumulative 14CO2 excretion and disappearance constant for bromosulphophthalein (BSP), the caffeine breath test is regarded as a quantitative measure of hepatic microsomal activity. The caffeine test is limited, however, in its practicability and is therefore not commonly applied in critically ill patients.

**Bromosulphophthalein clearance**

When injected intravenously, BSP is extracted fairly rapidly and exclusively by the liver. Most commonly, 5 mg/kg of BSP is administered and serum determinations are made at 30 and 45 min. In healthy volunteers, less than 10% is retained after 30 min and under 5% after 45 min [45,46]. The BSP clearance test is superior to laboratory tests for assessment of hepatic functional reserve, but the ICG retention rate at 15 min was found as the best discriminating preoperative test in patients undergoing liver resection [47]. Conti et al. [48] reported that BSP and ICG clearances correlated more closely than the MEGX test with the overall histological score. In summary, this test which may be associated with severe systemic reactions (possibly fatal) and requires special laboratory equipment has been largely abandoned in general clinical use.

**Amino acid clearance**

The amino acid clearance test relies on the ability of the liver to eliminate amino acids from the blood. In principle, patients who were fasted overnight receive a standardized continuous intravenous amino acid infusion over 18 h. After the end of infusion, amino acid concentrations in the plasma are measured and plasma amino acid clearance rate is calculated [49]. Lau et al. [24] performed a clinical study to identify the best test for assessment of the adequacy of hepatic functional reserve in patients before hepatectomy. Each patient was evaluated before operation with the ICG clearance test, the aminopyrine breathing test and the amino acid clearance test. In this study, ICG retention rate at 15 min was significantly different between survivors and nonsurvivors. By discriminant analysis, the safety limit of ICG retention rate at 15 min for major hepatectomy was 14% and the relative risk of hospital mortality was threefold. In summary, the ICG retention rate was the best discriminating preoperative test for evaluating hepatic functional reserve when compared to both other tests. The amino acid clearance test is time consuming and despite simplification of the procedure [50] it has only negligible relevance in the intensive care scenario.

**Galactose elimination capacity**

In the liver, galactose is phosphorylated by ATP to galactose-1-phosphate before undergoing further metabolism. For instance, 0.5 g/kg 25% D-galactose is administered as a short infusion. By plotting galactose serum concentrations over time (time point 0, end of infusion) the linear part of the curve, beginning at about 15–20 min, is used to extrapolate the time when the concentration was 0. The galactose elimination capacity (GEC) is calculated using the decay of the concentration curve and results are expressed in milligrams per kilogram per minute. GEC has been found to be reduced in hepatitis and cirrhosis but not steatosis. Data in critically ill patients, however, are rare. Christensen et al. [51] reported on patients admitted to their intensive care liver unit with acute hepatic encephalopathy induced by viral hepatitis, drugs, or pregnancy. The nonsurvivors (61%) had a higher bilirubin level and lower total cholic acid conjugation and glycine cholic acid conjugation than the survivors. Both aminopyrine clearance and GEC were significantly lower in the nonsurvivors. More recently, Jochum et al. [52] compared GEC, ICG half-life, and lidocaine half-life as markers for the quality of liver regeneration after liver transplant while studying living liver donors and their corresponding recipients at baseline and after 10 and 90 days. After liver transplant, GEC decreased (−42.6%) and ICG half-life increased (+50.6%) significantly in donors. ICG half-life and GEC remained significantly altered over 3 months in donors, however, with an improvement between days 10 and 90 (ICG half-life −9.1%; GEC +59.3%). In contrast, ICG half-life and GEC improved significantly in recipients between days 10 and 90 (ICG half-life −63.7%; GEC +16.3%). Noteworthy, lidocaine half-life showed no significant changes in this study.

In patients with end-stage liver disease, the basal GEC and MEGX tests were statistically significantly different between dead/transplanted patients and survivors. Child class and Model for End-stage Liver Disease (MELD) score, however, showed a higher prognostic accuracy than GEC and MEGX both of which were not independent predictors of survival. Repeated measures analysis of
GEC and MEGX did not increase the prognostic accuracy of these tests and did not add useful prognostic information on patient outcome during the following 6 months [53°]. In summary, although of clinical value, the GEC is limited because it is potentially dangerous (galactose intolerance) and too cumbersome for application in ICU patients.

Monoethyglycinxylidide test

The MEGX test is based on the hepatic conversion of lidocaine to MEGX which is related to the cytochrome P450 (CYP) system by sequential oxidative N-dealkylation to MEGX. In detail, the isoforms CYP3A/4A are involved in these drug interactions. Like all other liver tests, the MEGX test is dependent on hepatic metabolic capacity and blood flow. In practice, blood samples for determination of MEGX prior to and 15 min after intravenous injection of lidocaine (1 mg/kg) have been suggested [54]. MEGX peak concentration, however, may be missed by this approach since increased concentrations have been measured at 30 min after injection [55].

Quantification of MEGX serum concentration requires immunoassays, HPLC or gas liquid chromatography. Like ICG-PDR, the MEGX test may be used during liver surgery, since a relationship between the percentage remnant liver volume and the ratio of postoperative MEGX concentration was described [56]. Conti et al. [48] reported that MEGX values correlated negatively with ALAT activity and with the overall histological score and BSP and ICG clearances. A MEGX concentration of 25 ng/ml, however, had the highest prognostic properties with respect to 1-year survival in comparison to static tests or the Child classification in patients with liver cirrhosis [57]. An ICG half-life time of 20 min and MEGX under 10 µg/ml were comparable in separating nonsurvivors from survivors in pretransplant patients [57]. In critically ill patients, Schrotter [58] showed that median MEGX concentration on the fourth day after ICU admission was 23 ng/ml in nonsurvivors and significantly higher (53 ng/ml) in survivors. In another study, MEGX concentration on the third ICU day had the highest prognostic value when compared to all other liver function tests including ICG-PDR [59]. In a recent study, however, neither single nor repeated determinations of galactose elimination capacity and MEGX were found to be superior to the Child classification in predicting prognosis of patients with cirrhosis from viral hepatitis [53°].

In septic shock patients, increase in hepatic blood flow following N-acetylcysteine was associated with a parallel increase in MEGX formation [60]. Furthermore, patients with cirrhosis (Child A) and a MEGX concentration under 25 ng/ml after liver surgery had a significantly higher postoperative complication rate. Noteworthy, albumin, ammonium concentrations, prothrombin time, and cholinesterase activity were found to be significantly different in the two sub-groups of patients (i.e. MEGX concentration below or higher than 50 ng/ml). MEGX concentration was significantly lower in cirrhotic patients (35.6 ng/ml) than in patients without cirrhosis (77.8 ng/ml) [61].

In contrast to ICG-PDR, the MEGX test does not allow bedside assessment of liver function. Furthermore, since the MEGX test is related to metabolism of lidocaine, interactions with substances or drugs that result from the cytochrome CYP3A/4A system have to be considered [62]. For instance, antibiotics or antidepressives may inhibit MEGX formation due to their depression of CYP isoenzymes [63] while other drugs may induce CYP3A/4A and thus enhance MEGX production [64,65]. Noteworthy, median MEGX test results are different between both sexes (males 67 ng/ml, females 49 ng/ml). In females taking contraceptives, even a median of 25 ng/ml was reported [63]. In summary, all substances which influence or concur with the CYP3A/4A system may influence MEGX test results.

Recently, Ascione et al. [66°] studied patients with either off-pump or coronary artery bypass grafting with cardiopulmonary bypass (CPB) and assessed liver function by MEGX test and by serial measurements of transaminases, bilirubin, and alkaline phosphatase. MEGX results were not different in the two groups while transaminases were higher in the CPB group for the first postoperative day, but levels converged by day 3. Bilirubin level in the off-pump group, however, overshot the CPB group at 36 h before returning to a similar level 60 h postoperatively. These authors concluded that postoperative hepatocellular injury was worse in the CPB group.

In conclusion, the MEGX test is a clinically useful instrument for assessing liver function, but is limited by the need for laboratory equipment and potential influence by factors that may be present particularly in critically ill patients.

Aminopyrine test

The antipyrine breathing test is based on oral intake of radioactively labelled aminopyrine in which the 4-N-methyl groups contain 14C-atoms. After demethylation in the liver, exhaled 14CO2 is determined as marker of microsomal liver function [67]. So far, the aminopyrine test has most commonly been used for estimation of prognosis in patients with chronic liver disease [68,69]. Furthermore, estimation of functional liver reserve by antipyrine plasma clearance test in patients before cardiac surgery has been described to be in contrast to ICG-PDR independent from cardiac index and superior in terms of prediction of length of ICU stay [70]. General limitations are explained by exhalation of 14C (radioactive test) which may be influenced by general factors, gastrointestinal motility or basal
metabolic rate, resulting in a limited clinical value and reliability for the assessment of liver function [71]. Finally, this test is time consuming, requires specialized laboratory equipment and may involve radioactivity which prevents its use in the ICU.

Practical considerations

Still, there is no evidence-based guidance for when to assess liver function in critically ill patients and which therapeutic strategies to be used. Possible fields and circumstances in which liver monitoring may be useful and therapeutic aspects are summarized, however, in Table 1. Finally, the clinical value of combining different tests which may be useful due to the different partial functions assessed has not adequately been addressed yet and requires further investigation.

Conclusion

Real-time monitoring of liver function in critically ill patients is currently not available. In general, results of different tests may vary considerably since they assess different hepatic partial functions which per se makes a comparison difficult. Both ICG-PDR and MEGX test are clinically most valuable techniques, however, ICG-PDR has the advantage of being measurable noninvasively at the bedside and providing results within a few minutes.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as: **of special interest**  
* of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 242–244).


This study emphasized the usefulness of ICG-PDR in the field of liver transplantation.


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Table 1 Possible indications for liver function monitoring and therapeutic aspects

<table>
<thead>
<tr>
<th>Fields of indications</th>
<th>Therapeutic strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock of any underlying origin</td>
<td>Reduction or withdrawal of liver toxic drugs</td>
</tr>
<tr>
<td>Vasoactive drugs for haemodynamic support</td>
<td>Lowest possible airway pressures (mechanical ventilation)</td>
</tr>
<tr>
<td>SIRS/sepsis</td>
<td>Avoiding or reversal of fluid overload</td>
</tr>
<tr>
<td>ARDS</td>
<td>Increasing cardiac output by optimizing vasoactive drugs</td>
</tr>
<tr>
<td>Liver surgery</td>
<td>Increasing cardiac output by inotropics</td>
</tr>
<tr>
<td>Liver transplantation</td>
<td>Maintaining organ perfusion pressure (vasopressors)</td>
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<tr>
<td></td>
<td>N-acetylcysteine</td>
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<tr>
<td></td>
<td>Prostaglandins (Prostacyclin, iloprost)</td>
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</tbody>
</table>

SIRS, systemic inflammatory response syndrome; ARDS, acute respiratory distress syndrome.
This paper deals with the use of ICG-PDR for assessment of functional liver reserve in the field of liver resection.


Cirrhosis and Chronic Liver Failure: Part I. Diagnosis and Evaluation

JOEL J. HEIDELBAUGH, M.D., and MICHAEL BRUDERLY, M.D.
University of Michigan Medical School, Ann Arbor, Michigan

Cirrhosis and chronic liver failure are leading causes of morbidity and mortality in the United States, with the majority of preventable cases attributed to excessive alcohol consumption, viral hepatitis, or nonalcoholic fatty liver disease. Cirrhosis often is an indolent disease; most patients remain asymptomatic until the occurrence of decompensation, characterized by ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, or variceal bleeding from portal hypertension. Physical examination of patients with cirrhosis may reveal a variety of findings that necessitate a hepatic- or gastrointestinal-based work-up to determine the etiology. Some patients already may have had laboratory or radiographic tests that incidentally uncovered signs of cirrhosis and its comorbidities. No serologic or radiographic test can accurately diagnose cirrhosis. A significant correlation has been demonstrated between persistently elevated liver function tests and biopsy-proven underlying hepatic disease; thus, a more targeted serologic work-up is indicated in patients whose liver function test results are persistently abnormal. Unnecessary medications and surgical procedures should be avoided in patients with cirrhosis. Referral for liver biopsy should be considered only after a thorough, noninvasive serologic and radiographic evaluation has failed to confirm a diagnosis of cirrhosis; the benefit of biopsy outweighs the risk; and it is postulated that biopsy will have a favorable impact on the treatment of chronic liver disease. (Am Fam Physician 2006;74:756-62,781. Copyright © 2006 American Academy of Family Physicians.)

This is part I of a two-part article on cirrhosis and chronic liver failure. Part II, “Complications and Treatment,” appears in this issue of AFP on page 767.

► Patient information: A handout on cirrhosis and chronic liver failure, written by the authors of this article, is on page 781.

Cirrhosis and chronic liver failure together were the 12th most common cause of death in the United States in 2002, accounting for 27,257 deaths (9.5 per 100,000 persons), with a slight male predominance.1 Approximately 40 percent of patients with cirrhosis are asymptomatic, and the condition often is discovered during a routine examination with laboratory or radiographic studies, or at autopsy. In 2000, there were 360,000 U.S. hospital discharges related to cirrhosis and liver failure.1 This article, part I of a two-part series, outlines the diagnosis and evaluation of cirrhosis and chronic liver failure (Figure 1). Part II discusses complications and treatment.2

Single or multifactorial insults to the liver ultimately lead to cirrhosis, the most common being alcohol abuse, chronic hepatitis C, and obesity with concomitant nonalcoholic fatty liver disease (Table 1).3,4 Nonalcoholic fatty liver disease (NAFLD; formerly known as nonalcoholic steatohepatitis, or NASH) is an increasingly common cause of liver injury; risk factors include obesity, diabetes, hypertriglyceridemia, and profound weight loss after jejunoileal bypass.5

According to estimates from the United Network for Organ Sharing, 75 to 80 percent of cirrhosis cases could be prevented by eliminating alcohol abuse, and approximately 3.9 million Americans have chronic hepatitis C.6 In August 2005, there were 17,935 persons with cirrhosis (from various etiologies) in the United States who were awaiting a liver transplant.6 Mortality rates in patients with alcoholic liver disease are considerably higher than in patients with other forms of cirrhosis. The Centers for Disease Control and Prevention estimates that 75,766 deaths and 2.3 million years of potential life lost during 2001 were attributable to excessive alcohol use, an average of approximately 30 years of potential life lost for each alcohol-attributable death.7

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**SORT: KEY RECOMMENDATIONS FOR PRACTICE**

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Although no laboratory test can diagnose cirrhosis accurately, liver function tests, a complete blood count with platelets, and a prothrombin time test should be performed if a liver abnormality is suspected.</td>
<td>C</td>
<td>14</td>
</tr>
<tr>
<td>If clinical, laboratory, and radiographic data are inconclusive, but suspicion of cirrhosis remains, a diagnostic liver biopsy should be performed.</td>
<td>C</td>
<td>15, 17</td>
</tr>
<tr>
<td>If serum transaminase levels are greater than twice the upper limit of normal or remain elevated for longer than six months, additional serologic studies should be performed to evaluate for various etiologies of cirrhosis. If clinical suspicion for liver disease is high, further serologic work-up is warranted earlier.</td>
<td>C</td>
<td>15</td>
</tr>
<tr>
<td>Abdominal ultrasonography is a specific, reliable, noninvasive, fast, and cost-effective test that should be used as a first-line radiographic study for diagnosing cirrhosis.</td>
<td>C</td>
<td>20, 21</td>
</tr>
</tbody>
</table>

_A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 699 or http://www.aafp.org/afpsort.xml._

### Definitions and Etiologies

The liver aids greatly in the maintenance of metabolic homeostasis by processing dietary amino acids, carbohydrates, lipids, and vitamins; metabolizing cholesterol and toxins; producing clotting factors; and storing glycogen. Injury to the liver parenchyma associated with an influx of acute or chronic inflammatory cells is termed hepatitis. Cirrhosis refers to a progressive, diffuse, fibrosing, nodular condition that disrupts the entire normal architecture of the liver (Figures 2 through 4; Table 1).[^3][^4] Fibrosis

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[^3]: [Definition and Etiology of Cirrhosis](http://www.aafp.org/afpsort.xml)
[^4]: [Pathophysiology of Cirrhosis](http://www.aafp.org/afpsort.xml)
previously was thought to be an irreversible scarring process formed in response to inflammation or direct toxic insult to the liver, but current evidence suggests that fibrosis may be reversible in some patients with chronic hepatitis B after antiretroviral therapy.

Any chronic insult to the liver can cause progression to cirrhosis. Although numerous pathophysiologic mechanisms of injury exist, the final common pathway is persistent wound healing resulting in hepatic parenchymal fibrosis. In most persons, approximately 80 to 90 percent of the liver parenchyma must be destroyed before liver failure is manifested clinically. When complications of cirrhosis occur, they typically are related to impaired hepatic function or actual physical disruption and reorganization of the liver parenchyma.

Clinical Presentation

HISTORY

Cirrhosis often is a silent disease, with most patients remaining asymptomatic until decompensation occurs. Physicians should inquire about risk factors that predispose patients to cirrhosis (Figure 1). Quantity and duration of alcohol consumption is an important factor in the early diagnosis of cirrhosis. Other risk factors include those for hepatitis B and C transmission (e.g., birthplace in endemic areas, sexual history exposure risk, intranasal or intravenous drug use, body piercing or tattooing, accidental contamination with blood or body fluids), as well as transfusion history and personal or family history of autoimmune or hepatic diseases.

Early and well-compensated cirrhosis can manifest as anorexia and weight loss, weakness, fatigue, and even osteoporosis as a result of vitamin D malabsorption and subsequent calcium deficiency. Decompensated disease can result in complications such as ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and variceal bleeding from portal hypertension (discussed further in part II). Clinical symptoms at presentation may include jaundice of the eyes or skin, pruritus, gastrointestinal bleeding, coagulopathy, increasing abdominal girth, and mental status changes. Each of these clinical findings is the result of impaired hepatocellular function with or without physical obstruction secondary to cirrhosis. Because hepatic enzyme synthesis is required...
for drug metabolism, heightened sensitivity and medication toxicity may occur in patients with impaired hepatic enzyme synthesis.3,9

PHYSICAL EXAMINATION

Physical examination of patients with cirrhosis may reveal a variety of findings that should lead to a targeted hepatic- or gastrointestinal-based work-up (Table 2).10 Many patients will already have had serologic or radiographic tests or an unrelated surgical procedure that incidentally uncovered signs of cirrhosis.

Most patients with cirrhosis severe enough to lead to ascites have additional stigmata of cirrhosis on physical examination. Accurately diagnosing ascites depends upon the amount of fluid present in the abdomen, the technique used to examine the patient, and the patient’s habitus. The most useful physical finding in confirming the presence of ascites is flank dullness to

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**TABLE 1**

Etiologies of Hepatic Cirrhosis

<table>
<thead>
<tr>
<th>Most common causes</th>
<th>Less common causes</th>
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<tbody>
<tr>
<td>Alcohol (60 to 70 percent)</td>
<td>Autoimmune chronic hepatitis types 1, 2, and 3</td>
</tr>
<tr>
<td>Biliary obstruction (5 to 10 percent)</td>
<td>Drugs and toxins</td>
</tr>
<tr>
<td>Biliary atresia/neonatal hepatitis</td>
<td>Alpha-methylldopa (Aldomet)</td>
</tr>
<tr>
<td>Congenital biliary cysts</td>
<td>Amiodarone (Cordarone)</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Isoniazid (INH)</td>
</tr>
<tr>
<td>Primary or secondary biliary cirrhosis</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Chronic hepatitis B or C (10 percent)</td>
<td>Oxyphenisatin (Prulet)*</td>
</tr>
<tr>
<td>Hemochromatosis (5 to 10 percent)</td>
<td>Perhexiline*</td>
</tr>
<tr>
<td>NAFLD (10 percent)—most commonly resulting from obesity; also can occur after jejunoileal bypass</td>
<td>Troglitazone (Rezulin)*</td>
</tr>
<tr>
<td>Genetic metabolic disease</td>
<td>Vitamin A</td>
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<tr>
<td>α1-Antitrypsin deficiency</td>
<td>Genetic metabolic disease</td>
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<tr>
<td>Amino acid disorders (e.g., tyrosinemia)</td>
<td>α1-Antitrypsin deficiency</td>
</tr>
<tr>
<td>Bile acid disorders</td>
<td>Amino acid disorders (e.g., tyrosinemia)</td>
</tr>
<tr>
<td>Carbohydrate disorders (e.g., fructose intolerance, galactosemia, glycogen storage diseases)</td>
<td>Bile acid disorders</td>
</tr>
<tr>
<td>Lipid disorders (e.g., abetalipoproteinemia)</td>
<td>Carbohydrate disorders (e.g., fructose intolerance, galactosemia, glycogen storage diseases)</td>
</tr>
<tr>
<td>Porphyria</td>
<td>Lipid disorders (e.g., abetalipoproteinemia)</td>
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<tr>
<td>Urease cycle defects (e.g., ornithine carbamoyltransferase deficiency)</td>
<td>Porphyria</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>Urease cycle defects (e.g., ornithine carbamoyltransferase deficiency)</td>
</tr>
<tr>
<td>Idiopathic/miscellaneous</td>
<td>Wilson’s disease</td>
</tr>
<tr>
<td>Granulomatous liver disease (e.g., sarcoidosis)</td>
<td>Idiopathic portal fibrosis</td>
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<td>Idiopathic portal fibrosis</td>
<td>Indian childhood cirrhosis</td>
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<tr>
<td>Indian childhood cirrhosis</td>
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<td>Polycystic liver disease</td>
<td>Infection</td>
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<td>Brucellosis</td>
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<td>Congenital or tertiary syphilis</td>
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<td>Schistosomiasis</td>
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<tr>
<td>Schistosomiasis</td>
<td>Vascular abnormalities</td>
</tr>
<tr>
<td>Vascular abnormalities</td>
<td>Chronic, passive hepatic congestion caused by right-sided heart failure, pericarditis</td>
</tr>
<tr>
<td>Chronic, passive hepatic congestion caused by right-sided heart failure, pericarditis</td>
<td>Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)</td>
</tr>
<tr>
<td>Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease)</td>
<td>Veno-occlusive disease</td>
</tr>
</tbody>
</table>

NAFLD = nonalcoholic fatty liver disease.

*—Not available in the United States.

Information from references 3 and 4.

---

**TABLE 2**

Common Physical Examination Findings in Patients with Cirrhosis

| Abdominal wall vascular collaterals (caput medusa) |
| Ascites |
| Asterixis |
| Clubbing and hypertrophic osteoarthropathy |
| Constitutional symptoms, including anorexia, fatigue, weakness, and weight loss |
| Cruveilhier-Baumgarten murmur—a venous hum in patients with portal hypertension |
| Dupuytren’s contracture |
| Fetor hepaticus—a sweet, pungent breath odor |
| Gynecomastia |
| Hepatomegaly |
| Jaundice |
| Kayser-Fleischer ring—brown-green ring of copper deposit around the cornea, pathognomonic for Wilson’s disease |
| Nail changes: |
| Muehrcke’s nails—paired horizontal white bands separated by normal color |
| Terry’s nails—proximal two thirds of nail plate appears white, whereas the distal one third is red |
| Palmar erythema |
| Scleral icterus |
| Vascular spiders (spider telangiectasias, spider angioma) |
| Splenomegaly |
| Testicular atrophy |

Information from reference 10.
Cirrhosis and Chronic Liver Failure—Part I

Patients with numerous large vascular spiders are at increased risk for variceal hemorrhage.

Vascular spiders (spider angiomata, spider telangiectasias) are vascular lesions usually found on the trunk, face, and upper extremities. Although their pathogenesis is incompletely understood, it is believed that their presence in men is associated with an increase in the estradiol to free testosterone ratio. Vascular spiders are not specific for cirrhosis: they also occur during pregnancy, in patients with severe malnutrition, and in healthy persons. The number and size of vascular spiders have been shown to correlate with the severity of chronic liver disease. Patients with numerous large vascular spiders are at increased risk for variceal hemorrhage.13

**Laboratory Evaluation**

No serologic test can diagnose cirrhosis accurately. The term liver function tests is a misnomer because the assays in most standard liver panels do not reflect the function of the liver correctly. Although liver function tests may not correlate exactly with hepatic function, interpreting abnormal biochemical patterns in conjunction with the clinical picture may suggest certain liver diseases. When a liver abnormality is suspected or identified, a liver panel, a complete blood count (CBC) with platelets, and a prothrombin time test should be performed. Common tests in standard liver panels include the serum enzymes aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, and γ-glutamyltransferase; total, direct, and indirect serum bilirubin; and serum albumin. The ALT is thought to be the most cost-effective screening test for identifying metabolic or drug-induced hepatic injury, but like other liver function tests, it is of limited use in predicting degree of inflammation and of no use in estimating severity of fibrosis. One study found that a platelet count of less than 160 K per mm³ has a sensitivity of 80 percent for detecting cirrhosis in patients with chronic hepatitis C.16

A prospective study showed a strong correlation between liver function test results elevated to greater than twice the upper limit of normal for at least six months and underlying liver disease proved by liver biopsy. Additional serologic studies should be pursued in such circumstances to evaluate for various etiologies of cirrhosis (Table 3). If clinical suspicion for liver disease is high, then further serologic work-up is warranted within six months. If a patient has a persistently increased ALT level, viral hepatitis serologies should be assayed. If these are negative, the remaining serologic work-up should include an antinuclear antibodies test or anti–smooth muscle antibody test, or both, to evaluate for autoimmune hepatitis; and a fasting transferrin saturation level or unsaturated iron-binding capacity and ferritin level18 to evaluate for hereditary hemochromatosis. In patients younger than 40 years in whom Wilson’s disease is suspected, serum ceruloplasmin and copper levels should be measured, but screening all patients with chronic hepatic injury for Wilson’s disease is not indicated. Primary biliary cirrhosis or primary sclerosing cholangitis should be suspected in patients with chronic cholestasis. Testing for α₁-antitrypsin (A₁AT) deficiency may be of benefit in patients with chronic hepatic injury and no other apparent cause. Although the role of A₁AT deficiency in liver disease in adults is not clearly defined, testing is especially important in neonates with evidence of hepatic injury. Ultrasonography or biopsy is necessary to establish the diagnosis of NAFLD.

**Radiographic Studies**

Although various radiographic studies may suggest the presence of cirrhosis, no test is considered a diagnostic standard. The major use of radiographic studies is to detect ascites, hepatosplenomegaly, hepatic or portal vein thromboses, and hepatocellular carcinoma, all of which strongly suggest cirrhosis.

**ULTRASONOGRAPHY**

Abdominal ultrasonography with Doppler is a non-invasive, widely available modality that provides valuable information regarding the gross appearance of the liver and blood flow in the portal and hepatic veins in patients suspected to have cirrhosis. Ultrasonography should be the first radiographic study performed in the evaluation of cirrhosis because it is the least expensive and does not pose a radiation exposure risk or involve intravenous contrast with the potential for nephrotoxicity as does computed tomography (CT). Nodularity, irregularity, increased echogenicity, and atrophy are ultrasonographic hallmarks of cirrhosis. In advanced disease, the gross liver appears small and multinodular, ascites may be...
detected, and Doppler flow can be significantly decreased in the portal circulation. The discovery of hepatic nodules via ultrasonography warrants further evaluation because benign and malignant nodules can have similar ultrasonographic appearances. A study using high-resolution ultrasonography in patients with cirrhosis confirmed with biopsy or laparoscopy found a sensitivity and specificity for cirrhosis of 91.1 and 93.5 percent, respectively, and positive and negative predictive values of 93.2 and 91.5 percent, respectively.21

CT AND MRI

CT and magnetic resonance imaging (MRI) generally are poor at detecting morphologic changes associated with early cirrhosis, but they can accurately demonstrate nodularity and lobular atrophic and hypertrophic changes, as well as ascites and varices in advanced disease. Although MRI sometimes differentiates among regenerating or dysplastic nodules and hepatocellular carcinoma, it is best used as a follow-up study to determine whether lesions have changed in appearance and size. CT portal phase imaging can be used to assess portal vein patency, although flow volume and direction cannot be determined accurately.22

Although used rarely, magnetic resonance angiography (MRA) can assess portal hypertensive changes including flow volume and direction, as well as portal vein thrombosis.22 One study reported that MRI can accurately

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Clinical Laboratory Studies Used in Diagnosing Chronic Liver Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td><strong>Laboratory tests and results</strong></td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>AST:ALT ratio &gt; 2*&lt;br&gt;Elevated GGT</td>
</tr>
<tr>
<td>α1-Antitrypsin deficiency</td>
<td>Decreased serum α1-antitrypsin&lt;br&gt;Genetic screening recommended in equivocal cases</td>
</tr>
<tr>
<td>Autoimmune hepatitis (type 1)</td>
<td>Positive ANA and/or ASMA in high titer&lt;br&gt;Positive HBsAg and HBeAg qualitative assays&lt;br&gt;Once HBeAg is negative and HBeAb is positive, HBsAg should be monitored periodically to determine viral clearance.&lt;br&gt;Hepatitis B virus DNA quantification used to document viral clearance&lt;br&gt;Elevated AST and/or ALT*</td>
</tr>
<tr>
<td>Chronic hepatitis B</td>
<td>Elevated AST and/or ALT*</td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td>Positive hepatitis C virus antibody qualitative assay&lt;br&gt;HCV RNA quantification used to document viral clearance&lt;br&gt;HCV viral genotype to determine potential response to antiretroviral therapy</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>Elevated alpha fetoprotein, AST, and/or ALT*&lt;br&gt;Elevated ALP with obstruction or cholestasis</td>
</tr>
<tr>
<td>Hereditary hemochromatosis</td>
<td>Elevated fasting transferrin saturation, unsaturated iron-binding capacity, or ferritin. A transferrin saturation &gt; 45 percent or an unsaturated iron-binding capacity 155 mcg per dL (27.7 µmol per L) should be followed by analysis for HFE (hemochromatosis) gene mutations.</td>
</tr>
<tr>
<td>Nonalcoholic fatty liver disease</td>
<td>Elevated AST and/or ALT*&lt;br&gt;Ultrasonography or biopsy necessary to establish diagnosis.</td>
</tr>
<tr>
<td>Primary biliary cirrhosis and primary sclerosing cholangitis</td>
<td>Diagnosis made via contrast cholangiography, can be supported clinically by positive antimitochondrial antibody (primary biliary cirrhosis) or antineutrophil cytoplasmic antibody (primary sclerosing cholangitis) in high titers.&lt;br&gt;Elevated AST, ALT, and ALP common</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>Serum ceruloplasmin &lt; 20 mg per dL (200 mg per L) (normal: 20 to 60 mg per dL [200 to 600 mg per L]), or low serum copper level (normal: 80 to 160 mcg per dL [12.6 to 25.1 µmol per L])&lt;br&gt;Basal 24-hour urinary copper excretion &gt; 100 mcg (1.57 µmol) (normal: 10 to 80 mcg [0.16 to 1.26 µmol])&lt;br&gt;Genetic screening recommended in equivocal cases, but must be able to detect multiple mutations in Wilson’s disease gene.</td>
</tr>
</tbody>
</table>

AST = aspartate transaminase; ALT = alanine transaminase; GGT = γ-glutamyltransferase; ANA = antinuclear antibody; ASMA = anti-smooth muscle antibody; HBsAg = hepatitis B surface antigen; HBeAg = hepatitis B e antigen; HBeAb = hepatitis B e antibody; HCV = hepatitis C virus; ALP = alkaline phosphatase.

*—AST and ALT levels may be normal in advanced disease.

Information from references 14, 15, 18, and 19.
diagnose cirrhosis and provide correlation with its severity.\textsuperscript{23} Despite the potential of MRI and MRA in the diagnosis and evaluation of patients with cirrhosis, their widespread use is limited by their expense and by the ability of routine ultrasonography with Doppler to obtain adequate information for the diagnosis of cirrhosis and presence of complications.

**Liver Biopsy**

Referral for liver biopsy should be considered after a thorough, noninvasive serologic and radiographic evaluation has failed to confirm a diagnosis of cirrhosis; the benefit of biopsy outweighs the risk; and it is postulated that biopsy will have a favorable impact on the treatment of chronic liver disease. The sensitivity and specificity for an accurate diagnosis of cirrhosis and its etiology range from 80 to 100 percent, depending on the number and size of the histologic samples and on the sampling method.\textsuperscript{24}

Liver biopsy is performed via percutaneous, transjugular, laparoscopic, open operative, or ultrasonography- or CT-guided fine-needle approaches. Before the procedure, a CBC with platelets and prothrombin time measurement should be obtained. Patients should be advised to refrain from consumption of aspirin and nonsteroidal anti-inflammatory drugs for seven to 10 days before the biopsy to minimize the risk of bleeding.

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Author disclosure: Nothing to disclose.

**REFERENCES**


Cirrhosis and Chronic Liver Failure: Part II. Complications and Treatment

JOEL J. HEIDELBAUGH, M.D., and MARYANN SHERBONDY, M.D.
University of Michigan Medical School, Ann Arbor, Michigan

Major complications of cirrhosis include ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, portal hypertension, variceal bleeding, and hepatorenal syndrome. Diagnostic studies on ascitic fluid should include a differential leukocyte count, total protein level, a serum-ascites albumin gradient, and fluid cultures. Therapy consists of sodium restriction, diuretics, and complete abstention from alcohol. Patients with ascitic fluid polymorphonuclear leukocyte counts of 250 cells per mm³ or greater should receive empiric prophylaxis against spontaneous bacterial peritonitis with cefotaxime and albumin. Patients who survive an episode of spontaneous bacterial peritonitis should receive long-term prophylaxis with norfloxacin or trimethoprim/sulfamethoxazole. Patients with gastrointestinal hemorrhage and cirrhosis should receive norfloxacin or trimethoprim/sulfamethoxazole twice daily for seven days. Treatment of hepatic encephalopathy is directed toward improving mental status levels with lactulose; protein restriction is no longer recommended. Patients with cirrhosis and evidence of gastrointestinal bleeding should undergo upper endoscopy to evaluate for varices. Endoscopic banding is the standard treatment, but sclerotherapy with vasoconstrictors (e.g., octreotide) also may be used. Prophylaxis with propranolol is recommended in patients with cirrhosis once varices have been identified. Transjugular intrahepatic portosystemic shunt has been effective in reducing portal hypertension and improving symptoms of hepatorenal syndrome, and can reduce gastrointestinal bleeding in patients with refractory variceal hemorrhage. When medical therapy for treatment of cirrhosis has failed, liver transplantation should be considered. Survival rates in transplant recipients have improved as a result of advances in immunosuppression and proper risk stratification using the Model for End-Stage Liver Disease and Child-Turcotte-Pugh scoring systems. (Am Fam Physician 2006;74:767-76, 781. Copyright © 2006 American Academy of Family Physicians.)

This is part II of a two-part article on cirrhosis and chronic liver failure. Part I, “Diagnosis and Evaluation,” appears in this issue of AFP on page 756.

► Patient information: A handout on cirrhosis and chronic liver failure, written by the authors of this article, is on page 781.

Part I of this two-part series outlines the diagnosis and evaluation of cirrhosis and chronic liver failure.1 This article, part II, discusses complications and treatment. Major complications of cirrhosis include ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, portal hypertension, variceal bleeding, and hepatorenal syndrome.

Ascites

Ascites is defined as the pathologic accumulation of fluid in the peritoneal cavity. Approximately 85 percent of patients with ascites have cirrhosis, and the remaining 15 percent have a nonhepatic cause of fluid retention.2,3 The American Association for the Study of Liver Diseases recommends a diagnostic abdominal paracentesis be performed and ascitic fluid obtained from patients with clinically evident ascites.3 Paracentesis with ascitic fluid culture in blood culture bottles should be performed before the initiation of antibiotics to determine a true infection.

The initial laboratory investigation of ascitic fluid should include a differential leukocyte count, a total protein level, and a serum-ascites albumin gradient (SAAG). The SAAG is a useful prognosticator of portal pressure; it is calculated by subtracting the ascitic albumin concentration from the serum albumin concentration obtained on the same day.4 If the SAAG is 1.1 g per dL (11 g per L) or greater, there is a high likelihood of portal hypertension; if it is less than 1.1 g per dL, other causes of ascites should be explored, including peritoneal carcinomatosis, tuberculous peritonitis, and pancreatic ascites (Figure 1).4,5 The ascitic fluid total protein level typically has been used in defining ascitic fluid as transudative (protein content less than 2.5 g per dL [25 g per L]) or exudative (protein content of 2.5 g per dL or greater) and to help identify patients at higher risk of developing spontaneous bacterial peritonitis. However, this method is flawed because many patients with spontaneous bacterial peritonitis, in which ascitic fluid is infected, have a low rather
than high ascitic fluid total protein level, and many fluid samples from patients with portal hypertension secondary to heart failure have a high rather than the expected low ascitic fluid total protein level.\(^6\)

First-line treatment of patients with cirrhotic ascites consists of sodium restriction (i.e., no more than 2,000 mg per day) and diuretics (e.g., oral spironolactone [Aldactone], furosemide [Lasix]), as well as complete

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**Figure 1.** Algorithm for the differential diagnosis of ascites. (WBC = white blood cell; RBC = red blood cell; PMNL = polymorphonuclear leukocyte; TP = total protein; LDH = lactate dehydrogenase; CT = computed tomography.)

abstention from alcohol (Table 1). Fluid restriction is unnecessary unless serum sodium is less than 120 to 125 mEq per L (120 to 125 mmol per L). Patients who are sensitive to diuretics should be treated with sodium restriction and oral diuretics rather than with serial paracenteses, unless the ascites is refractory to these therapies or infection is suspected. Postparacentesis albumin infusion is unnecessary for a single paracentesis of less than 4 to 5 L, but for large-volume paracenteses, an albumin infusion of 8 to 10 g per liter of fluid removed can be considered. Referral for liver transplantation should be expedited for patients with refractory ascites. Transjugular intrahepatic portosystemic shunt (TIPS) should be considered in patients with refractory ascites who may require a transplant, whereas a peritoneovenous shunt should be considered in patients with refractory ascites who are not candidates for paracenteses, transplant, or TIPS.

### Spontaneous Bacterial Peritonitis

Patients with ascitic fluid polymorphonuclear leukocyte (PMNL) counts of 250 cells per mm³ or greater should receive empiric antibiotic therapy (e.g., cefotaxime [Claforan] 2 g intravenously every eight hours) and albumin (1.5 g per kg body weight within six hours of detection and 1 g per kg on day 3) to prevent spontaneous bacterial peritonitis (Table 1). Oral ofloxacin (Floxin; 400 mg twice daily) is an alternative to intravenous medications in patients without vomiting, shock, severe hepatic encephalopathy, or a creatinine level greater than 3 mg per dL (265 µmol per L). Patients with ascitic fluid PMNL counts less than 250 cells per mm³ and signs and symptoms of infection should receive empiric antibiotic therapy while awaiting culture results. Patients who survive an episode of spontaneous bacterial peritonitis should receive long-term prophylaxis with norfloxacin (Noroxin) or trimethoprim/sulfamethoxazole (Bactrim, Septra). Patients with gastrointestinal hemorrhage and cirrhosis should receive norfloxacin or trimethoprim/sulfamethoxazole twice daily for seven days (the drug is then discontinued).

### Hepatic Encephalopathy

Hepatic (portosystemic) encephalopathy represents a potentially reversible decrease in neuropsychiatric function caused by acute and chronic liver disease, occurring predominantly in patients with portal hypertension. The onset often is insidious and is characterized by subtle and sometimes intermittent changes in memory, personality, concentration, and reaction times. Hepatic encephalopathy is a diagnosis of exclusion; therefore, all other etiologies of altered mental status must be effectively ruled out. Treatment goals for hepatic encephalopathy include provision of supportive care, identification and removal of precipitating factors, reduction in the nitrogenous
load from the gut, and optimization of long-term therapy (Table 2). Therapy should be directed toward improving mental status via bowel cleansing with lactulose orally or with enemas (Table 1). One randomized trial demonstrated that diets with normal protein content can be followed safely during episodic hepatic encephalopathy caused by cirrhosis, and that protein restriction has no beneficial effect during such episodes. In patients who are refractory to lactulose alone, neomycin can be added. Increases in the ratio of plasma aromatic amino acids to branched-chain amino acids as a consequence of hepatic insufficiency also may contribute to encephalopathy. One meta-analysis suggested that mental recovery was consistently more rapid in patients whose treatment included a branched-chain amino acid infusion; three studies found lower mortality rates in patients who received this treatment, and two others suggested that the treatment increased mortality. Another physiologic theory of hepatic encephalopathy is that endogenous benzodiazepines may bind to \( \gamma \)-aminobutyric acid receptors and exert neuroinhibitory effects. Use of the benzodiazepine receptor antagonist flumazenil (Romazicon) may improve mental status transiently, whereas bromocriptine (Parlodel) may improve extrapyramidal symptoms. No formal recommendation for the routine use of any of these agents has been suggested.

**Portal Hypertension and Variceal Bleeding**

Regardless of the etiology of cirrhosis, the development of portal hypertension is nearly universal and results from an increased resistance to portal flow secondary to scarring, narrowing, and compression of the hepatic sinusoids. When the portal pressure exceeds a certain threshold, it results in the development of varices. Approximately 50 percent of patients with cirrhosis develop varices, most commonly in the distal 2 to 5 cm of the esophagus. Variceal hemorrhage is defined as bleeding from an esophageal or gastric varix at the time of endoscopy, or the presence of large esophageal varices with blood in the stomach and no other recognizable source of bleeding. The rate of variceal bleeding is approximately 10 to 30 percent per year.

The British Society of Gastroenterology guidelines for the management of variceal hemorrhage recommend

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line treatment of patients with cirrhotic ascites consists of sodium restriction (i.e., no more than 2,000 mg per day) and diuretics (e.g., oral spironolactone [Aldactone] and furosemide [Lasix]), as well as complete abstinence from alcohol.</td>
<td>A</td>
<td>3</td>
</tr>
<tr>
<td>TIPS should be considered in patients with refractory ascites who may require a transplant, whereas a peritoneovenous shunt should be considered in patients with refractory ascites who are not candidates for paracenteses, transplant, or TIPS.</td>
<td>B</td>
<td>3</td>
</tr>
<tr>
<td>Patients with ascitic fluid polymorphonuclear leukocyte counts of 250 cells per mm(^3) or greater should receive empiric antibiotic therapy (e.g., cefotaxime [Claforan] 2 g intravenously every eight hours) and albumin (1.5 g per kg body weight within six hours of detection and 1 g per kg on day 3) to prevent spontaneous bacterial peritonitis.</td>
<td>A</td>
<td>3</td>
</tr>
<tr>
<td>Patients who survive an episode of spontaneous bacterial peritonitis should receive long-term antibiotic prophylaxis with norfloxacin (Noroxin) or trimethoprim/sulfamethoxazole (Bactrim, Septra). Patients with gastrointestinal hemorrhage and cirrhosis should receive norfloxacin or trimethoprim/sulfamethoxazole twice daily for seven days.</td>
<td>A</td>
<td>3</td>
</tr>
<tr>
<td>Propranolol (Inderal) at a dosage of 40 mg twice daily is recommended for pharmacologic prophylaxis of variceal bleeding, increasing to 80 mg twice daily if necessary or a dosage titrated to a 25 percent reduction in pulse rate.</td>
<td>B</td>
<td>9, 15, 16</td>
</tr>
<tr>
<td>An early referral to a transplant subspecialist is recommended for potential transplant recipients to allow time for patients, families, referring physicians, and transplant centers to meet and identify any potential problems.</td>
<td>C</td>
<td>28</td>
</tr>
</tbody>
</table>

TIPS = transjugular intrahepatic portosystemic shunt.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 699 or http://www.aafp.org/afpsort.xml.
that patients with cirrhosis who present with evidence of upper gastrointestinal bleeding undergo an urgent upper endoscopic evaluation (Figure 2). If no varices are observed, these patients should have repeat endoscopy at three-year intervals. If small varices are diagnosed, patients should have repeat surveillance at one-year intervals. Primary prophylaxis of variceal bleeding is aimed at reducing the portal pressure gradient, azygous blood flow, and variceal pressure. These guidelines also suggest that the most effective pharmacotherapy is propranolol (Inderal) at a dosage of 40 mg twice daily, increasing to 80 mg twice daily if necessary (Table 1). If propranolol is contraindicated or not tolerated, isosorbide mononitrate (Ismo) at a dosage of 20 mg twice daily is the treatment of choice. Studies conducted since these guidelines have titrated the dosage of propranolol based on a reduction of the pulse rate by 25 percent.

The goals of treatment in acute variceal bleeding include hemodynamic resuscitation, treatment of active bleeding, and prevention of rebleeding. Band ligation is the standard for the control of variceal bleeding. If banding is difficult because of continued variceal bleeding, endoscopic sclerotherapy with vasoconstrictors (e.g., octreotide [Sandostatin]) or a Sengstaken-Blakemore tube insertion (with adequate airway protection) may be

### TABLE 1
Treatment of Complications of Cirrhosis

<table>
<thead>
<tr>
<th>Complication</th>
<th>Treatment</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascites</td>
<td>Sodium restriction</td>
<td>Maximum 2,000 mg per day&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Spironolactone (Aldactone)</td>
<td>Start 100 mg orally per day; maximum 400 mg orally per day&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Furosemide (Lasix)</td>
<td>Start 40 mg orally per day; maximum 160 mg orally per day&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Albumin</td>
<td>8 to 10 g IV per liter of fluid (if greater than 5 L) removed for paracenteses&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Fluid restriction</td>
<td>Recommended if serum sodium is less than 120 to 125 mEq per L (120 to 125 mmol per L)&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis&lt;sup&gt;††&lt;/sup&gt;</td>
<td>Cefotaxime (Claforan)</td>
<td>2 g IV every eight hours&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Albumin</td>
<td>1.5 g per kg IV within six hours of detection and 1 g per kg IV on day 3&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Norfloxacin (Noroxin)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>400 mg orally two times per day for treatment&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>400 mg orally two times per day for seven days with gastrointestinal hemorrhage&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Trimethoprim/sulfamethoxazole (Bactrim, Septra)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1 single-strength tablet orally per day for prophylaxis&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 single-strength tablet orally two times per day for seven days with gastrointestinal hemorrhage&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>Lactulose</td>
<td>30 to 45 mL syrup orally titrated up to three or four times per day or 300 mL retention enema until two to four bowel movements per day and mental status improvement&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Neomycin</td>
<td>4 to 12 g orally per day divided every six to eight hours; can be added to lactulose in patients who are refractory to lactulose alone&lt;sup&gt;7,8&lt;/sup&gt;</td>
</tr>
<tr>
<td>Portal hypertension and variceal bleeding</td>
<td>Propranolol (Inderal)</td>
<td>40 to 80 mg orally two times per day&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Isosorbide mononitrate (Ismo)</td>
<td>20 mg orally two times per day&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hepatorenal syndrome</td>
<td>Midodrine (ProAmatine) and octreotide (Sandostatin)</td>
<td>Dosed orally (midodrine) and IV (octreotide) to obtain a stable increase of at least 15 mm Hg mean arterial pressure&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Dopamine</td>
<td>2 to 4 mcg per kg per minute IV (nonpressor dosing to produce renal vasodilatation)&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>IV</sup> = intravenously; PMNL = polymorphonuclear leukocyte.

<sup>†</sup>—Patients with ascitic fluid PMNL counts greater than or equal to 250 cells per mm<sup>3</sup> should receive empiric antibiotic therapy; patients with ascitic fluid PMNL counts less than 250 cells per mm<sup>3</sup> and signs and symptoms of infection should receive empiric antibiotic therapy while awaiting culture results.

<sup>††</sup>—Patients who survive an episode of spontaneous bacterial peritonitis should receive long-term prophylaxis with norfloxacin or trimethoprim/sulfamethoxazole.

Information from references 3 and 7 through 10.
used until TIPS or surgical treatment can be arranged.9 TIPS has been shown to improve outcomes and is more cost-effective than endoscopic band ligation in reducing variceal bleeding, but it is associated with a higher risk of encephalopathy.9 This treatment option should be performed in medical centers with particular expertise. TIPS has been shown to reduce portal hypertension and can be effective in converting patients with diuretic-resistant ascites to diuretic-sensitive ascites, as well as reducing gastrointestinal bleeding in patients with refractory variceal hemorrhage. Evidence regarding whether or not TIPS improves survival is conflicting.3 Compared with large-volume paracentesis plus albumin, TIPS improves survival without liver transplantation in patients with refractory or recidivant ascites.17

After the cessation of active variceal hemorrhage, the subsequent six weeks carry a high risk of recurrent hemorrhage. The greatest risk of rebleeding is within the first 48 to 72 hours, with more than 50 percent of episodes occurring within the first 10 days.18 Risk factors for early rebleeding include age older than 60 years, renal failure, large varices, and severe initial bleeding (i.e., hemoglobin less than 8 g per dL [80 g per L] at admission).18 A retrospective study showed that in-hospital mortality of patients with cirrhosis and variceal bleeding decreased from 43 percent in 1980 to 15 percent in 2000, in concurrence with an early and combined use of pharmacologic and endoscopic therapies and short-term antibiotic prophylaxis.19

Hepatorenal Syndrome

Hepatorenal syndrome is defined as functional renal failure in cirrhotic patients in the absence of intrinsic renal disease.20 It is characterized by sodium and water retention in patients with renal vasoconstriction, resulting in decreased renal blood flow, glomerular filtration rate, and urinary output, which contribute to azotemia (Table 3).20 One prospective study of 229 patients with cirrhosis and ascites who did not have azotemia found an incidence of hepatorenal syndrome of 18 percent after one year and 39 percent after five years.21 The pathogenesis of hepatorenal syndrome is not completely understood, but it is likely the result of an extreme underfilling of the arterial circulation secondary to arterial vasodilation in the splanchnic circulation.22 Although hepatorenal syndrome can occur with most forms of severe hepatic disease, patients with primary biliary cirrhosis appear to be relatively protected.23

The International Ascites Club consensus conference on hepatorenal syndrome defined diagnostic criteria that distinguish between two types of hepatorenal syndrome.24 Type 1 hepatorenal syndrome is defined as a rapid deterioration of renal function indicated by a two-fold increase of serum creatinine to values above 2.5 mg per dL (221 µmol per L), or a decrease of creatinine clearance to values below 20 mL per minute (0.33 mL per second). This form of hepatorenal syndrome usually is precipitated by spontaneous bacterial peritonitis and occurs in approximately 25 percent of patients with spontaneous bacterial peritonitis, even with the clearance of infection. The median survival duration of these patients is less than two weeks without treatment, and almost all patients die within 10 weeks after the onset of renal failure.24 Patients with type 2 hepatorenal syndrome exhibit moderately increased serum creatinine levels above 1.5 mg per dL (133 µmol per L) that remain

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Hepatic encephalopathy is a diagnosis of exclusion; therefore, all other etiologies of altered mental status must be effectively ruled out.

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<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Treatment of Hepatic Encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identify and correct the precipitating causes:</td>
<td></td>
</tr>
<tr>
<td>1. Assess vital signs and volume status.</td>
<td></td>
</tr>
<tr>
<td>2. Evaluate for gastrointestinal bleeding.</td>
<td></td>
</tr>
<tr>
<td>3. Eliminate sedatives or tranquilizers.</td>
<td></td>
</tr>
<tr>
<td>4. Screen for hypoxia, hypoglycemia, anemia, hypokalemia, metabolic alkalosis, and other potential metabolic or endocrine factors; correct as indicated.</td>
<td></td>
</tr>
<tr>
<td>Initiate ammonia-lowering therapy:</td>
<td></td>
</tr>
<tr>
<td>1. Use nasogastric lavage, lactulose, and/or other cathartics or enemas to remove source of ammonia from colon.</td>
<td></td>
</tr>
<tr>
<td>2. Initiate treatment with lactulose or lactacid to produce two to four bowel movements per day.</td>
<td></td>
</tr>
<tr>
<td>3. Consider oral nonabsorbable antibiotics to reduce intestinal bacterial counts.</td>
<td></td>
</tr>
<tr>
<td>4. Consider treatment with flumazenil (Romazicon) or another benzodiazepine receptor antagonist.</td>
<td></td>
</tr>
<tr>
<td>Minimize potential complications of cirrhosis and depressed consciousness:</td>
<td></td>
</tr>
<tr>
<td>1. Provide supportive care with attention to airway, hemodynamic, and metabolic statuses.</td>
<td></td>
</tr>
</tbody>
</table>

stable over a longer period, and ascites that generally is resistant to diuretics. The median survival duration in these patients is three to six months.24

Hemodialysis often is used to control azotemia in hepatorenal syndrome and to correct electrolyte imbalances. Nonsteroidal anti-inflammatory drugs and potentially nephrotoxic medications should be avoided. One controlled trial demonstrated a substantial improvement in renal plasma flow, glomerular filtration rate, and urinary sodium excretion in patients with type 1 hepatorenal syndrome after 20 days of treatment with oral midodrine (ProAmatine) and parenteral octreotide compared with the use of nonpressor dose dopamine (Table 1).10 These therapies also appear to improve survival rates and may serve as a bridge to liver transplantation. In the future, endothelins, adenosine antagonists, long-acting vasoconstrictors, and antileukotriene antagonists may play a role in preventing and treating hepatorenal syndrome.25

Liver Transplantation

When standard medical and procedural therapy has failed to control the complications of cirrhosis, liver transplantation should be considered. Unnecessary surgical procedures should be avoided and risks versus benefits weighed before any surgical procedure is performed in patients with cirrhosis. Since the first successful liver transplant in 1967, there has been a growing disparity between the number of potential candidates and the number of donors. This disparity is attributed to a sixfold increase in patients on the transplant waiting list from 1991 to 2001 and a much slower rate of increase in the donor pool. A total of 6,169 liver transplants were performed in the United States in 2004; the current

Hepatorenal syndrome is defined as functional renal failure in cirrhotic patients in the absence of intrinsic renal disease.
The Clinical Practice Committee of the American Society of Transplantation suggests patients should be referred early to a transplant subspecialist to allow time for the patient, family, referring physician, and transplant center to meet and identify any potential problems. Transplant care is best provided by a team of health care professionals including a hepatologist, a surgeon, a psychiatrist, and a social worker. In addition to a standard medical evaluation, the initial assessment of a possible transplant recipient should incorporate education highlighting the risks and benefits of organ transplantation, including the potential for poor outcomes (i.e., organ rejection), and standard post-transplant care.

The statistical model for end-stage liver disease (MELD) predicts survival in patients with cirrhosis and has been adopted for routine use in the timing and allocation of transplantation (Figure 3). This system is an objective model based on the relationships among serum bilirubin, serum creatinine, and International Normalized Ratio values. The MELD score can be used as an accurate predictor of three-month mortality: a score of 40 out of 50 correlates to a three-month survival rate of less than 20 percent.

**INDICATIONS**

Potential candidates for liver transplantation include any patient with documented fulminant hepatic failure, decompensated cirrhosis (including hepatorenal syndrome), or a hepatocellular carcinoma with no single lesion greater than 5 cm or no more than three lesions with the largest being 3 cm or smaller. Fulminant hepatic failure is a rare syndrome that arises from the loss of hepatic parenchymal function accompanied by encephalopathy and coma in patients who have had liver disease for less than eight weeks.

The Child-Turcotte-Pugh (CTP) scoring classification, originally devised to risk-stratify patients undergoing shunt surgery for portal decompression, is a useful system to assess liver disease severity in patients with established cirrhosis (Table 4). In a retrospective study involving 92 patients with cirrhosis who underwent abdominal surgery, the mortality rate was 10 percent for patients with CTP grade A disease, 30 percent for those with grade B, and 82 percent for those with grade C. The CTP classification also correlates with the frequency

---

**TABLE 3**

**Diagnostic Criteria for Hepatorenal Syndrome**

<table>
<thead>
<tr>
<th>Major criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic or acute liver disease with advanced hepatic failure and portal hypertension</td>
</tr>
<tr>
<td>Low glomerular filtration rate, indicated by serum creatinine level &gt; 1.5 mg per dL (130 µmol per L) or creatinine clearance &lt; 40 mL per minute (0.67 mL per second)</td>
</tr>
<tr>
<td>Absence of treatment with nephrotoxic drugs, shock, infection, or significant recent fluid losses</td>
</tr>
<tr>
<td>No sustained improvement in renal function after diuretic withdrawal and volume expansion with 1.5 L isotonic saline</td>
</tr>
<tr>
<td>Proteinuria &lt; 0.5 g per dL (5 g per L) and no ultrasonographic evidence of obstruction or parenchymal renal disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine volume &lt; 500 mL per day</td>
</tr>
<tr>
<td>Urine sodium &lt; 10 mEq per L (10 mmol per L)</td>
</tr>
<tr>
<td>Urine osmolality greater than plasma osmolality</td>
</tr>
<tr>
<td>Urine red blood cells &lt; 50 per high-power field</td>
</tr>
<tr>
<td>Serum sodium concentration &lt; 130 mEq per L (130 mmol per L)</td>
</tr>
</tbody>
</table>

of postoperative complications including renal failure, hepatic encephalopathy, bleeding, infection, intractable ascites, and worsening liver failure.32

CONTRAINDICATIONS

Absolute contraindications to liver transplantation encompass clinical scenarios in which the expected outcome of transplantation is so poor that the procedure should not be considered. Examples include multisystem organ failure, extrahepatic or extrabiliary malignancy or infection, advanced cardiac or pulmonary disease, human immunodeficiency virus infection, and active alcohol or illicit substance abuse.34

Relative contraindications include comorbidities that have a potential to reduce survival but that allow for the option of transplantation. Examples include renal insufficiency, a primary hepatobiliary malignancy greater than 5 cm, hemochromatosis, spontaneous bacterial peritonitis, age older than 65 years, poor social support, and the inability to comply with an immunosuppression protocol.34

**Table 4**

<table>
<thead>
<tr>
<th>Clinical and laboratory measurements</th>
<th>Points scored for increased abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalopathy (grade)</td>
<td>1</td>
</tr>
<tr>
<td>Ascites</td>
<td>Mild (or controlled by diuretics)</td>
</tr>
<tr>
<td>Prothrombin time (seconds prolonged)</td>
<td>1</td>
</tr>
<tr>
<td>or INR</td>
<td>1.7</td>
</tr>
<tr>
<td>Albumin (g per dL)</td>
<td>1.7 to 2.3</td>
</tr>
<tr>
<td>Bilirubin (mg per dL)</td>
<td>2.8 to 3.5</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>

A score of 5 to 6 = grade A; 7 to 9 = grade B; 10 to 15 = grade C.
INR = International Normalized Ratio.


**REFERENCES**


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Cirrhosis and Chronic Liver Failure—Part II


CLINICAL PRACTICE

Non-invasive prediction of fluid responsiveness during major hepatic surgery†‡

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Background. The aim of this study was to evaluate potential predictors of fluid responsiveness obtained during major hepatic surgery. The predictors studied were invasive monitoring of intravascular pressures (radial and pulmonary artery catheter), including direct measurement of respiratory variation in arterial pulse pressure (PPVart), transoesophageal echocardiography (TOE), and non-invasive estimates of PPVart from the infrared photoplethysmography waveform from the Finapres® (PPVfina) and the pulse oximetry waveform (PPVsat).

Methods. We conducted a prospective study of 54 fluid challenges (250 ml colloid) given for haemodynamic instability in eight patients undergoing hepatic resection. Fluid responsiveness was defined as an increase in stroke volume index (SVI) >10%. The following variables were recorded before each fluid challenge: right atrial pressure (RAP), pulmonary artery occlusion pressure (PAOP), PPVart, PPVfina, PPVsat, and the TOE-derived variables left ventricular end-diastolic area index (LVEDAI), early/late (E/A) diastolic filling wave ratio, deceleration time of the E wave (MDT) of mitral flow and the systolic fraction of the pulmonary venous flow (SF).

Results. Only PPVfina, PPVart (both P<0.001), PPVsat (P=0.02), LVEDAI and MDT (both P=0.04) were different in responder vs non-responder fluid challenges. The areas under the receiver operating characteristic (ROC) curves were 0.81 (PPVfina), 0.79 (PPVart), 0.70 (LVEDAI), 0.68 (PPVsat and MDT), 0.63 (RAP), 0.62 (E/A), 0.55 (PAOP) and 0.42 (SF). The areas under the ROC curves for RAP, E/A, PAOP and SF were significantly less than that for PPVfina (P<0.05 in each case). Only PPVart (r=0.59, P=0.0001) and PPVfina (r=0.56, P=0.0001) correlated with the fluid challenge-induced changes in SVI.

Conclusions. PPVart and PPVfina predict fluid responsiveness during major hepatic surgery. This suggests that intraoperative monitoring of fluid responsiveness may be implemented simply and non-invasively.

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Recent studies have shown that intraoperative optimization of cardiac output (CO) by repeated volume loading reduces postoperative morbidity and shortens hospital stay following abdominal surgery.1 However, unnecessary i.v. fluids may be deleterious, and intraoperative fluid restriction has also been shown to improve clinical outcome.2 During major hepatic surgery, intravascular volume expansion is constantly required, but the safety margin in fluid management is quite narrow, as high central venous pressure may increase blood loss, transfusion requirements and length of


‡This article is accompanied by the Editorial.
hospital stay.\(^3\) Preload assessment is therefore crucial to guide fluid therapy and to prevent excessive fluid loading. Haemodynamic variables obtained through pulmonary artery catheterization have long been a mainstay for preload and volume status assessment, although increasingly questioned in critical care and perioperative monitoring.\(^4\) Over the past few years, new indices, often qualified as ‘dynamic’ (as opposed to ‘static’) indicators of cardiac preload, based on respiratory variations of invasively measured arterial pressure or of stroke volume [measured using transoesophageal echocardiography (TOE) or Doppler], have been shown to predict haemodynamic response to volume expansion in mechanically ventilated patients in the intensive care unit.\(^5\)–\(^7\) More specifically, these indices, when measured before a fluid challenge, distinguish between responders who will increase their stroke volume in response to fluid and non-responders whose stroke volume will not change.\(^5\)–\(^7\) From these studies, optimal threshold (cut-off) values to guide fluid administration have been determined and are now proposed for clinical practice.\(^7\)

Several studies have extended this assessment to the perioperative period, but, apart from one study in neurosurgery,\(^8\) measurements were performed exclusively before\(^6\)–\(^11\) or after surgery.\(^11\)–\(^14\) Such experimental conditions do not necessarily reflect intraoperative haemodynamic instability. In addition, tidal volumes, aortic compliance, peripheral resistance and abdominal pressure are likely to vary during abdominal surgery. As a result, threshold values for dynamic predictors during surgery may be different from those reported in other patients. Finally, because the widespread use of arterial catheters and transoesophageal echocardiography cannot be advocated in routine surgery, potential non-invasive predictors of fluid responsiveness, such as pulse oximetry plethysmographic waveform,\(^15\) should also be evaluated. The aims of the present study were to measure, before repeated fluid challenges, a number of static and dynamic variables derived from invasive and non-invasive monitoring, to determine their optimal thresholds for predicting fluid responsiveness and to compare their ability to predict fluid responsiveness in patients undergoing hepatic surgery. The hypotheses tested were that (i) dynamic indices predict fluid responsiveness better than static indices under intraoperative conditions and (ii) non-invasive dynamic indices are as sensitive and specific predictors as invasive indices for predicting fluid responsiveness.

**Patients and methods**

After institutional approval by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale de Lille and written informed consent, eight patients scheduled for major hepatic surgery were enrolled. Patients with valvular heart disease or a history of arrhythmias were excluded. Anaesthesia was induced with sufentanil 0.5 \(\mu g\) kg\(^{-1}\), propofol 2 mg kg\(^{-1}\) and atracurium 0.5 mg kg\(^{-1}\), and maintained with isoflurane at an expired fraction of 0.5% in a 50% oxygen/50% nitrogen mixture and continuous i.v. sufentanil 0.3 \(\mu g\) kg\(^{-1}\) h\(^{-1}\). Intraoperative muscle paralysis was maintained by the continuous i.v. administration of atracurium 0.5 mg kg\(^{-1}\) h\(^{-1}\). Controlled mechanical ventilation was maintained throughout the procedure with a tidal volume of 8–10 ml kg\(^{-1}\) and an inspiratory-expiratory ratio of 1:2. The ventilatory frequency was set to maintain an end-tidal \(PCO_2\) range of 3.8–4.7 kPa (Cato, Dräger, Lübeck, Germany). No changes to the ventilator settings were made during the study period. To minimize intraoperative hypothermia, patients were covered from sternum up to the shoulders with a forced-air warming blanket.

**Haemodynamic measurements**

All patients were monitored using a 20-G radial arterial catheter (Seldicath 3 French, Plastimed, Saint Lieu la Forêt, France) and a pulmonary artery catheter (PAC, Swan-Ganz catheter, 7.5 French; Baxter Edwards, Lifescience, LLC, Irvine, CA). In addition, finger arterial pressure was monitored non-invasively through a FinapresTM (Ohmeda Monitoring Systems, Englewood, CO). Transducers were positioned at the mid-axillary level with atmospheric pressure used as the zero reference level. Calibration of both monitors was confirmed using calibration tests providing series of 100 or 150 mm Hg square pulses. The correct position of the pulmonary artery catheter in West’s zone 3 was verified using a method described previously.\(^16\) Right atrial pressure (RAP) and pulmonary artery occlusion pressure (PAOP) were measured at end-expiration and averaged over three consecutive respiratory cycles. CO was measured by thermodilution, using the average of five measurements obtained by the injection of 10 ml of dextrose at room temperature randomly during the respiratory cycle. Cardiac index (CI) and stroke volume index (SVI) were calculated using standard formulas.

**Data acquisition**

To record the invasive arterial pressure and the pulse oximetry plethysmographic curve onto a computer (Machintosh LC III, Apple, Cupertino), the analog output (M1084, MP) from the anaesthesia monitor (Monitor Hewlett-Packard, M1165A, Model 56, Les Ulis, France) was converted using an analog-to-digital interface (Biopac MP 100, Systems Inc., Santa Barbara, CA) and acquired using Acknowledge software version 3.1.2 (Biopac. Systems Inc., Santa Barbara, CA). The non-invasive arterial pressure curve signal obtained from the FinapresTM device was simultaneously recorded via the same interface and software. Recordings were analysed off-line with the reviewer unaware of the haemodynamic data. After confirming the absence of artifact, arterial pressure (invasive and non-invasive) curves and pulse oximetry waveform were measured on a beat-to-beat basis. Pulse pressure (PP), the
difference between systolic and diastolic pressure of the preceding beat, was calculated from the invasive arterial (PPart) and Finapres™ non-invasive (PPfina) pressure curves. Likewise, the difference between the maximal and minimal values of the pulse oximetry curve was calculated beat-to-beat and assimilated to a pulse pressure (PPsat), expressed in arbitrary units. Maximal and minimal values for all the aforementioned PPs (PPmax and PPmin, respectively) were determined over a respiratory cycle. All PP measurements were automatically calculated by the software, thus preventing any inter- or intra-observer variations. The PP variation (PPV) was calculated as described previously: $PPV\% = \frac{PP_{max} - PP_{min}}{PP_{mean}} \times 100$.

During the surgical procedure, haemodynamic instability was suspected by the occurrence of a 20% decrease in invasive systolic arterial pressure, a 20% increase in heart rate, or both compared with preoperative baseline values. For each suspected episode of haemodynamic instability, a volume loading step (VLS) was performed using 250 ml of colloid solution (4% modified fluid gelatin, Gelofusine®, B. Braun Medical SAS, Boulogne Billancourt, France) over 10–15 min. A complete set of haemodynamic and echocardiographic measurements including all the studied variables (RAP, PAOP, PVArt, PVPsat, PPVfina, LVEDAI, E/A, MDT, and SF) was performed and recorded just before VLS (baseline values) and was repeated 2–5 min after VLS.

The SVI increase induced by volume expansion was used to classify each VLS as responder (≥10% increase in SVI) or non-responder (<10% increase in SVI). In responders, successive VLSs were performed until non-responder status was reached. When several suspected episodes of hypovolemia occurred during the surgical procedure, the whole protocol was repeated for each episode.

Because the validity of this analysis relies on the absence of haemodynamic changes other than the standardized increase in preload secondary to the 250 ml VLS, the protocol was interrupted before post-VLS measurements in case of evident interference (especially uncontrolled haemorrhage).

Statistical analysis
All haemodynamic and echocardiographic variables are presented as mean (SD). Comparisons between baseline and post-VLSs values used the Wilcoxon signed rank sum test for repeated measures. To assess the ability of the variables to discriminate between responder and non-responder VLSs, the values of each variable (PAOP, RAP, PVArt, PVPsat, PPVfina, LVEDAI, SF, E/A and MDT) measured before VLSs leading to a positive response were compared with those measured before a negative response using the Mann–Whitney U-test. Receiver operating characteristic (ROC) curves were generated for all the variables. The most discriminating threshold value (the cut-off value that maximized the sum of the sensitivity and specificity) was determined for each variable. The area under the curve (AUC) of each variable was calculated and AUCs were compared as described previously.18 Correlations between the pre VLS values of each variable and the SVI response to subsequent fluid infusion were determined using Spearman’s rank correlation coefficient calculation. Finally, agreement between the two non-invasive indices of PP variation (PPVfina and PPVsat) and PVArt was assessed using Bland–Altman analysis. Statistical analysis was performed using SPSS software, version 10.1 (SPSS Inc., Chicago, IL). For all comparisons, $P<0.05$ was considered significant.

Results
Patients were classified ASA I or II, with ages ranging between 45 and 71 yr. All underwent right hepatectomy.
Fluid responsiveness during hepatic surgery

Table 1 Changes in haemodynamic variables during volume loading steps (VLSs). Values are mean (SD). HR, heart rate; MAP, mean arterial pressure; CI, cardiac index; SVI, stroke volume index; SVRI, systemic vascular resistance index. *P<0.05 in comparison with responders at the same stage of volume loading. †P<0.05 in comparison with baseline

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline Responders</th>
<th>Baseline Non-responders</th>
<th>After 250 ml Responders</th>
<th>After 250 ml Non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats min⁻¹)</td>
<td>81 (14)</td>
<td>87 (14)</td>
<td>87 (14)</td>
<td>83 (13)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>73 (14)</td>
<td>70 (14)</td>
<td>70 (14)</td>
<td>73 (13)</td>
</tr>
<tr>
<td>CI (litre min⁻¹ m⁻²)</td>
<td>2.2 (0.5)</td>
<td>2.8 (0.5)*</td>
<td>2.8 (0.6)*</td>
<td>2.8 (0.6)</td>
</tr>
<tr>
<td>SVI (ml m⁻²)</td>
<td>34 (7)</td>
<td>44 (8)*</td>
<td>43 (6)†</td>
<td>42 (8)</td>
</tr>
<tr>
<td>SVRI (dyn cm⁻¹ m⁻³)</td>
<td>2202 (447)</td>
<td>1843 (475)*</td>
<td>1948 (505)†</td>
<td>1946 (467)</td>
</tr>
</tbody>
</table>

Table 2 Haemodynamic and echocardiographic indicators of fluid responsiveness measured before responder and non-responder volume loading steps (VLSs). Values are mean (SD). PPVfina, respiratory changes in non-invasive arterial pulse pressure; PPVart, respiratory changes in invasive arterial pulse pressure; PPVsat, respiratory changes in the pulse oximetry plethysmographic waveform; MDT, mitral deceleration time; LVEDAI, left ventricular end-diastolic area index; RAP, right atrial pressure; E/A, ratio of the early (E) and the late (A) peak velocities of the mitral flow; SF, systolic fraction; PAOP, pulmonary artery occlusion pressure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Responders VLSs</th>
<th>Non-responders VLSs</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPVfina (%)</td>
<td>16 (8)</td>
<td>8 (3)</td>
<td>0.0001</td>
</tr>
<tr>
<td>PPVart (%)</td>
<td>15 (7)</td>
<td>9 (4)</td>
<td>0.0005</td>
</tr>
<tr>
<td>PPVsat (%)</td>
<td>14 (11)</td>
<td>9 (7)</td>
<td>0.02</td>
</tr>
<tr>
<td>MDT (ms)</td>
<td>221 (42)</td>
<td>196 (37)</td>
<td>0.036</td>
</tr>
<tr>
<td>LVEDAI (cm² m⁻²)</td>
<td>9.8 (3.2)</td>
<td>12.1 (3.9)</td>
<td>0.038</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>6 (4)</td>
<td>8 (4)</td>
<td>0.09</td>
</tr>
<tr>
<td>E/A</td>
<td>1.48 (0.37)</td>
<td>1.72 (0.57)</td>
<td>0.17</td>
</tr>
<tr>
<td>SF (%)</td>
<td>53 (14)</td>
<td>55 (11)</td>
<td>0.38</td>
</tr>
<tr>
<td>PAOP (mm Hg)</td>
<td>8 (4)</td>
<td>9 (4)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Table 3 Receiver operating characteristic curve analysis of haemodynamic and echocardiographic parameters in prediction of fluid responsiveness. AUC (95% CI), area under ROC curve (95% CI); PPVfina, respiratory changes in non-invasive arterial pulse pressure; PPVart, respiratory changes in invasive arterial pulse pressure; LVEDAI, left ventricular end-diastolic area index; MDT, mitral deceleration time; PAOP, pulmonary artery occlusion pressure; SF, systolic fraction; NA, non applicable (AUC<0.5). *P<0.05 vs PPVart and PPVfina

<table>
<thead>
<tr>
<th>Variable</th>
<th>AUC (95% CI)</th>
<th>Optimal threshold value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPVfina</td>
<td>0.81 (0.70–0.93)</td>
<td>14.0%</td>
</tr>
<tr>
<td>PPVart</td>
<td>0.79 (0.67–0.92)</td>
<td>12.5%</td>
</tr>
<tr>
<td>LVEDAI</td>
<td>0.70 (0.53–0.88)</td>
<td>10.5 cm² m⁻²</td>
</tr>
<tr>
<td>PPVsat</td>
<td>0.68 (0.54–0.82)</td>
<td>9.5%</td>
</tr>
<tr>
<td>MDT</td>
<td>0.68 (0.52–0.84)</td>
<td>234 ms</td>
</tr>
<tr>
<td>RAP</td>
<td>0.63 (0.49–0.77)*</td>
<td>10 mm Hg</td>
</tr>
<tr>
<td>E/A</td>
<td>0.62 (0.45–0.78)*</td>
<td>1.84</td>
</tr>
<tr>
<td>PAOP</td>
<td>0.55 (0.39–0.70)*</td>
<td>8 mm Hg</td>
</tr>
<tr>
<td>SF</td>
<td>0.42 (0.26–0.60)*</td>
<td>NA</td>
</tr>
</tbody>
</table>

except one with left hepatic lobectomy. All remained in the supine position during surgery, and hepatic inflow cross clamping was not used. Initial echocardiographic measurements showed normal LV ejection fraction (>50%) in all patients. The mean estimated total blood loss was 820 ml (range: 200–1400 ml). A total of 54 VLSs (range 5–8 per patient) were performed. Twenty-three responder VLSs (increase in SVI ranging from 10 and 75%; 1–4 per patient) and 31 non-responder VLSs (change in SVI ranging from −30 and +9%; 2–5 per patient) were identified. No more than two successive responder VLSs was observed in any patient. Because of intraoperative conditions (gastric mobilization, compression by retractors, or both), echocardiographic data were obtained in only 48 (20 responder and 28 non-responder) VLSs for MDT, SF and E/A, and 39 (16 responder and 23 non-responder) VLSs for LVEDAI. Peak and plateau airway pressures before the first VLS ranged from 12 to 19 cm H₂O and from 9 to 17 cm H₂O, respectively. Moderate intraoperative variations in airway pressures without associated changes in tidal volume were observed in all patients, with the difference between the highest and the lowest plateau pressure ranging between 2 and 9 cm H₂O.

The main haemodynamic variables recorded before and after VLSs are summarized in Table 1. Comparison of variables measured immediately before responder and non-responder VLSs showed that PPVart, PPVfina, PPVsat and MDT were higher, and the LVEDAI lower, in the responder VLS group than in the non-responder group (Table 2). There was no significant difference in RAP, PAOP, E/A and SF between the two groups (Table 2). The performance of variables in discriminating responder and non-responder VLSs was evaluated by constructing ROC curves. The areas under the ROC curves and the optimal threshold value for each variable are reported in Table 3. Greater areas were obtained with indices derived from respiratory changes in arterial pressure (PPVart and PPVfina) while areas obtained with RAP, PAOP, E/A and SF were not significantly different from 0.5 (i.e. the test variable was no better than chance) (Fig. 1). A significant correlation with the VLS-induced change in SVI was found for only four variables measured before VLS: PPVart (r=0.59, P=0.0001), PPVfina (r=0.56, P=0.0001) (Fig. 2), PPVsat (r=0.29, P=0.04) and MDT (r=0.29, P=0.05). Bland–Altman analysis demonstrated a small bias between non-invasive estimates of PPV (PPVfina and PPVsat) and PPVart (mean difference: −0.1 and 1.0%, respectively), but precision, as assessed by the 95% limits of agreement, was better with PPVfina than with PPVsat (Fig. 3).
Discussion

Recent studies have consistently shown that intraoperative optimization of SVI by repeated volume loading (probably by preventing ‘occult’ peripheral hypoperfusion), and also i.v. fluid restriction (to avoid deleterious fluid overload), improves clinical outcome and shortens hospital stay following abdominal surgery. Accurate predictors of fluid responsiveness are thus needed in the operating theatre. The data from the present study demonstrate that PPVart is a better predictor of fluid responsiveness than static variables, including the TOE-derived ones, during hepatic surgery with haemodynamic instability. Moreover, non-invasive PPVfina provides a prediction as accurate as that obtained from invasive PPVart measurements. Estimated optimal thresholds for both dynamic indices were in the same range as those previously established for PPV in the ICU. This suggests that monitoring of fluid responsiveness may be implemented simply and non-invasively to optimize fluid therapy during surgery.
Haemodynamic monitoring to assess preload responsiveness using arterial pressure or LV stroke volume variation has been validated primarily in ICU patients.5–7 Several studies have extended this assessment to the perioperative period, but measurements in these studies were performed under conditions of haemodynamic stability before9–11 or after surgery.11–14 Our study is the first to determine the relevance of ventilation-induced arterial PP variation in cases of haemodynamic instability (recent hypotension, tachycardia, or both) while abdominal surgery is still underway. In contrast with intensive care patients, during major hepatic surgery, chest and abdominal compliance, airway pressures, aortic compliance and peripheral resistance are expected to vary over several minutes rather than several hours or days. In fact, we observed only moderate variations in airway pressure throughout surgery in all patients. Our findings strongly suggest that intraoperative conditions do not alter the clinical usefulness of respiratory variations in PP. Indeed, the optimal PPVart threshold value (12.5%) found in the present study is in the range of those previously obtained in ICU patients (from 11 to 13%).7

In agreement with previous reports, dynamic variables performed better than ventricular filling pressure-derived indices (RAP and PAOP) in predicting fluid responsiveness.5–7 The area under the ROC curve for PPVart in the present study (0.79) was lower than those found for ventilation-induced arterial pressure variation variables in ICU patients (between 0.94 and 0.98), but is in the same range as that established in most (0.819; 0.8212) but not all (0.87–0.96 11) studies before or after surgery. In the present study, this result appeared essentially to be because of ‘false negative cases’, that is patients responding to VLSs who were predicted to be non-responders (PPVart <12.5%) (the left upper quadrant in Fig. 2). Recent studies have shown that the degree of tidal volume and chest wall compliance influence the magnitude of PPVart, with small variations in pleural and transpulmonary pressures (resulting from small tidal volume or increased chest compliance)
leading to such false negative cases. However, in our study, patients responding to VLS with PPVart <12.5% and those with PPVart >12.5% (true positives) had similar tidal volumes and airway pressures (data not shown). In fact, most of the responders to VLS with PPVart value less than 12.5% had to moderate increases in SVI (between 10 and 20%), with pre-VLS values of PPVart greater than 8% (Fig. 2). This implies that PPVart values ranging from 8 to 13% may constitute an inconclusive or 'grey zone' where its predictive value is uncertain.

Non-invasiveness is of importance in anaesthesia. Improved outcome following intraoperative optimization of SVI by fluid therapy has been shown even in routine surgery, where invasive monitoring is usually not recommended. A major finding of the study is that PPVfina provides a reliable non-invasive index of fluid responsiveness. One preliminary report demonstrated good agreement between PPVfina and PPVart in ICU patients but did not assess the value of PPVfina itself in predicting SVI response to fluid loading. The Finapres is a non-invasive continuous beat to beat monitor of the finger arterial pressure waveform. The finger arteries are compressed at a fixed diameter, by applying an external pulsating pressure determined through infrared photoplethysmography in the finger cuff. Finapres data have not been found to be a reliable substitute for radial or brachial intra-arterial pressures in anesthetized patients. We also found a poor agreement between arterial pressure from the Finapres and invasive monitoring in our patients (data not shown). However, a recent article showed that, in experimental conditions, SVI variations can be modelled through pulse waveform analysis and PPV can be derived from the signal and is correlated for blood loss. Our results show not only a good agreement between PPVfina and PPVart but also that PPVfina has the same predictive value as PPVart in anesthetized patients undergoing hepatic surgery. The correlations between the VLS-induced change in SVI and PPVart and PPVfina, although not very close, confirm that these variables are associated, that is the VLS-induced changes in SVI tend to be higher for higher values of PPV.

Another surrogate variable for PPVart could be PPVsat. The pulse plethysmographic waveform represents pulse-dependent changes in volume of arterial blood and is related to stroke volume. Indeed, several reports have found a consistent correlation between dynamic indices derived from plethysmographic waveform and corresponding invasive variables. Changes in the plethysmographic waveform after blood withdrawal also correlate well with corresponding changes in the arterial waveform, but no study has tested the relation of these indices with fluid responsiveness. However, in our study, both the agreement between PPVsat and PPVart and the prediction of VLS-induced change in SVI with PPVsat were weak. This may be explained by the sensitivity of the plethysmographic signal to humoral and neurogenic factors. In addition, proprietary software included in pulse oximeters are designed to provide a graphic display for pulse oximetry monitoring and not for PP variation assessment. The software generates a signal that is substantially filtered, amplified and smoothed before display. As a result, whether using different pulse oximeters would provide similar results remains to be investigated.

While filling pressure-derived indices (RAP and PAOP) did not predict fluid responsiveness, the TOE-derived static variables exhibited contrasting results. TOE has been reported to be of value for fluid management during hepatic surgery. We found that LVEDAI was a potentially useful variable for TOE monitoring of fluid responsiveness with an AUC of 0.70, although there was no significant correlation between LVEDAI and VLS-induced changes in SVI. Previous reports on correlation between LVEDAI and SVI variation in response to volume expansion have led to conflicting results. Operator dependency and difficulty of measuring ventricular surfaces through manual planimetry in real-time may account for these discrepancies. In addition, the estimation of the LV end diastolic area by TOE does not always accurately reflect LVED volume and hence LV preload. Nevertheless, LVEDAI is usually considered an acceptable measure of LV preload in clinical practice, and its value as an index of preload responsiveness is thought to mainly depend on whether biventricular function is normal or not.

Doppler measurement of mitral flow allows indirect evaluation of the individual LV diastolic pressure/volume relationship and has been proposed as a predictor of the increase in CO after intravascular fluid challenge. E-wave deceleration time (expressed as MDT in the present study) has long been known as a preload-dependent transmural flow Doppler variable. Our study is the first to show that MDT predicts fluid responsiveness in patients, but it did not perform as well as dynamic variables. Although pulmonary vein flow has been found to be correlated to E-wave MDT, we did not find it to be of value for fluid responsiveness prediction.

Finally, only one study, performed by Lattik and colleagues, has shown that E/A may predict fluid responsiveness. Our data did not confirm the results of Lattik’s study, although the area under ROC curve obtained in our patients (0.62) was only slightly smaller than that reported in their study (0.71). The larger volume used for fluid challenges (twice that given in our study) and the definition of fluid responsiveness (20% increase in SVI) used in that study may account for these differences. In fact, several recent studies have shown that reliable prediction of fluid responsiveness by echocardiography is likely to require the use of dynamic indices.

The present study was designed to evaluate the predictive value of various indices during surgery conditions. It is possible that, despite our aiming to discard VLS with uncontrolled haemodynamic variations, changes other than the standardized increases in preload by 250 ml VLSs may have occurred between pre- and post-VLSs measurements and affected the validity of our results. Because we tested a
number of different measures as possible predictors of fluid responsiveness, the risk of type 1 error may have been underestimated. However, PPVart and PPVfina were the only predictors of fluid responsiveness, and very significant differences between responder and non-responder VLs were found only for these two variables (Table 2). In addition, repeated measurements were performed throughout surgery in each patient and then treated as independent observations for the analysis. However, this was done for all studied variables, and the large intra-individual haemodynamic variations that occur in any patient undergoing major hepatic surgery make it unlikely that these repeated measurements biased the analysis. We also verified that results were not biased by measurements derived from a particular patient (data not shown). Another limitation of our study was that some TOE measurements could not be performed, but this limitation must be acknowledged as representing real clinical practice. Non-invasive indices of PP variation could be measured in all patients throughout surgery. In practice, however, the signals of both the Finapres™ device and the pulse oximeter may be unstable or non-satisfactory, thus altering or preventing respiratory variation measurements, especially in patients with severe peripheral hypoperfusion. There are no monitors currently available that display these non-invasive indices of fluid responsiveness in real-time, and such measurements still necessitate off-line analysis of computer or graphic recordings. Finally, because no patient received epidural analgesia, whether the same results would be observed in patients with neuraxial blockade remains to be demonstrated.

Acknowledgements
The authors thank Drs Thierry Letourneau, MD (Department of Cardiology, University Hospital, Lille, France), Frederic Michard, MD, PhD, and Jean-Louis Teboul, MD, PhD (Department of Critical Care Medicine, Bicêtre University Hospital, AP-HP, Paris, France) for expert advice and assistance in data acquisition. Financial support was provided solely from institutional and departmental sources.

References
7 Michard F. Changes in arterial pressure during mechanical ventilation. Anesthesiology 2005; 103: 419–28
22 Michard F, Mercat A, Chemla D, Teboul JL. Noninvasive assessment of respiratory changes in arterial pulse pressure by infrared photoplethysmography (finapres®) in mechanically ventilated patients. Am J Respir Crit Care Med 1999; 159: A520
23 Stokes DN, Clutton-Brock T, Patel C, Thompson JM, Hutton P. Comparison of invasive and non-invasive measurements of
31 Lattik R, Couture P, Denault AY, et al. Mitral Doppler indices are superior to two-dimensional echocardiographic and hemodynamic variables in predicting responsiveness of cardiac output to a rapid intravenous infusion of colloid. Anesth Analg 2002; 94: 1092–9
Hepatopulmonary Syndrome — A Liver-Induced Lung Vascular Disorder

Roberto Rodríguez-Roisin, M.D., and Michael J. Krowka, M.D.

The hepatopulmonary syndrome is characterized by a defect in arterial oxygenation induced by pulmonary vascular dilatation in the setting of liver disease; patients of all ages can be affected. This clinical syndrome has three components: liver disease, pulmonary vascular dilatation, and a defect in oxygenation. A classification of the severity of the hepatopulmonary syndrome based on abnormalities in oxygenation is vital because severity influences survival and is useful in determining the timing and risks of liver transplantation (Table 1). The vascular component includes diffuse or localized dilated pulmonary capillaries and, less commonly, pleural and pulmonary arteriovenous communications. Arterial hypoxemia is common in the context of hepatic disease; its cause is often multifactorial (e.g., ascites, hepatic hydrothorax, and chronic obstructive pulmonary disease in patients with alcoholism), and in the particular case of the hepatopulmonary syndrome, the pathophysiological features are unique. The definition of arterial hypoxemia associated with the hepatopulmonary syndrome is based on measurements of the partial pressure of oxygen that are performed with the patient in a standardized position, preferably sitting and at rest. The use of the more sensitive alveolar–arterial oxygen gradient is important because it can increase abnormally before the partial pressure of oxygen itself becomes abnormally low as the gradient measure compensates for the reduced levels of arterial carbon dioxide and hyperventilation, along with respiratory alkalosis, that are common in cirrhosis (Table 1).

Contrast-enhanced transthoracic echocardiography with saline (shaken to produce microbubbles >10 μm in diameter) is the most practical method to detect pulmonary vascular dilatation (Fig. 1). After the administration of agitated saline in a peripheral vein in the arm, microbubble opacification of the left atrium within three to six cardiac cycles after right-atrial opacification indicates microbubble passage through an abnormally dilated vascular bed; microbubbles do not pass through normal capillaries (normal range of the capillary diameter, <8 to 15 μm). This qualitative approach is more sensitive and less invasive than the injection of technetium-99m–labeled macroaggregated albumin in the peripheral vein for lung scanning with quantitative uptake in the brain (Fig. 2). However, neither method can be used to discern discrete arteriovenous communications from diffuse precapillary and capillary dilatations or intracardiac shunt. The former distinction can be made by means of pulmonary angiography. The latter distinction can be made by means of transesophageal contrast-enhanced echocardiography that directly reveals the intraatrial septum, identifies the existence of an intraatrial right-to-left shunt, and shows the passage of microbubbles entering the left atrium through the atrial septal abnormality or pulmonary veins. In patients with the hepatopulmonary syndrome, pulmonary angiography should be performed only when the hypoxemia is severe (i.e., the partial pressure of oxygen is <60 mm Hg [8.0 kPa]), poorly responsive to administration of 100% oxygen, and when there is a strong suspicion (on the basis of a chest com-
Computed tomographic scan) of direct arteriovenous communications that would be amenable to embolization.6

**Clinical Manifestations**

Dyspnea on exertion, at rest, or both is the predominant presenting symptom, usually after years of liver disease. However, dyspnea is a nonspecific finding that is common in patients with advanced liver diseases because of the range of hepatic complications such as anemia, ascites and fluid retention, and muscle wasting. There are no signs, symptoms, or hallmarks of the hepatopulmonary syndrome on physical examination. However, the presence of spider nevi, digital clubbing, cyanosis, and severe hypoxemia (partial pressure of oxygen, <60 mm Hg) strongly suggests hepatopulmonary syndrome (Fig. 3).1 If the partial pressure of oxygen in arterial blood decreases by 5% or more or by 4 mm Hg (0.5 kPa) or more when the patient moves from a supine to an upright position (called orthodeoxia), he or she may describe worsening dyspnea (platypnea) related to further ventilation–perfusion mismatch.7 The chest radiograph is frequently nonspecific, perhaps suggesting a mild interstitial pattern in the lower lung that may reflect the existence of diffuse pulmonary vascular dilatation. Portopulmonary hypertension, which is sometimes associated with mild hypoxemia but rarely with severe hypoxemia, is frequently confused with the hepatopulmonary syndrome.8 In portopulmonary hypertension, obstruction of flow to the pulmonary arterial bed is caused by vasoconstriction, as well as proliferation of the endothelium and smooth muscle, in situ thrombosis, and plexogenic arteriopathy. Increasing pulmonary vascular resistance to flow leads to right heart failure and death.1 The diagnosis is made by means of right heart catheterization and according to pulmonary hemodynamic criteria (Table 2).

A decrease in the single-breath diffusing capacity for carbon monoxide is the only routine pulmonary-function test that is consistently abnormal result in patients with the hepatopulmonary syndrome.9 However, low diffusing capacity is not specific10 and may not normalize (as do other gas-exchange indexes) after liver transplantation,11,12

### Table 1. Diagnostic Criteria for the Hepatopulmonary Syndrome.1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygenation defect</td>
<td>Partial pressure of oxygen &lt;80 mm Hg or alveolar–arterial oxygen gradient ≥15 mm Hg while breathing ambient air</td>
</tr>
<tr>
<td>Pulmonary vascular dilatation</td>
<td>Positive findings on contrast-enhanced echocardiography or abnormal uptake in the brain (&gt;6%) with radioactive lung-perfusion scanning</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Portal hypertension (most common) with or without cirrhosis</td>
</tr>
<tr>
<td>Degree of severity</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Alveolar–arterial oxygen gradient ≥15 mm Hg, partial pressure of oxygen ≥80 mm Hg</td>
</tr>
<tr>
<td>Moderate</td>
<td>Alveolar–arterial oxygen gradient ≥15 mm Hg, partial pressure of oxygen ≥60 to &lt;80 mm Hg</td>
</tr>
<tr>
<td>Severe</td>
<td>Alveolar–arterial oxygen gradient ≥15 mm Hg, partial pressure of oxygen ≥50 to &lt;60 mm Hg</td>
</tr>
<tr>
<td>Very severe</td>
<td>Alveolar–arterial oxygen gradient ≥15 mm Hg, partial pressure of oxygen &lt;50 mm Hg (≤300 mm Hg while the patient is breathing 100% oxygen)</td>
</tr>
</tbody>
</table>

* All criteria were determined by means of positive contrast-enhanced echocardiography (i.e., microbubble opacification of the left heart chambers three to six cycles after right atrial passage). The abbreviated formula for the alveolar–arterial gradient is as follows:

\[
\text{PaO}_2 - \text{PaO}_2 = (F\text{I}O_2 \cdot [P_{atm} - PH_2O] - [\text{PaCO}_2/0.8]) - \text{PaO}_2,
\]

where \( \text{PaO}_2 \) denotes partial pressure of alveolar oxygen, \( \text{Pa}_2 \) partial pressure of arterial oxygen, \( F\text{I}O_2 \) fraction of inspired oxygen, \( P_{atm} \) atmospheric pressure, \( PH_2O \) partial pressure of water vapor at body temperature, and \( \text{PaCO}_2 \) partial pressure of arterial carbon dioxide (0.8 corresponds to the standard gas-exchange respiratory ratio at rest); the normal range is 4 to 8 mm Hg (0.5 to 1.1 kPa). The normal range for the partial pressure of oxygen is 80 to 100 mm Hg (10.7 to 13.3 kPa) at sea level, while the patient is at rest and breathing ambient air. For patients older than 64 years of age, a value of ≤70 mm Hg (9.3 kPa) for \( \text{PaO}_2 \) or ≥20 mm Hg for the alveolar-arterial gradient is often used. Ambient air is the respired gas unless otherwise indicated. To convert millimeters of mercury to kilopascals, multiply by 0.133.

† Data are from Rodríguez-Roisin et al.1
suggesting structural remodeling of the pulmonary vasculature.\textsuperscript{13}

Any acute or chronic form of liver disease can coexist with hypoxemia due to pulmonary vascular dilatation; thus, portal hypertension is not required for the syndrome to be manifested. Most cases of the hepatopulmonary syndrome are associated with clinical evidence of cirrhotic and noncirrhotic portal hypertension (e.g., gastroesophageal varices, splenomegaly, or ascites). Less appreciated is the fact that the criteria for the hepatopulmonary syndrome have been met in patients with acute liver failure and ischemic hepatitis.\textsuperscript{14} There is no relationship between the presence or severity of the hepatopulmonary syndrome and the severity of liver disease as assessed on the basis of the Child–Turcotte–Pugh classification or the Model for End-Stage Liver Disease (MELD).\textsuperscript{15}

Advanced liver disease associated with several pulmonary complications, pleural complications, or both (Table 3) is part of the differential diagnosis of the hepatopulmonary syndrome. Fortunately, the use of qualitative echocardiography, lung-scanning quantification with uptake in the brain, or both can distinguish hypoxemia induced by the hepatopulmonary syndrome from all other causes of hypoxemia.\textsuperscript{5} Clinical judgment may still be necessary, however, to unravel the severity of hypoxemia in the hepatopulmonary syndrome and in coexisting pulmonary conditions such as chronic obstructive pulmonary disease or pulmonary fibrosis; these conditions occur in up to 30% of patients with the hepatopulmonary syndrome.\textsuperscript{16}

The Rendu–Osler–Weber syndrome (also called hereditary hemorrhagic telangiectasia) and consequences of cavopulmonary anastomoses after operations for various congenital heart conditions\textsuperscript{17} also resemble the hepatopulmonary syndrome (Table 2). Both can be associated with severe hypoxemia caused by pulmonary vascular dilatation, which may be diffuse or discrete in nature.

**PREVALENCE AND NATURAL HISTORY**

The term “hepatopulmonary syndrome,” which was probably coined in 1977,\textsuperscript{18} was preceded by compelling descriptions based on autopsy and clinical findings.\textsuperscript{19–21} An autopsy study in patients with liver cirrhosis, reported in 1966 by Berthelot et al.,\textsuperscript{21} first suggested that marked pulmonary vascular dilatation may play a role in this condition.\textsuperscript{5}

Data from liver-transplantation centers indicate that the prevalence of the hepatopulmonary syndrome, including that involving mild stages (Table 1), ranges from 5 to 32%.\textsuperscript{22} No prospective, multicenter prevalence studies have been reported to date. The range in prevalence is primarily a function of varying cutoffs for the abnormal alveolar–arterial gradient and partial pressure of oxygen that are used to define gas-exchange abnormalities.\textsuperscript{22} A task force has recommended criteria that are reasonable from a clinical perspective for the alveolar–arterial gradient and the partial pressure of oxygen in patients of all ages (Table 1).\textsuperscript{1}

The natural history of the hepatopulmonary syndrome can be described by the assessment of

**Figure 1.** Transthoracic Echocardiographic Features of the Hepatopulmonary Syndrome.

The contrast-enhanced echocardiograms in Panels A and B show opacification of the right atrium (RA) and right ventricle (RV) with microbubbles and delayed opacification of the left atrium (LA) and left ventricle (LV), respectively. These findings are the standard for the diagnosis of the hepatopulmonary syndrome. A video showing the appearance of microbubbles in the right heart, followed by a delayed appearance of microbubbles (approximately five cardiac cycles later) in the left cardiac chambers, is available with the full text of this article at www.nejm.org.
survival among patients in two distinct cohorts: patients being considered for liver transplantation and those who are not candidates for this approach because of age or coexisting conditions.23 Studies have shown a median survival of 24 months and a 5-year survival rate of 23% among 37 patients who were not candidates for liver transplantation; in contrast, a control group of patients without the hepatopulmonary syndrome who did not undergo transplantation and who were matched for the cause and severity of liver disease according to the Child classification, age, and MELD score, had a median survival of 87 months, with a 5-year survival rate of 63%.15 Survival was significantly worse among patients with a partial pressure of oxygen of less than 50 mm Hg (6.7 kPa) at the time of diagnosis. These data are consistent with findings from a recent study indicating that the coexistence of the hepatopulmonary syndrome worsened the prognosis for patients with cirrhosis, even after adjustment for the Child classification of liver disease.24 The causes of death associated with the hepatopulmonary syndrome are usually multifactorial and related primarily to the complications of hepatic disease. It is rare for severe hypoxemic respiratory failure to be the primary cause of death.

**PATHOBIOLOGY**

The unique striking pathological feature of hepatopulmonary syndrome is gross dilatation of the pulmonary precapillary and capillary vessels (to 15 to 100 μm in diameter when the patient is at rest), coupled with an absolute increase in the number of dilated vessels visualized by means of injection at autopsy. In addition, a few pleural and pulmonary arteriovenous communications (shunts) and portopulmonary venous anastomoses can be seen.21 The increased wall thickness of small veins and capillary walls has also been observed.13 However, before the current definition of the syndrome and the availability of imaging techniques to identify pulmonary vascular dilatation, these findings were documented after death in patients with liver cirrhosis and various degrees of hypoxemia. Furthermore, the pulmonary vasculature in hepatic
Cirrhosis is characterized by the paradoxical combination of reduced or absent tone and some degree of inhibition of hypoxic pulmonary vasoconstriction.\textsuperscript{25}

The prerequisite of pulmonary vascular dilatation facilitates the passage of mixed venous blood either rapidly or even directly, through intrapulmonary shunt, into the pulmonary veins. The defect in oxygenation is due to a ventilation–perfusion mismatch characterized by increased blood flow while alveolar ventilation is uniformly preserved (Fig. 4), and in 30% of patients with cirrhosis, this blood flow is enhanced by the absence or impairment of hypoxic pulmonary vasoconstriction.\textsuperscript{25} The severity of hypoxemia appears to be directly related to the extent of intrapulmonary shunt, diffusion–perfusion impairment, or both; in contrast, the role of portopulmonary vascular communications is marginal.\textsuperscript{9,26-28} Ventilation–perfusion mismatch and shunt worsening constitute the key mechanisms of orthodeoxia in the hepatopulmonary syndrome, probably because of a more rigid and fixed pulmonary vascular tone, which is less liable to proportionately accommodate gravitational blood-flow changes to ventilation in dependent alveolar units.\textsuperscript{7} An increase in the partial pressure of oxygen to the breathing of 100% oxygen (\(\geq 300\) mm Hg [40.0 kPa])

\begin{table}
\centering
\caption{Differential Diagnosis and Treatment of Pulmonary Vascular Disorders Associated with Hepatic Abnormalities.\textsuperscript{9,25}}
\begin{tabular}{|l|c|c|c|c|}
\hline
Variable & Hepato-pulmonary Syndrome & Hereditary Hemorrhagic Telangiectasia & Cavo-pulmonary Anastomosis & Porto-pulmonary Hypertension \\
\hline
Type of disorder & & & & \\
Inherited & No & Yes & No & No \\
Acquired & Yes & No & Yes & Yes \\
\hline
Presentation & & & & \\
Pediatric & Yes & Yes & Yes & Yes \\
Adult & Yes & Yes & No & Yes \\
\hline
Documented genetic predisposition (familial with genetic polymorphisms) & No & Yes & No & No \\
\hline
Vascular dilatation & & & & \\
Diffuse & Yes & In rare cases & Yes & In rare cases \\
Discrete & In rare cases & Yes & Yes & No \\
Detection of lung abnormalities on contrast-enhanced echocardiography & Yes & Yes & Yes & Yes \\
Severe hypoxemia (\(\text{PaO}_2 < 50\) mm Hg [6.7 kPa]) & Yes & Yes & Yes & In rare cases \\
Normalization of hypoxemia on breathing 100% oxygen & Yes & No & No & Yes \\
\hline
Right heart catheterization and pulmonary angiography usually necessary & & & & \\
Diagnosis & In highly selected cases & Yes & Yes & Yes \\
Management & No & Yes & Rare & Yes \\
Treatment & & & & \\
Embolotherapy & In rare cases & Yes & Yes & No \\
Liver transplantation & Yes & In highly selected cases & No & In highly selected cases \\
Redirection of hepatic-vein flow & No & No & Yes & No \\
Pulmonary vasodilator therapy & No & No & No & Yes \\
\hline
\end{tabular}
\end{table}

* \(\text{PaO}_2\) denotes partial pressure of arterial oxygen.
often occurs in the hepatopulmonary syndrome.29 This response may be increased by an elevated cardiac output, indicating the complexity of gas-exchange abnormalities. An alveolar–capillary diffusion limitation to oxygen, essentially reflecting a diffusion–perfusion defect,30 predominates in advanced stages of the syndrome. These advanced stages aggravated by a high cardiac output resulting in a shorter transit time of red cells, are akin to a low diffusing capacity associated with hepatic dysfunction in general30 and with the hepatopulmonary syndrome in particular.9 The diffusing capacity may be reduced because the alveolar–capillary interface is too wide to allow for complete equilibration of carbon monoxide with hemoglobin.

Early, mild stages of the hepatopulmonary syndrome, characterized by an elevated alveolar–arterial gradient alone or a partial pressure of oxygen between 60 mm Hg and 80 mm Hg (10.7 kPa) while the patient is respiring ambient air are caused by ventilation–perfusion mismatch with or without modest shunt (<10%), whereas later, severe hepatopulmonary syndrome (partial pressure of oxygen, <60 mm Hg) may encompass all intrapulmonary determinants of abnormal gas exchange (Table 1).1 Arterial deoxygenation may also be reduced by hyperventilation, which increases the alveolar partial pressure of oxygen, and high cardiac output, which raises the mixed venous partial pressure of oxygen.

The correlation between the degree of hepatic dysfunction and portal hypertension and the prevalence and severity of the hepatopulmonary syndrome remains controversial. Rare congenital cardiac disorders without liver injury in which either hepatic venous blood flow does not reach the lung31 or portal venous blood reaches the inferior vena cava without passing through the liver (i.e., the type 1 Abernethy malformation)32 have clinical similarities to the hepatopulmonary syndrome; this provides support for the hypothesis that blood from the gut must cross the liver to prevent pulmonary vascular dilatation.

Enhanced pulmonary production of nitric oxide has been implicated as a key priming factor for the development of pulmonary vascular dilatation,33 but its relationship to the presence of portal hypertension, the hyperdynamic circulatory state, and the degree of liver injury remains unsettled. Although the levels of nitric oxide in exhaled air are increased, which is consistent with pulmonary overproduction, in the hepatopulmonary syndrome, there is normalization after liver transplantation.33 The use of nitric oxide inhibitors to treat the condition has had discrepant results. Methylene blue, an inhibitor of the soluble guanylate cyclase and cyclic guanosine monophosphate pathway, transiently improved arterial oxygenation,34 whereas N⁶-nitro-L-arginine methyl ester, through inhibition of nitric oxide synthase by competition with substrate, did not influence gas-exchange abnormalities in a wide spectrum of patients with the hepatopulmonary syndrome.35 In studies of the hepatopulmonary syndrome, pulmonary microvascular endothelial changes appeared to be induced by increased endothelial nitric oxide synthase–derived nitric oxide production as well as by enhanced expression of inducible nitric oxide synthase and activity in intravascular macrophages.36 Likewise, increased biliary production and the release of endothelin-1 and the enhanced expression of pulmonary vascular endothelin-B receptors, leading to endothelin-1–mediated endothelial nitric oxide synthase–derived nitric oxide overproduction, have been reported.37 In this context, norfloxacin decreased macrophage accumulation and normalized inducible nitric oxide synthase,38 a finding that supports the role of bacterial translocation in pulmonary macrophage accumulation and its contribution to pulmonary vascular dilatation. Similarly, experimental studies in which development of the hepatopulmonary syndrome was prevented by pentoxifylline, an inhibitor of the production of tumor necrosis factor α,39,40 suggest a pathogenetic role of this mediator in the hepatopulmonary syndrome. Other molecular vasodilating effects through nitric

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**Table 3. Major Pulmonary Consequences in Patients with Advanced, Nonmalignant Liver Disorders.**

<table>
<thead>
<tr>
<th>Location of Disorder</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenchyma</td>
<td>Lymphocytic or organizing pneumonitis (especially primary biliary cirrhosis), or both; panacinar emphysema (severe alpha1-antitrypsin deficiency); aspiration pneumonitis (due to hepatic encephalopathy)</td>
</tr>
<tr>
<td>Pleura or diaphragm</td>
<td>Hepatic hydrothorax (with or without ascites), chylothorax, pulmonary-function effect of massive ascites</td>
</tr>
<tr>
<td>Pulmonary vascularity</td>
<td>Hepatopulmonary syndrome, portopulmonary hypertension</td>
</tr>
</tbody>
</table>

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A Homogeneous lung

Mixed venous blood

Uniform ventilation

Alveolus

Alveolus

Uniform perfusion

Oxygenated arterial blood

B Hepatopulmonary syndrome

Mixed venous blood

Right-to-left shunt

Diffusion limitation

Nonuniform perfusion

Hypoxemic arterial blood

Ventilation–perfusion mismatch

Figure 4. Mechanisms of Arterial Hypoxemia in the Hepatopulmonary Syndrome in a Two-Compartment Model of Gas Exchange in the Lung.

In a homogeneous lung with uniform alveolar ventilation and pulmonary blood flow in a healthy person (Panel A), the diameter of the capillary ranges between 8 and 15 μm, oxygen diffuses properly into the vessel, and ventilation–perfusion is well balanced. In patients with the hepatopulmonary syndrome (Panel B), many capillaries are dilated, and blood flow is not uniform. Ventilation–perfusion mismatch emerges as the predominant mechanism, irrespective of the degree of clinical severity, either with or without intrapulmonary shunt, and coexists with restricted oxygen diffusion into the center of the dilated capillaries in the most advanced stages (bold arrows).

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oxide–independent molecular mechanisms have also been described; these include enzymatic carbon monoxide production by increased expression of heme oxygenase-1 and stimulation of calcium-activated potassium channels by endothelial-derived hyperpolarizing factor. The correlation between the partial pressure of oxygen and carboxyhemoglobin in patients with the hepatopulmonary syndrome points to the potential influence of increased carbon monoxide production in abnormal gas exchange.

TREATMENT

Currently, no effective medical therapies for the hepatopulmonary syndrome exist, and liver transplantation is the only successful treatment. However, both postoperative mortality and the interval between transplantation and the resolution of arterial hypoxemia have been shown to be increased in patients with severe pretransplantation hypoxemia due to this syndrome. In the largest single-institution series, patients with the hepatopulmonary syndrome had a 5-year survival rate of 76% after liver transplantation, a rate not significantly different from that among patients without the hepatopulmonary syndrome who underwent transplantation. The strongest predictor of death was a preoperative partial pressure of oxygen of 50 mm Hg or less and a lung scan with brain uptake of 20% or more. Because of the poor outcome without liver transplantation, the diagnosis of the hepatopulmonary syndrome associated with a partial pressure of oxygen of less than 60 mm Hg is considered to be an indication for liver transplantation, and patients with this syndrome are given a higher priority for transplantation than patients with other disorders.

Spontaneous resolution of the hepatopulmonary syndrome and the development of portopulmonary hypertension before or after liver transplantation for the hepatopulmonary syndrome is uncommon. In contrast, data from several uncontrolled trials and anecdotal evidence indicate that treatment with almitrine, antibiotics, beta-blockers, cyclooxygenase inhibitors, garlic preparation, systemic glucocorticoids and cyclophosphamide, inhaled nitric oxide, nitric oxide inhibitors, and somatostatin has been uniformly unsuccessful. Long-term oxygen therapy remains the most frequently recommended therapy for symptoms in patients with severe hypoxemia, although compliance with this treatment and its efficacy and cost–benefit value remain unsettled.

A few additional unproven therapeutic alternatives with uncertain results have been recommended. The use of a transjugular intrahepatic portosystemic shunt has been proposed to reduce portal pressure in patients with the hepatopulmonary syndrome. However, the limited available data, along with the risk of exacerbating the hyperkinetic circulatory state, thereby enhancing pulmonary vasodilatation and increasing the severity of the hepatopulmonary syndrome, do not provide support for its use as a palliative strategy. Cavoplasty has been shown to be an effective treatment for the hepatopulmonary syndrome when it is associated with the Budd–Chiari syndrome. In a single case report, coil embolization (embolotherapy) in the rare context of angiographic arteriovenous communications has been shown to improve arterial oxygenation temporarily.

In summary, screening for the hepatopulmonary syndrome with the use of arterial blood gases is recommended in patients with chronic liver disease who report dyspnea or who are candidates for liver transplantation. Future research should address the genetic polymorphisms associated with the hepatopulmonary syndrome, circulating factors emanating from the hepatic veins that may affect the pulmonary vascular tone, and angiogenic factors (including, among the most relevant factors, endothelin-1, vascular endothelial growth factor, and platelet-derived growth factor). Hepatic explants from patients with the hepatopulmonary syndrome who undergo liver transplantation should be examined for biomarker sentinel clinical correlates that could lead to effective medical interventions. Finally, the question of which patients with the hepatopulmonary syndrome should receive a high priority for liver transplantation should be answered on the basis of long-term outcomes of transplantation in patients with various degrees of severity of the syndrome and various causes of liver disease.

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No potential conflict of interest relevant to this article was reported.
REFERENCES


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Abstract

Patients with cirrhosis who develop tense ascites and hepatorenal syndrome have a very high mortality and present a management challenge. Current debate stems from a lack of studies evaluating changes in effective arterial blood volume following paracentesis or targeting fluid replacement with appropriate vascular physiological measures to ensure no paracentesis-related circulatory dysfunction. The study by Umgelter and colleagues addresses a goal-directed approach to fluid management in hepatorenal syndrome and raises several mechanistic questions, the answers to which are likely to improve our understanding of the pathophysiology in hepatorenal syndrome and to guide future management.

Decompensated cirrhosis is characterized by severe circulatory derangements including progressive splanchnic vasodilatation and portal hypertension. These derangements result in several of the complications of advanced cirrhosis, such as increasing ascites and hepatorenal syndrome (HRS). The splanchnic vasodilatation in turn results in relative arterial underfilling [1], with consequent activation of the neurohumoral system, leading to vasoconstriction of numerous vascular beds including the liver, the kidney and the brain [2]. The more advanced the disease, the greater the activation of these neurohumoral factors, most maximal in the state of HRS [3]. Management of tense ascites in the context of evolving HRS has been debated with the concern that a large-volume paracentesis may evoke paracentesis-induced circulatory dysfunction despite volume replacement, thereby further potentiating HRS.

The study reported by Umgelter and colleagues in the previous edition of Critical Care describes the single and combined effects on haemodynamics and renal function of plasma expansion with albumin and paracentesis in patients with tense ascites and HRS [4]. Maintenance of the global end-diastolic volume was achieved by invasive monitoring of the central volume. The study’s key findings were a demonstration that the cardiac index in HRS patients was fluid responsive despite a normal central venous pressure, and that the reduction in intra-abdominal pressure following paracentesis was associated with an improvement in renal function in the context of fluid substitution guided by assessment of the global end-diastolic volume. In their uncontrolled study, a transpulmonary thermodilution technique (the PiCCO system, Pulsion Medical Systems, AG) facilitated measurement of both cardiac output as well as intrathoracic and pulmonary blood volumes. A subtraction of the pulmonary blood volume from the intrathoracic blood volume enabled an estimate of the ‘central’ blood volume, referred to as the global end-diastolic volume index (GEDVI).

The authors are to be congratulated on their attention to haemodynamic monitoring, since in cirrhosis a mismatch exists between the capacity of the vascular system and the volume available to fill it; that is, there is a reduced ‘effective’ arterial blood volume [5]. Given the complexity of interpreting central venous pressure measurements in patients with increased intra-abdominal pressure and marked systemic vasodilatation, measurement of the central blood volume (the pulmonary, cardiac and central arterial tree contributions) as performed by Umgelter and colleagues is likely to reflect the closest estimation to this effective arterial volume [4]. The authors observed a significant early increase in the GEDVI after a 200 ml fluid load of 20% albumin despite no significant increase in central venous pressure and an actual reduction in the systemic vascular resistance. It is likely that this observation can be explained by a reduction of endogenous vasopressors (with unopposed vasodilatation) as a consequence of improved cardiac function, even though vasopressor activity was not specifically measured in this study.

GEDVI = global end-diastolic volume index; HRS = hepatorenal syndrome.
Previous studies investigating the effects of an albumin load in Child C cirrhosis [6] and in the treatment of bacterial peritonitis [7] have demonstrated a significant reduction in plasma renin activity following therapy. Moreover, it has been suggested that cirrhotic patients exist in a compensated systemic vasodilated state, with a greater contribution of vasoconstrictors such as noradrenaline, angiotensin II and endothelin-1, to maintain basal vascular tone. [8] The relative change in the balance between vasoconstrictors and vasodilators may also explain the drop in systemic vascular resistance observed in the study by Umgelter et al.

Another important finding of this study is the improvement in creatinine clearance and the fractional extraction of sodium following paracentesis, despite GEDVI subsequently increasing, by adopting a ‘goal directed’ target for fluid substitution [4]. This finding has significant clinical relevance given the reduction in systemic vascular resistance and the previously held concerns for potential to develop postparacentesis circulatory dysfunction, with an aggravation of the hypodynamic cirrhotic circulatory state.

Although 40 g albumin infusion does not expand the central blood volume in patients with advanced Child C cirrhosis, a study by Brinch and colleagues does show a significant improvement in the low effective arterial blood volume in these patients associated with a reduction in plasma renin levels alongside an increase in arterial compliance, which may be important in the prevention of circulatory dysfunction [6]. A not too dissimilar result has been achieved using vasoconstrictors and albumin prior to transjugular intrahepatic portosystemic stent shunt insertion in HRS patients, with improvement in fractional sodium excretion and renal function associated with a reduction in plasma renin levels after 1 year of follow-up [9]. A targeted approach to maintaining effective arterial blood volume through an associated decrease in activation of the renin–angiotensin mechanism will, therefore, have a positive effect on renal dysfunction.

Another factor worthy of note is the recognition that there is enhanced sympathetic activation with advancing liver disease – which has been suggested to interfere with renal blood flow autoregulation, causing increasing dependence of the renal blood flow on the renal perfusion pressure [3]. The suggested improvement in renal perfusion pressure observed by Umgelter and colleagues may therefore not only be the effect of reducing the intra-abdominal pressure but may also result from the effects of decreasing sympathetic activation, even though this was not measured in their study.

In summary, the data provided by Umgelter et al. provide important support for a goal-directed approach to fluid management in advanced cirrhosis and HRS, and emphasize that the cardiac index may be fluid responsive in such patients despite normal central venous pressure [4]. More extensive studies, however, are required to further validate the methodology to assess the GEDVI in cirrhotic patients before this measure can be implemented as the standard of care in the management of HRS.

Competing interests
The authors declare that they have no competing interests.

References
Intensive Care Management of Acute Liver Failure


ABSTRACT

The care of patients with acute liver failure (ALF) presents unique clinical challenges to the practicing physician. It combines the management of rapidly progressive, severe multiple organ failure, unpredictable and often devastating complications, and a need for urgent decision-making in the application of emergency liver transplantation. However, outcomes for patients with this condition have shown progressive improvement over the last four decades. In this article, practical clinical approaches to the care of critically ill patients with ALF are discussed, taking an organ systems-based perspective and discussing the underlying pathophysiological processes and major areas of uncertainty as to what constitutes best practice.

KEYWORDS: Acute liver failure, fulminant hepatic failure, intensive care, multiple organ failure

Despite recent advances, the practical intensive care (ICU) management of acute liver failure (ALF) remains among the most challenging of all critical illnesses. It has a unique combination of rapidly progressive, severe multiple organ failure, unpredictable and often devastating complications, and urgent decision-making that must be made in the application of the only effective therapy for those with advanced disease, emergency liver transplantation.

However, as documented in this and previous issues of Seminars in Liver Disease over the last four decades, in our unit, and in others worldwide, there has been progressive and substantial improvement in survival (Fig. 1). This may in part be attributed to the evolution in understanding of this complex multisystem illness and the improvements in supportive ICU management that have resulted.

In this article, we summarize some of our current approaches to the care of these patients, placing emphasis on those of primary practical importance and discussing major areas of uncertainty as to what constitutes best practice.

PRINCIPLES OF CARE

The general principles of care of the ICU management of patients with ALF are in essence straightforward (Table 1): first, to identify and either remove or ameliorate the insult causing hepatic injury and thus ALF; second, to provide organ systems support optimizing the patient’s physical condition such that maximal hepatic regeneration may occur for a return to premorbid levels of hepatic function; third, to anticipate and prevent the development of complications while this regeneration is occurring; and finally, to identify those patients in whom sufficient regeneration will not occur early in the course of their disease so that the possibility of successful transplantation may be maximized. To
achieve these goals, a comprehensive approach to the multiple organ systems involved is required. Survival in this illness is closely related to the overall severity of organ dysfunction.\(^1\)

While these general principles of care are relatively clear-cut, their practical application is more complex. The rarity of ALF and its severity of illness mean that few rigorous trials have been performed to determine what constitutes best practice and the evidence base is thus relatively small.\(^2\) Extrapolation to ALF from experience in other critical illness may not be appropriate and in some circumstances may even be detrimental. The evolution of clinical practice is thus in many instances the result of clinical experience alone.

Given these caveats, for the remainder of this article we will discuss in detail the practical management of patients with ALF, taking a systems-based approach to the recommendations for care.

**CARE BEFORE TRANSFER TO THE TRANSPLANTATION CENTER**

Given the possible need for emergency transplantation, it is frequently necessary to transfer patients with ALF from their presenting hospital to specialist centers. The ICU management of these patients should begin before their transfer to a transplantation center ICU, both to optimize their physical condition such that progression to other extrahepatic organ failures may be interrupted but also to ensure that the transfer is performed in such a way as to minimize risk to the patient. Several aspects of care are of particular importance here that are frequently underappreciated by medical and nursing staff unfamiliar with the management of these patients.

1. **Volume Resuscitation and Cardiovascular Monitoring**

At presentation, patients with ALF frequently have significant depletion of circulating volume as a consequence of poor oral intake and increased fluid losses though vomiting or diarrhea. Intravenous fluid repletion should commence immediately after presentation, guided by appropriate, and if required, invasive, monitoring. This approach may prevent or delay development of extrahepatic organ dysfunction, particularly renal failure, and in other critical illnesses improves outcomes.\(^3\) Both crystalloid and colloid may be required and sodium-containing formulations are acceptable.

2. **Intubation for Encephalopathy and Clinical Neurologic Monitoring**

In patients with ALF the progression of hepatic encephalopathy (HE) may be rapid and the development of airway compromise during transfer with a fall in conscious level may be unexpected and catastrophic. Any suggestion of evolving HE should be regarded as an indication for sedation, intubation, and mechanical ventilation prior to transfer. The development of intracranial hypertension (ICH) as a consequence of cerebral edema (CE) may also occur abruptly; staff performing the transfer should be specifically warned as to its possible development and instructed as to the importance of frequent pupillary examinations and appropriate therapeutic interventions should it develop.

<table>
<thead>
<tr>
<th>Table 1 Principles of Transplantation Center ICU Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Identification and removal of cause of hepatic injury</td>
</tr>
<tr>
<td>2. Optimization of conditions for hepatic regeneration</td>
</tr>
<tr>
<td>3. Anticipation and prevention of complications</td>
</tr>
<tr>
<td>4. Early identification and transplantation of “nonsurvivors”</td>
</tr>
</tbody>
</table>
3. Avoidance of Correction of Coagulopathy

There is no indication for the prophylactic administration of clotting factors to patients with ALF despite marked abnormalities of coagulation. Overt hemorrhage is uncommon; however, its presence may form an indication for therapy. Unnecessary correction of coagulopathy will remove one of the most important parameters for determining patient prognosis and further complicate the already difficult decision-making process around transplantation listing.

CARE AT THE TRANSPLANTATION CENTER

Following arrival at the transplantation center ICU, the patient is reassessed and further investigations performed to assess severity of illness, metabolic status, and the cause of disease. If not already begun, specific therapies for the agent responsible for hepatic injury should be commenced (Table 2). Our practice is to simultaneously follow a protocol-driven series of standards of care in relation to different forms of organ systems support.

Cardiovascular Support

Circulatory dysfunction is frequently present in patients with ALF and has a multifactorial origin; its severity is closely related to outcome. In addition to that resulting from fluid depletion, hypotension may also result from vasodilation and the development of a high cardiac output and low systemic vascular resistance condition, comparable to severe sepsis. The associated cardiovascular collapse and organ hypoperfusion may be central to the progression of multiple organ failure.

Relative adrenal insufficiency appears to be common in patients with ALF, and an inadequate cortisol response may contribute to hypotension through the resulting impairment of vascular pressor response to endogenous and exogenous adrenergic stimuli. Additionally, subclinical myocardial injury may be present as evidenced by elevated troponin levels and is associated with mortality, though the relation of troponin elevations to overt cardiac dysfunction has yet to be clarified. Anecdotally, cardiac output may initially be impaired as a consequence of metabolic disarray, particularly severe acidosis, and improve following biochemical normalization.

The early restoration of an appropriate circulating fluid volume, systemic perfusion, and oxygen delivery are crucial to the successful management of the patient with ALF. Hypotensive patients with ALF should receive an early volume challenge as above, with a failure to respond to fluid challenge regarded as an indication for other forms of hemodynamic assessment and monitoring.

There are currently few data to guide the choice of fluids administered in patients with ALF or to determine what constitute the optimal hemodynamic monitoring modality and the markers of achievement of euvolemia and an appropriate fluid load. Our practice is to utilize early continuous Pulse Contour Analysis (PiCCO; Pulson Medical Systems AG, Munich, Germany) for hemodynamic monitoring, administering a mixture of crystalloid and synthetic colloid solutions and assessing the response to fluid therapy from a combination of clinically observed and derived hemodynamic parameters.

In general, a cardiac index of less than 3.5 L/min/m² with evidence of inadequate tissue perfusion despite apparent euvolemia is treated with inotropic agents. A target mean arterial pressure of 65 mm Hg is generally sought and norepinephrine used as the primary vasopressor where necessary. In all patients who require vasopressors or large fluid volumes, adrenal function is assessed via a short synacthen test (SST; Cortrosyn® stimulation test) and replacement doses of intravenous hydrocortisone administered to those who display either inappropriately low baseline cortisol levels or inadequate incremental responses. In accordance with observation of other critical illnesses, while there are clear benefits of this approach in relation to shock reversal and reduced vasopressor requirement, improvements in mortality are less certain. However, in those patients awaiting transplantation this approach seems likely to extend the time to find a suitable donor. In those patients with refractory vasopressor-resistant hypotension, recent data would suggest that Terlipressin® may be better tolerated than initial evidence suggested and could provide a useful adjunctive agent, though for ease of administration and close control of blood pressure continuous infusion of low-dose vasopressin may be preferred.


day 1

Infection Control and Sepsis

Infection occurs commonly in patients with ALF and may be difficult to diagnose as the usual clinical signs of infection may be absent. In part, the high incidence of infection likely results from the complex multilevel
immune dysfunction that is seen in these patients. In
association with an abnormal acute-phase response and
impaired production of immunologically important sub-
stances including complement, defective leukocyte and
Kupffer’s cell function is seen.13–16 Neutrophil function
is impaired with abnormalities of movement, phagocy-
tosis, and intracellular killing.17,18 Recent studies have
indicated that monocyte dysfunction may further con-
tribute to relative immunosuppression and a “immuno-
paretic” state.19

The second major factor of likely importance in the
high incidence of infective episodes is requirement
for invasive medical procedures, intravascular lines, and
the need for intubation and ventilation. These factors are
likely to substantially increase risks of nosocomial in-
fection and indeed the pattern of infections seen suggests
that this may in fact be the case.12

The development of infection is of major prog-
nostic importance. It inhibits hepatic regeneration, is
associated with progression of HE, reduces rates of
successful transplantation, and increases mortality and
morbidity.11,20–23 Consequently the prevention and/or
effective treatment of infection is of primary practical
importance.

The importance of well-established universal pre-
cautions in the prevention of nosocomial infection cannot
be emphasized too strongly.24 Of particular
importance in this regard are the use and care of intra-
vascular catheters. In all patients close microbial surveil-
lance should be practiced with frequent and multisite
cultures.25

The place of antimicrobial prophylaxis in pa-
patients with ALF is more controversial. Data from early
studies suggest that the number of infective episodes
may be reduced and it may increase the proportion of
patients who remain suitable for transplantation. How-
ever, no mortality benefit has been demonstrated and
such treatment may favor the emergence of multiresis-
tant organisms.11,26,27 There also seems no addi-
tional benefit from the use of selective enteral
decomamination.26,27

Our pragmatic approach is to maintain a very low
threshold for the use of antimicrobials in patients with
ALF, administering antibacterial and antifungal agents
on admission to all patients with established HE or other
organ dysfunction, to those fulfilling or likely to fulfill
transplant criteria, and to those with acute hepatic
dysfunction without HE but with signs of significant
systemic inflammation. In those with rapidly improving
hepatic function and negative microbial cultures, as
typified by acetaminophen cases who do not fulfill trans-
plant criteria, truncated courses of 3 to 5 days may be
administered. In those patients who fulfill criteria, lon-
ger courses may be administered to cover the waiting
time on the transplant list and to provide pre- and
postoperative coverage.

**Renal Support**

Renal dysfunction frequently complicates ALF, partic-
ularly cases resulting from acetaminophen, and as an
indicator of the overall severity of illness, it is associated
with a poor prognosis.28–30 The pathogenesis of renal
dysfunction in the setting of ALF is incompletely under-
stood; published data suggest that both acute tubular
necrosis and functional (“hepatorenal”) processes may
occur.28,31,32 After restoration of normal levels of hepatic
function, either through spontaneous regeneration or
transplantation, recovery of renal function occurs in the
majority of survivors of ALF.

The more frequent occurrence in patients with
acetaminophen disease suggests that at least in this
etiologic group drug-mediated nephrotoxicity may be
important.33 An increased incidence is seen in those
patients in whom a delayed presentation to medical
attention occurs and thus may be in part as a conse-
quence of circulating volume depletion. The rapid and
effective restoration of appropriate intravascular volume
and renal perfusion may prevent the full evolution to
anuric renal failure and forms a key part of the initial care
of the patient with evolving ALF.

In patients with significant renal dysfunction,
continuous rather than intermittent forms of renal re-
placement therapy (RRT) should be utilized and insti-
tuted early in the course of illness. Continuous
hemofiltration is associated with greater hemodynamic
and metabolic stability than intermittent dialysis and is
better tolerated in those patients at risk of CE and
ICH.34 Most liver centers now use bicarbonate buffered
hemofiltration fluids rather than those containing ace-
tate or lactate, given the risks of worsening hyperlacta-
temia and acidemia in patients with limited hepatic
reserve.35

Our standard is to use hemofiltration “doses” of at
least 35 mL/kg/h, which in the general ICU population
have been associated with improved survival.36 The place
of higher volumes of filtration in this setting is yet to be
fully defined, but clinical experience suggests that it may
be effective in the control of otherwise refractory acidosis
and as an adjunct in the management of severe vaso-
pressor-dependent shock.37,38 When applied for these
indications, the evidence suggests that its application
may be most beneficial and cost-effective when applied
early and for limited periods of time.39

Novel indications for RRT in patients with ALF
include reduction of elevated circulating levels of am-
monia and for control of patient temperature. Con tin-
uous hemofiltration and particularly hemodiafiltration
appear to have clinically useful clearances of ammonia
and have been used in pediatric patients for control of
hyperammonemia.40,41 Their application in adults for
the reduction of ammonia levels has the potential to
arrest disease progression and reduced risk of severe HE
and ICH (Fig. 2). The active control of core temperature
through manipulation of RRT and the use of fluid warming and cooling via the hemofilter is straightforward and forms one means by which this may be accomplished. The general ICU literature suggests that cooling in this way may be accompanied by improvements in global hemodynamic status and systemic vascular resistance, importantly without apparently compromising hepatosplanchnic perfusion.

Respiratory Support

The most common indication for invasive respiratory support in ALF is for airway protection following the reduction in conscious level after the development of severe HE; our practice is for the intubation and ventilation of any patient who develops HE of grade 3 and above.

The exact prevalence of primary respiratory dysfunction is unknown; the clinical impression is that it is relatively uncommon, perhaps somewhat surprisingly given the frequent development of other organ system failures seen in ALF. However, lung injury does occur and is seen more commonly in those with acetaminophen-related disease and in those patients with severe multiple organ systems dysfunction, particularly a requirement for vasopressors and concurrent ICH.

Ventilatory strategies do not differ significantly from those employed in the general ICU population to minimize risks of pulmonary volu- and barotrauma. An early trial showed no benefit in respect of the incidence of ICH from routine hyperventilation; appropriate routine targets for partial pressure of carbon dioxide (pCO₂) are between 4 and 5 kPa. Our experience is that when required, the theoretical risks of increased intracranial pressure (ICP) are seldom a major clinical problem in the application of high levels of positive end-expiratory pressure (PEEP). Similarly, in occasional and selected patients we have successfully and without complication used prone ventilation in patients at risk of ICH and with severe lung injury, although its application without simultaneous monitoring of ICP is inadvisable.

Patients recovering from ALF often have a prolonged requirement for ventilatory support as a consequence of persistent HE and the delayed clearance of sedative agents. Tracheostomy is frequently required and is generally well tolerated if its insertion is delayed until the risks of ICH are minimal, when elevations in pCO₂ related to the procedure are likely to better tolerated.

Nutritional Support

Despite evidence of major nutritionally related metabolic disturbances of importance in the development of complications in patients with ALF, there is a paucity of data available upon which to base strategies for nutritional support. This is reflected in wide variation in clinical practice between units treating these patients.

Some forms of therapy appear to have been widely adopted and have a reasonable evidence base for their use. Loss of hepatic gluconeogenic capacity and glycogen capacity may result in clinically significant hypoglycemia and continuous intravenous infusion of glucose is a near-universal practice. This prevents the development of hypoglycemia, facilitates the administration of insulin for stable glycemic control, and may normalize the pattern of substrate oxidation used for energy expenditure.

In common with other critically ill patient groups, vitamin deficiency appears to be present in a significant proportion of patients with ALF, particularly in relation to vitamins B₁ and B₆, and have been associated with
compromised immune and antioxidant status.\textsuperscript{53–55} Losses of these and other water-soluble vitamins and trace elements may be substantially increased in those patients requiring RRT.\textsuperscript{56}

Vitamin supplementation in the critically ill, particularly via the parenteral route, appears safe, corrects deficiency, and may reduce mortality.\textsuperscript{54,57,58} Our practice is therefore to administer intravenous supplementation of vitamins B-complex, and C and trace elements from admission and for the duration of illness with appropriate dose adjustments, if RRT is required.\textsuperscript{56}

In normal individuals at rest, the liver is responsible for 20 to 25% of total energy expenditure. Several studies have demonstrated that despite a significant loss of functioning liver cell mass, high-energy expenditure is seen in patients with ALF, reaching levels of 20 to 30% greater than healthy controls.\textsuperscript{52,59} This high metabolic rate may reflect the severity of systemic inflammation in multiple organ failure and the response to hepatic injury.\textsuperscript{59} Additionally, patients with ALF exhibit high levels of protein catabolism and skeletal muscle breakdown.\textsuperscript{60,61} Amino acid losses may be substantially increased in those patients requiring RRT.\textsuperscript{56} To support high energy requirements and preserve muscle bulk and immune function, provision of artificial nutritional support is mandatory.

Current recommendations for nutritional support are for the use of the enteral rather than parenteral route and do not advocate the use of specific feed formulations.\textsuperscript{49,62,63} Enteral feeding should be commenced within 24 hours of ICU admission and provide 20 to 25 kcal/kg/d for the initial phase of the illness and 25 to 30 kcal/kg/d during recovery.\textsuperscript{62} The most beneficial composition of feed formula, particularly in relation to protein and amino-acid composition, is currently unknown. Concerns exist that a higher protein load might result in worsening of hyperammonemia; ammonia released by the intestine cannot be extracted sufficiently by the failing liver.\textsuperscript{49} There are currently no published data to substantiate this theoretical risk. Our pragmatic policy is to administer between 1.0 and 1.5 g/kg/d of protein and to frequently measure blood ammonia concentrations in those with markedly impaired liver function. In patients considered to be at high risk of ICH or in whom circulating ammonia is approaching or above 150 \mu mol/L, this protein load may be reduced for periods of 1 to 2 days only.

**Neurological Management**

The presence of HE is essential for the diagnosis of ALF.\textsuperscript{64,65} In ALF it encompasses a wide spectrum of neuropsychiatric disturbances ranging from minor confusion and disorientation to frank coma and CE resulting in intracranial hypertension and is graded from 1 to 4 depending on clinical severity (Table 3).

<table>
<thead>
<tr>
<th>Encephalopathy Grade</th>
<th>Clinical Features</th>
<th>Glasgow Coma Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>15</td>
</tr>
<tr>
<td>1</td>
<td>Shortened attention span</td>
<td>15–14</td>
</tr>
<tr>
<td>2</td>
<td>Minimal lack of awareness</td>
<td>13–11</td>
</tr>
<tr>
<td>3</td>
<td>Inappropriate behavior</td>
<td>10–8</td>
</tr>
<tr>
<td>4</td>
<td>Unresponsive to verbal stimuli</td>
<td>&lt; 8</td>
</tr>
</tbody>
</table>

Adapted from Mullen, KD. Review of the final report of the 1998 Working Party on definition, nomenclature and diagnosis of hepatic encephalopathy. Aliment Pharmacol Ther 2007;25:11–16.\textsuperscript{116}

The precise pathogenesis of HE in ALF is only partly understood, but clinical and experimental evidence suggests an important role for elevated circulating levels of neurotoxic substances, of which ammonia is of likely central importance. Experimental studies have demonstrated ammonia-induced changes in neurotransmitter synthesis and release, neuronal oxidative stress, impaired mitochondrial function, and osmotic disturbances resulting from astrocytic metabolism of ammonia to glutamine.\textsuperscript{66–68} The net result of these changes is marked alteration in cerebral function and astrocytic swelling.\textsuperscript{67–69} Clinical studies have suggested a clear relationship between the development of higher grades of HE and arterial ammonia levels.\textsuperscript{70–75}

While ICH is likely to represent the most extreme manifestation of HE, factors other than ammonia also appear to be important in its pathogenesis. While the risk of ICH appears clearly increased in those patients with arterial ammonia concentrations > 150 to 200 \mu mol/L, particularly if sustained, many patients develop the complication with lower levels.\textsuperscript{73–75} ICH tends to occur as part of a systemic process, in the context of more severe multiple organ failure than HE alone, and alterations of both cerebral metabolic rate (CMR) and cerebral blood flow (CBF) may be prominent. Clinical studies would suggest that in the evolution of ICH, the pattern of CMR and CBF vary over time.\textsuperscript{76,77} Initially both a reduction in CBF and CMR may develop, but in the later stages of advanced HE a loss of cerebral vascular autoregulation results in progressive cerebral vasodilation and hyperemia leading to an increase in cerebral blood volume and the clinical manifestations of ICH.\textsuperscript{77,78} Preternally there may be a marked reduction in CBF as a result of uncontrolled ICP and fall in cerebral perfusion pressure (CPP) with low CMR.\textsuperscript{79,80}
Recent observations suggest that the incidence of ICH appears to have fallen, particularly in series reporting results from transplantation centers. In contrast to earlier studies, ICH now appears to affect only a minority of those patients developing severe HE and is no longer the most common cause of death. Researchers are currently uncertain about the reasons underlying these observations, though the availability of transplantation may mean that the period during which patients are at risk of ICH is likely shorter. It may also be that the therapeutic strategies now employed in patients have been successful in reducing the incidence of ICH. Nonetheless, survival without transplantation remains poor in those patients who develop ICH and its successful management remains a major clinical challenge.

Prevention of Severe Encephalopathy
It may be that the progression to severe HE could be interrupted in some patients by reduction in circulating levels of ammonia, and several pharmacological and nonpharmaceutical therapies are now available that may be employed to this end. From a current practical perspective, continuous veno-venous hemofiltration may result in significant falls in arterial ammonia concentration and the additional effects upon core temperature and systemic hemodynamics may also be of benefit in this regard (Fig. 2). Similarly, the association between acquisition of infection and progression of HE is one of the strong arguments for the prophylactic use of antibiotics.

Management of Severe Encephalopathy
In those patients who develop HE of grade 3 or above, our approach is to undertake mandatory intubation and ventilation. Sedation may be given with a variety of compounds but our standard would be to utilize an intravenous opiate and a sedative such as propofol. In common with experiences in other neurocritical care, this agent would appear to have properties ideal for this setting, reducing CMR and ICP while maintaining cerebral reactivity to carbon dioxide and autoregulation. Importantly, liver failure does not influence propofol pharmacokinetics and thus a stable level of sedation may easily be achieved. The intubated and sedated patient with severe HE is then managed following a series of defined protocols (Table 4, Figs. 3, 4).

The patient’s head should be positioned at a 30-degree upright angle to improve jugular venous

Figure 3 Protocol for assessment of risk of intracranial hypertension in intubated patients with ALF and encephalopathy of grade 3 and above. ALF, acute liver failure; ICH, intracranial hypertension; SrjO2, reverse jugular venous oxygen saturation; JVO, jugular venous oximetry; CO, cardiac output; MAP, mean arterial pressure; PaCO2, partial pressure of carbon dioxide; ScvO2, central venous oxygen saturation; IV, intravenous; ICP, intracranial pressure.

Table 4 Goals of Care for ALF Patients Ventilated for Hepatic Encephalopathy of Grade 3 and Above

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.35–7.4</td>
</tr>
<tr>
<td>pO2</td>
<td>&gt; 10 kPa</td>
</tr>
<tr>
<td>pCO2</td>
<td>4–5 kPa</td>
</tr>
<tr>
<td>Glucose</td>
<td>4–6 mMol/L</td>
</tr>
<tr>
<td>Sodium</td>
<td>140–150 mMol/L</td>
</tr>
<tr>
<td>Temperature</td>
<td>&lt; 36.5° C</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>&gt; 65 mm Hg</td>
</tr>
<tr>
<td>Reverse jugular saturations</td>
<td>65–80%</td>
</tr>
</tbody>
</table>

ALF, acute liver failure; pO2, partial pressure of oxygen; pCO2, partial pressure of carbon dioxide.
outflow and optimize cerebral perfusion. Similarly, venous outflow should not be impeded by tapes securing endotracheal tubes or vascular catheters. Other nursing measures should attempt to reduce activities that are associated with surges in ICP including coughing, frequent head-turning, and endotracheal suctioning. However, the effective clearance of respiratory secretions with appropriate physiotherapy is essential and is probably beneficial in reducing the incidence of pulmonary infection. Routine neuromuscular blockade is avoided as it may mask clinical evidence of seizure activity. Other strategies used in this setting to reduce the likelihood of ICH include the active management of electrolytes, serum sodium, and magnesium and close control of temperature and pCO2. We maintain a serum sodium concentration of 145 to 155 mmol/L by low-rate infusion of hypertonic saline that may reduce ICP and delay the onset of ICH. Evidence does not support the prophylactic use of hyperventilation, though it may be employed in the short term to control ICP surges with concurrent jugular oximetry monitoring.

Temperature Control
Fever is closely related to adverse outcomes in neurocritical care and in patients with ALF has been associated with the development of ICH. Consequently, in most centers goals of care for patients with ALF include the maintenance of normothermia. Whether a greater degree of cooling is beneficial to patients as prophylaxis or treatment of ICH is the subject of ongoing research.

Apparently beneficial effects in relation to the severity of CE and ICH have been demonstrated in several animal models of ALF and in uncontrolled clinical series. Moderate hypothermia (32 to 33°C) has been reported to effectively control refractory ICH in ALF patients awaiting transplantation in association with improvements in systemic hemodynamic parameters. However, in patients who are actively cooled, the incidence of complications is closely related to the degree of hypothermia induced. While the risks of severe arrhythmias only become significant at temperatures below 30°C, more moderate hypothermia has been linked to other complications, including coagulation disturbances, impairment of hepatic regeneration, and, importantly, to an increased risk of infection. This infection risk appears highest in those patients cooled for longer periods of time (≥48 to 72 hours). While awaiting the results of ongoing randomized controlled trials of prophylactic hypothermia, our policy is for a standard of care of core temperature of 36°C in those intubated for HE and of 34°C in those developing

Figure 4  Schematic management of ICP in ALF patients. ICP, intracranial pressure; ALF, acute liver failure; CVVHF, continuous veno-venous hemofiltration; JVO, jugular venous oximetry; CPP, cerebral perfusion pressure; SrjO2, reverse jugular venous oxygen saturation.
ICH and without contraindications to its induction. Lower temperatures than this are reserved only for those with refractory ICH-fulfilling transplantation criteria and awaiting a graft.

**Neurological Monitoring**

In the discussion of cerebral monitoring modalities in patients with severe HE, the importance of frequent clinical examination is often underappreciated. Experience would suggest that changes in neurological signs, particularly in relation to changes in limb tonicity and the development of clonus, may be early indicators of evolving CE and ICH and predates pupillary abnormalities.

There is no clear consensus view as to the ideal mode(s) of other neurologic monitoring in patients with advanced HE. Though direct measurement of ICP is desirable, monitoring of ICP is associated with rare but definite risks of severe complications, particularly intracranial hemorrhage. Our policy is to defer insertion unless there is evidence from less invasive monitoring or clinical signs of evolving CE. Such noninvasive monitoring modalities include near infrared spectroscopy, transcranial Doppler, continuous electroencephalography, and jugular venous oximetry (JVO).

There may be a place for all these techniques in specific patients but our policy is to use JVO alone routinely in all patients intubated for HE; this permits real-time measurement of jugulovenous oxygen saturation (SVjO₂) providing a practical indication of cerebral oxygen delivery and consumption. High values of SVjO₂ may be indicative of cerebral hyperemia and low values of relative ischemia, providing both a guide for the targeting of ICP monitoring and for therapies likely to affect cerebral perfusion and metabolic activity, particularly those with vasoactive properties.

While there is no clear evidence to confirm that ICP monitoring improves outcome of patients with ALF, few if any monitoring devices have been shown to have such a property in isolation. Many centers reserve this monitoring modality for patients with deep HE who are considered to be at high risk of the development of ICH. In view of the potential for device-related complications, risk stratification is necessary to select those patients most likely to benefit from such an invasive procedure. We have recently examined the relationship between arterial ammonia concentrations and other potential clinical risk factors on admission to ICU to the risk of subsequent development of ICH. This was greatest in those with ammonia levels of > 200 μmol/L or with sustained high levels below this threshold. Younger patients and those with lower levels of ammonia but with concurrent renal dysfunction and vasopressor requirement also appeared to be at increased risk of ICH, and there may be other groups that could benefit from monitoring. The use of these parameters in the assessment of ICH risk in patients with severe HE is illustrated in Fig 3.

**Treatment of ICH**

Once inserted, ICP monitoring permits directed management of ICP and CCP (CCP calculated as mean arterial pressure minus intracranial pressure). Traditionally, prolonged ICP of > 40 mm Hg and CPP < 50 mm Hg have been associated with a poor outcome. However, personal observation and case series suggest that these cut-offs are not absolute and particularly that nonsustained ICP surges at significantly higher levels are compatible with full neurological recovery. In our patients CPP is optimized on the basis of clinical signs and multimodality monitoring, but is seldom below 40 mm Hg.

Sustained elevations in ICP of > 20 to 25 mm Hg or other signs of ICH are treated with a protocolized treatment regimen (Fig. 4). The various treatment options for the control of ICH have been recently and comprehensively reviewed. Therapies for ICH in ALF lower ICP by two major mechanisms. Mannitol and hypertonic saline act predominantly via osmotic effects, while indomethacin, hypothermia, and hyperventilation appear to decrease CBF. The use of multimodality monitoring of both ICP and JVO thus permits a rational approach to therapy dependent upon whether there are indications of cerebral hyperemia or oligemia while reducing the risk of inducing additional cerebral ischemia.

Our protocol-based approach to the therapy of ICH consists of optimizing sedation with or without neuromuscular blockade, followed by intravenous mannitol or hypertonic saline boluses. Refractory cases are treated with indomethacin and induced hypothermia (< 34°C). Of these agents, the best evidence exists for mannitol and hypertonic saline. In our and others’ experience indomethacin may be useful in selected patients as rescue treatment. However, its side effect profile and potential to induce cerebral ischemia limit its utility as a routine measure. Indomethacin should only be used in patients with hyperemia and concurrent JVO monitoring. Similarly, the side effect profile of both barbiturates and deep hypothermia cannot be recommended except in refractory cases. Hepatocellular damage remains an option best reserved for those patients with medically uncontrollable ICH and for whom a graft is available but not immediately accessible for transplantation.
CONCLUSION
ALF remains an uncommon critical illness whose management represents a major clinical challenge. The improvement in outcomes seen over the last four decades is a testament to the work of clinicians and researchers worldwide. Continued improvement in survival seems possible through the application of early and holistic multisystem supportive care and the better targeted use of transplantation. Many aspects of pathogenesis and therapy remain uncertain and the establishment of a sound evidence base to support the techniques and therapies applied to patients to ALF is of central importance if this is to occur. This will most likely result from the application of the results of completed and ongoing multicenter randomized controlled trials in these patients.

ABBREVIATIONS
ALF acute liver failure
CBF cerebral blood flow
CE cerebral edema
CMR cerebral metabolic rate
CPP cerebral perfusion pressure
HE hepatic encephalopathy
ICH intracranial hypertension
ICP intracranial pressure
ICU intensive care unit
JVO jugular venous oximetry
PEEP positive end-expiratory pressure
RRT renal replacement therapy
SVjO2 jugulo venous oxygen saturation

REFERENCES


89. Ng I, Lim J, Wong HB. Effects of head posture on cerebral hemodynamics: its influences on intracranial pressure, cerebral perfusion pressure, and cerebral oxygenation. Neurosurgery 2004;54:593–597; discussion 598
95. Diringer MN, Reaven NL, Funk SE, Uman GC. Elevated body temperature independently contributes to increased length of stay in neurologic intensive care unit patients [see comment]. Crit Care Med 2004;32:1489–1495
97. Munoz SJ. Hypothermia may impair hepatic regeneration in acute liver failure [comment]. Gastroenterology 2005;128: 1143–1144; author reply 1144–1145


Intensive care of patients with acute liver failure: Recommendations of the U.S. Acute Liver Failure Study Group

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LEARNING OBJECTIVES
On completion of this article, the reader should be able to:
1. Define acute liver failure.
2. Explain management of acute liver failure.
3. Use this information in a clinical setting.

Objective: To provide a uniform platform from which to study acute liver failure, the U.S. Acute Liver Failure Study Group has sought to standardize the management of patients with acute liver failure within participating centers.

Methods: In areas where consensus could not be reached because of divergent practices and a paucity of studies in acute liver failure patients, additional information was gleaned from the intensive care literature and literature on the management of intracranial hypertension in non-acute liver failure patients. Experts in diverse fields were included in the development of a standard study-wide management protocol.

Measurements and Main Results: Intracranial pressure monitoring is recommended in patients with advanced hepatic encephalopathy who are awaiting orthotopic liver transplantation. At an intracranial pressure of ≥25 mm Hg, osmotic therapy should be instituted with intravenous mannitol boluses. Patients with acute liver failure should be maintained in a mildly hyperosmotic state to minimize cerebral edema. Accordingly, serum sodium should be maintained at least within high normal limits, but hypertonic saline administered to 145–155 mmol/L may be considered in patients with intracranial hypertension refractory to mannitol. Data are insufficient to recommend further therapy in patients who fail osmotherapy, although the induction of moderate hypothermia appears to be promising as a bridge to orthotopic liver transplantation. Empirical broad-spectrum antibiotics should be administered to any patient with acute liver failure who develops signs of the systemic inflammatory response syndrome, or unexplained progression to higher grades of encephalopathy. Other recommendations encompassing specific hematologic, renal, pulmonary, and endocrine complications of acute liver failure patients are provided, including their management during and after orthotopic liver transplantation.

Conclusions: The present consensus details the intensive care management of patients with acute liver failure. Such guidelines may be useful not only for the management of individual patients with acute liver failure, but also to improve the uniformity of practices across academic centers for the purpose of collaborative studies. (Crit Care Med 2007; 35:2498–2508)

KEY WORDS: acute liver failure; standardized care; intracranial pressure monitoring; hepatic encephalopathy; orthotopic liver transplantation
Acute liver failure (ALF), defined as the onset of hepatic encephalopathy and coagulopathy within 26 wks of jaundice in a patient without preexisting liver disease, remains one of the most dramatic and highly mortal of all human afflictions. Nevertheless, the optimal management of patients with ALF remains very poorly defined and center-specific. Several reasons underlie the heterogeneous management of ALF, including the fact that ALF is a syndrome rather than a disease, representing the final manifestation of numerous etiologies. In addition, the syndrome is extremely difficult to study because of its high mortality and rarity (2,000 U.S. cases per yr) (1).

The Adult U.S. Acute Liver Failure Study Group (ALFSG) was founded in 1997 to define the epidemiology and management of patients with ALF. Since its inception, the group has collected data on >1,100 patients with ALF from 23 prominent liver transplant centers. To more uniformly manage patients with ALF at participating centers, the ALFSG convened in December 2005 to review the available literature on the management of ALF, to compare the intensive care of patients with intracranial hypertension of various etiologies, and to compare practices within participating centers. Investigators in specialties outside of hepatology—including neuro-intensive care, nephrology, and coagulation—were invited to participate in formulating a standard study-wide management protocol. Where possible, the protocol was based upon literature pertaining to patients with ALF; where studies specifically examining ALF did not exist, management recommendations were derived from other literature. Recommended measures were defined as those in which evidence-based studies suggest possible benefit in the clinical course or outcome of patients with ALF. Measures without supporting clinical data, but which potentially may be of benefit based upon a reasonable rationale, or supported by literature not specifically pertaining to patients with ALF, were deemed insufficient data to recommend. Finally, measures which clinical studies suggest may be detrimental were not recommended. The protocol was approved by the 23 member sites on September 23, 2006, and revisions were approved on May 10, 2007.

The present protocol expounds on a previous position paper (2) sanctioned by the American Association for the Study of Liver Diseases. The position paper offers the American Association for the Study of Liver Diseases. The position paper offers general guidelines targeted at nonintensivists, and is cited within the present protocol for completeness and to avoid duplication of publication.

GENERAL MANAGEMENT

Patients with evidence of acute liver injury should be admitted to the hospital when accompanied by significant hepatocellular insufficiency (e.g., international normalized ratio >1.5). Because neurologic deterioration may be very rapid, patients should be moved to an intensive care unit at the onset of hepatic encephalopathy, and a discussion should ensue between the referring physician and intensivists at the nearest liver transplant center regarding timely transfer after stabilization. Such discussion should include whether endotracheal intubation should be performed before transfer. To establish a diagnosis, estimate disease severity, and predict the need for orthotopic liver transplantation (OLT), a battery of initial tests should be performed on arrival at the transplant center (2).

Etiology-Specific Treatments. Specific treatments (antidotes) for ALF have been systematically studied only for acetaminophen overdose. N-acetylcysteine (NAC) administration is recommended even if there is doubt concerning the timing, dose ingested, or plasma concentration of acetaminophen, and should not be withheld even if the ingestion was 48–72 hrs before presentation (3). Oral NAC is recommended as first-line therapy only in patients with mild (grade 1) hepatic encephalopathy; intravenous NAC should be administered to patients with >grade 1 encephalopathy, hypotension, or other reason that oral dosing might not be tolerated (e.g., vomiting, compromised airway, postoperative state, ileus). Doses for oral NAC administration should include a 140 mg/kg loading dose, followed by 70 mg/kg every 4 hrs. Doses for intravenous NAC administration vary according to protocol; one suggested schedule includes a 150 mg/kg load for 15–60 mins (usually in 5% dextrose, but any crystallloid is acceptable), followed by a maintenance infusion (e.g., 12.5 mg/kg per hr for 4 hrs, then 6.25 mg/kg per hr). NAC administration is recommended until there is firm evidence of improved hepatic function (resolution of hepatic encephalopathy, improving coagulopathy [international normalized ratio <1.5], and declining transaminases). The length of NAC administration should be determined by clinical improvement or outcome (death or liver transplant) rather than by time or serum acetaminophen levels; it should be emphasized that this period of time may extend well beyond 72–96 hrs.

Except for women with acute fatty liver of pregnancy or the hemolysis-elevated liver enzymes–low platelet syndrome, in whom prompt delivery of the fetus readily reverses ALF (4), there are generally insufficient data to recommend specific therapies for ALF due to other etiologies. However, etiology-specific measures are recommended by the ALFSG based upon anecdotal experience, relative innocuousness of the measures, and the high mortality of the clinical syndrome (Table 1) (2).
Infection remains one of the principal causes of death in patients with ALF and may be subtle in clinical presentation (19). The most common site of bacterial infection is the lung, followed by urinary tract and blood, and the most commonly isolated organisms are Gram-positive cocci (Staphylococcus, Streptococcus) and enteric Gram-negative bacilli (20). Fungal infections, particularly Candida, may be present in one third of patients with ALF (21). Intra venous catheter-related sepsis represents a major source of avoidable infectious complications in patients with ALF (22); consequently, unnecessary intravenous catheters are to be avoided. Prophylactic parenteral and enteral antimicrobial regimens have not been shown to improve outcome or survival in patients with ALF, although key studies may have been underpowered (23). Therefore, there are insufficient data to recommend the routine use of antibiotic prophylaxis in all patients with ALF, particularly those with early stage hepatic encephalopathy. Although randomized studies exploring the use of daily bacterial surveillance cultures (blood and urine) and chest radiographs do not exist, such studies are recommended on the basis that patients with ALF frequently do not exhibit signs of infection, and early diagnosis of infection may improve outcome (20, 23). Empirical administration of antibiotics is recommended in the following circumstances where infection or the likelihood of impending sepsis is high: a) surveillance cultures reveal significant isolates (19); b) progression of, or advanced stage (III/IV), hepatic encephalopathy (22); c) refractory hypotension; or d) presence of systemic inflammatory response syndrome components (temperature >38°C or <36°C, white blood count >12,000 or <4,000/mm³, pulse >90 beats/min) (24). Empirical antibiotics (antibacterial and antifungal agents) also are recommended for patients listed for OLT, because developing infection often results in delisting and immunosuppression is imminent, acknowledging that specific data to support this practice do not exist. It should be recognized that the risk of developing infection with resistant organisms will increase with longer waiting times.

There are insufficient data to recommend specific antimicrobial agents for the indications above. However, broad-spectrum coverage for Gram-positive and Gram-negative bacteria, such as with a third-generation cephalosporin, should be chosen with consideration of patient-specific isolates from surveillance cultures, as well as historical hospital-specific isolates. Vancomycin is specifically recommended in all patients with possible intravenous catheter–related sepsis and/or risk factors for infection with meticillin-resistant Staphylococcus aureus. An antifungal agent also is recommended in any patient without prompt improvement in signs of infection after institution of antibiotic agents. Aminoglycosides are not recommended on the basis of risk of nephrotoxicity.

Sedation and Analgesia. Psychomotor agitation frequently contributes to intracranial hypertension in patients with ALF, especially as patients progress to stage III/IV hepatic encephalopathy (25). Pain also may increase intracranial pressure (26). Therefore, adequate analgesia and judicious sedation is required in patients who progress to stage III/IV hepatic encephalopathy, particularly before placement of invasive devices, such as intracranial pressure monitors or endotracheal tubes.

There are insufficient data to recommend a standard agent for sedation in patients with ALF. However, it should be recognized that both propofol and benzodiazepines, the most commonly used sedatives, increase γ-aminobutyric acid–ergic neurotransmission, and therefore may exacerbate hepatic encephalopathy.

**Table 1. Etiology-specific therapy of patients with acute lung failure**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Therapy</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>APAP</td>
<td>NAC oral: 140 mg/kg load, then 70 mg/kg every 4 hrs NAC IV: 150 mg/kg load, then 12.5 mg/kg hourly × 4 hrs, then 6.25 mg/kg hourly</td>
<td>Dr. Smilkstein and colleagues (5) Dr. Buckley and colleagues (6), Dr. Smilkstein and colleagues (7) Dr. Floersheim and colleagues (8), Dr. Broussard and colleagues (9) Dr. Peters and colleagues (10) Dr. Kessler and colleagues (11) Dr. Tillmann and colleagues (12) Dr. Mabie (4), Dr. Castro and colleagues (13)</td>
</tr>
<tr>
<td>Amanita</td>
<td>Penicillin G: 1 g/kg daily IV and NAC (as for APAP overdose)</td>
<td></td>
</tr>
<tr>
<td>HSV</td>
<td>Acracyclor: 30 mg/kg daily IV</td>
<td></td>
</tr>
<tr>
<td>AIH</td>
<td>Methylprednisolone 60 mg/day IV</td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>Lamivudine 100–150 mg/day orally</td>
<td></td>
</tr>
<tr>
<td>AFLP/HELLP</td>
<td>Delivery of fetus</td>
<td></td>
</tr>
</tbody>
</table>

APAP, acetaminophen; NAC, N-acetylcysteine; IV, intravenously; Amanita, mushroom intoxication; HSV, herpes simplex virus; AIH, autoimmune hepatitis; HBV, hepatitis B virus; AFLP/HELLP, acute fatty liver of pregnancy/hemolysis-elevated liver enzymes-low platelet syndrome.
transfusion requirements, obscures the
duce the risk of significant bleeding nor
recombinant factor VIIa (rFVIIa), is not recommended, as it does not re-
plasma to improve coagulopathy in ALF
spectively (38). Prophylactic fresh frozen
from decreased hepatic synthesis as well
function. Hypofibrinogenemia results
agulopathic, and frequently exhibit both
Patients with ALF are, by definition, co-
be administered immediately before a
planned procedure. The procedure should
be performed within 30–60 mins, although
the effect of rFVIIa usually persists for >2
hrs (42). The use of rFVIIa may increase
the risk of thrombotic complications in pa-
tients with ALF (43, 44), especially in
higher doses (90 μg/kg) or after repetitive
dosing (36). RFVIIa should not be given
to patients with a history of myocardial
infarction, stroke, or unstable angina
within 2 wks, or with active deep venous
thrombosis. Patients with ALF due to
pregnancy, Budd-Chiari syndrome, or
suspected malignant infiltration of the
liver also should not receive rFVIIa. In
subjects with persistent coagulopathy de-
spite fresh frozen plasma who have con-
traindications to rFVIIa, plasma exchange
is effective and should be considered (45).

The incidence of upper gastrointestinal
bleeding in ALF patients has been shown
to be decreased by gastric acid
suppression with intravenous his-
tamine-2 receptor antagonists (46). There-
fore, intravenous histamine-2 blockers,
or by inference, proton pump inhibitors
(intravenous or oral), are recommended.

Assessment of Prognosis and Liver
Transplant Listing Criteria. The ability to
predict the likelihood of spontaneous
recovery or death without OLT remains
of paramount importance in patients with
ALF. Many criteria have been proposed to
anticipate the probability of death with-
out OLT (Table 2), but there are insuffi-
cient data to recommend a particular
scheme, given none have been found to
be adequately sensitive and specific. A
cursory assessment regarding transplant
 candidacy should be made on admission
to the intensive care unit by the trans-
plant and intensive care teams with spe-
cific consideration of poor prognostic
factors included in the King’s College
criteria (Table 2). If no immediate con-
traindications are identified, an expedited
OLT evaluation should be undertaken
without delay (47). In addition to the
schemes outlined in Table 2, the etiology
and rapidity of evolution of ALF also must
be considered, because the likelihood of
spontaneous recovery without OLT de-
creases dramatically with the more sub-
acute presentations of fulminant hepatis-
tis B, idiosyncratic drug reactions, and
ALF of undetermined etiology (58).

Current requirements for listing a pa-
tient with ALF for OLT within the United
States must be consistent with Section 3.6.4.1 of the Policies and Bylaws of
the United Network for Organ Sharing (avail-
able at http://unos.org). However, it must
be emphasized that these policies are nei-
ther objective nor verifiable, nor are they
amenable to prospective operational def-
inition. The critical criteria include a) age
>18 yrs; b) a life expectancy without a
liver transplant of <7 days; c) onset of
hepatic encephalopathy within 8 wks of
the first symptoms of liver disease; d) the
absence of preexisting liver disease; e) re-
idence in an intensive care unit; and f) at
least one of the following: ventilator
dependence, requiring renal replacement
therapy, or an international normalized
ratio >2.0. Patients with acute decomp-
pensated Wilson disease also may be
listed for OLT because of their universally
poor prognosis for spontaneous recovery.

Nutrition. ALF is a catabolic state
characterized by negative nitrogen balance
and, consequently, immunodeficiency (59).
Patients with ALF also exhibit increased
resting energy expenditure compared with
healthy controls (60). Therefore, nutri-
tional support is recommended in patients
with ALF, although essentially no studies
exist to guide therapy (60, 61). Enteral
nutrition should be administered when-
ever possible, with higher caloric density
feeds preferred to avoid excessive free wa-
ter and hypo-osmolality, which may ex-
acerbate cerebral edema (see below). Par-
enteral nutrition (35–40 kcal/kg per day)
(61), delivered by a dedicated central ve-
nous catheter, should be reserved for pa-
tients with specific contraindications to
enteral nutrition. Monitoring for blood glucose should be performed at frequent regular intervals by finger stick (e.g., every 1–2 hrs). Intravenous glucose infusion (1.5–2.0 g/kg per day) is recommended in patients who develop hypoglycemia. Although single center clinical trials have suggested that the maintenance of tight glycemic control reduces mortality in critically ill patients (62, 63), and hyperglycemia may exacerbate intracranial hypertension in patients with ALF (64), ALF patients are at high risk for hypoglycemia. Thus, until further information is available, it is recommended that insulin infusions be used to maintain blood glucose levels <150 mg/dL, while also strictly avoiding hypoglycemia. Approximately 40 g protein per day (0.5–1.0 g/kg per day) should also be administered (65). There are insufficient data to recommend the use of branched-chain amino acids, which are also limited by cost (66). Lipid emulsions appear to be safe in ALF patients, and are recommended as a concentrated source of calories in volume-overloaded patients (61).

Seizure Prophylaxis and Surveillance. Nonconvulsive seizure activity has been documented in a high proportion of patients with ALF and advanced stages of hepatic encephalopathy (67). However, there are insufficient data to recommend prophylactic anticonvulsants in all patients with ALF because two studies using prophylactic phenytoin have reached conflicting conclusions (67, 68). It should be noted that propofol or benzodiazepine infusions used for sedation also provide potent antiseizure prophylaxis.

The performance of electroencephalogram, not necessarily continuously, is recommended for the following indications (68): a) grade III or IV hepatic encephalopathy; b) sudden unexplained deterioration in neurologic examination; c) myoclonus; or d) to titrate therapy when barbiturate coma is used to manage cerebral edema.

Treatment of Circulatory Dysfunction. In hypotensive patients with ALF, volume status should be assessed and hypovolemia corrected before the administration of vasopressors. Vasopressors are recommended for severe systemic hypotension (systolic blood pressure <90 mm Hg; mean arterial pressure <65 mm Hg) or to maintain a cerebral perfusion pressure (CPP) (equivalent to mean arterial pressure − ICP) of 50–80 mm Hg. Norepinephrine or dopamine are recommended, with norepinephrine preferred, because the former may provide a more consistent and predictable increase in cerebral perfusion than the latter in patients with traumatic brain injury (69). Low-dose dopamine is not recommended, as it has not been shown to be effective in decreasing the risk of renal failure in patients with systemic inflammatory response syndrome and early renal dysfunction (70). Epinephrine has been shown to decrease mesenteric blood flow in severe septic shock, and therefore may compromise hepatic blood flow in patients with ALF (71, 72). Vasopressin and analogs are not recommended, because they directly cause cerebral vasodilation and may exacerbate intracranial hypertension (73).

Relative adrenal insufficiency occurs frequently in patients with ALF, and may contribute to cardiovascular collapse (74). Moderate doses (200–300 mg/day) of hydrocortisone have been shown to improve the vasopressor response to norepinephrine in hypotensive patients with sepsis (75) and ALF (76). A trial of hydrocortisone should be considered in ALF patients with persistent hypotension despite a volume challenge and norepinephrine. Because of conflicting results in clinical trials, there are insufficient data to recommend the use of agents which purportedly improve peripheral tissue oxygenation, such as prostacyclin (77) and N-acetylcysteine (78, 79).

MANAGEMENT OF CEREBRAL EDEMA AND INTRACRANIAL HYPERTENSION

Intracranial hypertension due to cerebral edema remains one of the primary causes of morbidity and mortality in patients with ALF (80), with highest incidence in patients with more acute presentations (i.e., a jaundice-to-encephalopathy interval of <4 wks) (58). A head computed tomography is recommended in patients with ALF who progress to stage III/IV hepatic encephalopathy or experience an

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### Table 2. Proposed schemes for assessing prognosis and the need for orthotopic liver transplantation in patients with ALF

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Etiology of ALF</th>
<th>Criteria for Liver Transplantation</th>
<th>Reference</th>
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<tbody>
<tr>
<td>King’s College criteria</td>
<td>APAP Arterial pH &lt;7.3 OR all of the following: 1) PT &gt;100 secs (INR &gt;6.5) 2) creatinine &gt;3.4 mg/dL 3) grade 3/4 encephalopathy Non-APAP Arterial pH &lt;7.3 OR any of the following: 1) NANB/drug/halothane etiology 2) jaundice to encephalopathy &gt; 7 days 3) age &lt;10 or &gt;40 yrs 4) PT &gt;50 secs (INR &gt;3.5) 5) bilirubin &gt;17.4 mg/dL</td>
<td>Arterial pH &lt;7.3 OR all of the following: 1) PT &gt;100 secs (INR &gt;6.5) 2) creatinine &gt;3.4 mg/dL 3) grade 3/4 encephalopathy</td>
<td>Dr. O’Grady and colleagues (47)</td>
</tr>
</tbody>
</table>

ALF, acute liver failure; APAP, acetaminophen; PT, prothrombin time; INR, international normalized ratio; NANB, non-A, non-B viral hepatitis; Mixed, mixed etiologies; HBV, hepatitis B virus; APACHE, Acute Physiology and Chronic Health Evaluation; MELD, Model for End-Stage Liver Disease.

*Times of data collection vary between studies. See individual references.*

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acute change in mental status, or before ICP monitor placement. Although a head computed tomography will frequently demonstrate cerebral edema in ALF patients with advanced-stage hepatic encephalopathy (81), it is insensitive to intracranial hypertension (82, 83); therefore, its principal value is to rule out other uncommon intracranial pathology, most importantly bleeding. The physician must consider the potential risk of moving a patient from the intensive care unit to the computed tomography scanner.

The indications for placement of an ICP monitor remain one of the most contentious issues in managing patients with ALF, because there are no randomized, controlled studies to guide the physician. Indeed, ICP monitoring in nonrandomized subjects has not been shown to improve survival (84, 85). Therefore, there are insufficient data to recommend ICP monitor placement in all patients with ALF. However, most members of the ALFSG place ICP monitors in patients with advanced (stage III/IV) hepatic encephalopathy with the belief that monitoring improves the management of cerebral edema and provides important prognostic information regarding neurologic recovery after OLT (84, 85). Therefore, ICP monitor placement should be considered in all patients listed for OLT with stage III/IV hepatic encephalopathy. Some centers also insert ICP monitors in non-OLT candidates with advanced stage hepatic encephalopathy in whom intensive medical management offers a reasonable likelihood of spontaneous survival (e.g., in patients with acetaminophen-induced ALF).

Bleeding complications attributed to the placement of ICP monitors occur in 10% to 20% of patients with ALF, but are often mild and of questionable clinical significance (84–86). Therefore, treatment of the bleeding diathesis before insertion is recommended as outlined above. There are insufficient data to recommend a standard intracranial location for ICP monitor placement. While it has been observed that placement of ICP monitors in the epidural space may decrease the incidence of bleeding complications (84, 86), such monitors are less accurate than those that traverse the dura and they tend to overestimate ICP (87). Due to the risk of bleeding, intraventricular placement should be avoided. ICP monitor placement is not recommended in patients with mild hepatic encephalopathy (stages I/II), or with clinical evidence of diencephalic herniation and/or intractable arterial hypotension, in whom death is imminent.

Management of Intracranial Hypertension: General Recommendations. A quiet environment with limited stimulation is recommended for ALF patients with evidence of cerebral edema. Chest physiotherapy and endotracheal suctioning also may need to be minimized, and prophylactic intravenous lidocaine before endotracheal suctioning may be considered (88). To decrease ICP, the head should be maintained in a neutral position (89), and the head of the bed should be elevated to 30 degrees (90, 91), which will also reduce the risk of ventilator-associated aspiration pneumonia (92). During elevation of the head of the bed, mean arterial pressure should be maintained to avoid decreasing the cerebral perfusion pressure (93). Trendelenburg position, head flexion, head rotation, and sudden change of position to supine should be avoided except when necessary for placement of a central venous catheter (89).

Hyperventilation-induced hypocapnia induces cerebral vasoconstriction, decreases ICP (94, 95), and may improve cerebrovascular autoregulation (96). Spontaneous hyperventilation, therefore, which is usual in patients with ALF, should not be treated. However, prophylactic hyperventilation is not recommended in patients with ALF, because vasoconstriction can reduce cerebral oxygen utilization (94) and had no effect on the development of cerebral edema in one study (97). Consequently, maintenance of a PCO₂ between 30 and 40 mm Hg is a reasonable goal. Acute hyperventilation, however, is recommended as emergency rescue therapy of patients with evidence of diencephalic herniation.

Generally, maintenance of euthermaia (36.5–37.5°C) is recommended in patients with ALF, because fever exacerbates intracranial hypertension (25) and is independently associated with worse outcome in patients admitted to neurologic intensive care units (98). Fever should be treated aggressively with cooling blankets, fans, or other noninvasive devices, but nonsteroidal anti-inflammatory drugs and acetaminophen are not recommended because of possible nephro- and gastric mucosal toxicity, and possible potentiation of liver injury, respectively. Shivering, which may also increase ICP, should be treated with increased sedation, or with small doses of meperidine (12.5–25 mg). Mild spontaneous hypothermia (35–36.5°C), such as that observed during continuous renal replacement therapy, should not be treated. At this time, there are insufficient data to support the routine use of prophylactic hypothermia in patients with ALF. However, the induction of hypothermia may be considered in the treatment of intracranial hypertension refractory to mannitol (see below).

Cerebral edema in ALF results primarily from astrocyte swelling (cytotoxic cerebral edema) rather than a leaking blood brain barrier (vasogenic cerebral edema) (99). While vasogenic cerebral edema may respond to corticosteroids, cerebral edema in ALF has not been shown to improve after their administration (100); therefore, corticosteroids are not recommended.

Management of Intracranial Hypertension: Specific Recommendations. The absolute values and duration of abnormal ICP and CPP for optimal neurologic recovery after ALF have not been well defined. Therefore, there are insufficient data to recommend strict pressure goals. Suggested ICP based upon experience of individual liver transplant centers in patients with ALF (83, 101), and of other centers in patients with traumatic brain injury (102), include an ICP of <25 mm Hg and CPP between 50 and 80 mm Hg. There are also insufficient data to recommend criteria of ICP and CPP to contraindicate OLT, because rare cases of complete neurologic recovery after severe, prolonged, intracranial hypertension have been reported (103). It has been observed that severe (>40 mm Hg), sustained, intracranial hypertension refractory to medical therapy and/or a CPP <40 mm Hg for >2 hrs are associated with brainstem herniation or poor neurologic recovery after OLT (83). However, if a patient’s pupils remain reactive and a liver graft becomes available, some transplant surgeons would proceed with OLT (103).

The administration of mannitol is recommended as first-line therapy for intracranial hypertension. Mannitol should be administered when ICP ≥25 mm Hg for >10 mins, after the validity of the ICP calibration is confirmed. There are insufficient data to recommend a standard dose of mannitol to be administered. A range of doses (0.25–1.0 g/kg intravenous boluses) has been used both in patients with brain injury (104) and ALF (94, 105). Because lower doses reduce the risk of
severe osmotic disequilibrium and dehydration, and may be as effective as higher doses (104). 0.25–0.5 g/kg boluses are recommended. Serum osmolality should be assessed every 6 hrs, and mannitol boluses may be repeated if ICP remains >25 mm Hg and serum osmolality <320 mOsm/L. It should be noted that serum osmolality correlates poorly with mannitol concentrations, and a normal osmolar gap may be a more accurate measure of adequate mannitol clearance before the administration of subsequent doses (106).

There are insufficient data to recommend a standard therapy of intracranial hypertension refractory to mannitol. However, the following may be considered in the following order based upon ease and safety of administration, and efficacy based upon the available literature.

**Hypertonic saline** boluses have been used increasingly in neurocritical care patients, with efficacy similar or superior to mannitol (107–111). Many preparations and dosing strategies of hypertonic saline have been employed to treat cerebral edema, including 23.4% saline (30 mL) and 7.5% saline (2.0 mL/kg) boluses repeated every 2 hrs to 3 hrs (111). Serum sodium should be monitored at frequent intervals. Hypertonic saline also has been administered prophylactically to ALF patients with high grade encephalopathy as a constant infusion (30%, 5–20 mL/hr) to achieve a serum sodium of 145 mmol/L to 155 mmol/L. In one small, randomized trial, the incidence and severity of intracranial hypertension was reduced in those patients with induced hyponatremia (112). Although hyponatremia of short duration is not a contraindication to administering hypertonic saline in patients with ALF, the rate of correction should be inversely proportional to the duration of hyponatremia to minimize the risk of osmotic demyelination.

**Induced moderate hyperthermia** (32–33°C) may decrease ICP in ALF patients with intracranial hypertension refractory to mannitol (113), and stabilize ICP during OLT (114). Increasingly, units within the ALFSG have used hypothermia to bridge patients with osmotherapy-refractory intracranial hypertension to OLT, although the practice is not universally endorsed. Further studies also must document the safety of the practice, which may increase the risk of cardiovascular instability and/or infection.

**Barbiturate coma**, induced by pentobarbital (3–5 mg/kg intravenous loading bolus followed by 1–3 mg/kg per hr intravenous infusion) or thiopental (5–10 mg/kg loading bolus followed by 3–5 mg/kg per hr), also has been advocated in patients with ALF refractory to mannitol (83, 115). Potential severe adverse effects—including hypotension, hypothermia, immunosuppression, hypokalemia, and prolonged coma—mandate physician experience with the induction of barbiturate coma, and vasopressors to maintain cerebral perfusion pressure >50 mm Hg usually are required.

**Indomethacin** (25 mg infused intravenously over 1 min) also has been shown to acutely decrease ICP and increase CPP by causing cerebral vasoconstriction (116, 117). Indomethacin therefore may be considered as salvage therapy in patients with intracranial hypertension refractory to the above measures.

### OTHER SPECIAL PROCEDURES

**Mechanical Ventilation.** Recommended indications for endotracheal intubation include respiratory failure (hypoxemia, hypercapnia), airway protection in the setting of advanced encephalopathy (stage III/IV), agitation, and imminent ICP monitor placement. Laryngoscopy and endotracheal intubation may be associated with transient elevation in ICP and appropriate countermeasures (induction of anesthesia followed by constant sedation) are recommended.

There are insufficient data to recommend a standard mode of delivering mechanical ventilation to patients with ALF. Patients with ALF often develop acute respiratory distress syndrome with disease progression to cerebral edema (118), often in the setting of infection as part of systemic inflammatory response syndrome (24). Generally, tidal volume and plateau pressure should be limited (6 mL/kg predicted body weight and <30 cm H₂O, respectively) in intensive care unit patients with established acute lung injury, and low tidal volumes also may decrease the risk of progression to acute respiratory distress syndrome (119, 120). It must be appreciated that decrements in tidal volume will decrease minute ventilation and increase P_{CO₂}, and thereby increase ICP. Therefore, in patients with low tidal volumes, the respiratory rate should be increased to maintain a stable P_{CO₂}.

High levels of positive end-expiratory pressure also may increase ICP in patients with ALF, and decrease hepatic blood flow (121). However, in neurocritical care patients, the effects of positive end-expiratory pressure on ICP are inconsistent and not always clinically important (122). In general, the lowest level of positive end-expiratory pressure that achieves adequate oxygenation should be applied in patients with ALF.

**Renal Replacement Therapy (RRT); Management of Fluids and Electrolytes.** The evaluation of acute renal failure in patients with ALF should include analysis of urine sodium, which is low (<10 mEq/L) in prerenal azotemia and functional renal failure (hepatorenal syndrome) and high in acute tubular necrosis. Microscopic examination of the urine should be performed to detect casts and renal tubular cells, which suggest acute tubular necrosis. Assessment of intravascular volume by measurement of central venous pressure, or pulmonary capillary wedge pressure via pulmonary artery catheter, may be considered, but these measures poorly reflect intravascular volume (123). An intravenous fluid challenge (crystalloid and colloid; 1–1.5 L) is recommended to exclude prerenal azotemia, but large volumes of glucose-containing solutions should be avoided in consideration of the risk of hyperglycemia.

There are insufficient data to recommend specific criteria to start or discontinue renal replacement therapy (RRT) in patients with ALF. However, the decision to start RRT should be based upon the level of renal dysfunction, fluid balance, and metabolic derangements, and a need to create space for intravenous colloid (e.g., fresh frozen plasma) or parenteral nutrition. Goals of RRT should be clearly delineated before initiation of RRT. Conversely, a plan for discontinuing RRT also should be agreed upon before its institution, particularly in the event that a patient is no longer considered for OLT or fails to spontaneously improve (124).

Patients with ALF frequently tolerate intermittent hemodialysis poorly because of hemodynamic instability and fluid shifts. Furthermore, intermittent hemodialysis may increase ICP (125). Therefore, most members of the ALFSG prefer continuous RRT (126), even in hemodynamically stable patients (127). Mannitol removal may be accomplished by high volume continuous venovenous hemofiltration, but has not been well studied; conventional hemodialysis or continuous venovenous hemodiafiltration may be required for this purpose (128). A dedicated double-lumen catheter inserted in the internal jugular vein is recommended, un-
less the patient has significant intracranial hypertension, in which case the femoral route is preferred. If the catheter remains in place for >7 days, a tunneled catheter should be considered. Catheters should be locked with saline or citrate. During continuous venovenous hemofiltration, heparin anticoagulation should be avoided because of the risk of bleeding, and citrate is recommended, although ionized serum calcium must be monitored carefully. Bicarbonate buffer solutions are recommended, because citrate and lactate both require biotransformation to bicarbonate in the liver.

Electrolyte abnormalities of all types frequently accompany ALF, especially when complicated by renal failure, and may be particularly deleterious. Monitoring of serum electrolyte concentrations (once or twice daily) and prompt correction of abnormalities is recommended. Hyponatremia should be strictly avoided, because it may exacerbate cerebral edema. As noted above, a relative restriction of free water is recommended; for example, by administering higher caloric density enteral feeds and/or more concentrated glucose infusions in ALF patients with hypoglycemia. Although there are insufficient data to advise a rate of correction of serum sodium, the risk of osmotic demyelination may be lower than in other patient populations because of the short duration of hyponatremia. Therefore, hypertonic saline boluses or continuous RRT may be employed for this purpose (126), with adjustment of the rate of correction for the length of time of hyponatremia. Other electrolyte concentrations (phosphate, magnesium, bicarbonate) should be kept within the normal range.

Maintenance of euvolemia in ALF is recommended to avoid hemodynamic instability and underperfusion of critical vascular beds. Unfortunately, central venous pressure and pulmonary capillary wedge pressure reflect intravascular volume unreliably, and hypotensive ALF patients should first receive a volume challenge, as above. In volume-unresponsive subjects, echocardiography or other non-invasive measures of intrathoracic blood volume should be considered.

**MANAGEMENT OF ALF DURING AND AFTER OLT**

Many complications of ALF persist or become more acute during OLT. Unfortunately, there are insufficient data from clinical trials to recommend any specific management decision pertaining to OLT in ALF patients. However, based upon practices in the published literature and the experiences of centers in the ALFSG, the following guidelines have been endorsed.

**Intraoperative and Postoperative Monitoring.** ICP frequently increases during dissection of the native liver and during reperfusion of the graft (114), especially if the patient has experienced intracranial hypertension before OLT (129). Furthermore, intracranial hypertension may persist during the first 10–12 hrs after OLT for ALF (130). Therefore, if an ICP monitor has been placed before OLT, ICP should be continuously monitored during and early after OLT. OLT should not be delayed, however, for placement of an ICP monitor after an organ has become available, as long as the patient’s pupils remain active and the patient is not posturing (131). Monitoring in the operating suite also should include continuous arterial pressure. As in the case of pre–liver transplant patients, pressure goals include ICP <25 mm Hg, mean arterial pressure >90 mm Hg, and CPP 50 mm Hg to 80 mm Hg, and norepinephrine is preferred for pressor support (114). Osmotherapy with mannitol should be administered for ICP ≥25 mm Hg for >10 mins, and serum sodium should be maintained between 140–150 mmol/L.

**Graft Selection Considerations.** Survival after OLT for ALF decreases markedly after patients have progressed to stage IV hepatic encephalopathy (131). Therefore, in patients deemed to have poor prognosis by the schemes outlined in Table 2, OLT must be performed as soon as an organ becomes available and not delayed. In general, ABO-identical grafts are preferred, but ABO-compatible grafts have nearly comparable 1-yr survival after OLT for ALF and should be used without hesitation (132). The gravity of the clinical situation must dictate whether to use an ABO-incompatible graft, because 1-yr graft survival is decidedly lower (132). Evaluation of a possible living donor may be entertained by transplant centers with extensive experience with living donor liver transplantation in cirrhotic patients. Such an expedited evaluation has been shown to be feasible in the setting of ALF, with outcomes as good as OLT with a deceased donor graft (133).

**Other Surgical Considerations.** Transplant surgeons generally tailor other decisions regarding the surgical management of ALF patients to the particular clinical situation. Venovenous bypass has been advocated by some authorities (132), but not others (114), to minimize swings in cerebral perfusion during clamping of the inferior vena cava and portal vein, as well as during reperfusion. Similarly, hepatectomy of the native liver with temporary portocaval anastomosis may be considered in ALF patients with toxic liver syndrome (134–136).

**ACKNOWLEDGMENTS**

While the opinions expressed herein do not entirely reflect their practices, the authors wish to acknowledge the thoughtful comments of Drs. Julia Weldon (King’s College Hospital, London, UK) and Fin Larsen (University Hospital of Copenhagen, Denmark).

**REFERENCES**


59. O’Keefe SJ, El Zayadi AR, Carraher TE, et al:
Malnutrition and immuno-incompetence in patients with liver disease. **Lancet** 1980; 2:615–617


91. Ling GS, Neil CJ: Maintaining cerebral perfusion pressure is a worthy clinical goal. *Neurocrit Care* 2005; 2:75–81


129. Incidence and pathophysiology of pulmon-
INTRODUCTION

It is common for patients with liver disease to undergo surgery; as many as 10% of patients with advanced liver disease require a surgical procedure other than liver transplantation in the final 2 years of their life. In addition, asymptomatic patients with undiagnosed chronic liver disease might also undergo surgery. Underlying liver disease has an effect on the risk of morbidity and mortality from surgery. Appropriate preoperative evaluation and management of patients with liver disease is essential for counseling and selection of patients for surgical treatment, and might reduce the risks of surgery and improve outcomes for these patients.

PREOPERATIVE SCREENING FOR LIVER DISEASE

The goal of preoperative screening is to determine the presence of pre-existing liver disease without the need for extensive or invasive testing. A thorough history and physical examination will often provide important clues as to whether the patient has liver disease, or might identify specific risk factors for liver disease such as previous blood transfusions, illicit drug use, or excessive alcohol intake. A family history of jaundice, anemia or hereditary liver disease, or a history of prior adverse reactions to anesthesia should raise suspicion of liver disease. It is essential that a careful medication

SUMMARY

Patients with end-stage liver disease often undergo surgery for indications other than liver transplantation. These patients have an increased risk of morbidity and mortality that is related to their underlying liver disease. Assessments of surgical risk provide a basis for discussion of risks and benefits, treatment decision making, and for optimal management of patients for whom surgery is planned. The most useful indicators of surgical risk are indices that predict advanced disease, such as the Child–Turcotte–Pugh score, or those that predict prognosis, such as the Model for End-stage Liver Disease score. Careful preoperative risk assessment, patient selection, and management of various manifestations of advanced disease might decrease morbidity and mortality from nontransplant surgery in patients with liver disease.

KEYWORDS management, preoperative evaluation, risk assessment, surgery

REVIEW CRITERIA

PubMed was searched in November 2006 for all English-language publications that included the search terms "surgery," "preoperative," "anesthesia," "liver diseases," "cirrhosis," and "risk assessment." The full articles for identified records that were thought to be relevant were obtained.
history is taken that includes information on the use of over-the-counter analgesics and/or complementary alternative medications. The physical examination can identify signs that are consistent with underlying liver disease, such as temporal wasting, jaundice, spider nevi, ascites, hepatosplenomegaly, or palmar erythema.

The routine assessment of liver function is not recommended unless there is clinical suspicion of underlying liver disease, based on the patient’s history and physical examination findings. Despite the epidemics of viral hepatitis and obesity-related fatty liver disease, the overall prevalence of liver disease in the general population remains low. In one study of 7,620 patients who were scheduled for elective surgery over a period of 1 year, preoperative screening revealed abnormal liver function test results in only 11 patients. Routine liver function tests, therefore, have a low predictive value.

If the liver function test results are abnormal, elective surgery should be deferred until an extensive evaluation of the nature, acuity, and severity of the biochemical abnormalities has been completed. In general, for asymptomatic patients with mildly elevated alanine aminotransferase and aspartate aminotransferase levels, and a normal total bilirubin concentration, cancellation of surgery is rarely required. In patients with significant abnormalities, such as unexplained elevations in aspartate aminotransferase and alanine aminotransferase levels to greater than three times the upper limit of normal, or with any elevation in their total bilirubin concentration, detailed investigation is warranted to evaluate whether there is underlying cirrhosis (given the high perioperative risk observed in patients with cirrhosis). The need for further investigation in these patients is highlighted by studies that report an incidence of undiagnosed cirrhosis of 6–34% in asymptomatic patients with abnormal liver function test results.

**EFFECT OF LIVER DISEASE ON SURGERY AND ANESTHESIA**

The presence of liver disease can increase the risks of surgery and anesthesia in several ways. Hepatic dysfunction can significantly impair the metabolism of certain medications used perioperatively. The duration of action of many drugs can be increased as a result of altered metabolism by cytochrome P450 enzymes, a decreased concentration of plasma-binding proteins, and decreased biliary excretion. The perioperative use of certain narcotic opioids such as morphine and oxycodone should be avoided in patients with cirrhosis, because their bioavailability is markedly increased and their half-life prolonged. By contrast, metabolism of fentanyl does not seem to be affected by hepatic dysfunction. The metabolism of certain benzodiazepines (such as midazolam and diazepam) can also be slowed in patients with cirrhosis, whereas oxazepam and temazepam undergo conjugation without hepatic metabolism and their clearance rate is, therefore, not affected. In patients with hepatic dysfunction, the increased duration of action of benzodiazepines and narcotics can lead to prolonged depression of the central nervous system and hepatic encephalopathy; these agents should, therefore, be used with caution in the perioperative setting. Of the volatile anesthetics, isoflurane is generally recommended as it undergoes the least amount of hepatic metabolism and does not impair hepatic blood flow. By contrast, halothane undergoes significant hepatic metabolism and reduces hepatic blood flow. Halothane anesthesia carries with it a significant risk of drug-induced hepatitis.

One manifestation of advanced liver disease is a hyperdynamic circulation, with elevated cardiac output and decreased systemic vascular resistance. Progressive hepatic dysfunction results in progressive systemic and splanchnic vasodilation, with subsequent activation of the sympathetic nervous system and neurohormonal axis in an attempt to maintain arterial perfusion pressure. In addition, the compensatory inotropic and chronotropic response of the heart to pharmacologic and physiologic stressors, including surgery, is blunted in patients with cirrhosis. In patients with pre-existing hepatic dysfunction, these pathophysiologic changes exacerbate the effects of hemodynamic insult during surgery. Induction of anesthesia, hemorrhage, hypoxemia, hypotension, use of vasoactive medications—and even the patient’s position and the surgical technique used—can all decrease intraoperative and perioperative oxygen delivery to the liver and increase the risk of hepatic dysfunction.

**ESTIMATING THE RISK OF SURGERY**

Owing to the lack of large, prospective studies, the assessment of operative risk is an inexact science. Postoperative outcomes are markedly
influenced by the severity and nature of the underlying liver disease and the type of surgery being considered.16,17

**Nature of the underlying liver disease**

*Obstructive jaundice*

The presence of underlying obstructive jaundice markedly increases perioperative mortality, and several studies have reported risk factors for increased mortality in patients with this condition. These risk factors include an initial hematocrit of above 30%, a serum total bilirubin concentration above 11 mg/dl, the presence of malignancy, a serum creatinine concentration higher than 1.4 mg/dl, serum albumin concentration higher than 3.0 g/dl, age older than 65 years, aspartate aminotransferase concentration above 90 IU/l, and blood urea nitrogen concentration above 19 mg/dl.18–20

*Acute hepatitis*

Patients with acute hepatitis have increased morbidity and mortality associated with surgery.21,22 These increases probably occur as a result of the acute hepatocellular injury and associated hepatic dysfunction. As most cases of acute hepatitis are self-limited and symptoms ultimately resolve, elective surgery should be postponed until the patient’s clinical, biochemical and histologic parameters return to baseline. Similarly, overall morbidity and mortality are increased in patients with acute alcoholic hepatitis, and elective surgery is contraindicated in these patients.23

*Chronic hepatitis*

The etiology of chronic hepatitis does not seem to influence a patient’s perioperative risk, although specific conditions warrant special consideration (see below). Surgery is considered safe in asymptomatic patients with histologic evidence of mildly active hepatitis, whereas symptomatic patients with histologic evidence of severely active hepatitis have been shown to be at increased risk from surgery.24–26 The presence of underlying hepatic dysfunction increases perioperative risk. In patients with chronic hepatitis caused by either alcoholic or nonalcoholic steatohepatitis, one study reported a trend towards increased morbidity and mortality in patients with moderate to severe steatosis (>30%) who underwent major hepatic resection.27 These patients’ mean BMI was greater than 30 kg/m², and their preoperative bilirubin levels were elevated (mean 2.2 mg/dl), which indicated significant underlying hepatic dysfunction.27

*Cirrhosis*

In patients with cirrhosis, perioperative risk can be influenced by hepatic dysfunction, portal hypertension and complications such as intra-abdominal varices, ascites, renal dysfunction, and portopulmonary hypertension.

**Severity of the underlying liver disease**

An accurate assessment of the extent and severity of the patient’s underlying liver disease is required for an effective determination of their perioperative risk. The Child–Turcotte–Pugh (CTP) score and the Model for End-stage Liver Disease (MELD) score have both been used for this purpose.

*Child–Turcotte–Pugh score*

The CTP score was the first-described predictor of surgical risk—this score was originally designed by Child and Turcotte to predict mortality after portocaval shunt surgery, and was later modified by Pugh et al. to include prothrombin time in place of nutritional status for use in patients undergoing esophageal transsections of bleeding varices (Table 1).28,29 Although the CTP score has not been prospec- tively validated, it has stood the test of time, and has been widely used to assess disease severity in patients with cirrhosis and to predict their risks of perioperative morbidity and mortality for both elective and emergency surgery.30–32 In cirrhotic patients who undergo abdominal surgery, CTP classes A, B and C are associated with mortality of 10%, 30–31% and 76–82%, respectively.1,32

The subjective nature of the clinical parameters and the arbitrary cut-off points used for the biochemical parameters limit the accuracy of the CTP score as a predictor of surgical risk. An example of the limitations of the CTP score is shown by the fact that patients with CTP class A cirrhosis can still have ascites, hyperbilirubinemia and portal hypertension.33 For this reason, alternative systems have been sought that estimate the severity of underlying hepatic dysfunction more accurately.

*Model for End-Stage Liver Disease*

The MELD score was originally devised as a prognostic measure of short-term mortality in patients with cirrhosis who were undergoing
The MELD assigns the patient a score of 8–40, which is derived from a complex formula that incorporates three biochemical variables—the serum total bilirubin concentration, serum creatinine concentration, and international normalized ratio (INR, see Box 1). The MELD score has been prospectively validated as a prognostic marker of mortality in patients with cirrhosis, acute variceal bleeding or acute alcoholic hepatitis. A modified MELD score was adopted by the United Network for Organ Sharing in February 2002 for the purposes of donor liver allocation.

The MELD score was first evaluated for use in the preoperative evaluations of a series of patients with cirrhosis who were scheduled to undergo cholecystectomy (Figure 1). In this study, both the MELD and the CTP scores accurately predicted postoperative morbidity, with areas under the receiver operating characteristic curve (AUCs) of 0.938 and 0.839, respectively. Patients with a MELD score above 8 were more likely to have postoperative complications, including death, than those with a MELD score below 8 (44% vs 10%). Similarly, in a study of cirrhotic patients scheduled to undergo cardiac surgery with cardiopulmonary bypass, both the preoperative CTP and MELD scores correlated highly with postoperative hepatic decompensation and mortality, with AUCs of 0.84 and 0.89, respectively.

Other studies have evaluated the overall utility of the MELD score in patients with cirrhosis, but have included several different types of procedures. The type of surgery performed has a large effect on outcome (see below), and the results of these studies cannot, therefore, be directly applied to individuals. In one study of 40 cirrhotic patients who underwent various elective and emergency procedures, both MELD and CTP scores correlated with postoperative mortality at 1 and 3 months.

In another study of 53 cirrhotic patients who underwent abdominal surgery, a preoperative MELD score of 14 or greater was superior to CTP class C for prediction of either death or need for transplantation at 90 days (77% vs 23%). In a study by Northup et al., it was noted that the 30-day mortality from nontransplant surgery in cirrhotic patients increased by 1% for MELD scores between 6 and 20, with an additional 2% per point for scores above 20. This information has limited value for individual patient counseling, however; these analyses were reported on a per-procedure rather than per-patient basis.

### Table 1 Child–Turcotte–Pugh score

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<th>Component</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
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<tr>
<td>Total bilirubin concentration (μmol/l)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt;34</td>
<td>34–50</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Serum albumin concentration (g/l)</td>
<td>&gt;35</td>
<td>28–35</td>
<td>&lt;28</td>
</tr>
<tr>
<td>International normalized ratio</td>
<td>&lt;1.7</td>
<td>1.7–2.2</td>
<td>&gt;2.2</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Controlled with medication</td>
<td>Treatment-refractory</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>None</td>
<td>Grade I–II (or controlled with medication)</td>
<td>Grade III–IV (or treatment-refractory)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adapted from references 28 and 29. <sup>b</sup>Add up the points for each component, and use the total score to calculate the Child–Turcotte–Pugh class: Class A = 5–6 points, Class B = 7–9 points and Class C = 10–15 points. <sup>c</sup>For patients with chronic cholestatic diseases, assign 1 point for a bilirubin concentration of up to 68 μmol/l, 2 points for a bilirubin concentration of 68–170 μmol/l, and 3 points for a bilirubin concentration >170 μmol/l.

### Box 1 Model for End-stage Liver Disease score

\[
\text{MELD score} = (9.6 \times \log_{e} [\text{creatinine mg/dl}]) + (3.8 \times \log_{e} [\text{bilirubin mg/dl}]) + (11.2 \times \log_{e} [\text{INR}]) + 6.4
\]

The final score is rounded off to the nearest whole number and the maximum score is 40 (scores larger than 40 are assigned a value of 40). For any laboratory values less than 1.0 a value of 1.0 is used. The maximum creatinine concentration is 4.0 mg/dl (creatinine concentrations higher than 4.0 mg/dl are assigned a value of 4.0 mg/dl). If a patient has had dialysis twice within the previous week, the creatinine value is set as 4.0 mg/dl.

<sup>a</sup>Adapted from references 34–36. Abbreviation: INR, international normalized ratio.
The AUC of the MELD score when used to predict 30-day mortality for all procedures was 0.72, but was considerably higher for intra-abdominal surgery (0.87), which indicated that there are variations in risk for specific types of procedures and emphasized the need for procedure-specific outcomes data.

**Other approaches**

Alternative approaches used to determine the severity of hepatic disease include liver scintigraphy (using $^{99m}$Tc-galactosyl-labeled human serum albumin), the indocyanine-green retention test, the aminopyrine breath test, and measurement of the lidocaine metabolite monoethylglycinexylidide. Although these approaches can provide a quantitative assessment of hepatic function, these techniques are not widely available and are rarely used, except to assess a patient’s hepatic reserve during their evaluation as a candidate for resection.

**Type of surgery**

**Emergency surgery**

Several studies have shown that patients with cirrhosis who undergo any emergency surgery, especially emergency abdominal surgery or surgery as a result of trauma, have a higher mortality than patients with normal hepatic function. Patient outcomes worsen with increasing CTP scores.

**Abdominal surgery**

Abdominal surgical procedures—such as gastric bypass, biliary procedures, ulcer surgery and colonic resections—increase morbidity and mortality in patients with cirrhosis. Likewise, morbidity and mortality are also increased in patients with cirrhosis who undergo cholecystectomy, although the risk seems to be highest for those who undergo nonlaparoscopic and emergency cholecystectomy. Two small series have reported the pre-operative placement of transjugular intrahepatic portosystemic shunts in patients with cirrhosis and portal hypertension, for whom abdominal surgery would otherwise be contraindicated, to improve portal hypertension and allow surgery to be successfully completed.

**Cardiac surgery**

In patients with cirrhosis, cardiac surgery that requires cardiopulmonary bypass has an increased perioperative risk. The published studies reported are all small, but all have shown increases in postoperative complications and mortality. For example, in one study of 13 patients, no deaths were reported in patients with CTP class A cirrhosis, but mortality was 80% in patients with CTP class B cirrhosis or greater. The increased morbidity and mortality were caused by an elevated incidence of bleeding and sepsis and were felt to be unrelated to cardiac complications. A similar study of 18 patients who underwent cardiac surgery with cardiopulmonary bypass demonstrated mortality rates of 0%, 50%, and 100% for patients with CTP classes A, B, and C, cirrhosis, respectively.

In 2004, a relatively large study of 44 cirrhotic patients who underwent elective cardiac surgery (coronary artery bypass grafting, valve surgery, or pericardectomy) was published, which also noted a strong association between CTP score and postoperative mortality: patients with a CTP score of 8 or higher had significantly higher postoperative mortality than those with a CTP score below 8.

**Hepatic resection**

Surgical resection of localized hepatocellular carcinoma in patients with cirrhosis raises overall mortality from abdominal procedures was high, and procedure-specific mortality in this group was not reported. The AUC of the MELD score when used to predict 30-day mortality for all procedures was 0.72, but was considerably higher for intra-abdominal surgery (0.87), which indicated that there are variations in risk for specific types of procedures and emphasized the need for procedure-specific outcomes data.

### Figure 1

C-statistics for the use of the CTP or MELD score in prediction of 30-day postoperative mortality, or mortality and morbidity, in patients with cirrhosis. A high C-statistic value indicates the increased accuracy of the score. Both the CTP and the MELD scores are useful to predict outcomes after surgical procedures in patients with advanced liver disease. Data were obtained from references 39, 40 and 43. Abbreviations: CTP, Child–Turcotte–Pugh; MELD, Model for End-Stage Liver Disease.
concerns about the adequacy of residual hepatic reserve, especially in those who have advanced cirrhosis and portal hypertension. These patients have increased rates of perioperative complications, long-term hepatic decompensation, and death following resection, and thus patient selection is critical. \(^{57}\) Refinements in patient selection, early diagnosis and improved surgical techniques have, however, led to improved perioperative mortality and 5-year survival. \(^{58}\) The absence of portal hypertension measured by hepatic vein catheterization (a hepatic vein pressure gradient <10 mmHg) and a normal serum total bilirubin concentration have been shown to be superior predictors of outcome after surgery, with 5-year survival rates above 70%. By contrast, an elevated hepatic vein pressure gradient (>10 mmHg) and an elevated total bilirubin concentration of (>1 mg/dl) are associated with 5-year survival rates below 30%, regardless of the patient’s CTP classification. \(^{59}\)

### RECOMMENDATIONS FOR PREOPERATIVE EVALUATION

Although there have been no prospective studies that assess the usefulness of preoperative risk assessment with either the CTP or MELD scores, the published data provide a basis for general recommendations in the preoperative evaluation of patients with liver disease (Figure 2).

Elective surgery can proceed in patients with CTP class A cirrhosis. For patients with CTP class B cirrhosis, hepatic resection and cardiac surgery should be avoided, and the patient’s condition should be optimized before elective surgery. For patients with CTP class C cirrhosis, elective surgery is contraindicated and nonsurgical options should be pursued.

One advantage of the MELD score is that it provides a continuous scale that can be fine-tuned according to the type of surgery to be performed. In general, a patient with a MELD score below 10 can undergo elective surgery, whereas caution needs to be exercised for a patient with a MELD score of 10–15. For patients with a MELD score above 15, elective surgery should be avoided and the patient’s candidacy for liver transplantation should be considered. These general guidelines should be modified for specific circumstances. In particular, the risk of adverse outcomes from orthopedic or urologic procedures is lower than from abdominal or cardiac surgery.

Portal hypertension is a superior predictor of poor outcome in patients with cirrhosis who are undergoing hepatic resection, compared

**Figure 2** Proposed algorithm for the preoperative assessment of patients with liver disease.
with the CTP classification. Some authorities have proposed that portal pressure should be measured in cirrhotic patients during preoperative evaluations for surgical resection of hepatocellular cancer; however, this measurement is not routinely done. Clinically, the presence of underlying portal hypertension can be associated with the presence of varices, ascites or a platelet count below 100,000/mm$^3$ in the presence of splenomegaly. These findings might obviate the need for invasive measurement of the hepatic venous pressure gradient before surgery in some patients. A retrospective review of 587 patients who underwent resection of various hepatic lesions evaluated the predictive value of preoperative MELD scores in relation to postoperative outcomes. Although there was no significant association between MELD scores and morbidity or mortality after hepatic resection, 91% of the patients in this series had minimal or no preoperative evidence of liver dysfunction.

### PREOPERATIVE MANAGEMENT

In addition to risk stratification, optimal preoperative management of conditions related to an underlying hepatic dysfunction is essential (Table 2). Particular attention needs to be paid to the management of common complications of advanced liver disease, such as coagulopathy, thrombocytopenia, ascites, renal insufficiency, encephalopathy, and malnutrition, as well as to disease-specific factors. For example, the predisposition of cirrhotic patients to infection warrants consideration of the use of prophylactic antibiotics to prevent sepsis.

### Table 2 Preoperative management of the complications of advanced liver disease.

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>Management considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional status</td>
<td>Maintenance of an adequate protein intake (1–1.5 g/kg per day) Promotion of a balanced diet</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>Vitamin K supplementation (oral or parenteral) Fresh, frozen plasma transfusions Intravenous administration of cryoprecipitate Intravenous administration of recombinant factor VIIa Platelet transfusions</td>
</tr>
<tr>
<td>Ascites</td>
<td>Paracentesis with analysis of ascitic fluid for evidence of infection Dietary sodium restriction (&lt;2 g daily) Oral diuretic therapy with spironolactone and/or furosemide Fluid restriction (if sodium concentration is &lt;120 mmol/l) Avoidance of excessive saline administration Avoidance of NSAIDs</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>Avoidance of nephrotoxic insult Albumin infusion (with paracentesis volumes &gt;5 l)</td>
</tr>
<tr>
<td>Portosystemic encephalopathy</td>
<td>Correction of reversible metabolic factors Avoidance of sedatives and opioid narcotics, as far as possible Oral lactulose administration, titrated to ~3–4 bowel movements per day Administration of nonabsorbable antibiotics Decreased protein intake</td>
</tr>
<tr>
<td>Pulmonary hepatic vascular disorders</td>
<td>Supportive care Supplemental oxygen</td>
</tr>
</tbody>
</table>

**Coagulopathy**  
The etiology of coagulopathy can be multifactorial; it can result from malnutrition, poor absorption of nutrients as a consequence of cholestasis, or impaired synthesis of coagulation factors. Intramuscular administration of vitamin K and transfusions of fresh, frozen plasma can be used to correct the patient’s INR before surgery; however, it might not be possible to correct the INR by this method when coagulopathy is severe, and repeated transfusions of fresh, frozen plasma are associated with a large fluid load. Intravenous cryoprecipitate, which can be infused with a minimal volume load, contains large amounts of fibrinogen and von Willebrand factor in addition to clotting factors and can also be useful for correction of an underlying coagulopathy in patients with liver disease. Intravenous recombinant factor VIIa is a safe and effective means of correcting coagulopathy and normalizing the INR in patients with cirrhosis before some invasive procedures such as liver biopsy.
VIIa is costly, however, and studies on its perioperative use in patients who underwent partial hepatectomy have not consistently demonstrated a benefit in terms of reducing the need for blood transfusions. 66 For patients with pre-existing thrombocytopenia, transfusions of platelets to achieve a count of 100,000/mm³ or more are recommended. Prolonged bleeding times can be corrected using desmopressin acetate. 67

Ascites
Aggressive preoperative management and control of ascites can minimize the risks associated with perioperative respiratory compromise and postoperative wound dehiscence. 68 Long-term management involves dietary sodium restriction (to <2 g daily) and oral diuretic therapy with preoperative assessment of electrolytes and renal function. 69 Although rarely symptomatic, hyponatremia is common in patients with advanced cirrhosis as well as in those receiving diuretic agents, and fluid restriction is occasionally warranted if the serum sodium concentration is less than 120 mmol/l. 69 Rapid treatment options for moderate to severe ascites include large-volume paracentesis or removal of ascites during laparotomy. If paracentesis is performed, appropriate fluid analysis should be performed to rule out spontaneous bacterial peritonitis—for which, if present, appropriate antibiotic therapy should be initiated.

Postoperative reaccumulation of ascites is common and efforts should be made to minimize its occurrence. Preventive strategies include avoiding excessive oral intake of sodium, and minimizing the amount of saline in intravenous fluids used for drug administration or electrolyte replacement.

Renal dysfunction
Recognizing and preventing renal dysfunction in patients with liver disease who are scheduled to undergo surgery is essential to minimize the development of perioperative complications. As the severity of chronic liver disease progresses, the pathophysiologic changes that occur predispose patients to hypoperfusion of the kidneys. The avoidance of agents that can cause nephrotoxic insult is, therefore, important; such agents include aminoglycosides, NSAIDs, and intravenous dye loads. Paracentesis volumes in excess of 5 l should be accompanied by intravenous albumin infusion to decrease the risk of postparacentesis circulatory and renal dysfunction. 70

Portosystemic encephalopathy
Portosystemic encephalopathy (PSE) is a complication of liver disease that manifests as a wide array of neuropsychiatric symptoms that can range from mild confusion to deep coma. Although elevated serum ammonia levels are associated with PSE, the ultimate diagnosis is one of exclusion and should be based on clinical suspicion. PSE is often precipitated by a number of reversible factors, including metabolic derangements such as hypokalemia, alkalois, hypoglycemia and hypovolemia, and medications, especially benzodiazepines. Patients with portal hypertension who develop gastrointestinal bleeding, renal failure and active infection (especially spontaneous bacterial peritonitis) are prone to develop PSE. In those patients, elective surgery should be postponed until the patient's mental status improves. Treatment of PSE consists of identifying the reversible etiologic factors and attempting to correct them. 71

Although several options exist for the treatment of PSE that are widely used in clinical practice, they suffer from a lack of evidence-based support. Oral lactulose, which decreases ammonia absorption in the large bowel by lowering the pH of luminal contents, is commonly used and has been shown to improve symptoms of PSE when compared with placebo. 72 The lactulose dose is titrated until the goal of 3–4 soft stools per day is achieved. Oral rifaximin is of value, because of its lack of systemic absorption and high antibacterial activity; it can improve the symptoms of PSE and is useful for patients who are intolerant of lactulose. 73 Other antibiotics such as neomycin, metronidazole, and vancomycin are rarely used because of concerns about adverse effects associated with their use. Some small studies reported a benefit with zinc supplementation, although these findings have not been confirmed in large studies. 74, 75 Dietary protein restriction to 1–1.5 g/kg per day is often attempted, although there is no clinical evidence to support this practice and it has the potential to complicate the postoperative course in patients with pre-existing malnutrition. 76 In patients for whom malnutrition and adequate oral intake is a concern, supplemental feeding with enteral tube feeds is often required, in part because of the increased catabolic rate observed in patients with cirrhosis.

Pulmonary hepatic vascular disorders
The presence of either hepatopulmonary syndrome (HPS) or portopulmonary hypertension
can complicate advanced liver disease and portends a poor survival. The presence of platypnea, orthodeoxia, right heart failure, hypoxemia (arterial PO$_2$ <60 mmHg), or a postural change in arterial oxygen saturation as measured by pulse oximetry should raise clinical suspicion of HPS$^{78,79}$ Contrast-enhanced echocardiography and $^{99m}$Tc-labeled macroaggregated albumin lung perfusion scans provide useful screening tests for intrapulmonary vasodilatation in patients with suspected HPS, whereas Doppler echocardiography is useful to screen patients for portopulmonary hypertension.$^{80,81}$ There are no effective perioperative therapies that can improve the pulmonary vascular abnormalities, hypoxemia and ventilation–perfusion mismatches associated with HPS, but various therapies can reduce pulmonary arterial pressures in patients with portopulmonary hypertension.$^{82}$ The role of these therapies in preoperative management of patients scheduled for elective, nontransplant procedures is, however, unknown.

**Disease-specific factors**

In patients with certain liver diseases, specific factors can influence the risks of surgery. Early retrospective studies indicated that there was a possible benefit conferred by preoperative external biliary drainage in patients with obstructive jaundice. Subsequent prospective, randomized studies have shown, however, that preoperative biliary drainage (either by percutaneous or endoscopic approaches) does not improve the perioperative morbidity or mortality of patients in whom there is no evidence of infection, and is, therefore, not recommended.$^{83-86}$ In situations where there is clinical concern for the development of acute cholangitis, rapid biliary decompression and intravenous antibiotics should be administered preoperatively, and surgery should be delayed until the infection resolves.$^{87}$

In patients with liver disease and ongoing significant alcohol use, a period of abstinence is recommended before surgery to avoid the development of withdrawal symptoms perioperatively. In addition, patients who consume a substantial volume of alcohol are at increased risk for the development of acetaminophen-induced hepatotoxicity, and caution should be used in the administration of postoperative analgesia.

In patients who have autoimmune liver disease and are taking more than 10 mg daily of prednisone, consideration should be given to the perioperative administration of high-dose, or ‘stress’ dose hydrocortisone, although there remains considerable debate as to the efficacy of this practice. Patients with hemochromatosis should be preoperatively evaluated for diabetes and cardiomyopathy, as these conditions can influence postoperative outcomes. In patients with Wilson’s disease, penicillamine may impair postoperative wound healing, and the dose should be reduced 1–2 weeks before surgery. In addition, surgery may precipitate or worsen neurological symptoms.

**CONCLUSIONS**

Multiple factors contribute to the increased risks that patients with liver disease have when undergoing surgery. Accurate preoperative identification of patients with liver disease allows their treatment plans to be adjusted according to the severity and nature of the underlying liver disease, as well as the type of surgery being undertaken. In patients with acute liver disease, elective surgery should be postponed until symptoms resolve. In patients with chronic liver disease, perioperative risk increases with worsening severity of hepatic dysfunction as assessed by either the CTP classification or the MELD score. Hepatic resection poses unique risks in this patient population, and extensive evaluation is often required before their surgical candidacy can be determined. Finally, preoperative management of complications related to patients’ underlying liver disease is essential to optimize their outcomes.

**KEY POINTS**

- Elective surgery should be avoided in patients with acute liver diseases such as acute viral hepatitis or alcoholic hepatitis, if there is evidence of ongoing hepatic injury.

- For patients with chronic liver diseases, determine the severity of underlying disease and assess whether or not cirrhosis might be present before deciding whether to proceed with surgery.

- The Model for End-Stage Liver Disease and Child–Turcotte–Pugh scores can be used to stratify the risks of surgery for patients with chronic liver disease.

- Optimal preoperative management of the manifestations of advanced liver disease can reduce the risk of postoperative morbidity and mortality.
References

35 Wiesner RH et al. (2003) Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology 124: 91–96
38 Sheth M et al. (2002) Utility of the Mayo End-Stage Liver Disease (MELD) score in assessing prognosis of patients with alcoholic hepatitis. BMC Gastroenterol 2: 2
Completing interests
The authors declared that they have no competing interests.

Liver protection in the perioperative setting

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With recent advances in surgical and anaesthetic management, clinical medicine has responded to societal expectations and the number of operations in patients with a high-risk of perioperative liver failure has increased over the last decades. This review will outline important pathophysiological alterations common in patients with pre-existing liver impairment and thus highlight the anaesthetic challenge to minimise perioperative liver insults. It will focus on the intraoperative balancing act to reduce blood loss while maintaining adequate liver perfusion, the various anaesthetic agents used and their specific effects on hepatic function, perfusion and toxicity. Furthermore, it will discuss advances in pharmacological and ischaemic preconditioning and summarise the results of recent clinical trials.

Key words: liver; hepatotoxicity; perioperative; protection; anaesthesia; volatile; preconditioning; catecholamine.

INTRODUCTION

Estimates suggest that as many as 10% of all patients with advanced liver disease will undergo surgery in the last 2 years of their lives.1 In addition, the number of successful liver transplantations has increased dramatically over the last few years, in the USA alone the numbers have gone from 2931 procedures in 1991 to 4480 in 1999.2 With a recipient survival rate of about 88%3, more and more patients with post-transplant liver dysfunction may require further surgical intervention. Even seemingly healthy patients without clinical signs of liver impairment may present with subtle liver
dysfunction, as seen in about 1 in 700 patients with a pre-test classification of American Society of Anesthesiology physical status classification (ASA-1) admitted for elective surgery. Knowledge and evaluation of pre-operative liver impairment is extremely important, as the extent of perioperative liver injury caused by ischaemia and reperfusion depends primarily on the duration of ischaemia as well as on pre-existing liver diseases, such as cirrhosis or acute hepatitis. Hepatic ischaemia and subsequent liver dysfunction is associated with a profound deterioration in prognosis. Because of the central role of the liver in the metabolic and immunological response to stress, the increased mortality seen after perioperative liver failure is most likely due to progression to multiple organ failure. Pre-existing hepatic dysfunction poses a great risk even for non-hepatic surgery, as shown by the higher blood transfusion requirements, longer hospital stays, more complications and increased mortality rate of 16.3% in patients with cirrhosis compared to 3.5% in controls. A detailed understanding of the underlying pathophysiology and thorough evaluation and pre-operative optimisation by expert anaesthetic teams is, therefore, crucial to avoid perioperative liver insults.

**PRE-OPERATIVE CONSIDERATIONS AND ASSESSMENT**

Because of significant inter-individual differences and the often severely reduced functional reserve capacity of patients with liver dysfunction, the pre-operative work-up needs to be tailored to the individual patient. Assessing the general health and co-morbidities, e.g. coagulopathy, renal function, volume and electrolyte status and cardiovascular function, is essential for anticipating the need for invasive cardiovascular monitoring, transfusion requirements and prolonged post-operative monitoring in high-dependency areas to minimise the risk of perioperative liver insults (see Table 1).

The healthy liver has a substantial functional reserve capacity due to the dual blood supply from portal venous (75%) and hepatic arterial (25%) blood flow. Clinical manifestations of liver insults therefore occur only after substantial damage. However, patients with advanced liver disease lose a significant amount of hepatic reserve capacity and may have an inappropriate response to surgical stress, increased risk of bleeding and post-operative hepatic encephalopathy, as evidenced by their high perioperative mortality rate.

**Cardiovascular function**

The systemic circulation in patients with liver cirrhosis is best characterised as hyperdynamic and dysfunctional, with increased heart rate and cardiac output, decreased systemic vascular resistance and low, normal or decreased arterial blood pressure. Cirrhotic cardiomyopathy is characterised by impaired myocardial contractility, decreased β-adrenergic receptor function and downregulation, leading to clinically significant

<table>
<thead>
<tr>
<th>Table 1. Pre-operative assessment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular function: ECG, echocardiography, exercise/pharmacological stress-test</td>
</tr>
<tr>
<td>Pulmonary function: Detailed pre-operative blood gas analysis (right heart catheterisation)</td>
</tr>
<tr>
<td>Renal status: Electrolytes, urea and creatinine</td>
</tr>
<tr>
<td>Coagulation profile: INR, platelet number and function</td>
</tr>
<tr>
<td>Hepatic function: Liver function tests, Child–Pugh score</td>
</tr>
</tbody>
</table>

ECG, electrocardiography; INR, international normalised ratio.
cardiac dysfunction and a limited contractile reserve to meet perioperative haemodynamic challenges. Moreover, the response to exogenous norepinephrine and other potent vasoconstrictors, such as angiotensin II and vasopressin, is blunted in patients with liver cirrhosis.\textsuperscript{16,17} Thus, intraoperative cardiovascular stability maintaining adequate end-organ perfusion may be difficult to achieve and detailed pre-operative assessment of the functional reserve is warranted. Pre-operative echocardiography and either an exercise or pharmacological stress-test should be performed routinely. A 12-lead ECG may detect rate-corrected Q-T interval (QTc) prolongation, which is frequent in patients with cirrhosis and may predict severe arrhythmias and sudden cardiac death.\textsuperscript{18}

**Pulmonary function**

Two distinct pulmonary vascular disorders are known to occur in chronic liver disease – the hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH). The exact pathophysiological mechanisms are not known, but both are characterised by pulmonary vascular remodelling at different sites of the pulmonary microcirculation. Several pathophysiological abnormalities have been reported within the HPS, including diffuse or localised dilatation of pre- or post-capillary pulmonary vessels, increased intrapulmonary arterial–venous shunting and portal–venous anastomoses.\textsuperscript{19} The development of HPS does not seem to correlate uniformly with the degree of underlying liver impairment, but the clinical features of exertional dyspnoea, cyanosis and increased pulmonary arterial–venous shunting are seen in up to 15% of patients with chronic hepatic disease\textsuperscript{20} and may have deleterious effects on the attempt to maintain adequate perioperative liver perfusion and oxygenation.

The incidence of POPH, however, is about 10 times lower than that of HPS.\textsuperscript{19} Advanced POPH presents clinically with exertional dyspnoea, chest pain and syncope and the diagnosis is based primarily on pulmonary haemodynamic criteria obtained via right heart catheterisation, as defined at the third World Symposium on Pulmonary Artery Hypertension.\textsuperscript{21} Moderate and severe POPH can substantially increase the risk associated with liver transplant, increasing perioperative mortality to $>50\%$ with a pulmonary artery pressure of 35–45 mmHg and a pulmonary vascular resistance of $>250$ dynes/s/cm$^5$.\textsuperscript{22} The European Respiratory Society recommends screening for POPH with transthoracic Doppler echocardiography and right heart catheterisation.\textsuperscript{19} Since patients with cirrhosis present with a variable PaO$_2$ response to 100% inspiratory oxygen, detailed pre-operative blood gas analyses may help in understanding the underlying mechanism of hypoxia: if there is no improvement in PaO$_2$ under inhalation of 100% oxygen intra-pulmonary shunting is likely; a moderate increase of PaO$_2$ ($>300$ mmHg) does not rule out arteriovenous communications; a normal response with PaO$_2$ $>500$ mmHg can exclude intra-pulmonary shunting\textsuperscript{23}, making ventilation–perfusion mismatching or dilated alveolar capillaries more likely as the main factors responsible for arterial hypoxaemia.\textsuperscript{24}

**Renal assessment and electrolyte status**

Hepatorenal syndrome (HRS) is the renal disease most strongly associated with severe liver disease.\textsuperscript{25} HRS, a functional renal failure with histologically normal kidneys, is a diagnosis of exclusion, as it is caused by alterations in renal blood flow due to a reduction in effective intravascular volume from splanchnic vasodilatation.\textsuperscript{26,27} It usually presents with uraemia and oliguria in patients with advanced cirrhosis and ascites\textsuperscript{27} and may be
Exacerbated by perioperative fluid shifts and intravascular hypovolaemia. Electrolyte abnormalities, such as hyponatraemia, are common in patients with advanced liver disease, because of HRS, fluid retention, massive ascites and large-volume paracentesis. Symptomatic and severe hyponatraemia (< 125 mEq/l) must be treated and corrected carefully to avoid central pontine myelinolysis.

Coagulation profile

The liver plays a pivotal role in the coagulation process and coagulopathy is a prominent feature of acute and chronic liver failure. All coagulation factors are produced in the liver, except von Willebrand’s factor, which is produced in endothelial cells. The coagulopathy in liver disease results from impaired production of coagulation factors, alterations in vitamin K metabolism, a low grade disseminated intravascular coagulation, enhanced fibrinolytic activity and/or alterations in platelet number or function. An increased pre-operative prothrombin time is associated with post-operative liver decompensation and perioperative mortality. The coagulation profile should be assessed pre-operatively and coagulopathy corrected, depending on the surgical procedure and the expected blood loss. As hypothermia inhibits the enzymes of the coagulation cascade and thus further aggravates intraoperative blood loss, strict normothermia should be maintained using warmed fluids or warm-air devices. Portal hypertension is the most common cause for thrombocytopenia in liver disease and platelet sequestration in the spleen can increase from the normal 30% to as much as 90%. In addition, qualitative platelet dysfunction, including inhibition of platelet aggregation and alterations in platelet membrane composition, can impair perioperative haemostasis. Thus, care should be taken when considering neuraxial anaesthesia in patients with severe liver disease, as platelet function might be impaired despite a normal platelet count. Pre-operative assessment and correction of coagulopathy is important to minimise intraoperative blood loss and transfusion requirements. Application of vitamin K, infusion of fresh frozen plasma or cryoprecipitate can normalise coagulation factors and platelet transfusion may be indicated for low platelet numbers or abnormal intrinsic platelet function.

Quantified risk stratification

Patients with chronic liver disease have a reduced hepatic reserve capacity to cope with perioperative stress and are at increased risk for post-operative hepatic failure, coma or death. Thus, the decision to perform surgery in these patients needs to be made on the basis of the individual risk profile and the proposed surgical intervention. Comorbid conditions associated with perioperative morbidity and mortality need to be identified and assessed, as discussed in detail elsewhere. Two risk stratification schemes have been designed to assess the perioperative risk of patients with chronic and advanced liver disease – the Child–Pugh score (1984) and, more recently, in 1999, the Model of End-Stage Liver Disease (MELD). The Child–Pugh score (see Table 2) was originally derived from patients undergoing portosystemic shunting for variceal haemorrhage, but subsequent studies have shown its usefulness in estimating risks for patients with liver disease undergoing hepatic or non-hepatic surgery. On average, patients with a Child–Pugh class A score have a 10% perioperative morbidity and mortality rate with intra-abdominal surgery, those with a class B score about 30% and about 82% with class C. Patients with a Child–Pugh class B or C score were considered candidates for liver transplant until the Mayo Clinic developed a revised...
model in 1999. This Model of End-Stage Liver Disease (MELD) was designed to over-
come the ambiguity and interobserver variability due to the subjective parameters of
the Child–Pugh score. Initially aiming to predict 3-month mortality in patients with
chronic liver disease, it has been used since 2002 by the United Network for Organ
Sharing (UNOS) to prioritise patients awaiting liver transplantation. The MELD score
is based on biochemical parameters rather than the subjective assessment of clinical
features and is calculated from the patient’s serum creatinine (Crea), bilirubin (Bil)
and international normalised ratio (INR):

\[
\text{MELD Score} = 10 \left( 0.957 \ln(\text{Crea}) + 0.378 \ln(\text{Bil}) + 1.12 \ln(\text{INR}) + 0.643 \right)
\]

Even though the MELD score is a more objective predictor of post-operative mortality
than the Child–Pugh score, it is principally used to select patients for liver transplan-
tation and the Child–Pugh score remains the best validated predictor of perioperative
morbidity and mortality in patients with liver impairment.

**ANAESTHETIC CONSIDERATIONS AND INTRA-OPERATIVE
MANAGEMENT**

Patients with advanced liver disease are much more likely to suffer from hepatic de-
compensation due to anaesthesia and surgery. In a study of 733 patients with cirrhosis
who underwent surgery, the perioperative mortality within 30 days was 11.6% and the
complication rate was 30.1%, considerably higher than in patients without liver dys-
function. Post-operative pneumonia was the most frequent complication, with risk
factors including a high Child–Pugh score, diagnosis of cirrhosis, ascites, elevated se-
rum creatinine, pre-operative gastrointestinal bleeding and intraoperative hypotension.

Not only chronic liver impairment but also acute hepatitis increases the susceptibil-
ity for ischaemia following hypoperfusion, perhaps because of the hypermetabolic
state. Hepatic blood supply is complex and is regulated on different levels. Alterations
in blood flow on each of these levels can reduce hepatic nutritive blood supply and thus
contribute to subsequent hepatocellular injury; reduction in cardiac output or systemic
vascular resistance or an increase in right atrial pressure may all reduce hepatic blood
flow. The splanchnic blood supply is highly variable and does not necessarily

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**Table 2. Child–Pugh classification and interpretation.**

<table>
<thead>
<tr>
<th>A. Classification</th>
<th>Points</th>
<th>Classification</th>
<th>Albumin (g/dl)</th>
<th>Bilirubin (mg/dl)</th>
<th>INR</th>
<th>Ascites</th>
<th>Encephalopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Points</td>
<td>I</td>
<td>2</td>
<td>&gt;3.5</td>
<td>&gt;2.0</td>
<td>&lt;1.7</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>2</td>
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<td>&gt;2.0–3.0</td>
<td>1.7–2.3</td>
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<td>&gt;3.0</td>
<td>&gt;2.3</td>
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<th>2-year survival (%)</th>
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<td>C</td>
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</tbody>
</table>

INR, international normalised ratio.
increase even with stable or increased cardiac output.\textsuperscript{36,37} Hence, the regional macro and micro circulation is also actively modified to ensure an adequate nutritional blood supply. This so called ‘hepatic arterial buffer response’\textsuperscript{38} is partly mediated by locally released adenosine.\textsuperscript{39} Moreover, the endothelium itself is actively involved in the regulation of sinusoidal blood flow and various mediators such as nitric oxide, endothelin and carbon monoxide have already been identified.\textsuperscript{40–43} Interaction of the different anaesthetic agents with these microcirculatory mediators might partly explain the varying hepatotoxic effects of volatile anaesthetics and the subsequent perioperative liver insults.

General anaesthesia aggravates the already dysfunctional cardiovascular status present in many patients with chronic liver disease, further reducing the hepatic blood flow, especially that of the hepatic artery. Of the inhaled volatile anaesthetics, halothane and enflurane appear to reduce hepatic artery blood flow the most because of systemic vasodilatation and negative inotropic effects.\textsuperscript{44,45}

\textbf{Volatile agents}

It is commonly accepted that all volatile anaesthetics have the potential to impair liver function.

\textit{Halothane}

Halothane is associated with a risk for autoimmune hepatitis following exposure, with a reported incidence of about 1:6000–1:35000.\textsuperscript{46} A mild hepatic reaction is characterised by moderately increased liver enzymes, transient jaundice and a low mortality. Fulminant halothane-associated hepatitis, however, is associated with repeated exposure to halothane and the development of severe liver failure with high mortality. Specific circulating IgG antibodies were found in patients with fulminant hepatic failure after halothane exposure and these antibodies were shown to react with cell surface antigens of hepatocytes making them more susceptible to antibody dependent cell-mediated toxicity.\textsuperscript{47} In addition, a genetic susceptibility factor has been proposed, which would predispose certain patients to halothane hepatitis\textsuperscript{48} and thus makes an individual prediction about the safety of halothane very difficult.

\textit{Enflurane}

Enflurane has also been linked to post-operative liver damage\textsuperscript{49}, however, the exact mechanism remains unclear and controversy exists over whether enflurane is the causative agent.\textsuperscript{50,51} This might be partly explained by cross-sensitisation between enflurane and halothane, which has been shown for the protein products of enflurane metabolism.\textsuperscript{52}

\textit{Isoflurane}

Isoflurane, an isomer of enflurane, undergoes only a minimal biotransformation of 0.2%. Although this rate of biotransformation is thought to be minimal, several authors consider isoflurane to be the cause of a wide spectrum of hepatic injuries, ranging from post-operative transaminitis to fulminant hepatic failure and death.\textsuperscript{53–57} Isoflurane has been shown to have a positive effect on hepatic blood supply, possibly due to direct vasodilatation in the hepatic vascular bed.\textsuperscript{58} The exact mechanism is still being investigated,
but isoflurane, just like sevoflurane, has been shown to induce an upregulation of haem oxygenase-1 (HO-1). This enzyme catalyses the conversion of haem to biliverdin IX, free iron and carbon monoxide and thus decreases portal vascular resistance and may, therefore, exert hepatoprotective effects. Induction of HO-1 seems to be an individual feature of isoflurane and sevoflurane, since upregulation of HO-1 could not be seen with desflurane.

**Sevoflurane**

The metabolism of sevoflurane is rapid, with fluoride appearing in the plasma within minutes of administration. Although sevoflurane is also metabolised by cytochrome P450 (about 2–5%), this does not result in the formation of fluoroacetylated neoantigens. Sevoflurane causes a slight decrease in portal blood flow in animals, but in humans no difference in indocyanine green clearance has been shown and it appears to be as safe as isoflurane.

**Desflurane**

Desflurane increases hepatic blood flow, but there is no significant difference between it and isoflurane. Desflurane is metabolised by cytochrome P450 to only a very small degree (0.02%) and the reported hepatotoxicity in three patients was very low compared to that of other volatile anaesthetics.

The autoimmune antibody response that induces hepatic necrosis is directed at neo-antigens on trifluoroacetylated proteins. These are the products of cytochrome P450-dependent biotransformation. The production of antibodies should be related to the relative degree of metabolism of each volatile agent (apart from sevoflurane), that is: halothane (15–40%) > enflurane (2.5%) > isoflurane (0.2%) > desflurane (0.02%). Therefore, the formation of auto-antibodies should occur proportionately less frequently with isoflurane and desflurane.

**Regional anaesthesia**

Both general and regional anaesthesia cause reversible sympathectomy with peripheral vasodilatation and exacerbation of hypotension. No significant difference in liver function and hepatic perfusion was seen between general anaesthesia using isoflurane and spinal anaesthesia, provided the mean arterial pressure was maintained within normal limits. However, patients requiring vasopressors for more significant haemodynamic disturbances were excluded from that study. Because of the increased risk for spinal haematoma in patients with liver dysfunction and the better titration of volatile anaesthetics, isoflurane, sevoflurane or desflurane might be the more appropriate agents for anaesthesia in patients with pre-existing liver impairment.

**Haemodynamic management**

Patients with chronic liver disease have a reduced functional reserve capacity and are at greater risk of ischaemia and hypoperfusion, and therefore require tighter control of arterial blood pressure. However, macrohaemodynamic variables, such as mean arterial pressure and systemic vascular resistance, do not necessarily reflect nutritional organ blood supply, and oxygenation as well as microcirculatory blood flow cannot be reliably predicted from those variables. Vasoactive agents may, therefore, elicit their effects at
various levels, hindering detailed intra- and perioperative monitoring. Furthermore, vasoactive agents do not just alter cardiac output and systemic vascular resistance and thus oxygen delivery; they also modify regional oxygen consumption. Studies addressing the local nutritional blood supply have identified marked differences between physiological and pathophysiological conditions, although they have mainly been performed in septic patients or in animal models. It is, therefore, difficult to find detailed data about various vasoactive agents in patients with liver impairment and extrapolation of the results to a clinical setting needs to be done with great care.

Volume therapy

Intraoperative haemodynamic management is dictated by the surgical approach. Maintaining a low central venous pressure (CVP) between 2 and 5 mmHg limits the distension of hepatic veins and has been shown to reduce intraoperative blood loss during liver surgery. Once haemostasis is achieved, euvoaemia should be restored by fluid replacement, as the low-CVP approach exposes the patient to the risk of inadequate organ perfusion and reduces the volume reserve for meeting haemorrhagic challenges.

Epinephrine and norepinephrine

In a recent study Krejci et al. compared the effects of phenylephrine, epinephrine and norepinephrine on various splanchnic vascular beds in septic pigs, including blood flow through the superior mesenteric artery, microcirculatory blood flow in the intestinal mucosa of the stomach, jejunum and colon and the microcirculatory blood flow on the surface of the liver. Despite normovolaemia and an increased mean arterial pressure of about 20 mmHg above baseline, infusion of both epinephrine and norepinephrine had detrimental effects on regional mesenteric and microcirculatory blood flow in the jejunal mucosa. Blood flow in other organs (e.g. stomach, colon, liver and kidney) remained virtually unaffected despite an increased mean arterial blood pressure following epinephrine infusion. These results are similar to a report from de Backer et al. who found that epinephrine could impair splanchnic circulation in patients with septic shock and that the effect of epinephrine differed with the degree of underlying sepsis. For hepatosplanchnic blood flow measurement, indocyanine green clearance combined with hepatic vein catheterisation was used, thus representing metabolic variables rather than direct mucosal blood flow. These results imply that the effects on splanchnic perfusion do not only differ between vasoactive agents but are also dose dependent.

Dopamine, dobutamine and dopexamine

The effects of dopamine or dobutamine versus dopexamine on systemic, regional and local blood flow were studied in a porcine septic shock model, which showed no selective beneficial effect, improving microcirculatory blood flow only by increasing cardiac output. In patients with sepsis, dopexamine failed to selectively increase splanchnic blood flow and in a prospective, randomised controlled, double-blinded multicentre trial, dopexamine did not improve outcome after major abdominal surgery, had no effect on organ dysfunction, duration of intensive care unit or hospital stay and actually decreased gastric mucosal pH. The data on dopamine are very controversial, showing detrimental effects on gut mucosa perfusion in septic patients in one study, but improvements in splanchnic blood flow in septic patients in another. Interestingly, the effects of dopamine on
splanchnic blood flow may actually differ according to basal splanchnic perfusion, as seen in the small human study by Meier-Hellmann et al.\textsuperscript{81} Whether dobutamine has a specific effect on splanchnic mucosa is still debated. Cross-over studies in patients with septic shock comparing the combination of dobutamine and norepinephrine with epinephrine alone, showed a favourable effect of dobutamine/norepinephrine, with improved splanchnic blood flow and oxygen uptake, higher gastric pH and lower portal vein lactate concentration.\textsuperscript{82} A selectively beneficial effect of dobutamine, however, could not be confirmed in adequately fluid resuscitated septic patients, with an unaltered splanchnic oxygen consumption and a parallel increase in splanchnic blood flow and cardiac index being recorded.\textsuperscript{83}

**Vasopressin**

Vasopressin plays only a minor role in physiological blood pressure regulation. In the past few years clinical studies have shown that vasopressin can rapidly restore blood pressure in septic shock. However, the effects of vasopressin on splanchnic and hepatic blood flow are controversial and the subject of much discussion. In septic rats, vasopressin induced severe abnormalities in gut mucosa blood flow\textsuperscript{84} and this finding was confirmed in patients with septic shock; vasopressin altered the blood flow distribution pattern in the splanchnic area compared to norepinephrine, decreasing total splanchnic blood flow and doubling the pCO\(_2\) gap.\textsuperscript{85} Preliminary results of the completed Vasopressin and Septic Shock Trial (VASSST) were recently presented at the Society of Critical Care Medicine's 36th Critical Care Congress: data from 779 patients in septic shock, receiving either norepinephrine or vasopressin, were analysed. Overall, no difference in 28-day survival between groups could be found. However, a subgroup analysis showed improved survival with vasopressin in patients with less severe hypotension.

**Phosphodiesterase inhibitors**

Phosphodiesterase inhibitors used in septic patients showed promising results in a study from Kern et al.\textsuperscript{86} An increase in hepatosplanchnic oxygen consumption, an increased lignocaine metabolism and a decreased release of hepatic tumour necrosis factor (TNF)-alpha were found, all indicating an improvement in hepatosplanchnic function and anti-inflammatory properties after 12 hours of enoximone treatment. In a septic porcine model, olprinone showed beneficial effects in restoring systemic and hepatic circulation\textsuperscript{87}, suggesting a dose-dependent increase in splanchnic blood flow.

**Levosimendan**

This pyridazinone-dinitrite with both inotropic and vasodilating effects has been shown to selectively increase blood flow to the duodenum and to decrease splanchnic vascular resistance.\textsuperscript{88} Beneficial effects of levosimendan on gastric mucosa oxygenation, which were at least partially independent of systemic effects, were shown by Schwarte et al. in an animal model.\textsuperscript{89}

Few clinical trials have directly compared vasoactive agents and the use of surrogate endpoints, such as indocyanine green clearance, makes it very difficult to make recommendations with regard to the best choice for perioperative liver protection. Moreover, increased mean arterial pressure and/or cardiac output do not equate with regional or microcirculatory nutritive blood flow. The majority of evidence, however, suggests that vasopressin and epinephrine have adverse effects on splanchnic perfusion.
and that the combination of norepinephrine and dobutamine might be preferable. Newer agents, such as levosimendan and olprinone, appear to selectively improve splanchnic perfusion and their potential for perioperative liver protection warrants further research. The recommended approach to anaesthetic use is given in Table 3.

**PRECONDITIONING**

Ischaemia and reperfusion injury is a major cause of morbidity and mortality following liver surgery and transplantation. Iatrogenic occlusion of the supplying blood vessels, with the aim of reducing blood loss in hepatic trauma or resection, induces warm ischaemia, similar to haemorrhagic, cardiogenic or septic shock. Cold hepatic ischaemia is an integral component of liver transplantation. Liver tolerance for ischaemia is poor and the safe ischaemia time is not known. In addition to the direct ischaemic insult, hepatic injury occurs during reperfusion. The exact mechanisms, such as the activation of local macrophages and the production of reactive oxygen intermediates and pro-inflammatory cytokines, are still being investigated. The oxidative stress related to hepatic reperfusion injury has long been recognised, but is beyond the scope of this review and is discussed elsewhere in more detail.33,90

The recent discovery, in animal studies, of the promising endogenous cellular protective mechanism known as ischaemic preconditioning, has led to several clinical trials. The hypothesis that a short period of ischaemia, prior to subsequent prolonged clamping during the main surgical procedure, could reduce hepatic injury and improve outcome was investigated. In a recent prospective randomised study, Azoulay et al.91 investigated whether a 10 min period of prior ischaemic preconditioning in 60 patients requiring major hepatectomy would protect them against hepatic ischaemia–reperfusion injury. The results were disappointing, as ischaemic preconditioning in the clinical trial did not prevent ischaemia–reperfusion injury, nor did it have any impact on important clinical outcomes such as morbidity, length of hospitalisation and in-hospital mortality.91,92

In another prospective, randomised clinical trial with 100 patients undergoing major liver resection, Clavien et al.93 demonstrated an age-related beneficial effect of ischaemic preconditioning on post-operative aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. Interestingly, only patients younger than 60 years and those with steatosis benefitted – older patients and those with cirrhosis did not. Again, no benefit could be found in terms of morbidity, length of ICU or hospital stays, possibly due to the small sample size. This lack of improvement and the marked difference between age-groups indicates that the protocol for preconditioning might need to be tailored to the individual subgroup of patients. Furthermore, the positive effects seen in the surrogate endpoints (e.g. blood loss94, liver enzyme levels95 or ATP content97) used in animal and clinical studies, as summarised elsewhere90, need to be translated into clinical outcome and confirmed in larger trials.

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**Table 3. Recommended anaesthetic approach.**

- Isoflurane or sevoflurane (may exert hepatoprotective effects)
- Dobutamine and noradrenaline for haemodynamic control
- Volume therapy directed at minimising blood loss (low central venous pressure (CVP) in liver resection) while aiming at euvolaemia
Hospital mortality after elective liver resection is about 1% in patients without underlying liver disease and about 10% in patients with pre-existing disease. In a study on 478 patients, Belghiti et al. reported a post-operative complication rate of 22%, with pulmonary infection being the most frequent (11.9%), and abdominal abscess with or without biliary fistula (7.1%), haemorrhage (2%) and renal failure (0.7%) occurring less frequently. A hyperdynamic state with increased cardiac output and augmented splanchnic blood flow persists for at least 3 post-operative days after liver resection, with the development of mild-to-moderate pulmonary oedema and an incidence rate of transient ascites of about 50%. Because of an incidence rate of about 8% for major post-operative complications and 3% for re-operation, patients undergoing major liver resection or with significant preoperative liver impairment should be closely monitored for the early detection of post-operative complications.

Hepatic ischaemia and reperfusion injury is associated with high morbidity and mortality. One cornerstone of perioperative liver protection is to minimise the liver insult by optimising hepato-splanchnic perfusion and avoiding possible hepatotoxic agents. In addition, recent research has provided interesting data about ischaemic or drug-induced preconditioning and thus prevention of liver damage. Induction of hepatic enzymes (e.g. HO-1) has been shown to reduce hepatic reperfusion injury. Gene expression is up-regulated in response to a variety of stimuli, including isoflurane, sevoflurane, oxidative stress, hypoxia and other triggers. The exact mechanisms remain unclear and are subjects for further research, but specific preconditioning, whether ischaemic or pharmacological, and thus induction of protective mechanisms, e.g. haem oxygenase, might be able to limit subsequent liver injury. Despite promising results in animal studies, current regimens of ischaemic preconditioning have yet failed to improve morbidity and mortality in the clinical setting. Future research needs to be directed towards optimising ischaemic protocols, i.e. length of ischaemia, continuous versus intermittent, in order to translate positive effects on surrogate parameters into clinical outcome.

**Practice points**

- Pre-existing liver impairment increases susceptibility to ischaemia and affects non-hepatic organ systems, thus warranting detailed pre-operative assessment
- Maintenance of adequate hepatic perfusion and oxygenation is crucial for perioperative protection
- The volatile agents isoflurane or sevoflurane increases hepatic blood flow; using these agents in combination with norepinephrine and dobutamine for the maintenance of perfusion pressure may potentially provide benefits
**Research agenda**

- Microvascular regulation of blood supply warrants further research – can possible drug interactions be identified?
- Might certain anaesthetic agents selectively improve hepatic blood supply and oxygenation?
- What are the exact mechanisms of preconditioning and how do we improve morbidity and mortality?

**REFERENCES**


Immunosuppressive therapy for the prevention of rejection in solid-organ transplantation has made notable progress since the first successful nontwin kidney transplantation was performed in 1959. Early attempts with organ transplantation using total-body irradiation resulted in overimmunosuppression and overwhelming infections. Promising results with an antineoplastic agent, 6-mercaptopurine, in animal studies led to the introduction of its prodrug, azathioprine (AZA), in 1962. The application of AZA in combination with corticosteroids resulted in 1-year graft survival rates of 40% to 50%; this was considered revolutionary in clinical transplantation. Until that time, with hemodialysis in its earliest stages, survival with renal failure was exceedingly rare. Several more potent immunosuppressive agents have become available since then, leading to the successful transplantation of more than 25,000 organs annually in the United States, including nonrenal solid-organ transplants such as liver, pancreas, heart, and lung [1]. At 1 year, graft and patient survival rates of up to 95% and 98% can be achieved, respectively, with living donors, and 80% and 90% of patients are supported by a functioning deceased donor allograft, depending on the organ.

Current immunosuppressive regimens typically consist of two phases: induction phase and maintenance therapy. The various agents that are used in these two phases of immunosuppression will be reviewed in this article. The similarities and differences between the agents within each class, with respect to efficacy and tolerability, will also be discussed.
Induction therapy in solid-organ transplantation

The greatest risk of rejection of a transplanted organ occurs in the immediate period (weeks to months) after implantation. Thereafter, the risk of rejection is intermediate in the first year after placement and low, but omnipresent for the life of the transplanted organ. As such, induction strategies aim to reduce early acute rejection episodes and prolong long-term allograft survival. Most regimens for induction therapy also attempt to minimize the complications of maintenance immunosuppression. There are no standardized induction regimens, but most transplant centers use one of two basic strategies: (1) the use of high doses of conventional immunosuppressive agents, or (2) the use of polyclonal or monoclonal antibodies directed against T-cell antigens. This section discusses the agents used in the latter strategy.

The decision to use induction therapy with either polyclonal or monoclonal antibodies is dependent upon several factors including:

1. The organ transplanted: use of antibody induction is common in heart, lung, and kidney transplantation, occasional in liver transplantation, and almost universal with pancreas transplantation.
2. The immunologic risk of the recipient: induction agents are more commonly used in high-risk patients such as those of African decent, repeat (second or greater) transplants, and those patients with preformed anti-human leukocyte antigen (HLA) antibodies.
3. Planned minimization of maintenance immunosuppression, usually involving steroids or calcineurin inhibitors (cyclosporine and tacrolimus).

Polyclonal antibodies

There are two polyclonal agents in use today for induction therapy: horse antithymocyte globulin (ATGAM; Pharmacia-UpJohn, Kalamazoo, Michigan) and rabbit antithymocyte globulin (rATG; Thymoglobulin, Genzyme, Cambridge, Massachusetts). ATGAM is derived from horse sera immunized against human lymphocytes and Thymoglobulin from the sera of immunized rabbit. Both of these agents contain antibodies against a wide variety of T-cell surface antigens and act to deplete CD3-positive cells in the recipient. The depletion of lymphocytes occurs through a variety of mechanisms including complement-mediated and Fc-dependent opsonization and lysis [2]. Rabbit-ATG has become the polyclonal agent of choice, both for improved allograft survival as well as an observed decrease in delayed graft function (DGF) [3]. The original licensing for rATG was based on its efficacy for the treatment of acute rejection. The more frequent off-label use of the agent for immunosuppression induction follows from previous experience with polyclonal antibodies and the published experience within the transplant community. Both polyclonal agents have been used for the treatment of rejection, with rATG demonstrating superiority in both reversal of
rejection, as well as preventing recurrent rejection [4,5]. Some of this observed benefit might be related to the specific processing that makes rATG a more uniform product (less batch-to-batch variability), resulting in a more consistent clinical effect. Indeed, both the degree of lymphocyte depletion and the response to therapy are more predictable with the rATG product.

The use of polyclonal antibodies is associated with a “first-dose reaction,” manifesting as fevers and chills. This syndrome results from the release of inflammatory cytokines from lymphocytes as a consequence of activation, lysis, or destruction. Most centers administer steroids and often a combination of acetaminophen, antihistamines, pentoxifylline, and other agents to abrogate this response. Severe cases may be associated with capillary leak syndrome and pulmonary edema. Other reactions include anemia, thrombocytopenia, rash, pruritis, serum sickness, and rarely, anaphylaxis. The occurrence of adverse events is, in part, related to the timing and rate of administration, with intraoperative administration and slow infusion being less likely to produce severe first dose reactions.

**Monoclonal antibodies**

The oldest monoclonal antibody is Muromonab-CD3 (OKT-3, Orthoclone; Ortho Biotech, Bridgewater, New Jersey), which has been in use since 1986. OKT-3 is a murine IgG2 monoclonal antibody targeting the CD3 complex on T-lymphocytes, and like the polyclonal antibodies, induces a rapid depletion of T-lymphocytes [6]. OKT-3 has been used for both induction therapy and treatment of steroid resistant rejection. It is, however, associated with the release of several pro-inflammatory cytokines, and can cause the cytokine release syndrome, manifesting as fever, chills, headache, gastrointestinal symptoms, and most significantly, noncardiogenic pulmonary edema and acute respiratory distress syndrome [7]. These symptoms are ameliorated through premedication with steroids and antihistamines. OKT-3 also induces production of human antimouse antibodies (HAMA, antibodies generated against the agent) in nearly 50% of patients who undergo therapy with it, which may preclude future use [8].

Daclizumab (Zenapax; Roche Laboratories, Nutley, New Jersey) and basiliximab (Simulect; Novartis Pharmaceuticals, Inc, East Hanover, New Jersey) are monoclonal antibodies that do not cause depletion of T-cell populations but rather block IL-2 mediated T-cell activation, preventing rejection. Daclizumab is a humanized antibody, which combines a mouse hypervariable region with human IgG, and basiliximab is a chimeric antibody that combines mouse antigen-binding variable regions with human IgG constant regions. Both anti-IL2 receptor antibodies appear to have equal efficacy in clinical trials, reducing the incidence of acute rejection by 33% to 50% when added to maintenance immunosuppression. The two agents have not been compared against one another in direct studies.
A significant difference occurs in the dosage administration schedule as daclizumab is dosed at the time of transplant with four additional doses at 2-week intervals, whereas basiliximab is dosed on the day of surgery and the fourth postoperative day. Both of these agents are associated with minimal side effects compared with the other agents. They have no role in the treatment of acute rejection. Of interest is the observation that basiliximab, a drug with minimal side effects and presumably less “potent” than polyclonal antibodies, resulted in similar incidence of acute rejection compared with rATG in low-risk kidney transplant recipients [13].

Alemtuzumab (Campath-1H; Genzyme Oncology, Cambridge, Massachusetts) is the newest molecule to be used for induction therapy in solid-organ transplantation. The monoclonal antibody was developed for the treatment of chronic lymphocytic leukemia, with reports of full remissions. Alemtuzumab is specific for the common lymphocyte and monocyte antigen CD52. Its administration temporarily depletes mature lymphocytes and some monocytes without altering neutrophils or hematopoietic stem cells. The agent has a profound and long-lasting effect on the depletion of white blood cells [14].

Alemtuzumab has been used for induction in kidney, liver, heart, lung, and pancreas transplantation. Intravenous regimens of alemtuzumab, consisting of either a single 30 mg dose or two 20 mg doses, when used in conjunction with standard maintenance immunosuppressive agents, resulted in comparable rates of acute rejection, and patient and graft survival rates that are seen using induction therapy with rATG or anti-IL2 receptor antagonists [15–18]. Alemtuzumab also facilitates steroid-free immunosuppression in more than 80% of patients in conjunction with lower doses of other immunosuppressive agents such as calcineurin inhibitors [15–20]. Infusion-related adverse reactions have been associated with intravenous alemtuzumab administration, and can range from moderate symptoms such as fevers, chills, rigors, hypotension, and bronchospasm, to more life-threatening reactions such as arrhythmias, myocardial infarction, and respiratory or cardiac arrest. These adverse reactions can be avoided by premedicating with corticosteroids, acetaminophen, and diphenhydramine [21]. Alemtuzumab induction appears promising in the era of maintenance immunosuppression minimization; however, its potent effects on leukocyte depletion and the development of infection and malignancy requires evaluation in long-term controlled studies.

Maintenance immunosuppression

Standard maintenance immunosuppression regimens generally consist of a triple-drug combination, comprised of agents that act simultaneously at different levels of the immune cascade. Corticosteroids, calcineurin inhibitors, antiproliferatives, and mTOR inhibitors are the available immunosuppressive drug classes in use today. The most common regimen incorporates
a calcineurin inhibitor, an antiproliferative agent, and corticosteroids. Variations of this regimen are driven by the organ recipient’s immunologic risk for rejection, the immunogenicity of the allograft (lung > heart > kidney > liver) and medication-related toxicities that develop [22]. As a result, it is not uncommon for low-risk recipients and recipients of liver transplants to be on a single or two-drug regimen with stable allograft function.

Corticosteroids

Corticosteroids have been a key component of most maintenance immunosuppressive protocols across all solid organ transplants since the 1960s [1]. The mechanism of immunosuppressive action is incompletely understood, but it is known that corticosteroids block T- and B-cell activation via intracellular inhibition of interleukin (IL) and cytokine gene transcription [23]. Corticosteroids also induce a general lymphopenia by redirecting lymphocytes from the periphery to the lymphoid tissue and release of anti-inflammatory mediators leading to leukocytosis, elevated glucose concentrations, and central antipyretic effects [24].

Corticosteroid regimens vary widely, typically with higher doses initially and then tapered over a period of 3 to 6 months to maintenance doses equivalent to prednisone 5 to 10 mg, which is further tapered slowly over time. Intravenous high-dose corticosteroids are also commonly used for the treatment of acute rejection across all solid-organ transplants [1]. The main oral and intravenous corticosteroid agents used in practice are prednisone and methylprednisolone, respectively. The use of prednisolone is preferred in patients with hepatic insufficiency who cannot metabolize prednisone to its active counterpart. Dexamethasone has also been used in place of methylprednisolone with equal efficacy [25]. The equipotent doses and relative anti-inflammatory and mineralocorticoid potencies of these agents are summarized in Table 1 [26].

<table>
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<th>Corticosteroid</th>
<th>Route of administration</th>
<th>Anti-inflammatory potency</th>
<th>Equivalent dose (mg)</th>
<th>Mineralocorticoid activity</th>
<th>Duration of action (hours)</th>
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<td>8–12</td>
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<td>5</td>
<td>0.8</td>
<td>24</td>
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<tr>
<td>Prednisolone</td>
<td>PO</td>
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<td>5</td>
<td>0.8</td>
<td>24</td>
</tr>
<tr>
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<tr>
<td>Dexamethasone</td>
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<td>25</td>
<td>0.75</td>
<td>0</td>
<td>72</td>
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</tbody>
</table>

Corticosteroids are associated with numerous well-known adverse effects including hypertension (HTN), hyperlipidemia, posttransplant diabetes mellitus (PTDM), osteoporosis, and cataracts [27]. Of major concern, HTN, lipid abnormalities, and diabetes are all risk factors that are associated with cardiovascular disease (CVD). Concomitant use with other immunosuppressive agents can exacerbate these abnormalities [28]. There is a trend toward adopting corticosteroid minimization protocols in an effort to avoid these long-term adverse effects. Preventative strategies established in the general population may be applied to the transplant population when indicated [29]. Adrenal suppression can also occur as a long-term consequence of corticosteroid therapy and manifest as overt adrenal insufficiency with hypotension under stressful conditions such as general anesthesia and surgery. Recommendations for steroid replacement vary widely for transplant patients requiring nontransplant surgery. Simply continuing baseline doses of corticosteroids is sufficient in the majority of cases [30]. This may be particularly true as smaller doses of steroids become more widely adopted in clinical practice. Despite this experience and the absence of controlled studies that demonstrate a requirement for stress-dose steroids in this circumstance, most authors recommend a perioperative increase in steroids, typically hydrocortisone, with a rapid return to baseline doses based on the extent of the surgery and recovery [31].

**Calcineurin inhibitors**

Calcineurin inhibitors have been an integral part of immunosuppressive therapy for transplantation since the 1980s, and are currently used in the vast majority of transplant recipients upon discharge from the hospital after the transplant procedure [1]. Cyclosporine (CsA) and tacrolimus inhibit IL-2 mediated T-cell activation and lymphocyte proliferation through binding with their respective immunophilin proteins, cyclophilin and FK-binding protein [32,33]. This specific drug–immunophilin complex binds with and inhibits calcineurin, preventing transit of the transcription factor, nuclear factor of activated T cells, to the DNA promoter region thereby inhibiting IL-2 synthesis.

CsA was initially released as an oil-based oral formulation (Sandimmune; Novartis Pharmaceuticals, East Hanover, New Jersey), which was largely dependent on the extent of solubilization in bile, and thus had an erratic absorption profile. The microemulsion formulation (Neoral; Novartis Pharmaceuticals, East Hanover, New Jersey), with more predictable pharmacokinetics, has largely replaced the use of Sandimmune [32]. Generic formulations of CsA are also currently available, and although some of these products are rated as therapeutically equivalent (AB-rated) by the Food and Drug Administration, consistent use of one oral formulation is preferred versus routine switching between products. Further discussion of CsA in this review will refer to the microemulsion formulation. CsA can also be administered as an intermittent intravenous infusion at one-third
of the maintenance oral dose [34]. Tacrolimus is available for administration orally or intravenously as well; intravenous tacrolimus is administered as a 24-hour infusion versus an intermittent infusion, also at approximately one-third of the oral dose [35].

CsA and tacrolimus are both effective in reducing the incidence of acute rejection after transplantation [36,37]; however, improved outcomes have been observed with tacrolimus when used in blacks [38,39] and those with DGF [38]. The use of calcineurin inhibitors allows safe withdrawal of corticosteroid therapy in liver transplant recipients without increased risk for rejection [40]. Tacrolimus-based regimens also facilitate corticosteroid withdrawal and avoidance in kidney transplantation, particularly when used in conjunction with induction agents [41–43].

Routine therapeutic drug monitoring (TDM) is required for calcineurin inhibitors due to their narrow therapeutic index for efficacy and toxicity. Peak 2-hour (C2) CsA levels are better correlated with overall drug exposure than CsA trough (C0) levels; however, it is often logistically difficult to obtain these levels accurately; thus, C0 levels are more frequently used [32,34]. Target C0 and C2 levels range from 150 to 400 ng/mL and 800 to 2000 ng/mL, respectively. Tacrolimus target whole-blood C0 levels are generally 5 to 20 ng/mL [44]. Higher doses are usually required in black patients due to pharmacogenomic differences in p-glycoprotein and CYP450 enzyme expression [45,46]. Doses and target levels for both drugs vary, and are adjusted depending on the transplant type and the amount of time that has lapsed posttransplant.

The pharmacokinetic profiles of these calcineurin inhibitors are very similar. Both drugs undergo extensive first pass effect via p-glycoprotein and intestinal and hepatic CYP450 3A enzymes after oral administration. Both drugs are extensively metabolized in the liver by the same enzyme system. Metabolites are primarily eliminated in the bile, with a small percentage of the dose being excreted unchanged in the urine [32,44]. Calcineurin inhibitors have the potential for many drug–drug interactions due to their reliance on the CYP540 enzyme system for drug clearance. Concomitant use of drugs that induce or inhibit CYP450 enzymes should be used with caution. The most common class of agents includes antimicrobial agents such as azoles and macrolides. More vigilant TDM of CsA or tacrolimus drug levels is required; in some cases, dose adjustment should be made in addition, concurrent with commencing antimicrobial therapy [47]. Changes in gut motility can also affect the extent of drug absorption, and hence, overall drug exposure. One might expect reduced drug absorption due to decreased gut transit time as a result of diarrhea. Paradoxically, increases in tacrolimus trough concentrations requiring dose reduction have been observed in patients with persistent diarrhea. This is likely a result of decreased intestinal p-glycoprotein activity due to diarrhea-induced mucosal damage [48].

The most well-known adverse effect of calcineurin inhibitors is nephrotoxicity. Chronic allograft nephropathy is a major cause of graft failure in
kidney transplant recipients and calcineurin inhibitor-induced nephrotoxicity is a contributing factor [49]. Calcineurin inhibitor-induced renal toxicity has also been reported in about 10% to 20% of nonrenal transplant recipients [50]. Diabetes mellitus is another well-known adverse effect of calcineurin inhibitors and is a significant risk factor for CVD [51]. The incidence of nephrotoxicity and PTDM is similar between the two agents, although there are trends toward improved renal function with tacrolimus and improved glucose control with CsA [38,52]. Rates of PTDM of less than 5% have been reported for CsA and with regimens targeting lower tacrolimus trough levels when used in conjunction with minimal corticosteroid doses. Risk factors for developing PTDM include increased age, black ethnicity, hepatitis C virus, and concomitant administration of high-dose corticosteroids [53].

Other common adverse effects of calcineurin inhibitors include neurotoxicity, cardiovascular disturbances, and cosmetic effects [33]. Neurotoxic effects are more frequently associated with tacrolimus therapy, and can range from mild symptoms such as headache and tremor to more severe effects such as seizures, delirium, and coma. Alopecia and electrolyte disturbances, such as hyperkalemia and hypomagnesemia, are also more common with tacrolimus. Conversely, CsA is associated with a greater incidence of cardiovascular effects, such as hypertension and hyperlipidemia, and cosmetic effects, such as gingival hyperplasia and hirsutism [32,44]. Perhaps more so than the modest clinical improvements demonstrated for tacrolimus, these CsA-induced adverse effects on blood lipids and cosmesis resulted in tacrolimus gaining over 80% of the market in solid-organ transplantation.

Antiproliferatives

AZA, an inhibitor of purine nucleotide synthesis, was the first immunosuppressive agent to be used with significant success in clinical transplantation. AZA is metabolized via the enzymes thiopurine S-methyltransferase and xanthine oxidase to inactive metabolites, which are subsequently excreted in the urine [54]. Concomitant use of allopurinol in patients with gout should be approached with caution due to its inhibitory effect on xanthine oxidase. Doses of AZA should be reduced by at least two-thirds of the usual dose to avoid AZA-related toxicity [55]. Bone marrow suppression is a major dose-related adverse effect in almost 50% of patients. Gastrointestinal (GI) adverse effects such as nausea and vomiting, hepatitis, cholestasis, and rarely pancreatitis, can also occur with AZA therapy [54].

With the introduction of mycophenolate mofetil (MMF) in 1995, a noticeable shift has occurred with the declining use of AZA and a corresponding increase in MMF use over the last 10 years. MMF has largely replaced AZA as the antiproliferative agent in maintenance immunosuppression across the majority of solid-organ transplants [1]. MMF is the ester prodrug of
mycophenolic acid (MPA), a potent inhibitor of inosine monophosphate dehydrogenase (IMDPH). IMDPH is an enzyme expressed in T- and B-lymphocytes, and is required for de novo guanosine synthesis; inhibition of IMDPH results in the suppression of DNA synthesis and lymphocyte proliferation [56]. The usual starting dose is 2 g/d administered orally or intravenously in two divided doses [57]. Higher doses of 3 g/d may be required in black recipients [58].

After oral administration, MMF is rapidly hydrolyzed to its active metabolite MPA via the first pass effect. MPA is then metabolized mainly to its inactive glucuronide metabolite, MPAG, through the enzyme UDP-glucuronyltransferase (UDPGT) and excreted through the urine. MPAG also undergoes enterohepatic recirculation, whereby it is excreted in the bile, converted back to MPA by gut flora, specifically Gram-negative anaerobes, and is reabsorbed back into the circulation [57]. Both MPA and MPAG are bound to serum albumin; accumulation of MPAG can result in competition for albumin binding sites with MPA [59]. Finally, renal impairment results in MPAG accumulation, leading to displacement of MPA from albumin binding sites; uremia also has the same effect [60]. This may result in an increased risk of adverse effects in kidney transplant patients with delayed or slow graft function and calcineurin inhibitor-induced or other forms of renal dysfunction. Major complaints associated with MMF therapy are gastrointestinal adverse effects, such as nausea and diarrhea [61], and hematologic toxicities such as leukopenia and anemia [57]. An increased incidence of tissue invasive cytomegalovirus disease, particularly gastrointestinal, is also associated with MMF doses of greater than 2 g/d [62].

Enteric-coated mycophenolate sodium (Myfortic, EC-MPS) is a delayed-release formulation of MPA that was designed to reduce upper GI toxicity. It has similar efficacy and toxicity as MMF in de novo kidney transplant patients [63]. Administration of 720 mg doses resulted in similar MPA exposure as MMF doses of 1000 mg [64]. Patients who are intolerant of MMF due to GI adverse effects may be able to continue with therapy using EC-MPS; however, this potential benefit is controversial as GI adverse events correlate with systemic drug levels rather than local exposure [65]. To date, randomized trials of EC-MPS compared with MMF have demonstrated similar efficacy, and no clinically significant reduction in side effects.

Routine TDM is not required with antiproliferative therapy; however, its clinical value in MMF therapy is being explored [66]. MPA trough levels have been shown to predict acute rejection episodes and MMF-related toxicity such as diarrhea, leukopenia, anemia, and viral infections in kidney transplantation [67]. However, threshold values may vary depending on the type of organ transplant, and further study is required before TDM can be routinely advocated for MMF.

The potential for many drug–drug interactions to affect the pharmacokinetics of MPA exists, particularly when MMF is coadministered with other immunosuppressive agents [68]. Higher MPA trough levels are achieved in
patients receiving tacrolimus versus CsA, necessitating the use of lower MMF doses [69,70]. This primarily occurs due to the inhibitory effect of CsA on MPAG biliary excretion, thus interrupting enterohepatic circulation [71,72]. However, it has also been demonstrated that tacrolimus has an inhibitory effect on the UDPGT enzyme, leading to elevations in MPA levels due to decreased glucuronidation to MPAG [73]. Adverse effects or acute rejection may be precipitated, and should be considered when patients are switching from CsA to tacrolimus or vice versa, respectively. Corticosteroids are known inducers of drug-metabolizing enzymes, such as UDPGT; thus, withdrawal or avoidance can also result in relatively higher MPA levels [74]. Other drugs that have been shown to affect the pharmacokinetics of MPA include metronidazole, norfloxacin, antacids, and cholestyramine, all of which interfere with enterohepatic recirculation, reducing the overall exposure of MPA and MPAG. Concurrent administration of metronidazole and norfloxacin inhibit bacterial de-glucuronidation of MPAG to MPA. Although interactions with other antibiotics have not been reported, patients should be carefully observed for signs of acute rejection upon initiation of other antibiotic therapy with activity against Gram-negative organisms [75]. The interaction with antacids and cholestyramine is physicochemical in nature; they bind to MMF or MPA, respectively, leading to reduced absorption [59]. Thus, TDM of MPA may be important in optimizing MMF therapy in transplant patients, given the continuous fine tuning of immunosuppressive regimens based on individual patients’ therapeutic response and tolerance to adverse drug effects, as well as the trend toward minimization of immunosuppression as patient and graft survival increases.

mTOR inhibitors

Sirolimus (Rapamune; Wyeth Pharmaceuticals, Madison, New Jersey) was introduced into the armamentarium of immunosuppressive agents in 2000. Sirolimus complexes with mTOR via the FK-binding protein, resulting in arrest of the G1 to S phase of the cell cycle in various cell types. Sirolimus is effective when used in combination with calcineurin inhibitors or antiproliferative agents in all solid-organ transplants, and allows lower calcineurin inhibitor doses to be used to minimize the risk for nephrotoxicity. Patients exhibiting signs of chronic allograft dysfunction or calcineurin inhibitor-induced nephrotoxicity may also benefit from a switch to a sirolimus-based regimen as early as 3 months posttransplantation [76–79]. Incorporation of sirolimus into current immunosuppressive regimens may be advantageous in that it demonstrates antineoplastic properties; the risk of de novo malignancy and a nonskin de novo solid cancer was reduced by more than 50% in association with mTOR inhibitor therapy [80,81]. However, its use in liver and lung recipients immediately posttransplant is limited by the risk of hepatic artery thrombosis and airway anastomotic dehiscence, respectively [82–84]. In addition, risk of thrombotic microangiopathy is
associated with concomitant use of sirolimus and CsA in kidney and kidney–pancreas recipients [85].

Sirolimus is available in tablet and liquid formulations, but is not available as an injectable. Conversion between the tablet and liquid formulations can be made on a milligram-per-milligram basis based on pharmacokinetic studies demonstrating similar overall drug exposure [86]. The absolute bioavailability is low at about 15%, and is further reduced if the dose is administered with a high fat meal. Sirolimus is metabolized via the CYP450 3A enzyme system and p-glycoprotein; metabolites are primarily eliminated in the feces with minimal excretion in the urine [87]. Inhibitors or inducers of these two metabolic pathways that affect calcineurin inhibitors will likely also affect sirolimus. Lower CsA doses are required to maintain similar trough levels when administered with sirolimus. This is likely due to an interaction between sirolimus and CsA at the CYP450 and p-glycoprotein level.

Sirolimus has a long terminal half-life of 62 hours, which allows once-daily administration. Upon initiation of therapy, a loading dose of three times the maintenance dose is required to achieve steady-state concentrations more rapidly. Trough whole-blood sirolimus levels of less than 5 ng/ml and greater than 15 ng/ml are associated with the occurrence of acute rejection episodes and a greater incidence of adverse effects, respectively. TDM of trough whole-blood levels should occur no more often than weekly after initiation of therapy or dose changes [86,87].

The most common adverse effects observed with sirolimus include thrombocytopenia, leukopenia, anemia, hypertriglyceridemia, hypercholesterolemia, diarrhea, and acne/mouth ulcers. These dose-dependent toxicities are either self-limiting or can be managed with dose reductions [88]. Other less common, but important adverse effects occurs as a result of the antiproliferative properties of sirolimus. Despite its lack of nephrotoxicity, sirolimus may delay recovery after renal injury increasing the risk of DGF, as well as prolonging recovery from DGF [89]. Sirolimus is associated with an increased frequency of lymphoceles, nonlymphocele perinephric fluid collections, peripheral edema, and wound complications, particularly in the presence of other risk factors such as obesity, DM, infection, rejection, and increased age [90]. Finally, interstitial alveolar pneumonitis is a rare and potentially fatal complication of sirolimus therapy. Withdrawal of therapy results in symptomatic improvement within a few days to weeks with complete radiologic resolution within 3 to 10 months [91–94].

Emerging immunosuppressive agents

A number of new immunosuppressive agents are in the late stages of development and are entering clinical trials. FTY720 is a synthetic analog of Myriocin, which affects T-cell trafficking. Its mechanism of action involves the sequestration of lymphocytes in lymphoid organs, minimizing the number of circulating lymphocytes. It has been associated with a reduction of
acute rejection when used in combination with CsA and steroids [95]. An initial phase III trial in kidney transplant recipients failed to demonstrate equivalence with standard immunosuppression; however, the drug has shown promising therapeutic results in multiple sclerosis. LEA29Y is a receptor fusion protein that blocks T-cell activation by binding to CD80 and CD86. It is derived from a molecule, which has been shown to induce tolerance in rodent and primate models [96]. A great deal of promise exists for costimulatory blockade as a treatment strategy in transplantation based on several animal experiments, which demonstrated robust effects in the maintenance of allografts. LEA29Y is currently in phase II trials, and has been associated with less renal toxicity and less dyslipidemia. Leflunomide, an agent that inhibits de novo pyrimidine biosynthesis through the inhibition of the enzyme dihydroorotate dehydrogenase, is used off-label in transplantation as an antiproliferative agent [97]. Leflunomide has some antiviral properties, particularly against BK virus, creating a unique niche for this agent in kidney transplantation [97,98]. FK778 is a synthetic compound derived from the active metabolite of leflunomide. In preclinical trials, it appears to prevent the development of graft vasculopathy, which is typically seen in chronic rejection [99].

Summary

Immunosuppressive therapy for solid-organ transplantation has evolved dramatically; current regimens yield excellent 1-year patient and graft survival rates. Despite the efficacy of currently available agents, there is the potential for significant drug interactions and adverse effects that may interfere with patient management for nontransplant surgical procedures. Awareness of the nuances between agents will allow general surgeons to manage the complications of immunosuppression without compromising efficacy. Future immunosuppressive agents will hopefully facilitate further individualization of drug therapy based on patient response and tolerability, leading to improved long-term outcome.

References


The transplant recipient for nontransplant surgery

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Twenty-five thousand patients received solid-organ transplants in the United States, in 2002 [1]. The majority of these patients endured severe organ dysfunction before their transplants, and many continue to experience organ dysfunction after transplantation [2]. These patients have traded their life-threatening illness for a chronic medical condition [3–6]. As recipients of 21st Century medical care, transplant patients typically consume several prescription drugs, must attend medical appointments, and are subjected to routine invasive procedures (eg, biopsies). The social and emotional impact of organ transplantation on patient, family, and friends is substantial [7]. It is only after avoiding imminent death by transplantation that some patients and families are able to begin the process of grieving associated with loss of wellness. Only after transplantation do some patients and families begin to grasp the magnitude of human sacrifice associated with living donor and cadaveric-donor transplantation. Emotions resulting from this act of radical generosity can be those of joy and thankfulness but can also include feelings of guilt and unworthiness.

Essentially all survivors of transplantation are immune-compromised [8]. In transplant medicine, immunosuppressive agents render the recipient more susceptible to infection and malignancy [9]. Infection is a primary cause of death, particularly in the first year, after undergoing transplantation [10,11]. In using immunosuppressive regimens, attempts are made to prevent rejection while using doses that minimize the risk of infection [12]. Unfortunately, when transplant recipients require nontransplant surgery, immune competence can be altered from the stress of surgery, acute illness, or disruption of the regimen by inexperienced providers. Immunosuppressive medications are frequently adjusted to adapt to the immune imbalance brought on by severe stress. This period of immune system instability can result in acute infection or graft rejection, or both.
Veterans of transplantation frequently enter the operating room as patients who are acutely ill, chronically unwell, emotionally stressed, and acutely and chronically immune-compromised. These patients may be seeking surgical treatment for complications related to their transplant. They may also require surgical intervention for reasons unrelated to their organ transplant.

**Long-term effects of transplantation and immunosuppressive drugs**

Unlike 20 years ago, most patients survive organ transplantation for a long-term period (greater than 3 years). Data from United Network for Organ Sharing for the years 1996–2001 list the following 3-year patient survival figures for primary solid-organ transplants: heart-lung 43.9%, heart 78%, intestine 53.3%, kidney 90.9%, kidney-pancreas 89.9%, liver 79.7%, lung 58.3%, and pancreas 86.8% [1]. Susceptibility to infection results from treatment with immunosuppressive medications [10,11]. A drug regimen is selected and dosages are prescribed with the purpose of preventing graft rejection while minimizing the risk of infection [12]. The combination of several different drugs can provide a synergistic, rather than merely an additive immunosuppressive effect. Regimens can include medications from several categories, including antilymphocyte (eg, ALG) and antithymocyte globulins (eg, OKT3), monoclonal antibodies to cytokine receptors (eg, IL-2 antagonist), calcineurin inhibitors (eg, cyclosporine and tacrolimus), cytokine receptor signal transduction inhibitors (eg, sirolimus), nucleoside synthesis inhibitors (eg, azathioprine and mycophenolate), and steroids [13].

Immunosuppressive medications have side effects beyond their immunosuppressive properties. These toxicities are many and varied, depending on the particular agent. The popular regimen of the 1960s and 1970s (prednisone and azathioprine) was fraught with the complications of overimmunosuppression, myelosuppression, and an exogenous Cushing’s syndrome. The newer drugs have their own toxicities. Cyclosporine’s most troublesome side effect is nephrotoxicity, but premature atherosclerosis, hypertension, neurotoxicity, and hepatotoxicity are also associated with cyclosporine [14–16]. The toxicity profile of tacrolimus is similar but less severe than cyclosporine’s; however, tacrolimus is associated with hyperglycemia, and as many as 20% of tacrolimus recipients develop insulin-dependent diabetes [12]. Rapamycin is associated with troublesome hyperlipidemia [12]. The intravenous globulins are primarily used for induction therapy or for the treatment of acute rejection. Side effects from these therapies are related to the release of cytokines that occur at the time of administration. Patients can experience cardiovascular collapse and pulmonary edema. Application of several drugs in lower doses can sometimes spare the severe toxic effects of large doses of a single agent; however, transplant patients who come to the operating room for nontransplant surgery frequently have been exposed to several immunosuppressive medications in substantial doses throughout their posttransplant medical history and have accumulated many of the varied toxicities of these agents.
The “ideal” anesthetic for the “generic” transplant patient for nontransplant surgery

Because there is no such thing as a “generic” transplant patient, there is no single “ideal” anesthetic. There are, however, certain principles that can be applied to all transplant patients who undergo anesthesia and surgery. First, the patient should be thoroughly evaluated, with attention paid to the status of the transplanted organ. How is the graft functioning? Is the renal recipient again dialysis-dependent? Does yesterday’s echocardiogram of the heart transplant patient reveal a left ventricular ejection fraction of 20%? Is the INR of the liver recipient 3.0?

Second, the function of the transplanted organ should be optimized as much as possible before surgery. Should the heart transplant patient receive after-load reduction? Can the liver recipient receive fresh frozen plasma? Should the pancreas recipient be placed on an insulin drip?

Third, the anesthetic agents and techniques must be organized in a fashion that minimizes injury to the transplanted organ. Meticulous hygiene and sterile techniques can reduce exposure of these immune-compromised patients to infectious organisms. Antibiotics should continue during the time of the operation, as should the application of immunosuppressive medications. Stress doses of steroids will be required in most cases. For the lung transplant patient, low-volume protective ventilation should be applied. Transesophageal echocardiographic monitoring can be considered for volume and inotrope titration in the heart recipient. An adequate perfusion pressure should be provided for the renal graft. To facilitate hepatic blood flow, central venous pressures can be kept low in the liver transplant patient.

Fourth, the patient’s immediate postoperative care should be anticipated and organized from the operating room. Will the patient imminently require dialysis? Will the patient be able to tolerate conventional dialysis, or should continuous hemodialysis be arranged? Is it possible that the patient may require mechanical hemodynamic support, and should this be arranged? Careful communication between the anesthesiologist and the physicians, nurses, and respiratory therapists who will be caring for the patient during the immediate postoperative period is vital.

Special considerations for lung transplant recipients

The lung, arguably the most delicate of the transplantable organs, is the only allograft exposed to the external environment and is especially prone to complications and rejection [17,18]. The commonest indication for lung transplantation is chronic obstructive airways disease or emphysema (45% of all transplants) [19] followed by cystic fibrosis, idiopathic pulmonary fibrosis, primary pulmonary hypertension, Eisenmenger’s syndrome, and other rare indications.
Lung function after transplantation

Both single (SLT) and bilateral lung transplantation dramatically improve lung function in patients with either obstructive or restrictive lung disease [17]. Initially, postoperative pain, altered chest wall mechanics, acute lung injury, and respiratory muscle dysfunction may be limiting, but by 6 months the peak benefit is seen. Bilateral transplantation eventually results in normal pulmonary function. Pulmonary function after SLT will depend on the underlying disease in the native lung that will participate to a limited extent in ventilation [20], which has implications for subsequent anesthesia. After SLT for chronic obstructive disease, the forced expiratory volume (FEV) in 1 second increases to 50% to 60% of the predicted value [20,21], whereas patients who have undergone SLT for restrictive disease show persistence of a mild restrictive pattern [20,21]. Arterial oxygenation usually returns to normal, and supplemental oxygen is usually no longer required by the time of hospital discharge. Hypercapnia secondary to a blunted ventilatory response to carbon dioxide may persist for weeks in patients with emphysema [22,23], but eventually the pCO₂ and ventilatory response to a CO₂ challenge normalize. Persistent hypercapnia suggests allograft dysfunction or diaphragmatic dysfunction because of phrenic nerve injury [24]. Transplant recipients usually return to an active lifestyle, but peak exercise performance will not be normal [25], especially in recipients of SLTs [26]. Four percent of transplant recipients, however, remain dependent on assistance because of functional limitation, and these patients pose significant risks when undergoing anesthesia.

Hemodynamics

Both single and bilateral lung transplantation lead to an immediate and sustained normalization of pulmonary artery pressures and pulmonary vascular resistance [27]. Cardiac output increases, and remodeling of the right ventricle follows, leading to an improvement in right ventricular ejection fraction [28].

Innervation

Lung transplantation disrupts pulmonary innervation, lymphatics, and the bronchial circulation. The transplanted lung is denervated distal to the bronchial anastomosis, and reinnervation does not occur. In an SLT, the carinal receptors remain intact, and carinal stimulation elicits a cough reflex [29]. Patients with a tracheal anastomosis lose this cough reflex and are more prone to silent aspiration and retention of secretions. Rarely, bronchial hyperresponsiveness may occur [30]. Denervation appears to have minimal effects on respiratory rate or rhythm [31,32]. Mucociliary transport is impaired [33], and perioperative chest physiotherapy and secretion mobilization are important. Disruption of the pulmonary lymphatics increases the chance of pulmonary edema, requiring careful fluid management in the perioperative setting. The lymphatics do show evidence of reforming, but the extent and timing are unclear [34]. In patients with an SLT,
60% to 70% of pulmonary perfusion is directed toward the transplanted lung [35]. Hypoxic pulmonary vasoconstriction is unaffected by denervation, so during an episode of rejection, pulmonary blood flow may be directed away from the transplanted lung [36].

**Bronchiolitis obliterans**

Bronchiolitis obliterans (BO), which represents chronic rejection, limits patient survival after transplantation [37]. The allograft lung shows evidence of inflammation, submucosal fibrosis, and luminal obliteration of the small airways. BO may be classified by four stages (0 to 3) on the basis of measurements of FEV$_1$, with or without histologic confirmation. In stage 3, the most severe stage, FEV$_1$ is less than 50% of baseline. The clinical syndrome is characterized by progressive dyspnea, airflow limitation on functional testing, and impairment of gas exchange because of progressive, irreversible airway obstruction. Computed tomography scans show abnormalities long before conventional chest radiography [38]. BO is uncommon in the first 6 months after transplantation, but its prevalence subsequently increases steadily and is found in 60% to 70% of patients who survive for 5 years [17]. Two years after the diagnosis of BO, the mortality rate is 40% [17]. If rejection or infection is suspected, elective surgery should be postponed, and further investigation should be performed.

**Survival and complications**

Survival rates after lung transplantation are the lowest of any solid-organ transplant, making nontransplant anesthesiologists less likely to see them in the operating room than recipients of other organs. Early after transplantation, patients may present for surgery to control bleeding or to repair bronchial anastomotic leaks. Bronchoscopy (or open lung biopsy) may be required for the investigation of suspected infection. Abscesses may need surgical drainage, and osteomyelitis may need orthopedic intervention. Intense immunosuppression means that the incidence of posttransplantation lymphoproliferative disease is relatively high among lung transplant recipients [39], and tumors may need surgical excision. Transplant patients have a high risk of developing intra-abdominal conditions that require surgical intervention [40], and, of course, unrelated surgical conditions may require anesthesia [35].

Changes in surgical technique have decreased the incidence of airway problems after lung transplantation, and they now occur in less than 15% of patients [17,41]. Hemoptysis, dehiscence, and mediastinitis may still occur. Stenosis may present with wheezing, dyspnea, and recurrent lower respiratory tract infections [42]. If stent placement using fiber-optic bronchoscopy [43] is unsuccessful, rigid bronchoscopy under general anesthesia may be required. Laser ablation of granulation carries the usual hazards of anesthesia and surgery in the presence of laser energy.
Preoperative evaluation

The function of the transplanted lung and other organ systems, especially those that may be compromised by immunosuppressant medications, and the presence of infection or rejection should be assessed. In patients with single lung transplants, careful attention should be paid to establish the extent of disease and degree of compromise of the native lung because these factors may have implications for the provision of mechanical ventilation. As for every anesthetic, the proposed surgical procedure should be considered because it may have implications for the transplanted lung; for example, in the case of the potential cardiopulmonary effects of bone cement in total hip arthroplasty.

The patient should be asked about dyspnea, fatigue, fever, cough, sputum production, exercise tolerance, and continued need for supplemental oxygen. Dry cough and dyspnea occurring 8 to 12 months after transplantation are worrisome for BO. Inquiry also should be made about recent hospitalizations and details of previous infections or allograft rejection. The nature of the patient’s voice and the presence of stridor or wheezing may be clues to the presence of airway narrowing or compromise. Prolonged ventilator dependence or previous tracheostomy may indicate subglottic stenosis thus, influencing the size of endotracheal tube used or consideration of fiberoptic intubation.

Laboratory investigations

Laboratory investigations should include arterial blood gas analysis. An increased alveolar-arterial oxygen gradient or the presence of hypercapnia may form the basis for postponement of the case and referral to the transplant pulmonologist for further investigation. A complete blood count may indicate the presence of infection, anemia, or polycythemia. Levels of serum blood urea nitrogen, creatinine, and electrolytes may be abnormal because of immunosuppressants, and serum glucose should be evaluated because transplant recipients are likely to be on steroids which may cause glucose intolerance. An electrocardiogram may show evidence of right ventricular dysfunction or may suggest myocardial ischemia because of coronary disease which is common in lung transplant candidates and recipients [44]. Pulmonary function tests, or at least simple spirometry should be performed and the results compared with previous values. A trend showing deterioration should, in conjunction with the transplant team, prompt a search for rejection or infection [45]. Elective surgery should be delayed in this case. The chest radiograph should be reviewed for evidence of infection or rejection, although it may be clear even in their presence.

Premedication

While anxiolytic premedication may be useful in these medical “veterans,” caution should be exercised in patients with marginal gas exchange or CO₂ retention. Sedatives should be given in a monitored setting. If inspection of the
airways is being performed, an antiallogogue may be indicated. Steroid supplementation is not necessary for brief procedures such as bronchoscopy, but should be considered in all transplant recipients depending on when corticosteroids were last administered.

**Anesthetic technique**

Regional anesthesia, if appropriate for the surgical procedure, has some theoretical advantages over general anesthesia because a conduction technique decreases the chance of airway trauma and aspiration and allows earlier patient cooperation in postoperative pulmonary hygiene. Disruption of allograft lymphatics, however, may lead to pulmonary edema after fluid loading. Epidural anesthesia may be preferable to spinal because of the ability to titrate medications to establish an adequate block, but these issues have not been studied enough to give definitive recommendations. Irrespective of the technique chosen, incentive spirometry, chest physical therapy, postural drainage, and early mobilization are important in the postoperative period.

**Airway management**

If general anesthesia is chosen, airway management poses an interesting dilemma. Instrumentation of the airway may be difficult because of stenosis, as described above, and also increases the chance of infection. Some studies [18] have recommended strict aseptic technique and the use of air filters, sterile laryngoscopes, and breathing circuits. Nasotracheal intubation should be avoided in transplant patients because it increases the chance of bacteremia. Mask anesthesia or the use of a laryngeal mask may be satisfactory, but risks unrecognized aspiration in a patient with a decreased cough reflex. An endotracheal tube cuff should be placed just beyond the vocal cords to prevent damage to a tracheal anastomosis and decrease the chances of endobronchial intubation contralateral to the transplanted lung. Excessive positive airway pressure should be avoided, and the tidal volume and respiratory rate can be adjusted in an effort to keep peak airway pressures less than 40 cm H2O and preferably less than 30 cm H2O. The placement of double lumen tubes should be avoided if possible. If required, a double lumen tube should be chosen that avoids endobronchial intubation on the side of the transplanted lung. At the completion of the procedure, in most cases, tracheal extubation should be possible. “Deep extubation” is not appropriate for these patients, and they should be extubated only when they are awake and able to actively initiate coughing to avoid the problems of retained secretions.

**Differential lung ventilation**

In SLT patients, a native lung with emphysema will be highly compliant and at risk for dynamic hyperinflation, whereas the transplanted lung will have normal compliance or, potentially, (in the presence of rejection or infection) low
compliance. Compression of the transplanted lung by the native lung may occur when positive pressure ventilation begins. When the patient’s native lung has restrictive physiology (eg, pulmonary fibrosis), high airway pressures will be required for expansion. Distribution of this high-pressure flow may cause barotrauma and volutrauma to the lung allograft. Differential lung ventilation, requiring the placement of a double lumen tube, should be considered [46]. The use of two ventilators or mechanical ventilation to one lung coupled with manual ventilation of the other will provide for differential lung ventilation. Ventilation of the native emphysematous lung at reduced minute ventilation will allow for maximal expiratory time and a reduction in dynamic hyperinflation. The transplanted lung should be ventilated at standard settings with or without positive end-expiratory pressure (PEEP). If the transplanted lung shows evidence of acute lung injury, a low tidal volume strategy may be appropriate [47], but this has not been proven in this patient population. Standard operating room ventilators will be sufficient in many cases, but if difficulty with ventilation is anticipated, an intensive care unit ventilator should be used. With the development of adult high-frequency oscillators, this mode of ventilation may be used in the future [48]. Humidification of the inspired gas is important to optimize the performance of the mucociliary transport mechanism, but sterility of the humidified vapor is of great importance.

**Pulmonary blood flow**

The allograft generally receives the majority of pulmonary blood flow, with 60% to 80% of both ventilation and perfusion going to the transplanted lung. Positioning the patient in the lateral position may cause hypoxemia, especially if the allograft is in the dependent position. If possible, the transplanted lung should be nondependent. In surgical situations that require one-lung ventilation, because the allograft receives most of the blood flow and because it is the most functional lung, hypoxemia is likely to occur when allograft deflation is required to provide surgical exposure.

**Monitoring**

In addition to standard monitors, the condition of the patient and the surgical procedure should dictate the choice of additional monitoring. The risk of infection must be balanced against a desire for additional information. Routine placement of an arterial line is not appropriate, but an arterial line may be indicated for operations involving significant hemodynamic shifts, long cases, or in circumstances in which postoperative mechanical ventilation is likely. Central venous and even pulmonary artery catheters may be placed if the situation warrants and strict aseptic technique is used. There is no evidence to suggest that cannulating the vasculature on the side opposite the transplanted lung is safer, but it would seem reasonable [49].
Special considerations in heart transplant recipients

Orthotopic heart transplantation (OHT) is performed for severe heart failure, pulmonary hypertension, or congenital heart disease, in patients for whom other therapeutic modalities are failing [50]. Early after transplantation, patients may return to the operating room for bleeding and cardiac tamponade or for removal of a ventricular assist device. Later, minor surgical procedures such as incision and drainage of skin abscesses may require anesthesia. OHT recipients may be more susceptible to intra-abdominal catastrophes such as intestinal perforation because of their debilitated preoperative condition, hypoperfusion, nutritional defects, and the stress of cardiopulmonary bypass [51,52]. Surgical procedures for immunosuppressant-induced cancers may also be necessary. Additionally, peripheral vascular procedures [53], repair of aortic aneurysms [54], and flap procedures after sternal wound infections may require anesthesia.

Physiology of the denervated heart

During donor heart harvesting, sympathetic postganglionic and parasympathetic preganglionic efferent nerves and both sympathetic and parasympathetic afferents are transected [51]. The baseline heart rate is increased (typically at 90–100 beats/min) because the loss of vagal input causes an increase in automaticity of the sinoatrial and atrioventricular (AV) nodes [55]. The remnant recipient atria remain under intact vagal effects but are hemodynamically unimportant. The donor atrium is denervated and is responsible for the electrophysiologic responses of the allograft. There are two P waves on the electrocardiograph (ECG) of the OHT recipient, and right bundle branch block is common. Sensory input, such as the pain of myocardial ischemia, is impaired. The transplanted heart does not respond to carotid sinus massage, the Valsalva maneuver, or the sympathetic stimulation of laryngoscopy and may have a blunted heart rate response to inadequate anesthesia [56]. During exercise or hemodynamic stress, the denervated heart relies on circulating levels of catecholamines and the Frank-Starling mechanism to maintain adequate cardiac output by increasing stroke volume [57]. The denervated heart is preload-dependent and lacks the ability to mount a reflex tachycardia in response to hypovolemia. Eventually, however, endogenous or exogenous catecholamines will improve ventricular performance, as α- and β-adrenergic receptors are preserved. Compared with controls, the maximal exercise capacity of the transplanted heart is blunted [58]. Reinnervation occurs to a variable degree years after transplantation [59].

Effects of drugs on the transplanted heart

Drugs that act through the autonomic nervous system have minimal effects (or side effects) on the transplanted heart. Drugs include anticholinergics (atropine, glycopyrrolate, scopolamine), anticholinesterases (neostigmine, edrophonium, pyridostigmine, physostigmine), muscle relaxants that usually affect heart rate (pancuronium, gallamine), and nifedipine, phenylephrine, or sodium nitroprus-
Anticholinesterases normally act indirectly on the myocardium and should have no effect on the heart rate of the denervated heart, but neostigmine can cause bradycardia by direct activation of cholinergic receptors on cardiac ganglionic cells [60,61]. The cardiac allograft is responsive to isoproterenol, dobutamine, ephedrine, dopamine, glucagon, and the phosphodiesterase inhibitors (milrinone, amrinone) [62]. The inotropic effects of digoxin are preserved, but its effects on heart rate are not. Epinephrine and norepinephrine have an augmented effect in the cardiac allograft [56]. The denervated heart is also responsive to β-blockers. The effects of verapamil may be excessive.

**Arrhythmias**

First degree A V block is common in the transplanted heart, and bradyarrhythmias should be treated with epinephrine or isoproterenol [63]. Permanent pacemakers are required in 5% to 10% of patients. Re-entry dysrhythmias are rare, but supraventricular tachycardia may be treated with verapamil, procainamide, or quinidine. Atrial arrhythmias are suggestive of rejection and warrant further evaluation before elective surgery. Ventricular ectopy is common in the first weeks after transplantation. Lidocaine should be used with caution because of its negative inotropic actions.

**Functional capacity**

Most patients who have undergone OHT will regain good functional capacity. Preoperative evaluation includes early communication with the transplant center, particularly regarding immunosuppression regimens. Routine tests such as ECG, chest radiography, complete blood count, and electrolytes should be reviewed. If an indwelling pacemaker is present, its function should be checked; the mode of the pacemaker may need to be altered to prevent unwanted effects during the use of electrocautery. As with any transplanted organ, rejection is a major concern after OHT. Most rejection episodes occur within the first 3 months and are diagnosed by endomyocardial biopsy, and then they are treated with additional steroids. Troponin T levels may correlate with rejection [64]. Ongoing rejection may be indicated by both systolic and diastolic dysfunction [65]. Cardiac allograft vasculopathy [66] is an accelerated process of coronary atherosclerosis and is angiographically detectable in 20% of patients, 5 years after transplant. The condition may lead to fatal myocardial ischemia. Five years after transplantation, two thirds of recipients will have hypertension, which is often the result of cyclosporine therapy, and many will experience renal dysfunction [62,67].

**Monitoring**

Most patients undergoing noncardiac procedures in the years immediately after transplant can be managed with standard monitors. If central venous cannulation is necessary, the right internal jugular vein should be avoided if possible because it is the route by which endomyocardial biopsies are taken. Pulmonary
artery catheterization may be indicated because most hypotensive episodes may be treated with fluid administration, which will eventually cause pulmonary edema. Transesophageal echocardiography may be invaluable to assess preload and identify ischemia. Multilead ECG and ST-trend analysis should also be used.

Anesthetic technique

Heart transplant recipients have been managed with all types of anesthetic techniques [29,68,69]. Volatile agents may be used as long as the patient is not in a state of decompensated heart failure. There are some concerns with regard to the use of regional anesthesia because of the reliance of the denervated heart on preload and the potentially exaggerated response to hypovolemia. Diaphragmatic dysfunction is common in heart and heart-lung transplant recipients [70]. Judicious use of induction agents is more important than the recommendation of specific agents, and even propofol has been used in many (euvolemic) OHT recipients, despite its vasodilating properties. The patients usually have normal requirements for anesthetic agents, when any renal or hepatic dysfunction is allowed for [70]. Epinephrine and isoproterenol must be immediately available for the treatment of bradycardia.

Special considerations for liver transplant recipients

Orthotopic liver transplantation (OLT) is the surgical removal of a patient’s diseased liver and its replacement with a liver allograft. The procedure is the treatment of choice for irreversible, end-stage liver disease, and approximately 5000 such procedures are performed every year in the United States. The 1-year patient and graft survival rates are greater than 90% and 80%, respectively. The most common indications for OLT include cirrhosis caused by viruses, alcohol, and obstructive biliary disease. Fulminant hepatic failure and errors of metabolism are other reasons for transplantation. The transplantation procedure itself is major undertaking, but the anesthesia provider may need to anesthetize recipients of liver transplants in the subsequent months and years for a variety of reasons that are both related and unrelated to the transplantation procedure. The advent of living donor liver transplantation will further increase the number of OLT recipients in the general population [71].

Postoperative course

The anesthetic management of the liver transplant recipient for nontransplant surgery will depend on the length of time since transplant procedure and the function of the graft. Postoperatively, most OLT recipients spend some time in the intensive care unit and are usually mechanically ventilated for a number of hours. In most cases, after successful transplantation, the patient can leave the ICU on the day after the operation [72]. Ultra-fast tracking is gaining in popularity,
and some patients are extubated and managed for a number of hours in the recovery room before being transferred to a step-down unit [73].

A functioning graft is identified by the production of golden brown bile, the correction of preexisting coagulopathy, and improvement in metabolic parameters. Occasionally, “initial poor function” may be noted, typically, in livers from elderly donors or those patients who have been exposed to a prolonged ischemic period between harvest and re-implantation. “Primary non-function” is a separate immunologically mediated condition in which the newly implanted liver does not function. This requires urgent retransplantation, for which the anesthesia is usually the responsibility of the transplant anesthesia team.

Patients with preoperative encephalopathy will take longer to awaken after transplantation. If they require surgery in the early postoperative course, an attempt should be made to limit long-acting sedatives such as benzodiazepines and high-dose narcotics. Typically, in the early postoperative period after OLT, the hyperdynamic state seen in patients with end-stage liver disease persists. If the cardiac index is not elevated, it may be because of cirrhotic cardiomyopathy [74] or peritransplant myocardial dysfunction [75]. Abnormalities in serum sodium concentration are common. Patients with cirrhosis usually have hyponatremia, and overzealous correction of this may lead to central pontine myelolysis [76]. Nowadays, the need for massive transfusion during OLT is less common but still possible, and patients may present with metabolic alkalosis because of metabolism of citrate (in the transfused blood) to bicarbonate by the new liver. Sodium bicarbonate administration, which is now less common during the transplant procedure, may also contribute to the alkalosis. Concomitant hypocalcemia may be observed.

Early return to the operating room

Within the first 24 to 48 hours after transplantation, between 10% and 15% of patients experience some element of hemorrhage and may require reoperation. In some centers such patients are managed by the liver transplant team, but in other centers the nontransplant anesthesiologist may be responsible. Patients will likely have intra-abdominal compartment syndrome, with decreased urine output, increased airway pressure, and difficulty with oxygenation and ventilation. The endotracheal tube, invasive monitoring, and large-bore vascular access will usually still be in place. The anesthesiologist should be prepared for the possibility of cardiovascular collapse once the abdomen is opened, and any tamponading effect on the bleeding vessels is released. Arrangements should be made for a large volume of transfusion using a Rapid Infusion System (Haemonetics Corp., Braintree, MA) or Belmont fluid administration (Belmont Instrument Corp., Billerica, MA), or some similar system. Hemodynamic instability and difficulties with ventilation usually resolve once the intra-abdominal blood has been evacuated and the bleeding source identified (if possible). Surgical sources of bleeding include vascular anastomoses, the gallbladder bed and cystic artery, intra-abdominal varices, the adrenal gland, and the abdominal wall or a liver laceration or fracture.
The first two weeks after transplantation

The transplant recipient may present to the operating room for complications such as vascular thrombosis. Early hepatic artery thrombosis presents with elevated transaminases, hemodynamic and respiratory compromise, and will ultimately lead to graft failure, although surgical intervention may salvage the graft \([77]\). Occlusion of the hepatic artery that occurs later has a less dramatic presentation but may still cause graft failure. Reparative surgical procedures may be technically difficult from a surgical rather than an anesthesia standpoint. An infusion of prostaglandin E\(_1\) may be begun to maintain vascular patency; this will decrease the blood pressure, especially at higher doses. A hemoglobin concentration between 8 and 10 mg/dL is advisable to maintain optimal blood viscosity and rheology. Venous thrombosis (portal or hepatic vein) is less dramatic in its presentation but also requires surgical intervention in most cases. Veno-venous bypass is now used less frequently during the transplant procedure itself and is rare in operations subsequent to the OLT, unless the graft needs to be explanted. The procedure will require two large-bore venous lines. Biliary leaks are also problematic in the first weeks after OLT and may cause ongoing sepsis and require operative intervention.

General anesthesia is the norm for surgical procedures in the weeks after transplant because of the upper abdominal site of the surgery and the residual coagulopathy that may be present, even in the presence of a functioning liver graft. Surprisingly, analgesic requirements after liver transplantation are relatively low \([78]\), and most patients can be managed with intravenous morphine administered by patient-controlled analgesia and may be quickly transitioned to oral opiates for a few days. Relative bradycardia may be a feature in the weeks after transplantation.

Functional status after liver transplantation

Successful OLT eventually reverses the multisystem manifestations of end-stage liver disease. Transaminase levels are high in the immediate postoperative period but return to normal levels over the course of approximately 2 weeks. Recovery of the capacity for drug metabolism returns soon after reperfusion of the graft \([56]\), and considerable metabolic capacity for morphine and midazolam has been reported \([79]\). Oxygenation returns to normal because of the amelioration of multiple factors that impaired oxygenation and ventilation. Ventilation-perfusion mismatch is reversed as pleural effusions, ascites, and hepatic hydrothoraces gradually resolve. End-stage liver disease may be complicated by the hepatopulmonary syndrome (HPS) or portopulmonary hypertension (PPH) \([80]\). HPS, which results from intrapulmonary shunting and causes hypoxemia, may be an indication for transplantation. Oxygenation usually improves after transplantation, although this may take months, and the OLT recipient with a history of HPS may still require supplemental oxygen \([81]\). In most cases, adequate oxygenation is achieved, and intraoperative difficulty with oxygenation caused
by HPS in the recipient is very unusual. In a small number of cases the hypoxemia may not ever resolve fully. PPH, a thrombotic, vasoconstrictive process, occurs in a small number of patients with end-stage liver disease. Severe PPH is a contraindication to OLT, although patients with mild to moderate PPH will usually improve after transplantation. Depending on the length of time after transplantation, however, pulmonary hypertension may be an issue in the OLT recipient for nontransplant surgery. If the patient is on long-term epoprostenol (Flolan) infusion, it must be continued during the perioperative period. Even brief interruptions may be disastrous. Pulmonary hypertension will be made worse by hypoxia, hypercapnia, and acidosis, therefore these obvious interruptions should be avoided. Nitrates, inhaled nitric oxide [82], and sildenafil [83] may be used as additional measures to treat pulmonary hypertension. The OLT recipient’s ventilatory capacity may be affected by right hemidiaphragm dysfunction [84]. Hepatorenal syndrome may cause renal failure in patients with end-stage liver disease [85]. Although this syndrome will improve with transplantation, patients may need dialysis for a considerable length of time after OLT.

**Preoperative evaluation**

The patient should be questioned about symptoms related to graft function. The presence of jaundice, unexplained fevers, change in the color of urine or stools, pruritus, or evidence of fluid retention should be sought. Standard liver function tests should be obtained before elective surgery (ie, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma-glutamyl transpeptidase, bilirubin, international normalized ratio, activated partial thromboplastin time, and albumin.) Serum bilirubin is expected to be in the normal range by 3 months. If available, the thromboelastogram may provide useful information with regard to the coagulation status of the recipient. Elevations in aspartate aminotransferase may be related to the degree of immunosuppression, and the levels may not fall into the normal range for a number of years after OLT. Alkaline phosphatase and gamma-glutamyl transferase levels are the least likely to become normal after transplant, so trends are more important than the absolute numbers. After a successful transplant, liver synthetic function is usually normal. If it is not, rejection or biliary drainage problems should be considered, and liaison with the transplant hepatologist and surgeon is important. The presence of cytomegalovirus infection or recurrence of viral hepatitis should also be considered. Some centers also measure serum pseudocholinesterase as a measure of graft synthetic function. Clinical examination should include evaluation for asterixis, ascites, or edema, in addition to a search for side effects of immunosuppressant therapy (hypertension, fungal infections of the skin, and Cushing’s syndrome.) Coronary artery disease may be present in OLT recipients, but it is less common than in recipients of, for example, renal (underlying diabetes) or heart transplants (allograft vasculopathy). Screening for coronary artery disease has usually been performed before transplantation [86], and the patient presenting
for surgery weeks or months after OLT will have survived the major cardiovascular stress involved in the transplant procedure.

Implications for anesthetic drugs

Liver disease leads to hypoalbuminemia, and correction after transplantation may take weeks or months. Many anesthetic drugs (eg, opioids and barbiturates) are bound to albumin in the circulation, and a low albumin level may increase the free fraction of administered drugs, potentially resulting in an increased clinical effect. End-stage liver disease alters hepatic extraction and metabolism, renal excretion, and volume of distribution. The net effect on any given drug is unpredictable, especially in the period after transplantation, so titration of a drug to the desired effect is the safest approach. Muscle relaxants that are metabolized independently of liver and renal function, such as atracurium and cisatracurium, would seem to be prudent choices, but vecuronium, which is excreted through a biliary route, has also been used. Induction and maintenance of anesthesia may be achieved, and conventional induction agents and opiates such as fentanyl and morphine are reasonable choices for analgesia in the OLT recipient. Isoflurane has been suggested as the volatile agent of choice, and nitrous oxide may also be used.

Reasons for needing anesthesia

Recipients of OLT may require anesthesia months after transplantation for a variety of reasons. Diagnostic tests for complications of immunosuppressant therapy may include imaging such as computed tomography (CT) or magnetic resonance imaging (MRI), which may require general anesthesia depending on the condition of the patient. Bronchoscopy, performed to establish the cause of pneumonia, can usually be performed under sedation. Protocol biopsies for the surveillance of rejection are usually performed blind or under ultrasound guidance, and anesthesia is usually not required. Extrahepatic intra-abdominal complications of OLT include opportunistic infections of the peritoneal cavity, colonic perforation, and pneumatosis intestinales, for which surgical intervention may be required. Operations for incisional hernias are relatively common, given the large bilateral subcostal incision needed for the transplant procedure. Bowel obstruction may also require operative intervention. If portal hypertension persists after transplantation, resuscitation and anesthesia may be required for the surgical or endoscopic therapy of bleeding varices.

Biliary tract complications require surgical intervention in most of those recipients who develop them [87], and the cause of the problem depends on whether a choledochocholedochostomy or choledochojejunostomy (Roux-en-Y) was performed at the time of transplantation. Ductopenic rejection, or vanishing bile duct syndrome, indicates chronic rejection of the liver allograft. The cholestasis it produces may be confused with a surgical problem.
Other anesthesia considerations

Abdominal operations in OLT recipients have the potential for major bleeding, and the anesthesiologist should ensure that adequate vascular access is available. Placement of 8.5-F catheters in the antecubital fossae or the neck should be considered. During surgery, intravascular volume and systemic blood pressure should be maintained to avoid hypoperfusion of the transplanted organ. Avoidance of light anesthesia, hypoxia, hypercapnia, high airway pressures, and excessive PEEP will prevent increased splanchnic vascular resistance and decreased hepatic blood flow. The normal physiologic mechanisms that maintain liver blood flow are blunted after OLT. Administration of volatile anesthetic agents may decrease hepatic blood flow and may cause liver dysfunction but are routinely used in OLT recipients. Isoflurane may be the volatile anesthetic of choice. Very rarely, an immunologically mediated fulminant hepatic failure may occur from volatile agents [88]. Whether the transplanted liver is more susceptible to such damage is unknown. Physiologically, the liver may act as a blood reservoir, under the control of the sympathetic nervous system, which allows compensation for acute volume loss. The decreased responsiveness of the hepatic vasculature after OLT coupled with the blunting of the sympathetic response by anesthesia will lessen this compensatory mechanism. Drugs known to decrease hepatic blood flow such as cimetidine and propranolol should be avoided. Regional anesthesia or analgesia may also be considered providing there is no evidence of a coagulopathy. The potential for transmission of infectious agents (eg, viral hepatitis that was present before transplantation or was acquired secondary to transfusion during the transplant) to the anesthesia personnel must be recognized. Alcoholism may have been a precipitating factor in the patient’s liver disease, therefore consideration for OLT requires abstinence, but the effects of alcohol abuse may be manifested in other organs [89]. These factors should be considered in planning anesthesia for the OLT recipient.

Special considerations for kidney transplant recipients

Kidney transplantation is the most commonly performed solid-organ transplant, and the nontransplant anesthesiologist is likely to be faced with a renal transplant recipient for incidental surgery [90]. Diabetes mellitus, hypertensive nephrosclerosis, glomerulonephritis, and autosomal dominant polycystic kidney disease are the usual causes of end-stage renal disease. Recently, the number of kidney transplants, especially living donor transplants [91], performed annually has increased and comorbidities are less likely to be contraindications than before [92].

Patients who have undergone renal transplantation usually have multisystem disease. Although their quality of life is improved after a successful transplant and they no longer must undergo regular hemodialysis, their extra-renal manifestations or complications remain [93]. Thus, patients presenting for nontrans-
plant surgery may have hypertension, congestive heart failure, coronary artery disease, pulmonary disease, or diabetes. Coronary artery disease is common in this patient population, especially in diabetics [94], and stress testing or coronary angiography may have been performed before the transplant procedure [95]. Hypertension may have been present before transplantation and may also occur because of complications of immunosuppressant therapy [96]. Hyperlipidemia is common, and perioperative cardiovascular morbidity and mortality are increased in the renal transplant recipient. Compared with recipients of other solid-organ transplants, renal transplant recipients are likely to be older, with the concomitant problems related to anesthesia [97].

Reasons for requiring surgery

In the early postoperative course, often within the first 48 hours, renal transplant recipients may need exploratory surgery because of bleeding or inadequate urine output. Operative intervention may be possible to save a transplanted kidney if the cause of dysfunction is a kinked ureter or a technical error with the renal vasculature. Thrombosis of the allograft, which may be mediated by acute rejection, may necessitate removal of the transplanted kidney. Under these circumstances, the patient may be acutely ill with an ongoing systemic inflammatory response that may cause fever, vasodilation, hypotension, hypoxemia, and metabolic acidosis. Kidney transplant recipients may also subsequently require surgery for urologic complications, lymphoceles, wound infections, orthopedic problems caused by renal osteodystrophy [98] or steroids, gastrointestinal bleeding [99] or other gastrointestinal complications, and coronary artery bypass surgery [100]. If transplantation is unsuccessful, new AV fistulae for dialysis may need to be fashioned (often under axillary block or sedation).

Functional status after kidney transplantation

Although the serum creatinine of an adequately functioning renal allograft will be normal or nearly normal, the glomerular filtration rate and effective renal plasma flow will be lower than in normal individuals. The activity of excreted drugs may be prolonged, and the anesthesiologist should consider the use of anesthetic agents that do not require renal excretion [56]. Obviously, nephrotoxic drugs should be avoided, and although non-steroidal anti-inflammatory drugs such as ketorolac may be excellent perioperative analgesics, they should be used with extreme caution, if at all. Intravascular volume depletion should be avoided because renal hypoperfusion may occur [100,101]. Patients with allograft dysfunction who require dialysis are especially prone to hypovolemia in the perioperative setting. Many will have been dialyzed immediately before surgery to ensure normal electrolytes, and, when the patient is unable to take oral fluids and intravenous hydration is suboptimal, the fluid removed during dialysis may render the patient hypovolemic. Diuretics should not be administered until adequate intravascular volume is ensured. Hypokalemia may occur after dialysis,
and this may cause cardiac arrhythmias and increased susceptibility to muscle relaxants. Function of the allograft may be assessed by asking about urine output, previous episodes of rejection, the presence of symptoms related to uremia (pruritus, lethargy, nausea, skin pigmentation, and other symptoms) and by measuring serum blood urea nitrogen, creatinine, and electrolytes (including calcium and magnesium). As with other transplanted organs, suspicion for rejection should prompt discussion with the transplant nephrologist and surgeon, and elective cases should be postponed while investigation is ongoing. An electrocardiogram should be performed to look for changes related to ischemia or hypertension and to show evidence of electrolyte imbalance (especially signs of hyperkalemia).

If the transplant has not been successful or if allograft nephropathy has resulted in late allograft dysfunction [102], the patient may still require regular hemodialysis and may suffer from a variety of the pathophysiologic consequences of chronic renal failure, including anemia, platelet dysfunction, neuropathy, hypertension, central nervous system dysfunction, electrolyte imbalances, metabolic acidosis, nausea and vomiting, and problems related to dialysis.

Anesthesia techniques

Both regional and general anesthesia (balanced and total intravenous [103]) may be used for nontransplant surgery in the renal allograft recipient. The choice will depend on the nature of the surgery and patient and preference of the anesthesia provider. Central neuraxial blockade is relatively contraindicated in the presence of clinical evidence of uremic platelet dysfunction or severe hypovolemia. Uremic or diabetic peripheral neuropathy should also be considered. Most induction agents may be used, but caution should be exercised with ketamine because of the hypertension it can produce in patients who may already be hypertensive [104]. Isoflurane and desflurane are appropriate volatile agents. Enflurane should not be used because of potentially nephrotoxic inorganic fluoride metabolites, but clinically useful doses of sevoflurane are safe [105]. Muscle relaxants, that do not rely on renal excretion (such as cisatracurium, atracurium, mivacurium, and perhaps vecuronium) [106] are preferable in patients with some degree of renal dysfunction after transplantation. Even newly transplanted kidneys that are functional, however, are able to clear neuromuscular blockers and anticholinesterases at the same rate as they do in normal patients [56]. Delayed gastric emptying may be present because of diabetes, and for rapid sequence intubation, succinylcholine is safe if the $K^+$ level is less than 5.5 mEq/L, but rocuronium, mivacurium, or high doses of vecuronium or cisatracurium are alternatives. The commonly used opiate analgesics are often used in renal transplant recipients. Caution should be exercised, however, especially if the patient has some degree of renal dysfunction, because the active metabolites of meperidine (normeperidine) and morphine (morphine-6-glucuronide) may accumulate [107,108]. Benzodiazepines, phenothiazines, and butyrophenones are predominantly metabolized hepatically, but the duration and
activity of their metabolites are prolonged if residual renal dysfunction persists. Monitoring should be appropriate for the nature of the surgical procedure. It is of great importance that adequate intravascular volume is maintained in the perioperative period, because transplanted kidneys are sensitive to hypovolemia, and monitoring of the central venous pressure may be very useful.

**Special considerations for pancreas transplant recipients**

Pancreas transplantation (with or without kidney transplantation) [109] is associated with the highest surgical complication rate (as high as 35% in some series) of the solid-organ transplants, and patients may later present for treatment of such complications [49,110]. Postoperative sepsis is common, and 10% of patients have a prolonged initial hospitalization because of acute rejection or surgical complications, and more than 50% require readmission during their first posttransplant year. Rejection presents with unexplained abdominal tenderness, hyperglycemia, and urine hypoamylasemia (in patients with bladder drainage) and is often preceded by renal deterioration in simultaneous kidney-pancreas transplant patients [111]. A definitive diagnosis is determined by biopsy, and elective or even urgent surgery should be postponed.

**Reasons for requiring surgery**

Up to 25% of recipients may require laparotomy after transplantation, and this is associated with a decrease in both patient and graft survival [112]. Major bleeding (from the mesenteric axis and splenic hilar vessels or from AV fistulae) or more insidious hemorrhage (from small vessels on the surface of the pancreas) may occur. Transplant-related pseudoaneurysms [113] and AV fistulae may lead to graft loss. Volume resuscitation, blood transfusion, and the establishment of large-bore venous access are important in the anesthetic management of such patients.

Thrombosis of the graft, which occurs in 5% to 10% of patients, is a feared complication of the procedure, [114]. Low-dose heparin, dextran, or anti-platelet agents may be administered as prophylaxis. In addition to increasing the risk of bleeding that may require surgical intervention, this practice may also have implications for the performance of regional anesthesia. Early thrombosis is heralded by hyperglycemia, increased insulin requirements, and a fall in urine amylase. Hematuria, tenderness, and swelling of the graft and the ipsilateral lower extremity are evidence of venous thrombosis. Urgent removal of the graft is required, and the anesthesiologist should appreciate the potential for major, ongoing inflammatory and vasodilatory responses in such settings. Rarely, thrombectomy or reversal of a surgical technical error may save the graft.

**Drainage of the exocrine pancreas**

Unique among transplanted organs, the exocrine secretions of the pancreas may cause significant complications. Techniques to manage exocrine pancreas
drainage include enteric drainage into the proximal jejunum, synthetic polymer injection with occlusion of the pancreatic duct, and urinary drainage. Urinary drainage allows monitoring of urinary amylase as a guide to the function of the transplanted pancreas [115], although its value is questioned in the presence of a kidney transplant from the same donor because clinical and biochemical signs of kidney transplant rejection usually precede pancreatic allograft rejection [116]. Reflux of amylase-containing urine may cause allograft pancreatitis. Additionally, bladder drainage of pancreas grafts may lead to large bicarbonate losses resulting in severe, refractory metabolic acidosis and dehydration [117]. Acidosis does not occur in the enteric-drained pancreas recipient because bicarbonate is resorbed by the intestine. Between 6% and 20% of bladder drainage pancreas transplants are eventually converted to enteric diversion [118], and this is now an operation commonly performed within a number of months or years after the transplant surgery. In the first months after transplant, hematuria is common. Significant blood loss may occur, causing bladder distension and discomfort. Cystoscopy, clot evacuation, and surgical treatment of the bleeding site may be required. Bladder calculi may require cystoscopy and lithotripsy. Urine leakage may require intervention or may give rise to fistulae or abscesses that require surgical drainage. Duodenal segment leaks may require operative intervention [119]. Pancreatitis is common after transplantation, and although most cases are self-limited and because of ischemic preservation injury, peripancreatic fluid collections may occur and require operative drainage and debridement of necrotic tissue.

Anesthesia considerations

Transplanted patients are those most severely affected by diabetes and who have developed severe end-organ dysfunction, potentially affecting the conduct of anesthesia. A full range of diabetic complications may be seen, including diabetic stiff joint syndrome, which may affect the atlanto-occipital joint, making direct visualization of the vocal cords difficult or impossible [120]. Review of previous intubation attempts is important, and a fiberoptically guided technique with the patient awake may be necessary, but this is unusual. Diabetic gastroparesis will necessitate a rapid sequence induction or at least the application of cricoid pressure during induction. Autonomic neuropathy-induced loss of cholinergic tone in the airways may predispose diabetics to hypoxemia, especially in the presence of residual anesthetic agents. Positioning of the patient should seek to avoid exacerbating neuropathies and compression of any extremity AV fistula currently or previously used for dialysis. Pancreas transplant recipients may have required large doses of opiate analgesics because of recurrent episodes of allograft pancreatitis and may have a tolerance for opiates.

Insulin administration is not required to compensate for the stress response to surgery because successful pancreatic transplantation effectively restores normal glucose metabolism. It should be assumed that these patients have coronary artery disease and often are at high risk for asymptomatic ischemia [121]. Noninvasive testing may not be totally predictive, and many patients will have had coronary
angiography performed. The results of this testing, previous interventions, and current medical management should be established. Pancreas transplant recipients do not routinely need admission to the ICU after surgery, but this course should be considered if the patient has severe or unstable coronary artery disease or an ischemic cardiomyopathy. As with all patients with coronary artery disease, perioperative β-blockade is encouraged [122], but in patients with failed grafts, the possibility of hypoglycemia masking exists. Although pancreas transplantation may reverse the lesions of diabetic neuropathy, this reversal may take many years [123]. Autonomic neuropathy may cause cardiac denervation, and in a manner similar to that of the transplanted heart, the response to atropine may be absent, and epinephrine should be an early consideration in the treatment of bradycardia. Fluctuations in blood pressure, loss of beat-to-beat variability in heart rate, orthostasis, and silent ischemia may occur. If renal impairment is present, the anesthetic plan should account for this in a manner described elsewhere in this review.

Preoperative assessment

Preoperative assessment should also include assessment of metabolic status, including glucose control, acid-base status, electrolytes, and volume status. If possible, preoperative optimization should be attempted, and this may require ICU management if the patient is severely decompensated with, for example, congestive heart failure, severe electrolyte abnormalities, or diabetic ketoacidosis in the setting of a failed transplant. Formal recommendations for the perioperative management of glucose levels in pancreas transplant recipients are lacking, as are studies on the effect of anesthesia on the catecholamine and glucagon response to hypoglycemia after transplantation. In patients with failed pancreatic grafts, the management of glucose levels and acid-base status should be the same as for any diabetic patient [124]. Bicarbonate requirements should be assessed, especially if bladder drainage is present.

Islet transplantation

Transplantation of pancreatic islet cells is an alternative to transplantation of the entire organ [125]. This technique, although promising, has met with only modest success. The technique is usually performed under sedation by infusing cells into the portal vein through a catheter introduced using a percutaneous transhepatic technique. Postoperative complications and the need for further surgery should be less than with whole-organ transplantation, but anesthetic experience thus far is limited.

Special concerns in recipients of intestinal and multivisceral transplants

The indications for intestinal and “cluster” multiple-organ transplantation include loss of intestinal function related to surgically shortened gut (eg, after
resections for infarctions, atresia, strictures, or fistulae) or nonsurgical factors (eg, motility disorders, absorptive insufficiencies, polyposis syndromes, and certain tumors). The techniques for the care of reversible intestinal and total parenteral nutrition (TPN) failure are now standard [126]. These transplant patients require a high level of multidisciplinary support, and consideration should be given, if possible, to the referral of such patients back to the transplant center for all but emergency anesthesia and surgery.

Complications

Patients may present to surgery for the treatment of complications after transplantation. Postoperative hemorrhage is usually a technical problem, although it may be made worse by coagulopathy. Bleeding from vascular anastomoses or extensive raw peritoneal surfaces may need surgical intervention. Biliary leaks may occur during the first 2 weeks after transplantation, whereas biliary obstruction generally follows an anastomotic stricture and is a delayed complication; but both will need surgical intervention. Major arterial thrombosis is a life-threatening complication that leads to necrosis of the supplied organs and rapid clinical deterioration. Venous outflow thrombosis similarly presents with a major clinical deterioration. When providing anesthesia for a transplant recipient for repair of such a complication, the presence of severe metabolic acidosis and the requirements for large volume fluid resuscitation and pressor support should be expected. These patients should be left intubated at the end of the procedure and managed in the ICU. The proximal or distal gastrointestinal anastomosis may leak, requiring operative intervention to revise the anastomosis and eliminate peritoneal contamination. Again, such patients may be very ill.

Types of transplantation

There are basically four types of intestinal transplantation, from which an approach is selected depending on the cause and severity of dysfunction and the presence or absence of extra-intestinal dysfunction [56,127]. These types include isolated intestinal transplantation [128], combined intestine and liver transplantation, liver duodenum and pancreas (“organ cluster” transplantation), and multivisceral transplantation (stomach, duodenum, pancreas, liver, small bowel, and colon.)

Thrombotic disorders

Patients with protein C, S, or antithrombin III deficiency may be candidates for a combined liver-small intestine transplant, even in the absence of clinical liver disease because they develop mesenteric venous hypertension resulting from splanchnic thromboses. These patients are theoretically more likely to suffer from perioperative thrombotic events in the perioperative period of nontransplant surgery [129].
Venous access

Venous access may be difficult in patients who have undergone intestinal transplantation. TPN is the standard method of nutritional support before and for a variable period of time after transplantation. Recurrent episodes of infection or venous thromboses may cause severe damage to the venous system. Indeed, the lack of venous access for continued nutrition may prompt transplantation. Patients who present for surgery in the weeks or months after intestinal transplantation will most likely still have a long-term venous access device (such as a Hickman catheter) in situ. Provided that strict aseptic technique is used and care is taken to remove any indwelling heparin, the line may be used during the anesthesia. If no such device is present, potential difficulty in gaining venous access should not be underestimated. Electrolyte imbalance is common in this patient population and may be caused by the difficulties inherent in long-term TPN or because of diarrhea, which may occur in the posttransplant period [130].

Anesthesia considerations

Intestinal transplant recipients are prone to infection because denervation and lymphatic dysfunction affect intestinal permeability and absorption during the posttransplant period. Ischemia, rejection, or enteritis may damage the intestinal mucosal barrier causing bacterial translocation and subsequent sepsis. A vasodilated state may exist that requires the administration of pressors in addition to fluids to treat hypotension [130].

When abdominal surgery is performed on recipients of bowel transplants, a difficult surgical dissection should be anticipated. These patients may have undergone multiple laparotomies in the past, and adhesions may be severe, leading to major bleeding and a large volume of fluid resuscitation. The surgical procedure may be very long, especially if attempts are being made to ameliorate complications after transplantation, which may involve refashioning of anastomoses. Appropriate venous access, invasive monitoring, blood products, and methods to preserve temperature should be available.

Liver dysfunction is common in recipients of multivisceral, liver-small bowel, or cluster grafts. The anesthesiologist should be aware of this possibility, and the principles of management of the liver transplant recipient as detailed earlier in this discussion apply. Recipients of isolated small bowel transplants are generally less ill than those in whom multiple organs have been transplanted.

Postoperative ventilation may be necessary because these patients are often weak and debilitated, especially if upper abdominal or thoracic surgery is performed. Indeed, a significant percentage of these patients may have undergone tracheostomy in the period after their transplant because of prolonged ventilator dependence. Hypoproteinemia increases the risk for the development of pleural effusions, and ascites, which further compromises respiration and the right hemidiaphragm, may be compromised after liver transplantation [84]. If coagu-
lopathy and infection are not active problems, epidural catheter placement for postoperative local anesthetic and opiate administration should be considered because incisional pain may prevent coughing and deep breathing, both of which are necessary to prevent and treat atelectasis. Incentive spirometry and chest physical therapy are very useful after liberation from mechanical ventilation.

These patients may have renal dysfunction resulting from repeated insults such as hypovolemia, and antibiotic and immunosuppressant therapy around the time of their transplant. Allowance should be made for a decreased glomerular filtration rate in both the choice and dosage of anesthetic and other drugs.

As with other organ transplant procedures, the presence of rejection should be sought, and elective or even urgent surgical procedures should be postponed if it is present. Graft surveillance relies on inspection of the stoma, and distal ileum and routine enteroscopy is performed. Anesthesiologists may be asked to aid with sedation for such procedures, although endoscopy through the allograft ileostomy usually requires minimal sedation. The presence of blood in the stool may indicate an anemia but more ominously indicates rejection until proven otherwise. Rejection weakens the mucosal barrier of the intestinal allograft, allowing bacterial translocation and potential systemic sepsis \[131\]. Enteritis caused by the Epstein-Barr virus may also cause systemic symptoms.

The transplanted small bowel is unique among vascularized solid-organ grafts in its ability to elicit a graft-versus-host response, probably because of the large number of lymphocytes present in the graft and their ability to translocate between the graft and the patient’s circulation. Graft-versus-host disease is manifested by skin rash, diarrhea, pancytopenia, altered mental status, and pneumonitis \[132\]. Although the disease is a theoretical possibility, its clinical impact has been less than was originally feared. Treatment is increased immunosuppression, although it may be life-threatening.

The nutritional support of patients with intestinal transplants is vital. The patient is gradually weaned from TPN while oral or enteral feedings (through a gastric or jejunal tube) are advanced. This often highly-individualized nutritional regimen may be altered by the need for incidental surgery or be an intercurrent illness. Fluid and electrolyte imbalances, which may be serious, should be noted. Consultation with the transplant team and dietitian for should be sought for perioperative advice. After small bowel transplantation, intestinal motility returns after 1 to 2 weeks, but gastric emptying may continue to be delayed for a longer period \[133\]. Rapid sequence induction with cricoid pressure is desirable because of the possibility of intestinal dysfunction and regurgitation. Pre-anesthetic laboratory investigations should include an assessment of the patient’s liver and renal functions. The increased immunosuppression necessary in this group of patients may cause an elevation of serum creatinine. If liver or renal function is impaired, appropriate allowances should be made in the anesthetic technique, as detailed in the sections on liver and renal impairment. Other considerations in this group of patients include the possibility of the presence of secretory tumors (such as carcinoid), which may have prompted transplantation in the first instance, and if this is the case, octreotide should be available \[134\].
Special considerations for hematopoietic stem cell transplant recipients

Bone marrow transplantation, or more properly, hematopoietic stem cell transplantation (HSCT), is an accepted therapeutic modality for a variety of malignant and nonmalignant diseases [135]. Between 40,000 and 50,000 patients per year receive HSCT, and the practice is increasing at a rate of 15% to 20% per year [136]. Autologous transplantation involves removing stem cells from the patient (harvesting), removing tumor cells, treating the patient with high-dose chemotherapy or total body irradiation, and then reinfecting the cells into the patient. The patient’s stem cells may be obtained by aspirating a large volume of bone marrow or, more commonly now, by removing peripheral blood stem cells after pretreatment with a granulocyte or granulocyte-macrophage colony stimulating factor. Autotransplants are associated with lower mortality, the absence of graft-versus-host disease, and faster marrow recovery. Allogeneic transplantation involves infusion of stem cells from a related or unrelated donor. The stem cells are obtained from the donor’s iliac crest bone marrow, umbilical cord blood, or from the peripheral blood.

Indications

The indications for HSCT continue to evolve, but they include leukemias and lymphomas, multiple myeloma, inherited metabolic disorders such as thalassemia and immunodeficiency syndromes, and other, experimental uses. After the initial diagnosis and induction chemotherapy, many of these patients can be treated as outpatients but may need to be hospitalized for complications of therapy or infection. HSCT is associated with substantial morbidity and mortality, and these patients may present a formidable challenge to the anesthesiologist.

Complications

Organ-specific complications may occur as a result of the disease process, chemotherapeutic agents, or infectious or immunologic sequelae. The anesthesiologist should be aware of the potential for or diagnosis of such complications. Cardiac insufficiency may be related to cyclophosphamide or anthracycline administration, mediastinal irradiation, malignant pericardial effusions and tamponade, or restrictive cardiomyopathies produced by disease processes such as amyloidosis. Such patients may need invasive monitoring for all but the most minimally invasive surgical procedures. Choices and doses of induction agents should be made in light of such patients’ poor cardiac reserve, potentially slow circulation, and the possibility of malignant arrhythmias or cardiac decompensation at any time. Pericardial tamponade or pre-tamponade physiology may be detected by clinical and echocardiographic signs and should be treated before anesthesia if possible. Sepsis with concomitant vasodilatory shock may require the administration of vasopressin, phenylephrine, dopamine, or norepinephrine.

Pulmonary complications occur in approximately half of patients who undergo HSCT. Oropharyngeal mucositis is extremely common and predisposes to both
infection and aspiration. Chemotherapeutic agents such as carmustine (1,3-bis-(2-chloroethyl)-1-nitrosourea [BCNU]), bleomycin, busulfan, and alkylating agents may cause a process of diffuse alveolar damage leading to airspace consolidation, hypoxemia, and oxygen free-radical toxicity. Diffuse bilateral pulmonary infiltrates and acute lung injury or the acute respiratory distress syndrome may be caused by drugs, cytokines from recovering marrow elements, pulmonary infection, or systemic sepsis. The causes of pulmonary infections vary from common bacterial organisms such as Streptococcus or Staphylococcus to opportunistic organisms such as Pneumocystis carinii, Nocardia, or fungi. Pulmonary edema may occur secondary to fluid overload, cardiogenic causes, and permeability edema. Diffuse alveolar hemorrhage may lead to hypoxemia and anemia and is treated, with some degree of success, by high-dose steroid administration [137]. The “idiopathic pneumonia syndrome” is a diagnosis of exclusion of multifactorial causes in recipients of HSCT. Progressive bronchiolitis obliterans may develop in patients with graft-versus-host disease and is similar to the disorder seen in patients with lung transplants [138]. Although patients who required mechanical ventilation after HSCT have tended to have a poor prognosis [139], the recent prognostic data have shown an improvement [140].

The liver may be affected by veno-occlusive disease, which is a life-threatening consequence of the pretransplant conditioning regimen [141]. Hyperbilirubinemia, elevated transaminases, thrombocytopenia, and refractoriness to platelet transfusions may be associated with veno-occlusive disease. Refractory thrombocytopenia may also be associated with platelet antibodies, which may develop in patients with hematologic malignancies. The anesthesiologist should be aware of patients with such antibodies and allow extra time (sometimes even days) to have platelets available for transfusion. Renal insufficiency is a common complication of HSCT and occurs because of drugs (anti-neoplastic agents, immunosuppressants, and antimicrobials), irradiation, hypovolemia, or sepsis [142].

Anesthesia considerations

Bone marrow transplant recipients may need anesthesia for a variety of reasons. Commonly, long-term catheters, such as Hickman or Ash-split catheters, are placed for laboratory blood draws and the administration of chemotherapy and fluids. At the author’s institution, such procedures in adults are usually performed under monitored anesthesia care using midazolam, fentanyl, and propofol sedation. Even these relatively simple cases may be complicated because of the patient’s cardiorespiratory disease. Diagnostic bone marrow biopsies and aspirates are performed under sedation in many centers.

In the pretransplant stage, most stem cells are now harvested from the peripheral blood through a large-bore central line after stimulation with hematopoietic growth factors. In certain circumstances, however, bone marrow is harvested, from either the patient (autologous transplant) or from a healthy donor (allogeneic transplant). Anesthetic management for these procedures is reviewed elsewhere in this issue.
Bronchoscopy and bronchoalveolar lavage may be necessary to investigate the cause of pulmonary infiltrates and respiratory failure. These are usually performed in the ICU if the patient is on mechanical ventilation, but the anesthesiologist may be asked to sedate such patients in the operating room or bronchoscopy suite. General anesthesia and double lumen endotracheal tube placement may be required for video-assisted thoracoscopic surgery or for investigation of pulmonary infiltrates or nodules, or for procedures related to recurrent malignant effusions. Open lung biopsy is less commonly used these days.

Neutropenic colitis is a complication occurring in the period after transplantation but before engraftment. It is usually managed by conservative measures, but colonic perforation may force the need for laparotomy. Patients tend to be very ill, will often be on pressors for shock, and may have a severe metabolic acidosis as well as multiple-organ dysfunction syndrome. Patients with respiratory failure may require sophisticated intensive care ventilatory management (inverse-ratio ventilation, high PEEP, low tidal volume ventilation \[47\]), and the operating room anesthesiologist should seek to replicate these protective strategies during surgery. An ICU ventilator may need to be brought to the operating room because conventional anesthesia ventilators may not have sufficient capability. Airway management may be more difficult in the patient after HSCT. Amyloidosis, which may be a feature of hematologic malignancies, may involve the airway and make intubation difficult. Mucositis and the bleeding tendency caused by thrombocytopenia may also serve to make any airway manipulation fraught with difficulty, and care must be taken with the placement of oro- and nasogastric tubes. The risk-benefit ratio of the use of esophageal stethoscopes must be considered.

The anesthesiologist may be asked to care for recipients of HSCT in remote locations such as the CT or MRI suite as diagnostic tests (eg, MRI of the brain looking for the cause of mental status deterioration \[143\]) or therapeutic interventions (eg, CT-guided abdominal abscess drainage) are performed.

Many children do very well after chemotherapy and HSCT, so these therapeutic modalities are frequently performed in the pediatric population. The same principles applied to adult HSCT recipients may be applied to children, but it is more likely that general anesthesia as opposed to sedation or local anesthesia will be required. Intravenous induction is usually possible because of the presence of long-term vascular access. Like other pediatric transplant recipients, these children may be medically sophisticated and their psychologic state may be a help or a hindrance to the performance of a smooth anesthesia \[144\].

**Summary**

Barring a social or economic upheaval of revolutionary proportions, organ transplantation will be performed in greater numbers in the future. Considering the prospects for liver transplantation alone, the number of patients currently infected with the hepatitis C virus in the United States is estimated at 4.9 million \[145\]. If 20% of these patients develop cirrhosis, 1 million patients may
eventually become candidates for liver transplantation [146]. From where will come the personnel, organ, and monetary resources? As more transplant recipients require routine medical and surgical care, the generalist anesthesiologist will need to become an expert in providing these needs. So that the anesthesiologist is supplied with information relevant to the care of transplant patients, residency programs and continuing education programs will need to be refocused and reorganized.

The future of solid-organ transplantation is ultimately dependent on the availability of transplantable grafts [147]. Twenty-five thousand solid-organ transplants were performed in the United States, in 2002. [1] Approximately three quarters of these grafts came from deceased donors [1]. Although the proportion of organs supplied by living donation has been increasing yearly, the numbers still pale compared with the current and anticipated demand for transplantable organs. As of December 20, 2003, there were 83,900 patients on the solid-organ candidate waiting list provided by United Network for Organ Sharing [1]. Many of these patients, especially those waiting for lung, heart, and liver grafts, will succumb if they do not receive a transplant in a timely manner. Xenotransplants and stem cells as alternative sources of replacement organs are discussed elsewhere in this issue.

Skilled and highly educated anesthesiology personnel, an abundance of transplantable tissue, and highly sophisticated immunosuppression will be for naught if society is unwilling or unable to accept the monetary burden associated with the widespread practice of organ transplantation. The cost of surgical transplantation, immunosuppression, hospitalization, ongoing clinic visits, and other requirements can amount to hundreds of thousands of dollars for a single patient. The patient who is successfully transplanted has traded an acute illness for a chronic condition that still requires financial disbursement, close monitoring, and occasional medical and surgical intervention. The anesthesiology community must be readied to respond to the current and future demands of this growing population of patients.

References


[98] Vautour LM, Melton LJ, Clarke BL, Achenbach SJ, Oberg AL, McCarthy JT. Long-


