CHAPTER 72
Liver Transplantation
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INTRODUCTION
Liver failure or end-stage liver disease (ESLD) is the fourth leading cause of death in the United States in patients 45 to 54 years of age, and 12th among all age groups (1). Liver transplantation (LT) is the only definitive cure for irreversible liver failure. The first successful transplant was performed in 1967, but it remained a difficult procedure with suboptimal outcomes until the early 1980s when patient survival rates more than doubled. Improvements in surgical and anesthetic techniques, the introduction of the University of Wisconsin solution, which extended cold preservation time, and advancements in immunosuppressive drugs have resulted in even lower graft failure rates and improved patient and graft survival rates since the early 1980s (Figs. 72.1 and 72.2). Currently, 1- and 5-year survival rates exceed 85% and 74%, respectively, according to the Scientific Registry of Transplant Recipients (2). In 2012, 6,256 liver transplants were performed and more than 65,000 liver transplant recipients were alive in the United States (Fig. 72.3). According to the Organ Procurement and Transplantation Network (OPTN) there were 15,275 patients wait listed for LT at 165 liver transplant centers in the United States as of April, 2015; only about 25% of these centers perform more than 70 transplants annually (2). It is important for intensive care unit (ICU) physicians to understand the process of LT, including preoperative assessment, organ allocation, and the postoperative ICU course as they care for patients with ESLD and acute liver failure (ALF) being considered for LT.

PRESURGICAL PROCESS, ISSUES, AND EVALUATION
Patients with decompensation of chronic liver disease or ALF are often admitted to an ICU. In some cases this may be their first contact with the transplant system and pretransplant evaluation may be initiated during their ICU stay. A multidisciplinary approach to the evaluation of these patients should include hepatology, transplant surgery, transplant anesthesia, and, if the clinical situation warrants, the expertise of nephrology, cardiology, and pulmonology.

Organ Allocation
The appropriate assignment and prioritization of solid organs remains a challenge for organizations, such as United Network for Organ Sharing (UNOS) and the American Society of Transplantation (AST), that strive to achieve optimal and fair distribution for transplantation. Since 2002, the MELD (Model for End-Stage Liver Disease) scoring system has been the method of liver allocation and its accuracy of predicting 3-month mortality on the transplant waiting list has been validated (3–5); it is calculated as shown in Table 72.1 using easily obtained serum indices: bilirubin, international standardized ratio (INR) for prothrombin time (PT), and creatinine. Any patient who is on dialysis receives an automatic 4 mg/dL for creatinine score. An exception to the MELD scoring system is made for LT candidates who present with acute fulminant liver failure without history of chronic liver disease; they receive first priority (4,5). An increasing score predicts increasing likelihood of 30-day mortality. For example, a MELD of 10 indicates a 3-month mortality rate of nearly 0% and a score of 40 approaching 90% (Fig. 72.4); UNOS has modified the system to an upper limit cap of 40 for the purpose of allocation for LT (4).

There are still subsets of patients at higher risk for mortality than predicted by their MELD score. Periodically, the system is adjusted to make allocation fair for all patients with ESLD. OPTN continuously monitors wait-list dropouts and reviews patient scores to maintain impartiality. For example, studies reveal a higher wait-list mortality rate in patients with hyponatremia compared to those with a normal serum sodium at the same MELD (6,7). The proposal to add serum sodium to the MELD score calculation was approved with an amendment by the OPTN board in June of 2014. Upon implementation by 2016, approximately 34% of candidates will have a different MELD score and will receive 1 to 13 additional MELD points depending on the serum sodium level. A survival benefit has been shown for earlier transplantation in patients with hyponatremia and a baseline MELD of at least 12 (7).

Other subsets of patients who are at higher risk of death than predicted by their MELD score include, but are not limited to, those with portopulmonary hypertension (PoPH), hepatopulmonary syndrome (HPS), hereditary hemorrhagic telangiectasias, and hepatocellular carcinoma. These patients are assigned a “MELD exception” score based on the expected mortality predictions related to the associated condition. An in-depth discussion of the conditions for which a MELD exception may be assigned and the evidence supporting these decisions is available online (8). Other patients may be considered on a case-by-case basis for exception as published by the MELD exception study group (9).

Cardiovascular Issues and Pretransplantation Evaluation
Hemodynamic Physiology
The classic hemodynamic physiology of ESLD is characterized by a hyperdynamic profile with a high cardiac output (CO) state and low systemic vascular resistance (SVR); as the liver

A calculator for the MELD score can also be found at the OPTN website: http://optn.transplant.hrsa.gov/converge/resources/MeldPeldCalculator.asp?index=98.
Liver transplantation

Essentials of the Cardiac Evaluation

In addition to a thorough history and physical examination, adult patients undergoing evaluation for LT should have an ECG, looking for findings that suggest the presence of underlying ischemic, conductive, or structural cardiac disease; if present, this should prompt further testing. Transthoracic echocardiography (TTE) is an excellent noninvasive test that to the abdominal cavity, which results in total body volume overload secondary to ascites and interstitial edema. High output cardiac failure may be present, as defined by a high CO and elevated left ventricular (LV) end-diastolic pressure. These collective processes decrease end-organ perfusion and predispose to complications such as the hepatorenal syndrome (HRS) (discussed below), peritonitis, and bacteremia due to intestinal bacterial translocation (10–12).

Cardiovascular complications are the leading cause of non-graft-related mortality and morbidity following LT in the acute transplant period and remain the number one cause of 1-year mortality (13). Therefore, an important element of the pretransplant evaluation is the assessment of the cardiovascular system. LT is a hemodynamically challenging procedure and individuals must have adequate cardiovascular reserve to tolerate the surgery.

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## Table 72.1 Model for End-Stage Liver Disease (MELD) Scoring System

<table>
<thead>
<tr>
<th>Scoring System</th>
<th>Formula</th>
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<tbody>
<tr>
<td>MELD</td>
<td>$3.78 \cdot \log_e [\text{serum bilirubin (mg/dL)}] + 11.20 \cdot \log_e [\text{INR}] + 9.57 \cdot \log_e [\text{serum creatinine (mg/dL)}] + 6.43$</td>
</tr>
</tbody>
</table>

INR: International normalized ratio.

*Use 1 for any value less than 1 to prevent scores below 0.
*If the patient has undergone dialysis twice within the previous 7 days, use 4.0 as the serum creatinine value.

should be considered in all patients under consideration for LT. Much information can be garnered from a TTE including, but not limited to, diastolic and systolic ventricular function, presence of cardiomyopathies, structural defects, valvular abnormalities, evidence of an intrapulmonary shunt on the bubble contrast study, and the presence of pulmonary artery (PA) hypertension. There are several significant cardiopulmonary conditions associated with ESLD outlined below which can be safely ruled out on a screening TTE.

**Coronary Artery Disease.** It has been reported that the prevalence of CAD in patients with ESLD approaches 30%, clearly exceeding that of the general population (14,15). This is at least in part due to the increasing age of patients receiving LT combined with comorbidities considered risk factors for CAD. In fact, the number of recipients older than 65 years has more than doubled from 2002 to 2012 (11,16). Chronic HCV infection is also independently associated with presence of metabolic conditions—insulin resistance, type 2 diabetes mellitus, and hypertension—which are established risk factors for CAD (17). Patients with nonalcoholic steatohepatitis (NASH), in particular, are more likely to be older, obese, hypertensive, diabetic, have chronic kidney disease, and have hyperlipidemia or metabolic syndrome, all risk factors for CAD, and to suffer posttransplant cardiovascular events (18,19). In fact, growing evidence suggests that NASH itself is an independent risk factor for cardiovascular disease (20). LT candidates with two or more of the following traditional cardiac risk factors (21) are more likely to have obstructive CAD (11,19,22–25):

- **Age:** male 45 or older, female 55 or older or premature menopause without estrogen replacement therapy
- **Family history of premature coronary disease:** definite myocardial infarction or sudden death before age 55 years in male first-degree relative and before age 65 in female first-degree relative
- **Current cigarette smoking**
- **Hypertension:** blood pressure over 140/90 mmHg, or an antihypertensive medication
- **HDL cholesterol below 40 mg/dL (1.03 mmol/L)**

The presence of even nonobstructive CAD has been shown to negatively impact short and long-term mortality outcomes in LT (26–31). Therefore, it is important to identify and treat patients at risk for CAD prior to LT given the risk of perioperative cardiac complications (29,32,33); in some cases the burden of CAD may be severe enough to prohibit LT.

![FIGURE 72.4 Estimated 3-month survival as a function of MELD score. (Adapted from Wiesner R, Edwards E, Freeman R, et al; The United Network for Organ Sharing Liver Disease Severity Score Committee. Model for end-stage liver disease (MELD) and allocation of donor liver. Gastroenterology. 2003;124(1):91–96.)](image)

Approximately one-fourth of LT candidates with traditional coronary risk factors may have developed clinically significant CAD even while asymptomatic. As patients with ESLD often are sedentary and encephalopathic, typical signs of myocardial ischemia may be masked. Extrapolating from currently accepted preoperative, cardiac evaluation guidelines created for the general population that place emphasis on symptomatology may not be prudent in the setting of LT (34,35).

The evaluation for the presence of inducible ischemia with noninvasive exercise or pharmacologic stress testing has limited predictive value in LT candidates (36). The inability to achieve target heart rate or adequate peak double product due to impaired adrenergic and chronotropic responses is associated with an increased risk of postoperative cardiovascular events (37). In the ICU setting, hemodynamic instability, use of vasopressors, mechanical ventilation (MV), and kidney injury make noninvasive stress testing impractical and unlikely to yield findings worthy of interpretation. The decision to pursue stress testing should be based on individualized evaluation of the candidate's pretest probability for having CAD.

Coronary angiography (CA) should be considered for LT candidates with high pretest probability of CAD (two or more traditional coronary risk factors) those who cannot undergo stress testing, have suboptimal response to pharmacologic stress testing, or who have inducible ischemia on stress imaging. CA can be performed safely in LT candidates even with renal dysfunction and elevated bleeding risk (38–40). CA via the transradial approach, if possible, is the preferred method in LT candidates, to improve hemostasis and reduce perioperative complications (41–43).

Revascularization of obstructive CAD may be pursued in order to improve symptoms and cardiovascular mortality per ACC/AHA guidelines, and in cases where the burden of obstructive CAD would prohibit LT in an otherwise appropriate surgical candidate (36,44–46). There is evidence suggesting revascularization will improve post-LT outcomes (47,48). Increases in the frequencies of CA and percutaneous coronary intervention (PCI) corresponded to significant reductions in postoperative MIs and 1-year all-cause mortality rates in LT through reductions in the incidence of both fatal and nonfatal MIs (36,49).

**Cardiomyopathy.** Cirrhotic cardiomyopathy is a physiologic syndrome unique to patients with ESLD. Despite a hyperdynamic circulation, there is both clinical and experimental evidence that liver failure itself can lead to impaired cardiac function. Cirrhotic cardiomyopathy is a syndrome of diminished chronotropic and inotropic response to stress and diastolic and/or systolic dysfunction. Diastolic dysfunction, which limits passive and active filling of the LV, is the most common clinical feature present in cirrhotic cardiomyopathy (50,51). LV systolic function is typically normal at rest, but inadequate reserve with a decreased stroke volume in response to stress is the hallmark of this entity (51–57). This impaired inotropic response, combined with the diminished capacity for a chronotropic response in patients with ESLD limits cardiac reserve during times of stress.

A common electrophysiologic abnormality associated with cirrhotic cardiomyopathy is a prolonged QT interval on ECG. A rate-corrected QT interval of greater than 440 ms has been estimated to be present in 30% to 60% of patients...
with cirrhotic cardiomyopathy (58). However, the incidence of sudden cardiac death in patients with cirrhosis who develop a prolonged QT interval does not seem to be elevated (59–61). The clinical significance of a prolonged QT interval associated with cirrhotic cardiomyopathy remains unknown, but drugs that prolong ventricular repolarization should be avoided.

There is no standard treatment for cirrhotic cardiomyopathy. Down regulation of β-adrenergic receptors and attenuation of response to chronotropic and inotropic drugs is a common feature of this entity and, therefore, β-agonists may not elicit the expected response (62–64). β-Blockers may be beneficial as they improve QTc interval prolongation and may oppose the downregulation of adrenoreceptor density. However, it is unknown if they have an effect on long-term contractile function in cirrhotic cardiomyopathy (65–68). Mineralocorticoid antagonists (aldosterone) and angiotensin-converting enzyme (ACE) inhibitors have not shown long-term benefit in cirrhotic cardiomyopathy (65,69). Fortunately, there is strong evidence that LT reverses the majority of cirrhotic cardiomyopathy (70–73). After LT, heart function parameters improve and the QT interval normalizes in the majority of patients (74). Nonetheless, immediate perioperative stresses may precipitate myocardial dysfunction in the perioperative period (75).

Cardiomyopathies are myocardial diseases presenting as structural or functional disorders of the heart. The prevalence of secondary causes of cardiomyopathy is significantly higher in LT candidates compared with the general population. Certain indications for LT, such as alcoholism, hemochromatosis, and amyloidosis, may also have both direct and indirect toxic myocardial effects. In fact, alcohol is the main cause of nonischemic, dilated cardiomyopathy in the western world (76,77). Careful pretransplant cardiac evaluation is essential and diagnosis of cardiac involvement in these disorders requires a high index of clinical suspicion and coordinated multidisciplinary evaluation for LT candidacy. Decompensated congestive heart failure can be difficult to appreciate as peripheral edema, dyspnea, orthopnea, and elevated jugular venous pressure are frequent findings of ESLD.

The presence of preoperative LV dysfunction is not an absolute contraindication to LT per se, but is a risk factor for perioperative cardiovascular complications and mortality. Most centers restrict LT to those with LV ejection fraction (EF) over 40%; there is general consensus that patients with worse function do not have the reserve to withstand the rigorous hemodynamic insults associated with LT (78). As the typical pretransplant hemodynamic profile is one of low SVR, cirrhotics are considered to be “auto-afterload reduced” and LV systolic dysfunction may be masked or under appreciated. With successful transplantation there is an abrupt increase in SVR and afterload, and patients may develop decompensated congestive heart failure. A decrease in cardiac index (CI) or CO is seen in most recipients after LT acutely, but nonsurvivors typically have lower EF prior to transplant than the survivors indicating poorer cardiac reserve (13,79–81).

### Pulmonary Issues and Pretransplantation Evaluation

There are several reasons for pulmonary disease to co-exist with liver failure. Some are related to the cause of liver failure itself, such as emphysema in α-1 antitrypsin deficiency and fibrosing alveolitis associated with primary biliary cirrhosis. Additionally, complications of portal hypertension, regardless of etiology of liver failure, can affect lung function. Ascites and hepatic hydrothorax cause physiologic restriction and decreased functional residual capacity. However, the pulmonary issues that receive the most attention include the vascular abnormalities of HPS and PoPH (82).

### Hepatopulmonary Syndrome

The term hepatopulmonary syndrome (HPS) was first used in 1977 and was preceded by autopsy descriptions of marked pulmonary vascular vasodilation correlating with clinical findings of hypoxemia. Enhanced NO production has been implicated as the key factor for the development of pulmonary vascular vasodilation leading to a ventilation–perfusion mismatch and hypoxemia. NO-synthase (NOS) activity in the endothelium and intravascular macrophages appears to be responsible for the enhanced NO production in the lungs (83). Data from multiple liver transplant centers suggest that the incidence of HPS, including mild stages, ranges from 5% to 32% (84). Even after the adjustment for severity of liver disease, the presence of HPS infers a worse survival rate with a median survival of 24 months and 5-year mortality rate of 28% without LT; for patients with severe HPS, the mortality is much worse (Table 72.2) (84–86).

Dyspnea, resting or exertional, is the primary but nonspecific symptom in HPS. Platypnea, dyspnea that increases in the upright position and improves when supine, is a somewhat more specific complaint encountered in HPS. Physical findings of clubbing, cyanosis, hypoxemia, and spider nevi are suggestive of HPS. Severe hypoxemia (PaO₂ below 60 mmHg) without another cause and orthodeoxia (a decrease in PaO₂ by >15 mmHg while breathing 100% oxygen) is suggestive of HPS. Severe hypoxemia (PaO₂ below 60 mmHg) without another cause and orthodeoxia (a decrease in PaO₂ by >15% or more with change from supine to upright position) are strongly suggestive of HPS (84).

The gold standard and most practical method in the diagnosis of HPS is contrast echocardiogram demonstrating intrapulmonary shunting. Microbubble opacification of the left atrium following three to six cardiac cycles after its appearance in the right atrium indicates passage through an abnormally dilated pulmonary vascular bed; microbubbles will not pass through normal capillaries (<8–15 μm) (84,87,88). A more invasive

### Table 72.2 Diagnostic Criteria for Hepatopulmonary Syndrome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Criterion</th>
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<tbody>
<tr>
<td>Oxygenation defect</td>
<td>Partial pressure of oxygen &lt;80 mmHg or Aa oxygen gradient ≥15 mmHg 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 (&lt;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>Aa oxygen gradient ≥15 mmHg, PaO₂ ≥80 mmHg</td>
</tr>
<tr>
<td>Moderate</td>
<td>Aa oxygen gradient ≥15 mmHg, PaO₂ ≥60 to &lt;80 mmHg</td>
</tr>
<tr>
<td>Severe</td>
<td>Aa oxygen gradient ≥15 mmHg, PaO₂ ≥50 to &lt;60 mmHg</td>
</tr>
<tr>
<td>Very severe</td>
<td>Aa oxygen gradient ≥15 mmHg, partial PaO₂ &lt;50 mmHg while the patient is breathing 100% oxygen</td>
</tr>
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Aa, alveolar–arterial; PaO₂, partial pressure of oxygen.
and less sensitive approach is a technetium-99m–labeled, microaggregated albumin lung scan with quantitative uptake in the brain (84).

LT is the only therapy for HPS and results in resolution in 85% of patients transplanted, but there remains an inability to predict reversibility (82,84,85,89). The duration of time after LT until improvement can be quite variable, ranging from a few days to 2 years. The overall 5-year survival rate of all stages of HPS following LT is 76%. The duration of time to improvement and postoperative mortality are both increased in those with severe pretransplantation HPS (84). Because of the high mortality without LT in those with HPS and a PaO₂ below 60 mmHg, LT should be considered in these patients who are otherwise adequate candidates for transplantation. A room air PaO₂ of at least 50 mmHg is the greatest predictor of posttransplant mortality; most centers choose a transplantation cut-off of a PaO₂ somewhere between 40 and 50 mmHg (84,85).

Identification of HPS on pretransplant evaluation requires a multidisciplinary approach to evaluation and management. Consultation with a pulmonologist who is familiar with the syndrome is recommended. In patients with severe HPS who are not considered to be candidates for LT, referral to palliative care is a reasonable option.

**Portopulmonary Hypertension**

PoPH is a condition involving the pulmonary circulation in cirrhotic patients with portal hypertension (90–92). The definition of PoPH consists of three essential elements:

1. Mean pulmonary arterial pressure (mPAP) greater than 25 mmHg
2. Pulmonary vascular resistance (PVR) greater than 240 dynes·sec·cm⁻²
3. Pulmonary arterial occlusion pressure (PAOP) less than or equal to 15 mmHg (93,94)

About 8% of patients on the wait list for LT have PoPH and its presence profoundly impacts survival. Patients with PoPH are candidates for a MELD exception to expedite LT (Table 72.3). A retrospective study from the Mayo Clinic composed of PoPH patients from 1994 until 2007 revealed a median survival of 15 months and a 5-year survival of 14% in those not treated with pulmonary vasodilators (95). For individuals who received pulmonary vasodilators, the median survival improved to 46 months with a 5-year survival of 45%. The perioperative mortality of LT in patients with untreated PoPH is profound. An early study by Krowka et al. (96) revealed an mPAP greater than 50 mmHg to be associated with 100% mortality, while a mPAP between 35 and 50 mmHg with a PVR above 250 dynes·sec·cm⁻² had a 50% mortality rate.

**TABLE 72.3 Criteria for MELD Exception**

<table>
<thead>
<tr>
<th>Initial abnormal mPAP and PVR</th>
<th>Documentation of pulmonary vasodilator treatment</th>
<th>Posttreatment achievement of mPAP &lt;35 mmHg and PVR &lt;400 dynes·sec·cm⁻²</th>
<th>Transpulmonary gradient (mPAP – PAOP) ≥12 mmHg to correct for volume overload</th>
</tr>
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<tbody>
<tr>
<td>MELD score of 22 if above met</td>
<td>MELD score increases by 10% every 3 mo if hemodynamic parameters are maintained by left ventricular catheterization</td>
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All potential LT recipients should be screened for PoPH, given the associated mortality; PoPH is reported present in up to 16% of patients with cirrhosis and refractory ascites, but 4% or less in those without refractory ascites (97). Mild PoPH may be asymptomatic and the symptoms associated with more severe PoPH, such as peripheral edema, ascites, and dyspnea on exertion, mimic those of ESLD and are easily overlooked or misinterpreted (94). An ECG with findings of right atrial or right ventricular (RV) enlargement or RBBB and chest radiographic findings of enlarged pulmonary arteries and cardiomegaly should raise suspicion for PoPH, but both CXR and ECG have low sensitivity for the diagnosis. TTE is an excellent screening tool, with a sensitivity of 98% and specificity of 96% when using a cutoff value for the RV systolic pressure of 40 mmHg; the diagnosis of pulmonary hypertension is confirmed by right heart catheterization (94).

In the past the presence of PoPH was considered a contraindication to LT given the profound perioperative mortality rates. Now, most centers treat these patients with pulmonary vasodilators. LT may commence if there is adequate response to treatment based on improved mPAP and RV function. This is a laborious and costly undertaking; it requires close follow-up with frequent echocardiography and/or right heart catheterization to monitor the response to treatment. The medical regimens are intense and require close attention to detail and unfailing compliance by the patient. The treatment may require an infusion pump and continuous supply of a refrigerated drug such as epoprostenol. Ideally, a pulmonologist or other expert in pulmonary vascular disorders should manage these patients. Many centers will proceed with LT if mPAP is reduced below 35 mmHg and RV function improves. Adequate RV function is likely the best predictor of operative survival, although no studies are available to support assessment (97–100). In some patients LT reverses PoPH and they are eventually weaned from the pulmonary vasodilators over a period of time. Currently, there are no means to predict who will respond and who will need continued treatment for PoPH for life (94,97).

Compliance with the pulmonary vasodilator therapy before, during, and after surgery is essential. These drugs have varying half-lives and abrupt cessation or changes in dosing can cause a precipitous decline in RV systolic function, serious systemic hypotension, and death. Close consultation with the prescribing physician may be necessary during the acute perioperative period or during any ICU stay for patients with PoPH who are on these therapies.

**Hepatorenal Syndrome**

HRS is a functional renal impairment that occurs in 11.4% of patients with liver failure within 5 years of the first episode of significant ascites (101). There are two types, both potentially reversible with LT. HRS 1 is rapidly progressive, with doubling of initial creatinine to above 2.5 mg/dL, oliguria, or 50% reduction of creatinine clearance to less than 20 mL/min occurring in less than 2 weeks. HRS 2 is associated with a more moderate, steady decline in renal function and ascites refractory to diuretics (102). Criteria for the diagnosis of HRS include the following (103):

- Cirrhosis with ascites
- Serum creatinine over 1.5 mg/dL
• No improvement in serum creatinine after 2 days of treatment with diuretics and volume expansion with albumin (1 g/kg to a maximum of 100 g/day)
• Absence of shock
• No current or recent exposure to nephrotoxic agents
• Absence of signs of parenchymal renal disease as suggested by proteinuria or hematuria or abnormal renal ultrasound results

Arterial vasodilation in the splanchic circulation caused by portal hypertension plays a primary role in the pathogenesis of HRS. As liver failure progresses, despite the increases in CO and decreased SVR, there are local increases in renal vascular resistance due to the activation of the renin–angiotensin system, followed by a further decline in renal perfusion and glomerular filtration rate (GFR) and impaired sodium and water excretion. It is important to bear in mind that the true reduction in GFR may be disguised by a relatively normal serum creatinine as muscle mass in patients with long-standing liver disease and cirrhosis is usually significantly reduced (102,104).

Without the recovery of hepatic function, the prognosis for patients with HRS is very poor overall, with an approximate survival rate of 50% in 1 month even with dialysis (102,105,106). Kidney function may recover if liver failure resolves or LT is performed. The potential for renal recovery, however, is difficult to predict and is negatively impacted the longer dialysis is needed. Deciding which patients will require a combined liver/kidney transplant remains in evolution and requires a multidisciplinary approach (107).

Patients with HRS 1 are often managed in an ICU setting as they are likely to deteriorate. In most cases diuretics should be stopped, particularly potassium-sparing diuretics. Early management may include large volume paracentesis if the abdomen is tense, followed by albumin infusion of 8 g for each liter of ascitic fluid removed. Early paracentesis may improve intrabdominal pressure and renal perfusion and allow assessment for peritonitis (79). Maintenance of euvoolema, preferably with albumin, and vasoconstrictor therapy to improve mean arterial pressure (MAP) is the mainstay of treatment (102,108). Terlipressin, a vasopressin analogue, is the treatment of choice in some countries, but is not approved in the United States or Canada (102,109–111). The efficacy of treating HRS with terlipressin versus norepinephrine appears similar, but adverse events (particularly abdominal pain, chest pain, ischemic events, and arrhythmias) are more frequently encountered with terlipressin. The cost of terlipressin is more than threefold that of norepinephrine (112,113). Norepinephrine is the vasopressor of choice in the United States for the treatment of HRS in the ICU. Oral midodrine, a selective α-1 adrenergic agonist, may be used in patients not considered critically ill. Octreotide, a somatostatin analogue, inhibits endogenous vasodilator release and increases splanchnic vasoconstriction. Octreotide, combined with a vasoconstrictor, theoretically improves renal and splanchnic hemodynamics. There is limited evidence that supports the efficacy and safety of octreotide use in combination with a vasoconstrictor for patients with HRS (114,115).

In select patients with HRS who fail to respond to medical therapy, placement of a transjugular intrahepatic portosystemic shunt (TIPS) is a possible therapeutic option (103,116). Some patients appear to benefit exhibiting improvement in creatinine clearance, reduction in serum creatinine, and increased urinary sodium excretion. Patients in the ICU may be too ill to tolerate placement of TIPS and there are complications that occur following TIPS placement, including hepatic encephalopathy, worsened hepatic function, further renal injury from the use of IV contrast agents during TIPS placement, and death. Mortality rates from HRS are still substantial following TIPS without LT or return of hepatic function (116).

Early consultation with nephrologists knowledgeable about HRS is recommended. Renal replacement therapy (RRT) is an option for appropriate patients who fail medical therapy. In the ICU continuous renal replacement therapy (CRRT) is often required due to concomitant hemodynamic instability. Patients who have the potential to recover from acute hepatic failure or those on the LT waiting list are more likely to benefit. Benefit is less clear in patients with HRS who do not have recoverable liver failure and who are not transplant candidates (102). Since recovery of liver function is the greatest hope for survival in HRS, urgent assessment for possible LT should transpire in appropriate patients. In those patients with non-recoverable liver failure who are deemed not to be candidates for LT, realistic expectations and outcomes should be communicated to the patient and family; palliative care is a reasonable approach to treatment in this situation.

**OBESITY IN LIVER TRANSPLANTATION**

Obesity is a global pandemic; patients presenting for consideration of LT are no exception. This has made NASH one of the fastest growing indications for LT. Currently, it is the third most common etiology of liver disease in patients who have had LT in the United States (2,117) and the second most common etiology of liver failure on the transplant waiting list (118). It has been predicted that NASH may exceed hepatitis C and alcohol as the most common reason for LT within the next decade (117–119). NASH is the hepatic manifestation of metabolic syndrome, which is a combination of increased abdominal girth, hypertension, hyperglycemia, and hyperlipidemia. Patients with NASH have increased risk for early postoperative and delayed morbidity and mortality, particularly cardiovascular events (18,19,117). The impact of obesity itself on mortality following LT remains uncertain; early analyses and reviews suggest that obese patients have worse survival outcomes. However, the findings of more recent single-center and multicenter reviews contradict the earlier findings (119–121). Given that obese patients are more likely to have comorbid conditions such as metabolic syndrome, obstructive sleep apnea, diabetes mellitus, and coronary artery disease, and are often less functional than nonobese candidates, it is not surprising that they appear to be at increased risk for postoperative morbidity and increased resource utilization. These are evidenced by longer ICU and hospital stays, operative times, transfusion needs, wound complications, infectious complications, cardiovascular events, and biliary complications requiring interventions (19,120,121). Hence, LT in the morbidly obese is not a trivial undertaking. But, given that patient and graft survival appear to be similar to that in nonobese patients, obesity itself should not be considered an absolute contraindication (117,121). Preoperative LT assessment of obese patients should include a thorough evaluation for cardiac, pulmonary, endocrine, and nutritional disturbances commonly associated
with obesity. Sustained weight loss through diet and exercise is the most effective strategy for NASH and a multidisciplinary approach to the pretransplantation and posttransplantation weight management should be utilized (117).

**COAGULOPATHY OF LIVER FAILURE AND TRANSFUSION**

Patients with cirrhosis have a true bleeding-clotting diathesis. Several pathophysiologic abnormalities, other than low levels of procoagulants, may promote bleeding complications in ESLD. The vascular phase of hemostasis is impaired by vasodilation and a reduced vascular constrictive response to injury. Hemodynamic alterations of portal hypertension cause vascular congestion, especially of the mesenteric vessels. This, combined with the fragility of esophageal varices, explains the proclivity of these patients to present with gastrointestinal bleeding rather than a coagulopathy. Other factors may promote bleeding, including thrombocytopenia, which is secondary to hypersplenism, bone marrow suppression, and decreased thrombopoietin production in ESLD. Fibrinolysis may be poorly regulated due to elevated levels of tissue plasminogen activator (tPA), as well as poor hepatic clearance and increased extravascular production of tPA (122–124).

Historically, it was suggested that patients with liver failure are “auto-anticoagulated.” This old dogma was based on abnormal findings of traditional tests of coagulation, such as PT, international normalized ratio (INR), platelet count, and partial thromboplastin time (PTT) suggesting risk for bleeding and poor coagulation. The emerging model of coagulation in patients with ESLD is one of “rebalanced hemostasis” (Fig. 72.5). This theory takes into account that procoagulant and anticoagulant factors are decreased in parallel, since most are manufactured by the liver (122–124). In ESLD, the INR does not accurately predict the need for transfusion or the risk of bleeding during invasive procedures (125–130). Furthermore, there is a lack of supportive evidence that transfusion with FFP for the purpose of normalizing the INR prior to an invasive procedure reduces transfusion needs and bleeding risk. In fact, it may actually increase the risk of bleeding by increasing central venous pressure (CVP) and vascular congestion (127–129,131,132,133). Blood from patients with ESLD generates as much thrombin as normal controls when an invasive procedure reduces transfusion needs and bleeding risk. In fact, it may actually increase the risk of bleeding by increasing central venous pressure (CVP) and vascular congestion (127–129,131,132,133). Blood from patients with ESLD generates as much thrombin as normal controls when methods of dynamic testing, such as thromboelastography (TEG), are used; this represents the activity of both procoagulants and anticoagulants (122,125,134–138). TEG is an accepted alternative to traditional tests of coagulation to assess coagulation and guide transfusion in ESLD, as most serum component markers of coagulation are reflected in the intricate dynamics of whole blood clotting.

Even more interesting, patients with cirrhosis have a nearly twofold increased risk for spontaneous venous thromboembolism (VTE) compared to age-matched population controls (139). There are several mechanisms that tip the hemostatic balance in favor of coagulation and thrombin generation (122,123,134–139). Important contributors include elevated levels of factor VIII and Von Willebrand factor in ESLD. Activated protein C downregulates thrombin formation, and thrombomodulin is the primary activator of protein C; levels of both are low in ESLD. ADAMTS 13, which normally limits the function of VWF on platelets, is present at lower levels than normal in ESLD. This elevated level of VWF and the greater affinity of VWF for platelets may explain why platelet adhesion to injured vascular endothelium is maintained, despite lower platelet counts. Factor VIII plays a key role in thrombin generation, and circulating levels actually increase as the severity of liver disease progresses (122–124,135). Given the tendency toward increased VTE risk, consideration should be given to the use of antithrombotic prophylaxis for patients with ESLD in the ICU.

**FULMINANT HEPATIC FAILURE**

ALF may be defined as the abrupt loss of liver function, characterized by hepatic encephalopathy and coagulopathy within 26 weeks of the onset of symptoms—classically jaundice—in a patient without previous liver disease. Although ALF frequently results in death, many will recover with supportive medical therapy. In the past 20 years, improved critical care management has substantially improved survival in ALF without LT (140). When LT for ALF transpires, the burden of neurologic and infectious complications of ALF extend into the posttransplant period, resulting in inferior survival rates compared to those of elective LT. This combination of improved survival without LT and suboptimal survival after LT makes accurate identification of those patients who will actually benefit from LT complex (141–143).

The prognosis of fulminant liver failure is determined by four key elements (144):

- **Etiology**
- **Rate of progression**
- **Age of the patient**
- **Laboratory markers of disease severity**

Since the pace of the evolution of ALF has important implications on mortality, it may be subdivided based on the jaundice-to-encephalopathy interval. With hyperacute liver failure the interval is 7 days or less; ALF has an interval of 8 to 28 days; and subacute liver failure more than 28 days. In general, patients with hyperacute liver failure have a more favorable rate of spontaneous survival without LT. This group is more likely to have acetaminophen (APAP) overdose or acute hepatitis A as the etiology of ALF, but are also more likely to have cerebral edema; in contrast, subacute liver failure patients have a worse rate of spontaneous survival. APAP overdose constitutes nearly 50% of the cases of ALF in the United States (Fig. 72.6) (140).

Infection occurs in 80% of patients with fulminant hepatic failure. The use of prophylactic antibiotics may increase the risk of fungal infections, often fatal, which occur in roughly one-third of patients with ALF. Encephalopathy inversely correlates with prognosis; Table 72.4 summarizes the four stages of encephalopathy that are seen in FHF. Cerebral edema occurs in most cases that progress to stage 4. Typical symptoms of severe cerebral edema are the Cushing reflex, decerebrate rigidity, disconjugate eye movements, and a loss of pupillary reflexes (145).

The King’s College Hospital criteria, described in 1989, were the first to differentiate between APAP-induced ALF and other causes; Table 72.5 summarizes the King’s College criteria for LT (146). The sensitivity and specificity of the King’s College criteria for LT in ALF have been evaluated in
FIGURE 72.5 Schematic presentation of the balance between procoagulant and anticoagulant factors in patients with liver disease. Both sides of the balance are functionally reduced, resulting in a more or less rebalancing of the hemostatic system in these patients, although at a lower level with smaller margins. FVIII, factor VIII; YTAI, thrombin activatable fibrinolysis inhibitor; tPA, tissue plasminogen activator; VWF, von Willebrand factor. (Adapted from Warnaar N, Lisman T, Porte R. The two tales of coagulation in liver transplantation. Curr Opin Organ Transplant. 2008;13(3):298–303.)

several meta-analysis and systematic reviews, with reported overall specificity of 82% for non-APAP etiologies and 92% to 95% for APAP-induced ALF (144,146–149). When considering whether or not to proceed with LT, reduced sensitivity leads to failure to transplant a patient with ALF who will die without LT, but reduced specificity carries the risk of unnecessary transplantation in a patient likely to recover spontaneously. In this setting, the MELD score has a high sensitivity and negative predictive value, but a low specificity. Use of the MELD score in conjunction with King’s College criteria may be beneficial to the decision-making process (144,150). One of the main components of both scores is the INR, hence unnecessary correction of the INR may affect prognostication. The use of liver biopsy for prognostication in patients
with ALF is controversial. Assessing the volume of viable hepatocytes may have prognostic value, but sampling error is a point of contention. A critical mass of at least 25% to 40% viable hepatocytes is considered to have a good prognosis. Hepatomegaly may warrant biopsy to rule out a malignant infiltrative process or consideration of alcoholic hepatitis as the etiology of ALF (151).

Intracranial hypertension (ICH) and cerebral edema are a frequent cause of death, second only to infection, both before and after LT in ALF. In patients with severe or progressive encephalopathy, empiric strategies to prevent or reduce ICH include mild respiratory alkalosis (PaCO₂ of 30–35 mmHg), elevating head of bed to at least 30 degrees, mild hypervolaemia (Na⁺ 145–155 mEq/L), and avoiding noxious stimulation. Vasopressors will often be required to treat hypotension and maintain cerebral perfusion pressure. Osmotically active agents (e.g., mannitol) have been successfully used to decrease cerebral edema. Other therapeutic maneuvers employed for severe encephalopathy and ICH have included barbiturate coma and induced hypothermia (140). The utilization of intracranial pressure (ICP) monitors to manage ICH in ALF is controversial. Institutional practices vary widely from standard practice in some to never in others. Major points of contention include significant risk of associated intracranial bleeding and lack of evidence supporting improved outcomes. The rate of fatal intracranial bleeding associated with ICP placement in this situation is approximately 3.5% (140). Despite a lack of evidence, many experts believe ICP monitors improve management and outcomes, but may also provide information as to when the process may not be recoverable. The US Acute Liver Failure Study Group has supported the use of ICP for patients

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**TABLE 72.4 Hepatic Encephalopathy in Fulminant Hepatic Failure**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Mental Status</th>
<th>EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Confusion, slow mentation and affect, slurred speech, disordered sleep</td>
<td>Normal</td>
</tr>
<tr>
<td>II</td>
<td>Accentuation of stage I, drowsy, inappropriate, loss of sphincter control</td>
<td>Slowing</td>
</tr>
<tr>
<td>III</td>
<td>Marked confusion, sleeps mostly but arousable, incoherent</td>
<td>Abnormal</td>
</tr>
<tr>
<td>IV</td>
<td>Not arousable, may or may not respond to painful stimuli</td>
<td>Abnormal</td>
</tr>
</tbody>
</table>

EEG, electroencephalograph.  
(From Sass DA, Shiff AG. Fulminant hepatic failure. Liver Transplant. 2005;11(6):594-605, with permission.)

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**TABLE 72.5 King’s College Criteria for Liver Transplantation in Fulminant Hepatic Failure**

**ACETAMINOPHEN**
- pH < 7.3 (irrespective of encephalopathy)
- All three of the following:
  - Grade III or IV encephalopathy
  - PT > 100 sec or INR > 6.5
  - Serum creatinine > 3.4 mg/dL

**ALL OTHER CAUSES**
- PT > 100 sec or INR > 6.5 (irrespective of encephalopathy)
- All three of the following:
  - Age <10 or >40 yrs
  - Cause: non-A, non-B hepatitis; halothane; idiosyncratic drug reaction; Wilson disease
  - Length of time from jaundice to encephalopathy > 7 days
  - PT > 50 sec or INR > 3.5
  - Serum bilirubin > 17.5 mg/dL

PT, prothrombin time; INR, international normalized ratio.  
with ALF, particularly in those with severe encephalopathy who will go on to LT or who have a high likelihood of spontaneous recovery (140,152).

Due to improved ICU management, the past two decades have witnessed improved outcomes of ALF with and without transplantation. There is now some doubt about the benefit of LT in patients with APAP-induced ALF, the prompt recognition of which is critical, since a specific antidote, N-acetylcysteine (NAC), effectively limits hepatocellular injury by replenishing glutathione, the putative scavenger of the reactive APAP metabolite (N-acetyl-p-benzoquinoneimine), and preventing its binding to hepatocellular proteins. King’s College Hospital treated 3,300 patients with ALF between 1973 and 2008, with overall survival rate increasing from 16.7% to 62.2%. This improvement followed the introduction of NAC and LT as treatment for APAP-induced ALF; more notably, survival without transplantation improved to 48% (144). A prospective study of 275 APAP-related ALF carried out by the US Acute Liver Failure Group included 72 patients who were placed on the waiting list for transplantation. The overall survival rate was 73%, increasing to only 78% after LT; more remarkable, over half of the patients placed on the wait list recovered without being transplanted. There was no statistically significant difference in survival after listing for transplantation based on whether or not a transplant took place (149). In both European (ELTR) and US (UNOS) transplant databases, neurologic complications account for 13% of post-transplant mortality in ALF. Both databases attribute death to infection in 18% to 24% of cases of which approximately 25% are fungal infections (141–143).

There are few more difficult decisions in critical care than the determination as to whether a patient with ALF should be listed for LT. In ALF the clinical condition can change significantly within short time intervals. The implication is that their clinical status may markedly improve or deteriorate from the time of their placement on the wait list to organ allocation, making LT irrelevant, either because they are now recovering with supportive care or too ill to proceed with LT. Defining the point when the anticipated outcome no longer justifies the utilization of the organ is difficult from an evidence-based standpoint. An outline of some indicators of when to proceed with LT including:

- Criteria of poor prognosis persist
- Absence of comorbidity independent of liver failure that precludes transplant
- Absence of complications related to liver transplant that reduce survival
- Absence of psychosocial profile suggestive of poor graft or patient survival following transplant

**Surgical Management**

As described by Starzl, the original surgical procedures were prolonged and required complete cross-clamping of the portal vein (PV) and the inferior vena cava (IVC) above and below the liver. Venovenous bypass (VVB) was introduced to combat the hemodynamic challenges and mesenteric congestion created by the interruption of the IVC and PV. However, VVB carries complications of its own including vascular and nerve injury, fatal air- or thromboembolism, hemorrhage, lymphenema, prolongation of ischemic times of the graft, hypothermia, and infections. In the late 1980s, the piggyback technique, a caval-sparing technique, with end-to-side or side-to-side caval anastomosis was introduced and is generally the procedure of choice for most primary liver transplants today (Fig. 72.7). It spares the IVC and results in improved outflow of the allograft. This technique has resulted in shortened operative and ischemic times and diminished transfusion needs (153,154). A few centers still use VVB routinely, but many feel the shortened anhepatic time of the piggyback technique and partial, rather than complete, clamping of the IVC minimizes mesenteric congestion. VVB may be used occasionally for select, high-risk cases, such as redotransplantations or transplantation for ALF.

**Anesthetic Management**

Dramatic improvements in anesthetic management have positively impacted outcomes in LT at least equal to that of surgical advancements. These changes include improvements in clinical care as well as evidenced-based administrative practices.

Massive intraoperative blood loss and transfusion requirements were nearly insurmountable prior to the last two decades. Now, bloodless LT is a reality and many transplants transpire with few or no blood products transfused. This is of paramount significance in improving LT outcomes as transfusion is linked increased complication rates, morbidity, and

**SURGICAL AND ANESTHETIC MANAGEMENT**

LT is one of the most complex surgical procedures, requiring intensive resources and multidisciplinary care. However, in the past two decades improved outcomes have reached levels that would have been inconceivable previously. This success has been achieved through enhancements of care by all involved in LT including:

- Enhanced donor management
- Improved surgical techniques
- Advances in anesthetic management
- Superior immunosuppressive medications

**TABLE 72.6 Kings College Criteria Guidelines for Urgent Liver Transplantation in Acute Liver Failure**

<table>
<thead>
<tr>
<th>PROCEED</th>
<th>WAIT</th>
<th>STOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria of poor prognosis persist</td>
<td>Evidence of sustained clinical improvement suggesting favorable prognosis without transplant</td>
<td>Evidence of compromised brain stem function</td>
</tr>
<tr>
<td>Absence of comorbidity independent of liver failure that precludes transplant</td>
<td>Acetaminophen-induced acute liver failure without grade III-IV encephalopathy regardless of coagulopathy</td>
<td>Invasive fungal infection</td>
</tr>
<tr>
<td>Absence of complications related to liver transplant that reduce survival</td>
<td>Acetaminophen-induced acute liver failure with severe lactic acidosis that responds rapidly to resuscitative measures</td>
<td>Rapidly escalating vasopressor and inotrope requirements</td>
</tr>
<tr>
<td>Absence of psychosocial profile suggestive of poor graft</td>
<td>Allocated liver is septic from an advanced age donor, non-ABO compatible or otherwise marginal</td>
<td>Severe pancreatitis</td>
</tr>
</tbody>
</table>

mortality (155,156). Several anesthetic practices have been credited in the reduction of transfusion needs. Lower CVP and fluid restriction during hepatic dissection reduces hepatic and vascular congestion and, consequently, bleeding (157). In addition, avoiding excess intravenous fluid also prevents dilutional coagulopathy and hypothermia, and results in a less edematous allograft with improved function. Using vasoressors to maintain adequate MAP rather than fluids is now standard management in LT. Normovolemic hemodilution, another method utilized to decrease both bleeding and allogeneic transfusion needs in patients with adequate hematocrit, is used successfully in donor hepatectomies for live donor LT to prevent unnecessary transfusions in this otherwise healthy population (158). Anesthesiologists are vigilant in preventing and treating hypothermia and correcting hypocalcemia to further minimize intraoperative bleeding (159,160).

Understanding the rebalanced hemostasis of ESLD and avoiding “prophylactic” transfusion with FFP, platelets and cryoprecipitate to unnecessarily correct abnormal tests of coagulation is key. Transfusion begets more transfusion, due at least in part to increased CVP, splanchnic congestion, and increased serum citrate concentration (124,129). Accepting lower transfusion thresholds, using point of care testing, such as TEG, and accepting lower transfusion thresholds, using point of care testing, such as TEG, and serum citrate concentration (124,129). Accepting lower transfusion thresholds, using point of care testing, such as TEG, and clinical assessment of hemostasis on the surgical field to guide transfusion should have become standard of care in LT.

Antifibrinolytic drugs have been used successfully to improve hemostasis in LT in the past, but controversy surrounds this practice, given the risk of thrombosis. Although there is no conclusive evidence to link the use of antifibrinolytics to thrombosis in LT, when thrombosis occurs it is associated with a high mortality rate (161). Logic dictates empiric use be avoided when there is a history of VTE, evidence of hypercoagulability on tests such as TEG or the patient has a condition with a predisposition to thrombosis such as cancer or primary biliary cirrhosis. Use on demand when there is excess bleeding and evidence of thrombolyis by TEG may be a more acceptable approach.

Mannitol is often administered just prior to, or during, the anhepatic stage of the procedure to increase CVP and improve hemodynamic tolerance during IVC clamp. Its oxygen radical scavenging properties may protect the allograft and the kidney from ischemia–reperfusion injury, and its osmotic effects have the added benefit of preventing or reducing mesenteric edema, unlike crystalloid solutions. Furthermore, mannitol appears to temper postreperfusion syndrome, the marked hemodynamic instability that occurs immediately after initial perfusion of the new allograft (162).

The marked intraoperative circulatory challenges require a comprehensive evaluation of preload, afterload, and cardiac function by the anesthesiologist. At a minimum, this includes standard American Society of Anesthesiology (ASA) monitors, an arterial catheter for invasive blood pressure monitoring, and a large-bore central venous catheter for CVP monitoring. The latter also allows optimal access for volume resuscitation and vasopressors. The use of PA catheters for LT has been largely replaced by transesophageal echocardiography (TEE) in many transplant centers; risk of hemorrhage from variceal injury during placement is minimal. TEE allows for direct visualization and assessment of preload, volume status, and cardiac contractility. It offers the added benefit of rapid diagnosis of intracardiac thrombosis which is an uncommon, but often catastrophic, event unique to LT. Air embolism, tension pneumothorax, and large pericardial effusions or tamponade can also be detected immediately (163). As absolute values cannot be calculated with TEE, one indication for PA catheters may be PoPH; the PA pressure measurement often drives management decisions in this scenario. More over, TEE allows visual assessment of function of the right ventricle (RV) which is crucial, not only in PoPH, but during massive transfusion. Pressure and volume overload of the RV can lead to overstretching of the ventricle and ischemia; using TEE to guide preload and volume may prevent RV failure in this instance.

Traditionally, patients who had LT remained intubated after surgery for 1 or 2 days or longer. This practice was founded in the belief that remaining intubated reduced physiologic stress. In the last decade, there has been a movement toward early, or “fast-track” extubation. Patients are now extubated immediately in the operating suite or within a few hours of ICU admission if they meet criteria, such as adequate oxygenation, adequate mental status, and hemodynamic stability. This practice has shortened ICU and hospital stays (164). While “fast-tracking” facilitates decreased cost and resource utilization, it may also help to prevent complications, such as nosocomial infections and others associated with longer ICU stays and hospitalizations.

In 2008, Hevesi et al. (165) reported on the benefits of a dedicated liver transplant anesthesia team at the University of Wisconsin. This team included a small, core group of anesthesiologists who provided anesthesia for all LT and a director who worked closely with the transplant surgery department in many of the administrative and clinical duties associated with LT. This was the first such description of a collaboration between two disciplines that substantially improved outcomes (165). Prior to this, there was enormous institutional variation in practices and resource utilization. The core team of anesthesiologists employed consistent clinical practices that resulted in less transfusion, decreased MV time, and shorter ICU stays. The director also became intimately involved in the preoperative evaluation to insure selection of recipients able to tolerate LT, which is tantamount to appropriate organ allocation. This approach to care yielded improved communication and
professional partnership between the surgeons and anesthesiologists. Although an unmeasurable element, this type of collaboration and satisfaction likely leads to improved quality of care. The success of this program led the ASA and UNOS to adopt this model as the standard for institutions that provide LT.

**POSTOPERATIVE ICU MANAGEMENT**

Physiologic perturbations of the preoperative and intraoperative periods accompany the patient into the acute postoperative phase. In most cases, the patient will be admitted to the ICU following LT for continued resuscitation, ongoing transfusion and hemostasis, support of organ systems, and close monitoring of the graft function. The approach to the postoperative care of the liver transplant patient should include coordination between the intensivists, transplant surgeons, and hepatologists, along with other subspecialty management as necessary.

**Cardiovascular Management**

Hypotension and hemodynamic instability in the immediate posttransplant phase have multiple causes, including surgical bleeding, underresuscitation, baseline infiltrative disease, ischemic cardiomyopathy, new dilated cardiomyopathy, bleeding due to coagulopathy, abdominal hypertension, heart failure, dysrhythmias, infection, inflammatory response, electrolyte and acid/base derangements, and graft failure, to name some (166). The patient will usually arrive to the ICU following LT for continued resuscitation, ongoing transfusion and hemostasis, support of organ systems, and close monitoring of the graft function. Fluid and protein shifts in the allograft are less when the sinusoids. Extravasation of fluid also increases abdominal congestion of the graft, mesentery and abdominal hypertension. Crystalloids in the early posttransplant period rapidly exit the intravascular space causing edema and congestion of the sinusoïds. Extravasation of fluid also increases abdominal compartment pressure further compromising allograft perfusion. Fluid and protein shifts in the allograft are less when

outcome and graft function, not to mention failing to treat the true problem. For example, volume resuscitation in a nonfluid responsive state can cause pulmonary edema and vascular congestion of the graft, mesentery and abdominal hypertension, which will worsen allograft function. Alternatively, treatment of hypotension with vasopressors in a nonvasodilatory state may worsen graft perfusion due to splanchnic vasoconstriction. In the case of a failing left ventricle (LV) increasing SVR will further compromise CO. Therefore, it is crucial for patient and graft survival to methodically assess hypotension for cardiac, hypovolemic, and distributive causes.

**Volume Resuscitation, Electrolyte, and Acid–Base Management**

Hypovolemia in the immediate postoperative phase of LT is commonly encountered. Ongoing bleeding, either surgical or coagulopathic, continued production of ascites, fluid shifts, and inadequate intraoperative resuscitation are a few of the causes. Treatment of hypovolemia is necessary to maintain adequate perfusion of the allograft. In a stable situation compensatory responses will allow for a 25% to 30% loss of blood volume without a decrease in systemic blood pressure, but the splanchnic vasculature and, therefore, the liver are compromised by a 10% reduction (167). It is imperative that close observation of hematocrit and tests of coagulation accompany hemodynamic monitoring in the first 48 to 72 hours after LT. The goal of volume resuscitation is euvolemia, while avoiding excess volume administration leading to elevated CVP, portal hypertension, and hepatic and pulmonary edema.

Several options are available for the treatment of hypovolemia. Crystalloids are cost-effective, readily available, and do not carry the risks of blood product transfusion. Conventional wisdom and evidence support minimizing transfusion; however, the newly transplanted liver patient presents different challenges and is not represented well in standard transfusion practice guidelines. Vascular barrier permeability in the allograft has been compromised by ischemia–reperfusion injury. Crystalloids in the early posttransplant period rapidly exit the intravascular space causing edema and congestion of the sinusoïds. Extravasation of fluid also increases abdominal compartment pressure further compromising allograft perfusion. Fluid and protein shifts in the allograft are less when

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using blood products, as opposed to crystalloids, for volume expansion (168). Colloids may be considered during attempts at fluid resuscitation as they have a more sustained effect than crystalloids, but the effects are still transient and colloids are also prone to causing edema of the graft (169). Given that hypovolemia is frequently due to bleeding from coagulopathy, blood products have the added benefit of correcting these, whereas, crystalloids may worsen coagulopathy by dilution. Colloid starch solutions are best used judiciously, if at all, during this phase of care given the inherent risks associated with them. It is important to prevent and treat hypothermia during volume resuscitation as it will worsen coagulopathy. Active warming of the patient, blood products, and fluids along with the room are measures that can be utilized for this purpose.

Abnormal levels of all electrolytes are commonly encountered after LT. Sodium, potassium, calcium, phosphorous, and magnesium should be monitored closely and corrected judiciously. It is reasonable to follow these serum values three or four times a day in the first 48 to 72 hours. Hypocalcemia is a frequent occurrence. To prevent clots, citrate is often used in CRRT systems and blood banking. Between the amount of citrate administered during CRRT and that from blood products, hypocalcemia may develop with resultant hypotension; serum ionized calcium should be monitored closely and replaced accordingly.

Hypokalemia occurs in many LT recipients and represents another cause for caution when considering crystalloid administration after LT given the risk of central pontine myelinolysis (CPM), discussed in further detail below. Normal saline is hyponatremic to serum and may raise sodium levels inappropriately in patients with hyponatremia. Albumin also contains sodium and caution is advised with infusion of it as well (170,171).

Metabolic acidosis is frequently encountered in the LT perioperative period. It is important to treat the underlying cause of the acidosis. The new graft may have reduced ability to metabolize lactate, particularly in times of increased production. Poor tissue oxygenation and perfusion due to hypotension, poor CO, hypovolemia and severe anemia, complications of infection, and intestinal ischemia are common causes of lactate production. Acute kidney injury (AKI) and chronic renal failure cause further metabolic acidosis. During volume resuscitation excessive use of normal saline solutions should be avoided as this may lead to worsened acidosis due to hyperchloremia. Severe metabolic acidosis may be encountered in delayed or poor graft function. It is important to optimize hemodynamic parameters and minute ventilation in the face of metabolic acidosis. Severe metabolic acidosis may require sodium bicarbonate or tromethamine (THAM) administration. Correction of severe metabolic acidosis may be faster and safer with the use of CRRT compared to sodium bicarbonate or THAM infusions (172).

Attempting to maintain euvolemia in patients with ESLD particularly acutely after liver transplant leads into a discussion of diuretic administration. Despite the fact that total-body volume overload is usually present, intravascular volume depletion is the norm. The use of diuretics in the acute posttransplant period is inadvisable if there are ongoing fluid shifts from intra- to extravascular spaces, hemodynamic instability, ongoing transfusion, or vaspressor needs as it may worsen intravascular volume depletion and organ perfusion. Diuretics may be administered cautiously in the case of significant intravascular volume overload in a patient who is otherwise hemodynamically stable. If diuresis is considered necessary, the concomitant use of diuretics or CRRT and transfusion or colloid infusion can improve preload and splanchnic perfusion while minimizing allograft edema.

**Cardiogenic Shock**

The incidence of new heart failure following LT has been reported in several series to be between 7% and 31% (80). In the posttransplant setting, findings of hypotension and poor end-organ perfusion should prompt an assessment of cardiac function. As discussed previously, cirrhotic physiology is one of an “auto-afterload” reduced state. Abrupt increases in SVR following transplantation, the surgical stresses, and myocardial ischemia can lead to depressed systolic function or unmask previously unrecognized myocardial dysfunction. This is usually a temporary or reversible state, but if severe heart failure occurs within the first 12 hours of LT, death and multiorgan failure have been described (173). Bedside echocardiography is a valuable, noninvasive tool in establishing the diagnosis of myocardial dysfunction. A PA catheter may also be useful if parameters suggesting cardiac failure are present. A mixed venous oxygen saturation below 60% is also indicative of a poor CO. Inotropes, adequate preload, and lowered afterload are the mainstay of care for a failing LV. Cardiology assistance in the management of these patients is frequently necessary and valuable.

Hemodynamic instability in the perioperative period is a complex issue in patients with PoPH. Right heart failure can lead to cardiogenic shock and inotropic agents should be considered the mainstay of therapy. Lowering of the PVR with inhaled NO or prostacyclins to achieve afterload reduction of the RV may also be beneficial. Perioperatively, close attention to fluid management is critical. It is essential to optimize preload while avoiding volume overload and RV wall stress (98,99,173). Some patients will have been prescribed pulmonary vasodilators prior to LT and these should be continued perioperatively without fail. TEE or TTE and PA catheters may be useful in guiding intraoperative and postoperative LT management in patients with PoPH.

**Vasodilatory Hypotension**

Vasodilation and vasopressor responsive hypotension are also encountered after LT and have multiple etiologies in this setting. Hypocalcemia, infections/sepsis, and inflammatory responses are common causes of vasodilation and hypotension following LT. Adrenal crisis is an unlikely cause as patients receive large doses of corticosteroids as part of their immunosuppression induction. The mainstay of treatment for distributive shock is vasopressor administration. Vasodilation creates a relative increase in vascular capacity, so attention should be given to achieving normovolemia as well. The persistence of the cirrhotic physiology, high CO and low SVR, into the postoperative period may be a concerning indicator of a poorly functioning allograft or primary nonfunction (PNF). Graft-versus-host disease (GvHD) is an unusual cause of hypotension in the immediate, posttransplant ICU setting. GvHD occurs in only about 1% of liver transplants and presents 1 to 6 weeks after LT. Rarely, it may present in a fulminant fashion that mimics septic shock with fever, abdominal pain, hypotension, and multiorgan failure. Cytopenia may accompany the most severe cases and severe neutropenia is an indicator of poor prognosis. Treatment is high-dose corticosteroids with modifications or decrease in other immunosuppressive medication dosages.
If suspected, the transplant team should be consulted to assist with management of the immunosuppression regimen. Short tandem repeat (STR) levels of over 20% for CD3+ donor lymphocytes in the peripheral blood is confirmatory. Skin biopsy, if a rash is present, or intestinal biopsy may also aid in the diagnosis. Risk factors include a discrepancy between the age of the donor and the recipient. Younger donors have a greater number of lymphocytes in the liver. Older recipients (>65 years) are less able to reject the donor lymphocytes. The risk of severe GvHD increases when the age difference is over 40 years (174).

Certain drugs received in the peritransplant period may also cause vasodilation and refractory hypotension. Antithymocyte globulin (ATG) is an immunosuppressive agent that is more often used in kidney transplant recipients, but is used occasionally in liver transplant recipients considered at high risk for rejection. ATG is known to cause a systemic response that mimics septic shock due to cytokine release syndrome (CRS). This syndrome is particularly likely to occur when infusions are administered too rapidly. Fever, chills, hypotension, shock, pulmonary edema, or even death may occur from CRS in patients receiving ATG. Patients receiving ATG should be monitored closely during infusions.

**General Postoperative ICU Care**

**Mechanical Ventilation and Extubation**

Traditionally, patients remained intubated and on MV in the ICU following LT, often for over 48 hours. Although there is variability in practice among centers, early extubation or “fast tracking” has increased over the past decade. Many patients are now extubated safely in the OR immediately following LT, or within hours of admission to the ICU. This practice has been associated with decreased cost and ICU length of stay. It has also been suggested that avoiding the positive pressure of MV has beneficial effects on splanchnic and liver perfusion (164,175). For many reasons, this practice is not feasible in all patients. Hemodynamic instability, ongoing bleeding, a complicated or prolonged intraoperative course, massive transfusion, pulmonary edema, need for repeat laparotomies, and nonfunction of the allograft are some of the circumstances leading to a need for continued MV. Patient-specific factors limiting early extubation include obesity, pretransplant encephalopathy, prolonged hospitalization, prolonged ICU stay, severe malnutrition, hydrothorax, underlying lung disease, and severe deconditioning. HPS or PoPH may also delay liberation from MV. Patient selection is key to the success of early extubation.

Management of MV in this population is no different from others in the ICU. While patients are ventilated, standards of care for stress ulcer prophylaxis with either an H2-blocker or proton pump inhibitor therapy should be maintained. Strategies to prevent ventilator-associated pneumonia should be adhered to, including keeping the head of bed elevated to at least 30 degrees, oropharyngeal decontamination with chlorhexidine, secretion management, and high-volume, low-pressure endotracheal tube cuffs. Daily sedation holidays and spontaneous breathing trials should be practiced in this population. Use of PAD bundles (pain, agitation, and delirium protocols) to direct sedation and analgesia have been shown to be effective in decreasing time on MV when paired with daily sedation holidays. It may be prudent to limit the use of benzodiazepines, particularly long-acting formulations, as hepatic clearance may be limited in liver transplant recipients. Early mobility and early enteral nutrition have also been associated with decreased complications, improved outcomes, and decreased time to extubation and ICU days (176,177).

A central concern is the development of acute respiratory distress syndrome (ARDS) following LT. Inflammatory responses related to the surgery, massive transfusion, organ failure, and infections are all risks for ARDS. Fundamental MV management requires lung-protective ventilatory strategies for all liver recipients, given this concern and, particularly, in patients exhibiting hypoxia or evidence of ARDS. In severe cases of refractory hypoxemia, rescue strategies include prone positioning, inhaled NO, inhaled prostaglandin, or extracorporeal membrane oxygenation. There is an overall lack of evidence that these maneuvers will improve survival, but there are supportive case reports (177,178).

Successful weaning and freedom from the ventilator may take hours to weeks depending on the clinical situation as outlined above. Parameters for extubation are no different for LT recipients than other ICU patients. In general, the patient should be oxygenating adequately on lower levels (<50%–60%) of inspired oxygen, hemodynamically stable, have adequate mental status, ability to manage secretions and airway, satisfactory cough and gag reflex, and adequate capacity to meet their minute ventilation requirements (166,177). Furthering their chance of successful extubation, their overall clinical status should be one of steady improvement without evidence of impending or ongoing deterioration such as new bleeding, untreated or refractory infection, and worsening AKI.

**Glycemic Management**

Because of the presence of cirrhosis-induced insulin resistance, the increase in stress hormones during surgery, and the use of high-dose steroids, patients may become quite hyperglycemic even if there were no glucose control issues prior to surgery (179). Hyperglycemia is a marker of poorer outcomes in LT. It has been related to sepsis, poor wound healing, and wound infection and suboptimal graft function (166). Hyperglycemia in the perioperative period can enhance ischemia–reperfusion injury and certain inflammatory mediators, leading to increased risk of rejection and poorer graft function (180). The ideal management of glucose in the ICU is a matter of debate; hyperglycemia has many negative consequences, but tight glucose control was associated with increased mortality in the NICE-SUGAR trial (181). A rational plan may be to avoid hypoglycemia with a glucose goal of 100 to 150 mg/dL. This will require frequent glucose measurements and, often, an insulin infusion while in the ICU. Hypoglycemia may be encountered when poor graft function occurs following transplant and may require treatment with glucose-containing solutions and enhanced glucose monitoring.

**Nutrition**

Early initiation of enteral nutrition is an important part of ICU care, perhaps more so in LT recipients. Early enteral nutrition in critically ill patients appears to lower mortality and infection. Nutrition plays an important role in recovery following LT, as the stresses of LT result in a catabolic state. Many patients presenting for LT have nutritional deficiencies at baseline, so early intervention is even more crucial. The ability to achieve adequate oral intake may be impacted by prolonged MV, encephalopathy, prolonged ileus, or poor appetite. Early consideration should be given to placement of an enteral feeding tube for nutritional purposes in select patients (180).
In such patients this will have the added benefit of allowing enteral access for medications, reducing the need for intravenous catheters and, therefore, catheter-related septicemia.

ACUTE POSTTRANSPLANT COMPLICATIONS

Acute Kidney Injury

AKI is an all too common phenomenon following LT, with estimates of 20% to 80%, frequently presenting within the first 48 hours post transplant. AKI after LT requiring RRT impacts mortality negatively, with early reports of 30-day mortality at 40% to 50% (182). As defined by the Acute Kidney Injury Network (AKIN), AKI is an abrupt (within 48 hours) reduction in kidney function presenting with an absolute increase in serum creatinine of at least 0.3 mg/dL (26.4 mmol/L), a percentage increase in serum creatinine of 50% or higher (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 mL/kg/hr for more than 6 hours) (183). Severe chronic kidney disease will develop in approximately 4% of LT recipients who survive 1 year and with at least half requiring RRT (184). Predictors of posttransplant AKI include pretransplant renal dysfunction, diabetes mellitus, allograft dysfunction or PNF, intraoperative hypotension, intraoperative prolonged caval and PV cross clamp, massive transfusion, abdominal hypertension, sepsis, exposure to intravenous contrast, and acute cardiogenic shock. Hemolytic uremic syndrome (HUS) has also been described acutely in the posttransplant recipient in the ICU, triggered by calcineurin inhibitors (CNIs).

Early recognition of AKI is crucial to prevent further injury and initiate treatment. The most common etiology of post-LT AKI is acute tubular necrosis (ATN). The cause is usually multifactorial due to any combination of the previously described risk factors. Initial treatment should include optimization of volume status, CO, and renal perfusion. Abdominal hypertension that compromises renal perfusion may require paracentesis or laparotomy for decompression. Avoidance of nephrotoxins and contrast dye is principal to the recovery of AKI. Consultation with transplant surgery or hepatology regarding immunosuppression management and adjustment of dosages is essential. Early consultation with nephrology for assistance in evaluation and management is vital to care, as well. Loop diuretics may be administered in an effort to stimulate urine output, but if the patient does not respond and renal failure progresses these should be discontinued to avoid further renal injury. RRT will be required when severe oliguria or anuria, volume overload, severe uremia, electrolyte derangements, or acidosis is present. Intermittent hemodialysis may be adequate for patients who are hemodynamically stable. CRRT, such as continuous venovenous hemodialysis, is more appropriate for patients with hemodynamic instability who cannot tolerate intermittent hemodialysis (166,180). Patients who required RRT pretransplant for AKI or HRS will most likely continue to require treatment posttransplant for an indefinite period while awaiting the return of renal function. In patients who have not been maintained on RRT for a prolonged period, most will undergo liver-only transplantation in hopes of reversal of AKI, but the degree is unpredictable. In time, if kidney failure persists then consideration may be given to kidney transplantation. In patients who have been on RRT for a longer period of time prior to LT, the likelihood of reversal is diminished and consideration may be given to a combined liver–kidney transplant. However, there is not an accurate model to predict recovery of pretransplant HRS or AKI following LT (102,104,105,107).

Infection

Infection is one of the most common causes of shock and mortality and morbidity in LT recipients, despite advances in techniques and antimicrobial prophylaxis. Infectious complications are more common in LT recipients than in any other organ recipient, and mortality from infection is currently below 10%, significantly lower than in earlier days of LT when it approached 50% to 60% (185). Infections are most common in the first 6 months, but may occur at any time following LT. Discussion here will be limited to infections in the acute, posttransplant period.

Risk factors for posttransplant infections start in the pretransplant phase. Fulminant hepatic failure, renal failure, ICU status, MV, high MELD score, pre-existing infections, diabetes mellitus, and malnutrition are all risk factors for infection following transplant. Latent infections, such as cytomegalovirus and tuberculosis, may reactivate in the face of induction immunosuppression following LT. Surgical and intraoperative events that increase the likelihood of infection include prolonged surgical time, massive transfusion, disruption of the gastrointestinal tract, vascular complications that lead to tissue necrosis, and repeat laparotomy; rarely, infections may be acquired from the donor liver. Retransplantation, prolonged ICU stay, protracted MV, renal failure, CRRT, antimicrobial pressure, vascular catheters, colonization with resistant flora, and immunosuppression after LT further increase the likelihood of infection in the recipient (185–187).

The locale of the infection, such as central line–associated bloodstream infection (CLA-BSI), pneumonia, intra-abdominal wound or urinary tract infection, may be predictive of the microorganisms that are isolated. Intra-abdominal infections are frequently polymicrobial and may include fungi. In the early posttransplant period (<1 month) most infections are bacterial, followed by fungal. Common bacterial pathogens in this setting include methicillin-sensitive and methicillin-resistant Staphylococcus aureus (respectively, MSSA, and MRSA), coagulase-negative staphylococci, Enterococcus faecalis, Enterobacteriaceae, and Pseudomonas aeruginosa. The occurrence of bacteremia from gram-positive organisms and gram-negative bacilli in the early transplant period is nearly equal, with a slight predisposition toward gram-positive pathogens (185,186). Vancomycin-resistant enterococci (VRE) infections and colonization are on the rise in liver transplant patients; invasive infections carry a poor prognosis in this population with mortality reported to be 60% to 80%. VRE is more commonly seen in patients with prolonged hospital and ICU stays, renal failure, repeat laparotomies, intensive antimicrobial pressure, and the presence of other infections (188).

Fungal infections occur in approximately 10% of LT recipients; indeed, liver recipients have the highest incidence of fungal infection of all organ recipients. Ninety percent of all invasive fungal infections occur in the first 2 months after transplant, with most being a Candida species. Aspergillus is the second most common fungal infection, compromising about 10% to 20% of fungal infections; unfortunately, invasive Aspergillus infections are frequently fatal, and Aspergillus
Infections of the central nervous system are nearly universally fatal (185,186,189,190).

Viral infections are much less common in the acute posttransplant phase, although herpes simplex virus (HSV) may be encountered occasionally, despite prophylaxis. HSV infection most commonly presents as a mucosal infection, involving the oropharynx or esophagus, but hepatitis, encephalitis, or disseminated herpes are reported as well (191).

When sepsis is suspected adequate empirical therapy should be instituted, with haste, guided by suspected site of infection, probable flora, prior pathogens isolated, institutional microorganism susceptibility patterns, and the presence of renal insufficiency. A thorough examination is necessary along with cultures of the blood, lower respiratory tract, and urine to identify the source of the infection. The need for other studies, such as computed tomography of the abdomen or examination of the cerebrospinal fluid or ascites, are indicated based on the differential diagnosis garnered from the initial assessment. Once the source and organisms have been identified, then specific therapy can begin. Source control is vital in cases that require evacuation or surgical debridement of a discrete infectious collection. Removal of infected catheters and devices are necessary to abolish the infection. Infections in LT patients have become increasingly complex with complicated resistance patterns. Assistance from an infectious disease consultant, particularly one experienced in the care of transplant recipients and knowledgeable regarding institutional patterns, is instrumental in delivering appropriate antimicrobial regimens, both empiric and specific.

Neurologic Complications

Neurologic complications occur in about 25% of LT recipients, with CPM a particularly serious and dreaded neurologic complication. Fortunately the incidence is below 1% following LT despite the frequent presence of hyponatremia in ESLD; when it does occur, however, CPM can be devastating (192). Symptoms include paralysis, depressed consciousness, dysarthria, and dysphagia; pre-existing hepatic encephalopathy may mask symptoms of CPM acutely. Care is supportive and primarily preventative by avoiding rapid changes in serum sodium in patients with hyponatremia. Reality dictates that this can be extremely difficult during periods of rapid fluid and blood losses, such as during the transplant surgery. There is not a definitive serum sodium level that is a contraindication to LT. However, levels below 125 mEq/L are associated with an increased risk of CPM (192). Correction of severe or symptomatic hyponatremia in the ICU should occur slowly with close monitoring. A universally accepted, established rate of correction which insures prevention of CPM does not exist, but many experts consider an increase of less than 12 mEq/L/day (0.5 mEq/L/hr) to be a reasonably safe therapeutic goal. Diagnosis of CPM is made when magnetic resonance imaging of the head shows areas of T2 signal intensity in the pons in conjunction with clinical suspicion; there are no therapies to reverse the syndrome (180,192).

Encephalopathy is a frequent complication of cirrhosis and will often persist into the posttransplant phase. Although transplant usually improves encephalopathy, poor graft function will delay resolution. Medications such as benzodiazepines and narcotics may have impaired metabolism and complicate, or prolong, encephalopathy as well. Uremia and persistent hyperbilirubinemia may also worsen or delay recovery of encephalopathy. Care is supportive with close attention to neurologic examination, correction of metabolic disturbances, such as uremia, and avoidance of drugs that will further suppress consciousness (180).

CNIs are associated with several neurologic complications. Posterior reversible encephalopathy syndrome (PRES) is one such complication. PRES may present as altered mentation or coma. PRES is more likely to occur when CNIs are administered to patients with more severe, pre-existing encephalopathy; blood–brain barrier defects are present and increase the susceptibility to PRES when CNIs are administered (193,194).

Seizures are another adverse effect of CNIs. Seizures may also result from infection, hyponatremia, alkalosis, substance withdrawal, and cerebrovascular accidents. In addition to determining the cause of the seizure, all potential neurotoxic substances should be withheld. Basic care includes airway protection, ventilation, reversal of electrolyte and metabolic derangements, and antiepileptic medications. Acutely, benzodiazepines may be required for refractory or recurrent seizures; levetiracetam is usually the drug of choice for suppression of seizures. Imaging studies or sampling of the CSF may be warranted to determine the cause of the seizures. Electroencephalography (EEG) may be necessary to assess for the presence of subclinical seizures or a seizure focus (180,194).

Cerebrovascular complications or strokes are uncommonly reported following LT but, when they occur, are associated with significant morbidity and mortality. Several recent investigations of LT cohorts report incidence rates for stroke within the first 30 days of LT ranging from 0.6% to 4% (193–196). Perioperative stroke in LT is associated with an in-hospital mortality of up to 10%. More compelling is of the remaining survivors, 33% will die within a year and less than 50% will make full recovery and gain independence; more than half are institutionalized (194).

Perioperative hemorrhagic strokes appear to be more common than ischemic strokes in LT, compared with other types of surgery (196). Global hyperperfusion of the central nervous system occurs in LT during periods of sustained blood and fluid loss, hyponatremia, and anemia. Patients with ESLD are known to have abnormalities in cerebral perfusion and cerebral edema, which may increase the risk of injury from central nervous system hyperperfusion and, thereby, intracranial hemorrhage. The presence of a patent foramen ovale (PFO) may theoretically increase the risk of paradoxical embolic stroke due to events inherent in LT, particularly following reperfusion of the new liver graft (193,194,196).

When cerebrovascular accidents occur in the setting of LT, treatment is generally supportive. Correction of coagulopathy is important in hemorrhagic CVAs. Adequate airway protection and ventilation should be established along with optimization of the blood pressure and CO to ensure adequate cerebral perfusion while avoiding increase of the ICP. Craniotomy for management of intracranial hemorrhage in this population has been reported to be universally futile (197).

Graft-Related Complications

Primary Nonfunction and Delayed Function

Some degree of allograft dysfunction immediately following transplantation is not uncommon, but resolution is expected, given the regenerative capacity of the liver. Some patients, however, may develop graft failure or PNF. Although no formal
Vascular Occlusions

The most common occlusive vascular complications following LT involve the hepatic artery. Hepatic artery thrombosis (HAT) is reported in 4% to 15% of transplantations and hepatic artery stenosis in 5% to 13% (201). Both may exist concomitantly as stenosis may lead to HAT. HAT usually occurs in the first month following transplant, often within 72 hours, but can also have a delayed presentation. Clinical manifestations of HAT and stenosis are similar and vary with the most severe of these usually presenting early after transplant. The worst complications of HAT are hepatic necrosis and fulminant failure, which are associated with a high mortality rate and often require retransplantation. Significantly elevated transaminases, fever and new abdominal pain should prompt urgent investigation. Delayed presentations include ischemic cholangiopathy with necrosis of bile ducts, bile leak, peritonitis, and sepsis, also with a high mortality rate. Recurrent cholangitis and bacteremia carry a mortality rate of 30% and often requires retransplantation (202).

Although angiography is historically the gold standard for diagnosis of HAT and hepatic artery stenosis, Doppler ultrasonography has become the primary technique. It is noninvasive and has a high sensitivity (75%–100%) with the added convenience of its ability to be performed at the bedside. CT angiography (CTA) and magnetic resonance angiography (MRA) have also been established as accurate diagnostic tools to identify HAT (201).

The treatment of HAT and stenosis depends upon the severity of the clinical presentation. Those with fulminant failure require aggressive support in the ICU and, often, retransplantation. Alternative management including surgical reconstruction of the hepatic artery or thrombectomy; vascular interventions such as angioplasty and stenting or thrombolysis may be appropriate for less symptomatic patients with the intent of graft salvage (201,202). However, about 50% of patients in this scenario will still require retransplantation. There is insufficient data to evaluate the efficacy of such procedures and long-term patency rates remain a problem (203). In the least severe or asymptomatic cases expectant management and systemic anticoagulation are considered adequate (201).

Portal vein thrombosis (PVT) is present in about 12% of patients at the time of transplant. Pre-existing PVT makes surgery more challenging and increases the risk of rethrombosis after transplantation, but it has not been shown to alter mortality (204). The incidence of PVT presenting after transplantation is 2% to 7%, with most occurrences early after transplant (202). In addition to a prior history of PVT, risk factors include a hypercoagulable state, perioperative hypotension, and allograft cirrhosis. PVT may also result from technical complications due to stricture at the anastomotic site, malalignment, and vascular kinks. Acutely, it can lead to hepatic failure, but chronically it has a more insidious presentation involving portal hypertension with ascites and varices (199). Transaminases are typically elevated; diagnosis is made by Doppler ultrasonography or magnetic resonance venogram (204).

Hepatic vein thrombosis (HVT) is very unusual following LT; usually related, when it occurs, to technical complications such as kinking of the hepatic veins, small allografts that rotate, or a hypercoagulable state. Patients who have undergone transplantation for Budd-Chiari syndrome and have subtherapeutic anticoagulation are also at risk for HVT. Diagnosis is often made by Doppler ultrasonography; hepatic venography is confirmatory. Treatment depends on the severity of the presentation. Extensive thrombosis can result in graft failure. Options for treatment include surgical reconstruction and repositioning, thrombectomy, stenting, anticoagulation, or expectant management (202).

Rejection

Not only is rejection less common in LT than in other solid organ transplants, but less rejection occurs in the latter group when performed in the setting of a concurrent or previous liver transplant (205). In addition, rejection that occurs early after the liver is transplanted does not necessarily affect overall graft survival (206). This effect is not due to antigenic difference, but instead to an active immune system process for which there are several theoretical causes. Microchimerism is one such hypothesis where donor hematopoietic cells persist in the recipient, producing tolerance through a balance of graft-versus-host and host-versus-graft reactions (205). Nonetheless, transplantation tolerance is not attainable consistently, and complete cessation of immune suppression is associated with about a 30% incidence of rejection (206).

In most institutions, high-dose corticosteroids are typically used for induction immunosuppression. Many patients can be tapered off corticosteroid immune suppression after transplantation with CNIs as the mainstay of therapy. In those with
renal insufficiency, an antimetabolite such as a mycophenolate compound combined with a low-dose CNI or corticosteroid may be used as maintenance (206, 207). The immunosuppressives commonly used in LT and their side effects are listed in Table 72.7 (206); side effects will result in the alteration of which medications are used (205–207).

Acute rejection occurs within the first 5 to 15 days after transplantation, manifested by fever, graft enlargement, tenderness, leukocytosis with increased eosinophils, and reduced bile production. Biopsies are done only when symptoms are present because the morphologic features consistent with acute rejection can be present in a significant percentage of patients in the early posttransplant period (208). Treatment for acute rejection is 3 to 5 days of 500 to 1,000 mg of methylprednisolone daily, resulting in about 75% resolution; a second course is sufficient for treatment in an additional 10%. The rest require an antilymphocyte therapy, with the rare case requiring retransplantation (209). Patients who develop rejection in the setting of complete immune suppressive cessation have been shown to develop jaundice, coagulopathy, delayed synthetic function, avascular necrosis, growth retardation, Cushingoid features, psychosis, poor wound healing, adrenal suppression, cataracts.

Biliary Complications

Despite the increased use of organs donated after cardiac death, biliary complications following LT have decreased from early estimates of 50% to currently reported 5% to 25% (210). However, they are still a significant cause of mortality and morbidity. There are a wide range of types and presentations of biliary complications, with biliary leaks and strictures being the most common. About two-thirds will present within the first 3 months following LT; complaints of abdominal pain, anorexia, ileus, and fever may be associated with biliary tract disorders. The serum markers, total bilirubin and γ-glutamyltransferase, are the most sensitive indicators of biliary complications (211). Initial imaging for diagnosis is usually Doppler ultrasonography; abnormalities can be further followed up with CT, cholangiography (direct via T tube or endoscopic), or magnetic resonance cholangiography (MRCP).

Biliary complications can often be managed with endoscopic or percutaneous stenting or strategic placement of a drain, and require surgery only if a major leak is present (212). The transplant surgeons will be intimately involved with the treatment and evaluation of potential biliary complications. A very rare syndrome of diffuse biliary necrosis may require retransplantation; in this scenario, patients present with a combination of sepsis, cholestasis, and bile leakage in which temporizing measures are useless. However, most cases of biliary dysfunction are not a cause for retransplantation or mortality (212).

Living Donor Liver Transplantation and Small-for-Size Syndrome

For the most part, the recipient receives essentially the same measures, however, there is an increased risk of vascular and biliary problems postoperatively. Unique to this type of transplantation is small-for-size syndrome. Although, this syndrome can occur in whole-organ grafts, it is a feared complication of living donor partial grafts. Small-for-size syndrome is defined as dysfunction during the first posttransplant week and requires the presence of two of the following findings on 3 consecutive days: total bilirubin over 5.8 mg/dL, INR above 2, and grade III or IV encephalopathy (213). Essentially, the patient develops jaundice, coagulopathy, delayed synthetic function, encephalopathy, and ascites in the first week. These patients are at risk for sepsis and have increased mortality (213). A similar situation may affect patients who receive a split liver from deceased donors as well. The mechanism of this syndrome appears to be acute, severe portal hypertension combined with an overwhelmed metabolic capacity of the allograft; sinusoidal injury occurs from portal pressures that exceed sinusoidal compliance. Experimental evidence supports this theory and suggests these events cause failure of graft regeneration (214).

SUMMARY

The patient undergoing LT has a significantly altered physiology and undergoes specific management to ensure optimal outcome. Coordinated care from the perioperative physician, surgeon, hepatologist, and anesthesiologist can minimize the risks from this procedure so the intensivist is in the position to positively affect prognosis.

Key Points

- Understand the presurgical selection, allocation, and evaluation of potential liver transplant recipients
- Identify the comorbidities and physiology associated with liver failure
- Understand the complex coagulopathy and transfusion decisions in ESLD
- An update of the advances in surgical and anesthetic management of LT
- Standard ICU management and practices following LT
- Defining and recognizing of the complications of LT

References


