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Introduction

Liver transplantation for both acute and chronic liver failure results in excellent outcomes. Patient and graft outcomes are closely monitored on a national level and 1-year survival is between 80 and 92 % (<http://optn.transplant.hrsa.gov/latest-Data/rptStrat.asp> accessed 10/19/13). Perhaps more than with any other surgical program, graft and patient outcomes for liver transplantation reflect the combined efforts of several interrelated services. The success stems from a multidisciplinary approach with close involvement of gastroenterologists, anesthesiologists, surgeons, and intensivists. This chapter will review the concerns related to postoperative care of the liver transplant patient in the intensive care unit. Existing evidence on potential early concerns such as hemodynamic monitoring, respiratory failure, neurologic management, electrolyte and glucose correction, coagulation management, systemic immunosuppression, graft function and rejection, and technical problems will be reviewed. The chapter will conclude with brief mention of long-term complications related to recurrence of disease that may lead to future ICU admissions.

Monitoring Hemodynamics

Monitoring hemodynamics after liver transplantation is critical in the postoperative setting. Acute changes in hemodynamics that are not properly diagnosed or treated can result in impaired graft function, prolonged ICU stay, and increased mortality. Postoperative management of hemodynamics

begins with a thorough understanding of the underlying pathophysiology. End-stage liver disease typically results in high cardiac output and low systemic vascular resistance. Following successful transplantation this process begins to reverse, leading to a reduction in cardiac output and an increase in systemic vascular resistance with improved maintenance of systolic blood pressure [1].

Blood Pressure and Fluid Status Measurement

Real-time monitoring of blood pressure in the postoperative setting is crucial and invasive hemodynamic monitoring should be maintained for at least the first 24 h following transplant. Hemodynamic monitoring for liver transplantation should include arterial and central venous catheters at a minimum. Beyond central venous pressure (CVP) monitoring, utilization of a pulmonary artery catheter (PAC), echocardiography, or noninvasive continuous cardiac output [2] has been described. The type of monitoring differs among transplant centers and is determined by individual or institutional practice. For example, Schumann et al. surveyed 62 transplant centers in the United States and found that PACs were used in 30 % and transesophageal echocardiography was used in 11.3 % during the intra-operative period [3].

The PAC had previously been the standard for fluid monitoring for liver transplantation at most centers. Evidence that PACs fail to improve outcomes in critical care [4, 5], and their potential to induce ventricular arrhythmias [6] has led to less-invasive monitoring for the orthotopic liver transplant (OLT) patient. An increasing number of transplant centers now rely on CVP monitoring alone with only selective PAC usage, while others continue to routinely use PAC monitoring for all their patients.

Due to limitations of central venous and pulmonary artery catheters, the use of dynamic methods of fluid responsiveness is currently being explored. Presumably dynamic measurements based on physiologic responses will be more

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accurate than static indicators [7]. The measurements, including systolic pressure variations (SPV) and pulse pressure variations (PPV), are derived from algorithms that abstract data from an arterial line and allow beat-to-beat monitoring for the purpose of predicting fluid responsiveness. Although the data are promising under anesthesia [8, 9], these monitors have not been validated in the ICU. Furthermore, in order to obtain accurate calculations, patients must be in sinus rhythm, have a closed chest, have normal intra-abdominal pressures, and be on controlled ventilation with positive end expiratory pressure (PEEP) of 0–5 cm H₂O [10]. Perhaps the most prudent approach from all this data is to base management on clinical examination findings and appropriately titrate fluid according to the patient's hemodynamic trends. The preferred choice of monitoring tool (central venous line, PAC, or echocardiography) remains controversial due to the lack of evidence indicating a difference in patient outcomes. Overall choice of monitoring for cardiac function and fluid status is probably best decided based on the expertise of the center and the familiarity and ease of access to different options.

Portopulmonary Hypertension

A detailed discussion of the underlying etiology of pulmonary hypertension in the liver transplant patient can be found in other chapters, but a discussion of their management deserves quick mentioning here.

Portopulmonary syndrome is defined as pulmonary hypertension in association with portal hypertension. Diagnostic criteria vary, but it is important to note that pulmonary pressures should be verified with right heart catheterization pre-transplant if suspicion for pulmonary hypertension arises on echocardiography [11]. Prevalence of portopulmonary syndrome in liver transplant is approximately 6% as found in a prospective study evaluating 165 patients [12]. Due to the effect on postoperative mortality, most patients with portopulmonary hypertension will have been identified in the preoperative setting; this information is vital to the physician caring for the patient postoperatively. Of particular importance are both the severity of disease and treatments the patient received prior to transplant. Disease severity is a predictor of postoperative mortality. Severe portopulmonary hypertension (mean pulmonary artery pressure >45 mmHg) is associated with a perioperative mortality of 40% [13]. Mild pulmonary hypertension (mean pulmonary artery pressure <35 mmHg) is not associated with decreased survival and current case series suggest that if pulmonary pressures can be reduced medically to less than 35 mmHg, then outcomes are acceptable [14].

If evidence of pulmonary hypertension is identified on echocardiography, then fluid status should be optimized, as

volume overload can be an exacerbating factor. Inotropic support and inhaled agents for pulmonary hypertension, for example dobutamine, milrinone, and inhaled nitric oxide, can be used for more severe cases, particularly if the patient was requiring these agents prior to transplantation. Right heart function should be improved if possible, because prolonged failure will impair graft perfusion and lead to graft failure due to decreased left heart output (secondary to decreased left ventricular filling) and worsened venous congestion from right heart failure.

Randomized clinical trials for the treatment of portopulmonary hypertension are lacking and most therapies are derived from known treatments for primary pulmonary hypertension. These include epoprostenol (prostacyclin), endothelin receptor antagonists such as bosentan, and phosphodiesterase-5 inhibitors such as sildenafil. While definitive data in the liver transplant setting does not exist, these agents are frequently used to improve a patient's pulmonary hemodynamics so that the patient can be considered for transplant [15]. The continuation of pulmonary vasodilators is critical in the postoperative setting. Additionally, repeat echocardiography and/or a pulmonary artery catheterization may be beneficial in directing further therapy if right ventricular failure develops in the ICU.

Respiratory Issues

Pulmonary complications can be very common in the postoperative setting. Many liver transplant patients will have a tenuous respiratory status requiring care ranging from close observation to prolonged mechanical ventilation. While the incidence varies, prompt recognition and treatment is essential to improve the patient's outcome [16]. Predisposing factors in the pre-operative setting include underlying pulmonary disease (in particular a restrictive pattern on pulmonary function tests) and smoking [17]. In addition, patients intubated pre-operatively are at risk for mechanical ventilation needs postoperatively due to the underlying disease.

Early Extubation

Early extubation after liver transplant is often possible due to improvements in both surgical and anesthetic techniques. The concept of early postoperative tracheal extubation began with cardiac surgery and was applied to select liver transplant patients in the late 1990s [18]. Proponents argued that early extubation reduced the risk of ventilator-associated pneumonia and improved both splanchnic and hepatic blood flow. Early extubation has been shown to decrease ICU length of stay and resource utilization [19]. In some centers, early extubation is performed in as many as 70–80% of cases

[20]. Although these results are promising, extubation immediately following OLT is not a routine practice at all transplant centers.

Variables predictive of delayed tracheal extubation include: primary graft dysfunction, renal and/or cardiovascular failure, serious neurological impairment, transfusion of more than 12 units of intraoperative red blood cells and pulmonary edema [21]. Interestingly, severity of liver disease, duration of surgery, and duration of cold ischemia did not predict prolonged intubations. Glanemann and colleagues demonstrated that patients that were extubated immediately following surgery actually had a lower rate of reintubation when compared with patients who were extubated on average 5 h postoperatively, or those requiring prolonged mechanical ventilation of more than 24 h [22]. In a multicenter trial conducted to evaluate the safety of early extubation [23], extubation rates varied from 5 to 67% despite a uniform set of extubation criteria. The authors concluded that there were likely institutional-specific practices that were not measured or controlled by the study. The differences in outcomes among the centers revealed that variability persists despite efforts to provide protocolized care.

At this time, there is no consensus among transplant centers regarding early extubation following OLT, and whether it should be a therapeutic goal remains debatable [24, 25]. However, for the correctly selected patient, this can be a valid strategy to reduce hospital costs and ICU length of stay (Table 29.1). Patients that are good candidates for extubation

are hemodynamically stable, demonstrate low risk for surgical re-exploration, and have received few intraoperative blood products. Additional trials are required to establish indications for early extubation.

Mechanical Ventilation Management

Liver transplant patients who are not candidates for early extubation in the operating room are common, particularly among patients with pre-existing pulmonary pathology. A subset of patients will require prolonged mechanical ventilation and may develop additional pulmonary complications in the postoperative period. It is critical for the intensivist to recognize these patients and work to prevent ventilator associated lung injury.

Post-liver transplant patients in the ICU may develop acute respiratory distress syndrome [26]. The differential for ARDS is broad and includes infection [including ventilator-associated pneumonia (VAP)], systemic reperfusion injury, transfusion reaction, or graft failure. Patients who meet criteria for ARDS should be placed on low tidal volume ventilation [27]. While patients with severe liver disease were excluded from the ARDSNet study, there currently is no evidence to suggest that low tidal volume ventilation is harmful. In fact, recent studies have shown expanded benefit of low tidal volume ventilation even in patients who do not have ARDS [28].

The data in regards to other forms of mechanical ventilation are minimal for all critical care patients, and nonexistent for the post-OLT patient with ARDS. Airway pressure release ventilation [29], high-frequency oscillatory ventilation [30, 31], prone ventilation [32], inhaled nitric oxide [33], neuromuscular blocking agents [34], and recruitment maneuvers [35] have all been studied, but for most randomized studies, patients with cirrhosis and liver failure were excluded. All the studies have shown the ability to improve oxygenation; some have shown a mortality benefit, but none have been as definitive as ARDSnet. Lung-protective mechanical ventilation should be the underlying ventilator support strategy of post-liver transplant patients with ARDS requiring mechanical ventilation.

Several theoretical concerns related to liver transplant patients and ARDSNet ventilation exist. In the ARDSNet protocol, permissive hypercapnia is used. There is some concern that this elevated PCO₂ may affect graft function, but there is currently no significant data addressing this potential complication. A second concern has been the administration of positive end-expiratory pressure (PEEP) and the corresponding increase in intrathoracic pressure, which in turn may impede venous return from the new liver. No studies have addressed high PEEP, but there is published evidence that PEEP up to 10 cm H₂O does not adversely affect graft function [36].

Table 29.1 Data on early extubation after liver transplantation

Study	Type	Comment
Glanemann et al. [154]	Retrospective analysis	546 patients analyzed, immediate extubation in 18.7%. No increased incidence of reintubation when compared with patients successfully extubated later.
Mandell et al. [19]	Prospective trial	147 sequential patients, 111 successfully extubated immediately. 83 patients transferred directly to surgical ward. 1 day ICU reduction in 75.5% of patients with no problems reported with patient safety.
Biancofiore et al. [155]	Prospective trial	207 out of 354 patients extubated immediately, two re-intubated. In the final year of the study 82.5% of patients were successfully extubated immediately.
Mandell et al. [23]	Multicenter prospective trial	391 patients who met criteria for early extubation. Complication rate of 7.7%, however was skewed as two institutions had higher complication rates. Removing these two centers the complication rate fell to 3.6%. This difference may be related to a center's experience with early extubation.

A subset of posttransplant patients will be difficult to wean from ventilator support and can prove challenging. Liver transplant patients should be treated like other patients who are mechanically ventilated and when feasible, given daily sedation holidays and spontaneous breathing trials in an effort to evaluate readiness for extubation. For patients with prolonged ventilation requirements, tracheostomy should be considered as with other intubated patients in the ICU setting.

Hepatopulmonary Syndrome

Hepatopulmonary syndrome is a complication of cirrhosis that adds unique concerns to the postoperative course. The presence of hepatopulmonary syndrome can lead to increased postoperative mortality, particularly for severe cases of hepatopulmonary syndrome ($\text{PaO}_2 < 50$ mmHg on room air) [37]. Diagnosis and intra-operative management of hepatopulmonary syndrome is covered in other chapters.

The complication most commonly seen in patients with hepatopulmonary syndrome is prolonged hypoxia in the postoperative setting. Management of hypoxia is important, as prolonged mechanical ventilation in these immunosuppressed patients is associated with an increased risk of adverse events. There have been case reports of using nitric oxide to improve oxygenation, but no randomized trials exist to demonstrate the efficacy of this therapy [38]. In some patients with severe hepatopulmonary syndrome, the recovery of oxygenation may be prolonged. Recent data from two Canadian centers reported a mean rate of increase in PaO_2 of 3.1 ± 2.3 mmHg/month, and mean time to resolution of the intrapulmonary shunt of 4.5–18 months (median 11 months posttransplant) [39]. For these patients, prolonged mechanical ventilation may not be the most appropriate therapy and it may be appropriate to consider extubation with administration of supplemental oxygen or noninvasive ventilation. This strategy can be effective in reducing ventilator related complications and will allow for a postoperative patient to leave the ICU and avoid a prolonged stay. Further studies will be necessary to determine the feasibility of this approach.

Neurologic Issues

Sedation

Sedation of the mechanically ventilated patient is challenging; this is especially true in the post-liver transplant patient. Mental status changes can be an early clue to graft dysfunction and efforts should be made to avoid excessive sedation. Benzodiazepines are not recommended as they

have been shown to increase delirium in the ICU setting [40]. Propofol and dexmedetomidine have become popular sedatives due to their favorable pharmacokinetics. A recent meta-analysis suggested that use of dexmedetomidine or propofol infusions rather than a benzodiazepine infusion in critically ill adults reduced ICU length of stay and duration of mechanical ventilation [41]. There have been only a few recent case reports of safe use of dexmedetomidine infusions in post-liver transplant patients [42, 43]. The short acting agents have a favorable profile and allow for serial neurologic exams while still providing adequate sedation and anxiolysis.

Pain Management

Liver transplant is a major surgical procedure and may be accompanied by significant postoperative surgical pain. Pain control intra- and postoperatively is usually achieved with fentanyl, via infusion or intermittent bolus. Other opioids such as morphine and hydromorphone are avoided if possible due to their prolonged half-lives in liver failure. Fentanyl derivatives such as sufentanil, alfentanil, and remifentanyl have superior pharmacokinetic properties but are not routinely used in the postoperative setting due to higher cost, insufficient staff experience, and lack of data showing improved efficacy. Some patients may require use of a patient controlled analgesia (PCA) pump along with longer acting agents, or transition to around-the-clock oral medications if pain persists.

Thoracic epidurals are beneficial for pain control following abdominal surgery [44], however they are not routine for liver transplant patients. The varied coagulation status of posttransplant patients raises concerns regarding the use of thoracic epidurals for postoperative analgesia. Hypotension from the epidural also raises concern that graft function may be compromised, particularly in posttransplant patients who have complex hemodynamic indices. For certain patients, other than transplant recipients (i.e.: hepatectomy patients) thoracic epidurals may be an acceptable option for postoperative analgesia.

Non-opioid adjuncts for pain control have received significant attention. While there have been few studies examining these agents in liver transplant patients, some generalizations can be made. Nonsteroidal anti-inflammatory drugs (NSAIDs), while efficacious for pain, should probably be avoided in the setting of increased bleeding risk and potential renal insufficiency. Acetaminophen is usually given at lower doses (2 g/day) for liver failure patients and should be avoided in the immediate postoperative period. However, for patients with functioning grafts, it is reasonable to consider acetaminophen administration due to its synergy with opioids.

Unfortunately there does not exist a one-size-fits all approach to pain management in the liver transplant patients. Each patient's individual risk for postoperative pain must be weighed against potential side effects. At this point, opioids such as fentanyl remain the mainstay of therapy until further studies are completed that can validate the safety of other interventions.

Hepatic Encephalopathy

Patients with liver failure often suffer from hepatic encephalopathy. The underlying etiology of hepatic encephalopathy is not entirely understood but current theories suggest that increased ammonia in the systemic circulation crosses the blood brain barrier where it is converted into glutamine by astrocytes. The glutamine causes swelling of the astrocytes, which impairs neurotransmission regulation. Interestingly, the level of ammonia does not correlate with neurologic symptom severity, so trending ammonia levels may not be helpful. In the postoperative period, a patient with a newly functioning liver should have steady clearance of toxins and a continual improvement in mental status. If there is no improvement or mental status declines, then a workup for graft nonfunction and infection should be undertaken and electrolyte imbalances corrected. Given the extreme changes in coagulation status, there should also be a low threshold to obtain imaging if there is concern for intracranial hemorrhage.

Osmotic Demyelination Syndrome

Hyponatremia in the setting of liver failure will be discussed below. However, it is important to note a potential neurologic complication that is associated with rapid correction of hyponatremia: central pontine myelinolysis or osmotic demyelination syndrome. The exact etiology of osmotic demyelination syndrome is unknown. The symptoms are usually seen 1–6 days after the insult of rapid sodium correction [45]. The most common clinical manifestation is fluctuations in consciousness. Eventually, pseudobulbar palsy and quadriplegia may develop. If a patient is known to be hyponatremic preoperatively, then clinicians must closely monitor electrolytes and choose intravenous fluids appropriately to avoid rapid over correction postoperatively.

Electrolyte and Endocrine Issues

Adequate management of electrolytes can be challenging in posttransplant patients. The patients often have numerous abnormalities that should be closely monitored and

corrected. Treatment of the more common electrolyte abnormalities found in posttransplant patients will be discussed below.

Sodium Homeostasis

Alterations in sodium levels are very common in pre- and posttransplant patients. In fact, there is clinical evidence to suggest that adding serum sodium to model for ESLD (MELD) scoring improves mortality prediction [46]. The first step in management is to determine the acuity of the situation. Patients with acute hyponatremia (development in under 48 h) are at risk for developing neurologic impairment and, consequently, require prompt correction of serum sodium levels. Administration of a hypertonic (3%) saline infusion may be necessary for this situation. In patients with more chronic hyponatremia (development in over 48 h), rapid correction of hyponatremia is an independent risk factor for the development of posttransplant neurological complications [47]. Serum sodium correction should be performed in a controlled manner in this instance. The goal is usually 1–2 mmol/L per hour for the first 48 h. If the level rises too quickly, then hypotonic intravenous fluids should be started to restore the goal correction rate.

Hypernatremia is a less-frequent complication associated with liver transplant patients. The etiology is frequently related to excessive loss of free water in patients using an osmotic laxative (such as lactulose) to reduce hepatic encephalopathy. These patients are unable to adequately regulate their own free water balance due to impaired thirst mechanisms. This derangement may continue into the postoperative setting. As the mental status improves, the patient should begin to appropriately regulate water intake. For a hypernatremic patient who is unable to tolerate oral free water boluses, hypotonic maintenance fluids are recommended with close monitoring of electrolytes.

Hyperkalemia

Hyperkalemia may be the most lethal electrolyte abnormality due to the rapid progression of arrhythmias and death. The causes of hyperkalemia in the posttransplant patient are often multifactorial. Many liver transplant patients either have pre-existing renal dysfunction [48] or will develop transient renal dysfunction in the perioperative period which can impair mechanisms of potassium homeostasis.

For patients that had significant blood loss and transfusion requirements during the operation, there may be a significant potassium burden in the form of lysed cells from aged units that are transfused. Many liver transplant centers have a high usage rate of blood products and will often be

assigned aged units by the blood bank because they are unlikely to be wasted. While this is an excellent use of resources, these units contain less-functional cells and correspondingly represent a higher potassium load to the patient. Washing the cells before transfusion can partially attenuate the hyperkalemia, but frequent potassium monitoring remains necessary.

Hyperkalemia can be exacerbated acutely by reperfusion of the preserved graft and release of a significant potassium load from ischemic tissues. This is often managed with temporizing measures such as administration of calcium, sodium bicarbonate, and insulin with glucose, but the total body potassium may continue to be elevated in the postoperative setting. Dialysis may be needed if renal insufficiency and hyperkalemia persist in the ICU.

Hypocalcemia

Hypocalcemia is frequently identified in liver transplant patients. However, it is important to remember that these patients often have low albumin levels and the total calcium is not necessarily reflective of free calcium levels [49]. Ionized calcium levels are more accurate in this situation. Low calcium levels can result from chelation with the anticoagulant citrate, found in blood products and renal replacement therapy infusions. Hypocalcemia should be suspected in a patient with hypotension despite adequate resuscitation. Calcium gluconate or calcium chloride can be used for replacement.

Glucose Levels

Glucose levels following liver transplantation have significant implications for both prognosis and complications. Hypoglycemia in the postoperative period may be a marker for sepsis or poor graft function [2]. Hyperglycemia, which is much more common in the postoperative setting, may be a reflection of underlying diabetes, stress response, or steroid administration. Severe hyperglycemia (glucose > 200 mg/dL) is associated with an increased risk of liver allograft rejection [50], surgical site infection [51], and increased mortality [52]. Hyperglycemia is known to aggravate ischemia reperfusion injury in several organ systems.

Although hyperglycemia has complications, tight glucose control (between 80 and 120 mg/dL) is not recommended due to poor outcomes in the ICU setting [53, 54]. The best approach is to achieve modest glucose control (150–180 mg/dL), which is consistent with current ICU guidelines. In the immediate postoperative setting, an insulin infusion with frequent blood glucose checks is often required, as fluctuations in the stress response make steady state dosing difficult.

Renal Complications

Renal insufficiency following liver transplant is a common occurrence. Some studies report up to a 50% incidence, though numbers vary widely due to the lack of a uniform definition. Acute ischemic tubular necrosis (ATN) is the most common cause of early renal failure following liver transplant [55]. A number of contributing factors increase the risk of renal dysfunction postoperatively. They include: hepatorenal syndrome, hepatitis C, diabetes mellitus, intraoperative and postoperative hemodynamic instability, massive transfusion, vasopressor infusions, infections, frequent radiologic studies, and nephrotoxic immunosuppressants and antibiotics [56, 57]. Management usually includes judicious fluid management, medication dose reductions based on creatinine clearance, and avoidance of further renal insults.

Eight to seventeen percent of patients with posttransplant acute kidney injury go on to require renal replacement therapy despite supportive care [2]. Risk factors for renal replacement therapy (RRT) following transplant include preoperative serum creatinine (Cr) greater than 1.9 mg/dL, blood urea nitrogen (BUN) greater than 27 mg/dL, ICU duration of greater than 3 days, and MELD score greater than 21 [55]. Some patients will progress to end stage renal disease (ESRD) and require kidney transplantation in the future. One percent of all kidney transplant patients in the United States are prior liver transplant patients with ESRD. The risk for kidney injury is further increased in recipients of living donor liver transplantation. These patients may develop small for size syndrome (see section below), which worsens fluid and hemodynamic derangements [58].

Hepatorenal syndrome (HRS) involves severe vasoconstriction of the renal vasculature and renal hypoperfusion in the presence of decreased systemic vascular resistance and normal renal parenchyma [59, 60]. Patients with HRS pre-liver transplant have been found to require longer ICU stays postoperatively and more dialysis, and are more likely to progress to ESRD following transplant than patients without HRS. Calcineurin inhibitor (CNI) initiation should be withheld for the first several days following transplantation to allow for reversal of HRS physiology and recovery of renal function [56].

Monitoring renal function in liver transplant patients is challenging, as elevations in serum creatinine are late indicators of renal insufficiency and proteinuria may not develop in the presence of calcineurin inhibitors [61]. A formula for calculating glomerular filtration rate should be utilized for the detection of renal dysfunction, but the results may be less reliable in patients with liver disease. A recent study suggested that cystatin C levels in the immediate posttransplant period are superior to creatinine based equations for estimation of GFR and may be useful as a confirmatory test for

kidney injury [62]. Although it may be more accurate, cystatin C is not universally available, and it is more expensive. Until better markers are discovered and validated, serum creatinine will remain the main criterion used for the diagnosis of AKI.

Calcineurin-Induced Nephropathy

Once renal failure begins to develop, nephrotoxic immunosuppressants, namely CNIs, should be withdrawn, and immunosuppression should be maintained with renal-sparing protocols. CNI-induced nephropathy results from afferent arteriolar vasoconstriction and subsequent decrease in renal perfusion [63]. Using a reduced dose of cyclosporine, or replacing cyclosporine with mycophenolate mofetil (MMF) and sirolimus reduces the incidence of CNI-induced renal injury [64]. While CNI-induced nephropathy was reduced with MMF and sirolimus, the incidence of biopsy-proven acute rejection in the liver increased. Fortunately, this was not associated with increased rates of graft loss. A recently conducted Cochrane review of the literature surrounding CNI toxicity did not reach a conclusion regarding the role of CNI minimization in preventing nephrotoxicity in liver transplant patients [65]. Many centers now delay the administration of these drugs following surgery. The dosages used today are also substantially lower than those prescribed in the past in order to reduce the subsequent risk of chronic kidney disease [56].

Infectious Complications

Infections are the leading cause of morbidity and mortality after liver transplantation. The early posttransplant course (first month) is often complicated by surgical site infections and infections related to hospitalization including urinary tract infections, pneumonias, blood stream infections, and pseudomembranous colitis [66]. Patients post-liver transplant are at particular risk for developing bacterial infections of the liver and surgical site including abscesses, cholangitis, and peritonitis. Standard perioperative antibiotic prophylaxis with third generation cephalosporins should be used to reduce the risk of infections [67]. Although prior studies had suggested that selective bowel decontamination with prolonged antibiotic use prior to transplantation may help reduce the occurrence of infections, a Cochrane Database analysis concluded that there was no clear benefit of this intervention, and that decontamination may in fact increase the risk of infection and length of hospital stay [68]. Prebiotics and probiotics may provide some benefit, and should be further studied.

Opportunistic Infections

Opportunistic infections generally occur in the second through sixth months, when immunosuppression is most profound. Trimethoprim/sulfamethoxazole (TMP-SMX) prophylaxis for *Pneumocystis jirovecii* should be instituted for the first 6 months following transplant, and continued in patients requiring monoclonal OKT3 antibodies for rejection and in patients with graft dysfunction. An additional benefit of TMP-SMX administration is prophylaxis for *Toxoplasma gondii*, *Listeria monocytogenes*, and *Nocardia asteroides* [66].

CMV infection is notable for its association with increased opportunistic infections in liver transplant patients, including fungemia and bacteremia, and its association with transplant rejection [69]. Infection with CMV within the first year of transplant is associated with increased mortality. Effective prophylaxis can be provided with ganciclovir or valganciclovir for 3 months following transplant [70]. Herpes simplex virus (HSV) reactivation may occur posttransplantation, but antivirals used for CMV prophylaxis should also be effective in these patients. If the patient is not receiving CMV prophylaxis, acyclovir can be used for the prevention of HSV. Varicella vaccination should be administered prior to transplantation. Beyond 6 months, patients are no longer at risk for most opportunistic infections if the level of immunosuppression has been reduced.

Candida is the most common fungal pathogen following liver transplantation and accounts for nearly 80% of postoperative fungal infections, followed by *Aspergillus*. Most fungal infections occur within the first 2 months following transplantation. Risk factors for opportunistic fungal infections are retransplantation, renal failure, and reoperation involving the thoracic or abdominal cavity [71]. The use of antifungal prophylaxis is highly variable between liver transplant centers, and can include nystatin suspension, fluconazole, amphotericin B, or no empiric prophylaxis [72].

Hematologic Issues

Transfusion Triggers

Blood transfusions for bleeding are indicated to maintain adequate oxygen delivery. No firm transfusion threshold exists, but evidence in other patient populations suggests that a more restrictive strategy is appropriate. In the most recent clinical practice guidelines published, the taskforce, comprised of surgeons, anesthesiologists, and intensivists, felt there was good evidence to recommend a restrictive strategy of red blood cell (RBC) transfusion (hemoglobin < 7 g/dL) in critically ill patients with hemodynamically stable anemia [73].

Acute blood loss with hemodynamic instability should probably be addressed by more aggressive resuscitation with blood products. Further trials testing rigorous transfusion protocols are necessary, but the trend has been toward more restrictive transfusion practices.

Colloid Versus Crystalloid

No evidence for the superiority of albumin over crystalloid has been found in the critical care literature, but it is important to note that liver transplant patients were excluded from the trial [74]. Either crystalloid or colloid can be used effectively when administered in bolus doses for hypotension. In a patient with significant ascites, colloids may be the fluid of choice for resuscitation. It does appear that among colloids, albumin may be safer than hydroxyethyl starches because of the lower incidence of anaphylactic reactions, coagulation disorders, renal or liver failure, pruritus, and better hemodynamic stability [75]. Hydroxyethyl starch has also been found to increase the need for renal replacement therapy when compared with normal saline [76] and lactate ringers [77].

Thoughtful selection of crystalloid is essential as significant electrolyte derangements may be present in the postoperative setting. Boniatti and colleagues showed recently that hyperchloremia, possibly due to the administration of normal saline, is the primary cause of metabolic acidosis in liver transplant recipients [78]. Among critically ill patients with sepsis, large chloride loads from saline resuscitation have been associated with increased renal failure [79], and hospital mortality [80]. While this has not been exhaustively studied in the posttransplant setting, this concept may translate to the care of liver transplant patients as well. Future studies are needed to assess the utility of various balanced salt solutions in the care of patients post-OLT.

Coagulation Deficits

Coagulopathy does not resolve immediately after transplantation and often persists into the postoperative ICU period. The etiology is multifactorial and can involve hyperfibrinolysis, disseminated intravascular coagulopathy, platelet activation, platelet sequestration within the graft, and the presence of heparin-like effect (HLE). Some patients are actually hypercoagulable posttransplant, which further complicates the evaluation of their coagulation status [81]. The cause of this hypercoagulability is not entirely clear but maybe due to impaired synthesis of antithrombin by the liver.

As the new graft improves in function, synthesis of coagulation factors should improve and laboratory values should return to baseline. While laboratory value correction may not correlate well with bleeding risk, it does correlate with improved graft function. Failure to see improvement in coag-

ulopathy should prompt a work up for graft nonfunction and infection, two serious causes of impaired coagulation in the postoperative setting. Routine transfusion for laboratory abnormalities is not indicated unless there is evidence for ongoing bleeding and hemostatic problems [82]. Aggressive transfusion can worsen cardiac function and consequently graft perfusion, so it should be reserved as therapy for clinically significant bleeding.

Fibrinolysis

In addition to hypofibrinogenemia from transfusions and blood loss, the new graft releases t-PA and tissue factor, which results in an accelerated fibrinolytic state that frequently causes significant consumption of fibrinogen in the post-reperfusion setting [83, 84]. Refractory bleeding should prompt an investigation for low fibrinogen and fibrinolysis. Administration of antifibrinolytic drugs has shown benefit in reduction of transfusion requirements, and with the small number of patients studied so far, there does not appear to be an increased risk in thrombotic events (Table 29.2). Due to the lack of definitive data, it is not routine practice to administer antifibrinolytics, but practice patterns may change with further results.

Heparin-Like Effect (HLE)

The prevalence of HLE in patients undergoing liver transplant is not uncommon, and can range from 25 to 95% of cases [85]. Patients who have acute liver failure, primary nonfunction of the liver graft or require retransplant have a higher prevalence of HLE. The problem appears to be worse in patients with acute liver failure; however, the problem can persist in the posttransplant period regardless of the etiology of the liver failure [86].

The HLE can come from an exogenous source as well as an endogenous source. Residual heparin bound to the endothelium of the donor liver, which is perfused with heparin before clamping, is the exogenous source of heparin. The endogenous source comes from substances known as heparinoids. The increased release of heparinoids is thought to occur from activation of macrophages or hepatocytes following ischemic injury to the liver. There is currently no evidence for reversing the HLE and supportive care is the best treatment option. An infusion of protamine sulfate has been attempted, but did not result in reduced bleeding or transfusion requirements [87]. If impaired coagulation persists several days into the postoperative period, then a sepsis workup is indicated as infection can worsen the production of these heparin-like molecules.

Table 29.2 Trials on use of antifibrinolytic agents in liver transplantation

Study	Type	Drug	Comments
Boylan et al. [156]	Randomized controlled trial	Tranexemic Acid	TXA: 25 patients, Controls: 20 patients. Statistically significant reduction in intraoperative blood loss (20.5 units vs. 43.5 units). No difference in hepatic artery or portal venous thrombosis.
Kaspar et al. [157]	Randomized controlled trial	Tranexemic Acid	32 patients randomized to TXA or control. No difference in transfusion, but decreased fibrinolysis seen on TEG
Dalmou et al. [158]	Randomized controlled trial	Tranexemic Acid/ ϵ -Aminocaproic Acid	132 patients randomized to TXA, ϵ -aminocaproic acid, or placebo. Statistically significant reduction in intraoperative transfusion for TXA, not for ϵ -aminocaproic acid. No differences in thrombotic events or post-operative transfusion.
Dalmou et al. [159]	Randomized controlled trial	Tranexemic Acid/Aprotinin	127 patients randomized to TXA or Aprotinin. No difference in transfusion requirements or thrombotic complications.
Ickx et al. [160]	Randomized controlled trial	Tranexemic Acid/Aprotinin	51 patients randomized to TXA or Aprotinin. No difference between intraoperative blood loss or transfusion requirements.
Molenaar et al. [161]	Meta-analysis	TXA/Aprotinin/ ϵ -Aminocaproic Acid	Meta-analysis including the above trials showing no increased risk of thrombotic complications with antifibrinolytic agents.
Gurusamy et al. [162]	Meta-analysis	TXA/Aprotinin (additionally looked at other interventions to reduce blood loss)	Only aprotinin may reduce blood transfusion requirements. No difference seen between TXA and controls; no difference seen between aprotinin and TXA (only 3 trials included comparing the two).

TXA tranexemic acid, TEG thromboelastography

Thrombocytopenia

Low platelet counts are a commonly seen abnormality in the posttransplant patient. The etiology for the thrombocytopenia is varied but is related to decreased circulation and decreased production. With severe cirrhosis, there is often significant sequestration of platelets in the spleen due to portal hypertension, and the new graft will also sequester platelets. There is decreased platelet production because of low thrombopoietin levels in liver failure patients [88]. In the postoperative period, massive blood transfusions can result in a dilutional thrombocytopenia. Finally, even if the platelet count is adequate, platelets in a patient with liver disease may have decreased function because of adenosine diphosphate-induced and collagen-induced aggregation [89]. Platelet function may be further impaired by uremia in the setting of coexistent renal dysfunction. Thromboelastography (TEG) may be beneficial in measuring platelet function [90], but definitive studies relating use of TEG in liver transplant patients are needed.

Coagulation Factor Deficiencies

All coagulation factors except for factor VIII and von Willebrand factor are synthesized by the liver and are therefore decreased in the setting of severe hepatic impairment. Fresh frozen plasma (FFP) can replace these factors, but administration of plasma carries the risk of transfusion reactions and large volumes are often needed to reverse the laboratory coagulopathy [91].

For patients with refractory bleeding, many clinicians have used recombinant activated factor VII (rFVIIa) [92]. No randomized clinical trials have been conducted in postoperative liver transplant patients; however, case series have shown some benefit. There are risks associated with the off-label use of rFVIIa. Mayer and colleagues demonstrated increased risk of thrombosis with rFVIIa administration in patients presenting with intracerebral hemorrhages [77]. The exact role of rFVIIa in liver transplantation is unclear due to lack of data. Given the uncertainty, recommendations are that rFVIIa should be used only as “rescue therapy” in patients with severe life-threatening bleeding where other therapies have failed.

Immunosuppression

Posttransplant immunosuppression is necessary to prevent rejection of the donor organ. However, immunosuppression must be balanced with the maintenance of other immunologic functions, especially the prevention or recurrence of infection and malignancy. Fortunately, the rejection of transplanted livers occurs less frequently than in other organs [93], so lower dosages can be used. Side effects and complications can still occur in the postoperative period, so the intensivist should be familiar with the indications and side effects of immunosuppressants (Table 29.3).

The immunosuppressive effects of corticosteroids include a decrease in IL-1-induced lymphocyte activation, a decrease in CD4+ T-cells, and a decrease in antigen presentation by dendritic cells [94]. Steroids are used for induction and

Table 29.3 Immunosuppressants: their mechanisms of action and side effects

Class	Name	Mechanism of action	Side effects
Corticosteroids	– Prednisone	Reduce antigen presentation and lymphocyte activation	– HCV recurrence – HCC recurrence – Metabolic effects – Hepatic fibrosis
Calcineurin inhibitors	– Cyclosporine – Tacrolimus	Reduce IL-2-mediated T cell activation	– Nephrotoxicity – Neurotoxicity – Metabolic effects – HCC recurrence – PTLD
Mycophenolic acid	– Mycophenolate mofetil	Inhibit DNA synthesis	– GI distress – Bone marrow suppression
mTOR inhibitors	– Sirolimus – Everolimus	Reduce IL-2-mediated T cell activation	– Bone marrow suppression – Pneumonitis – Delayed wound healing

maintenance during the first year following transplant, and also for treating episodes of acute rejection. Concern exists for the use of high-dose corticosteroids accelerating rates of HCV recurrence, HCC recurrence, and hepatic fibrosis. However, the avoidance of steroids in immunosuppression has not been shown to be beneficial in HCV positive transplant recipients [95]. Commonly seen acute side effects from high-dose steroids include: hypertension, glucose intolerance, agitation/insomnia, infection risk, and poor wound healing. Most of the signs and symptoms can be managed, so corticosteroid cessation is rare.

The calcineurin inhibitors (CNIs), cyclosporine and tacrolimus, are used frequently in order to prevent rejection. Calcineurin inhibition results in a decrease in the pro-inflammatory cytokine IL-2 and subsequent decrease in T-cell activation. Both CNIs undergo metabolism by the cytochrome P450 system, and require careful monitoring of levels, especially when used in conjunction with other medications that induce or inhibit cytochrome P450 [93]. Common side effects of CNIs include nephrotoxicity and neurotoxicity, including seizures, delirium, cognitive impairment, neuropathy, and coma. If a posttransplant patient develops concerning neurologic symptoms, tacrolimus levels should be checked. Unfortunately, neurologic symptoms can develop even at therapeutic levels of tacrolimus. Treatment is largely supportive as there is no way to acutely lower tacrolimus levels other than dose adjustment. A strategy of using low dose CNI for maintenance of immunosuppression has been suggested in order to minimize renal dysfunction [96, 97]. Additional side effects from CNIs include hypertension, hyperlipidemia, metabolic acidosis, and diabetes. CNIs have also been found to increase levels of the transcription factor TGF-beta, which may increase the risk of hepatocellular carcinoma recurrence or posttransplant lymphoproliferative disorder [93, 94].

Mycophenolate mofetil (MMF) undergoes metabolism into mycophenolic acid (MPA). MPA inhibits the synthesis of guanosine nucleotides, necessary for DNA transcription, and subsequently decreases lymphocyte proliferation [93]. Side effects of MMF include gastrointestinal distress and bone marrow suppression. An advantage of MMF is its lack of renal toxicity, and MMF levels do not need to be regularly monitored. Unfortunately, monotherapy with MMF is associated with higher rates of rejection, so the combination of MMF with a low dose CNI has been proposed as a strategy for reducing renal dysfunction and graft rejection [98].

The mammalian target of rapamycin (mTOR) inhibitors, sirolimus and everolimus, are similar to the CNIs in many ways. They too inhibit IL-2-mediated activation of T-cells, and are metabolized by the cytochrome P450 system [93]. There is some concern for increased risk of hepatic artery thrombosis [32] with sirolimus when used as de novo therapy [99], and the FDA has issued a black-box warning in regards to this risk. Side effects of the mTOR inhibitors include bone marrow suppression, interstitial pneumonitis, edema, and delayed wound healing. In patients with CNI-induced nephrotoxicity, early conversion to sirolimus helps to prevent kidney damage. However, the recently published PROTECT trial did not demonstrate any benefit with the early substitution of everolimus for CNI in patients with a normal baseline renal function [100].

The role of mTOR inhibitors versus CNIs in patients with HCV remains controversial [101, 102]. Antiangiogenic properties of mTOR inhibitors may prevent recurrence of HCC, when used in conjunction with systemic chemotherapy posttransplant [103]. The data are strong enough that the American Association for the Study of Liver Diseases recommended patients undergoing transplant for hepatocellular carcinoma (HCC) receive sirolimus for immunosuppression [61].

Rejection

After liver transplantation, there are many types of graft rejection that may occur. Rejection of the allograft can be hyperacute, acute, chronic, or graft-versus-host (GVHD). Since chronic rejection is not usually an issue for the ICU patient, it will not be covered in this chapter.

Hyperacute rejection, mediated by antibodies, occurs within minutes to hours after the transplant procedure. Sixty percent of the cases of hyperacute rejection are due to ABO-incompatible allografts. In the presence of ABO-incompatible transplants, plasmapheresis, splenectomy, and the CD20 monoclonal antibody, rituximab, have been reported to prevent hyperacute rejection [104], but immediate retransplantation is often the only lasting option. Because antibody-mediated rejection with ABO-compatible allografts is so rare, due to the liver's relative resistance to the humoral immune system, a positive crossmatch does not necessarily preclude liver transplantation. However, evidence does suggest that the presence of preformed donor-specific HLA-antibodies can increase the risk of acute cellular rejection and chronic rejection [26].

Unlike hyperacute rejection, which is B cell mediated, acute rejection is mediated by T cells. Acute rejection is usually seen within days or weeks of the transplant and occurs in 36–75% of liver transplant patients. Acute rejection is characterized by mononuclear inflammation and active cell damage, and episodes refractory to antirejection medications (usually high-dose steroids) can progress to chronic rejection [105]. Risk factors for the development of steroid unresponsive acute rejection include pre-liver transplant steroid administration, ABO incompatibility, recurrent rejection, low serum cyclosporine levels, and high liver function tests. A rising or persistent elevation of alanine aminotransferase (ALT) levels should prompt a biopsy to exclude rejection. Treatment options for a positive biopsy depend on the severity and include: optimization of maintenance immunosuppression for mild rejection, steroid pulses for moderate or severe rejection, and T cell depletion therapies for severe rejection.

GVHD occurs in 1–2% of liver transplant recipients and is associated with an 85% mortality rate. In the case of solid organ transplant, donor lymphocytes remaining in the parenchyma become detectable in the recipient weeks after transplant. These immunocompetent cells react against the different cellular antigens found in the host. A humoral response leading to hemolysis can also occur due to organ ABO incompatibility [106]. GVHD is divided between acute (occurring within 100 days of transplant) and chronic (after 100 days) presentations. Risk factors associated with the development of GVHD include alcoholic liver disease, hepatocellular carcinoma, and diabetes mellitus. It has also been suggested that GVHD is more likely to occur in the setting of

close HLA matching and autoimmune hepatitis. Symptoms usually develop 2–6 weeks posttransplant, and include fever, diarrhea, rash, and pancytopenia. Similar to treatment for acute rejection, treatment of GVHD includes administration of corticosteroids, increasing the current immunosuppressant regimen, or administration of medications for the antagonism of T cells. Mortality following the development of GVHD can be as high as 85% [107]. Prevention includes limiting recipient exposure to donor lymphocytes, such as graft irradiation or treatment with monoclonal antibodies, and limitation of blood products to those that have been leukocyte reduced and irradiated.

Surgical Concerns

Aside from the medical complications discussed above, there are some posttransplant complications that occur secondary to surgical technique. Successful liver transplant services have close collaboration between the internists, surgeons, and intensivists. Complications that necessitate relisting the patient or urgent return to the operating room are discussed among the services and the risks and benefits are weighed carefully.

Primary Nonfunction

Primary nonfunction occurs in 4–8% of deceased-donor liver transplants. Although uncommon, it is the most serious and life threatening condition in the immediate postoperative period and can be the most challenging for the transplant service. It is caused by reperfusion injury of the new liver, and results in irreversible graft failure. The diagnosis of primary nonfunction can only be made in the absence of technical or immunologic causes for graft dysfunction [108]. The acute destruction of hepatocytes results in decreased bile production, coagulopathy, encephalopathy, hypoglycemia, lactic acidosis, and hemodynamic instability. Signs often are present intraoperatively, but correction of the metabolic disturbances will need to be aggressively continued in the intensive care unit. The risk factors for primary nonfunction are numerous, and include: prolonged cold ischemic time, increased donor age, donor hypernatremia, donor length of stay in the ICU, male recipients with female donors, reduced graft size, racial mismatch between donors, retransplantation, and hepatic steatosis [109–111].

The only treatment for primary nonfunction is early retransplantation, and primary nonfunction is the most common reason for early retransplantation [110]. Without retransplantation, mortality is high. In addition to the complications from liver failure, cardiovascular, renal, and respiratory failure can often result from the release of

vasoactive mediators from the nonfunctioning liver. Often times, removal of the failing graft can lead to a dramatic improvement in the patient's clinical status. In the absence of an immediately available liver, a rescue hepatectomy with portocaval anastomosis can be performed with subsequent liver transplantation occurring 24–48 h following hepatectomy [112].

The effect of iloprost, a synthetic PGI₂ analogue, is currently being evaluated for its utility in preventing reperfusion injury and reducing the rate of primary allograft nonfunction [113]. Artificial liver support systems can theoretically be used to provide temporary support to patients as they await retransplantation. Artificial support systems provide hemodialysis combined with adsorption by albumin or charcoal in order to remove toxic metabolites. Bioartificial systems additionally use hepatocytes to provide synthetic function. Unfortunately, a meta-analysis of these systems did not demonstrate a mortality benefit in patients with severe liver failure. Furthermore, these systems can be associated with serious side effects, including bleeding, disseminated intravascular coagulopathy, fever, shock, and acute renal failure [114]. They also have not been studied specifically for use in patients with primary nonfunction.

Patients that undergo retransplantation for PNF demonstrate a 57% survival if retransplantation occurs within the first 3 days of transplant (presumably before multiorgan failure occurs). Retransplantation between postoperative days 8–30 is associated with worse prognosis [115]. The principal issues that determine feasibility of retransplant include the extent of advanced liver failure and its comorbid conditions, such as brain herniation, refractory sepsis, or severe hemodynamic impairment. As little data exist to guide decisions for retransplant in such settings, the decision is based on the experience and judgment of the surgical team. Patients who require a second or third retransplant for primary nonfunction have poor survival (57% mortality), and the feasibility of allocating another organ to the patient needs to be weighed against organ shortages.

Initial Poor Graft Function

Initial poor graft function (IPGF) is a poorly defined entity occurring in approximately 20% of OLTs. It can result in decreased graft survival, renal failure, severe bleeding, sepsis, and progression to primary nonfunction of the graft. Risk factors for the development of initial poor function include the quality of the graft, ischemic time, primary disease, and operative techniques [116]. Definitions of IPGF vary, but include findings of transaminitis and coagulopathy within 7 days of transplant [117]. Although graft and recipient outcome after IPGF remains unpredictable [118], early identification does allow for close monitoring and a low threshold to

return for exploratory laparotomy. The monitoring of static serum lactate levels does not predict liver function after transplantation, but Wu et al. studied lactate clearance, which has been suggested as an alternative biomarker for the development of IPGF [119]. Patients with early lactate clearance less than 24.6% had a higher rate of IPGF (OR=169). Further studies are necessary to determine if poor lactate clearance can prompt intensivists and surgeons to institute more aggressive interventions and improve mortality.

Hepatic Artery Thrombosis

Hepatic artery thrombosis occurs in up to 5% of transplanted patients, with a higher incidence in pediatric patients, and is associated with a high rate of graft failure and mortality [32]. It is the most common vascular complication of liver transplantation and the second most common cause of liver graft failure after primary nonfunction [120]. Risk factors for the development of hepatic artery thrombosis include unmatched vessels, vascular damage during anastomosis construction, retransplantation, low recipient weight, and anatomic variance. Nonsurgical risk factors include diabetes, hypercoagulable state, CMV mismatch, primary sclerosing cholangitis, and donor age [121].

The clinical presentation depends on the time of onset of HAT and the existence of collateral vessels. Early HAT can present with biliary tract necrosis followed by sepsis, altered mental status, and coagulopathy. Late HAT usually presents as biliary tract complications leading to necrosis and abscess formation and liver ischemia. The key is early diagnosis so that treatment can be initiated in order to avoid graft loss. Posttransplant grafts can be monitored with Doppler ultrasound to detect presence or absence of hepatic artery flow, and definitive diagnosis is made with angiography or surgical exploration. If the diagnosis is made early, and there is no liver graft damage, surgical reconstruction of the hepatic artery is the best treatment [122]. Retransplant may be necessary if there is accompanying biliary tract damage and parenchymal necrosis.

Portal Vein Thrombosis

Portal vein thrombosis is rare in adults, occurring in only 0.5–15% of liver transplants, and usually in the early transplant period [67]. Patients with portal vein thrombosis can present with transaminitis, ascites, portal hypertension, and graft failure. Risk factors for the development of portal vein thrombosis include technical difficulties during surgery, pretransplant portal vein thrombosis, small portal vein size, prior splenectomy, and the use of venous conduits [123]. Surgical treatments include thrombectomy and anastomotic

revision, or retransplantation. Thrombolysis in interventional radiology is generally not recommended because of the risk of re-occlusion and concern for anastomotic disruption.

Hepatic Vein and Inferior Vena Cava Thrombosis

Hepatic vein and inferior vena cava (IVC) thrombosis are also rare, occurring in 1–6% of transplants [124]. Symptoms include lower extremity edema, portal hypertension, and ascites. Surgical technique, which may result in narrow vessels and decrease flow into the IVC, and underlying hypercoagulability are risk factors. Percutaneous angioplasty is the treatment for thrombosis, but may be complicated by restenosis and repeat procedures may be necessary [125]. Stenting may also be considered. Retransplantation may be necessary if there is massive necrosis. Unfortunately, there is no provision for priority listing for patients with portal vein or hepatic vein thrombosis from UNOS. Most centers will start long-term anticoagulation after revision or retransplantation for vascular thrombosis [67].

Biliary Tract Stenosis

Biliary tract complications are the most common technical problem after OLT and occur in 5–20% of patients post-liver transplant [126]. They are often referred to as the “Achilles heel” of liver transplantation. These can be complicated by graft dysfunction or secondary infection. Strictures and leaks are the most common cause of complications. While leaks can occur early, strictures usually occur late following transplantation (after 3 months). Risk factors include vascular insufficiency, ischemia/reperfusion injury, or poor surgical technique. The rate of anastomotic stricture is higher in patients undergoing living donor transplants [127]. Non-anastomotic leaks can also occur as a result of vascular, infectious, or immune-mediated dysfunction. These usually present earlier than anastomotic leaks and are associated with worse outcomes.

Evaluation for biliary irregularities can be difficult as elevations in bilirubin, alkaline phosphatase, and gamma glutamyl transferase can be nonspecific. Endoscopic retrograde cholangiopancreatography (ERCP) with dilation and stent placement is generally the initial approach to treating biliary anastomotic strictures. ERCP has a high success rate (75%) in the treatment of biliary strictures. In the event of ERCP failure, percutaneous transhepatic biliary drainage or surgical reconstruction with a Roux-en-Y hepaticojejunostomy can be performed [128]. Intraoperative placement of a T-tube to stent the biliary tract may help to prevent stricture formation, monitor bile output and perform cholangiography [129]; however, the increased risk of peritonitis and cholangitis limits the utility of T-tubes.

Small-for-Size Syndrome

Compared with cadaveric transplantation, living donor transplantation is complicated with a unique set of concerns—including donor safety, graft size, technical difficulties with biliary tree and outflow tract repairs, and of course ethical considerations. The liver volume required to avoid small-for-size syndrome (SFSS) is characterized by a graft-to-recipient weight ratio of 0.8. Small for size grafts are grafts that are less than 0.8–1% of the recipient’s weight, or less than 30–50% of the expected full sized liver [130]. Although its exact mechanism is unknown, SFSS appears to result from portal hypoperfusion and inadequate hepatocellular regeneration. SFSS results in delayed synthetic function and decreased graft survival. Severe cases may progress to liver failure within weeks of transplant. Strategies to decrease portal hypertension may be effective treatments for SFSS such as splenic artery embolization, transjugular intrahepatic portosystemic shunt, or mesocaval or portocaval shunts [131, 132].

Long-Term Complications

Because outcomes in the early posttransplant period continue to improve, management of complications in the later posttransplant period is becoming even more integral to the overall care of the liver transplant patient. These late complications are largely related to the consequences of prolonged immunosuppression, but recurrence of the original disease (HBV, HCV, HCC) remains of concern. The intensivist should be aware of the treatments and indications so that these important therapies are not missed in the immediate postoperative period.

Hepatitis B Virus

Hepatitis B virus (HBV) recurs nearly universally in previously infected liver transplant patients. HBV recurrence contributed significantly to post-liver transplant mortality and followed a particularly aggressive course, including rapidly progressing cirrhosis or fulminant hepatitis, prior to the introduction of current prophylaxis regimens. Consequently, HBV infection had previously been a relative contraindication to liver transplantation at certain transplant centers [109]. The risk of HBV recurrence is increased depending on the type of pretransplant disease. For instance, the presence of HBV DNA seropositivity or HBV-associated cirrhosis prior to transplant results in an increased risk of HBV recurrence. Patients with fulminant hepatitis or a superimposed delta virus have a lower risk of reinfection [133].

The introduction of anti-hepatitis B surface antigen (anti-HBs) immune globulin, or HBIG, has reduced the recurrence

of HBV following liver transplantation from 80 to 20% [134]. Specifically, long-term treatment with HBIG (greater than 6 months) afforded a longer time to recurrence, decreased rate of recurrence, and increased rate of survival [133]. Although the mechanism for this protective action has not yet been elucidated, the goal for treatment with HBIG is HBsAb greater than 500 IU/L for the first 6 months following transplant [135, 136]. Unfortunately, the long-term use of HBIG is associated with high costs, and HBIG has been less effective in patients with high viral loads [134].

For patients at high risk of HBV recurrence (those with high viral load and pretransplant viral replication), a nucleoside analogue antiviral should also be considered [135]. The combination of HBIG and antivirals has improved 5 year survival to greater than 90% in patients undergoing OLT for HBV [137]. Lamivudine is often used in the pretransplant period to lower HBV load prior to transplant. However, a HBV polymerase mutation, YMDD, has limited the utility of lamivudine [138]. In the presence of lamivudine resistance, alternative antivirals such as adefovir, entecavir, or tenofovir may be considered. Monotherapy with antivirals posttransplant has not been found to be as effective in preventing the recurrence of disease. Currently, there are two strategies for discontinuing HBIG postoperatively. The first is HBIG withdrawal after initial combination therapy, and addition of a second oral antiviral agent. The second is a completely HBIG-free regimen using one or two oral antiviral agents [139].

Hepatitis C Virus

Hepatitis C recurrence posttransplantation follows a particularly aggressive course. Up to 30% of all patients with disease recurrence will progress to cirrhosis of the allograft within 5 years of transplant [109]. Factors that may contribute to more aggressive disease course include donor age, graft steatosis, ischemia/reperfusion injury, diabetes, immunosuppression, and cold ischemic time [61, 140]. Low viral load prior to transplant has been demonstrated to reduce the risk of severe HCV recurrence. Unlike with HBV, no role for hepatitis C virus immune globulin has been found for the treatment of these patients [137].

Following transplant, there is no role for prophylactic antiviral therapy. High levels of immunosuppression make antiviral therapy ineffective, and these treatments are poorly tolerated. Antivirals should be used in patients with severe inflammation or mild to moderate fibrosis on biopsy [61]. Currently, pegylated interferon and ribavirin are being used, and new protease inhibitors are being evaluated for their utility in treating HCV.

Historically, retransplantation for liver failure secondary to recurrent HCV infection has been associated with a particularly poor survival [141], but there are conflicting results in the literature [142]. The current practice is not to perform

retransplant for recurrent HCV, but this controversy remains to be decided, and perhaps will be influenced by advances in antiviral therapy.

Posttransplant Cancers

OLT recipients are at least twice as likely to develop cancer as the matched population, and cancer accounts for approximately 11% of all deaths after transplant [143]. Most posttransplant malignancies are cutaneous. Of the noncutaneous malignancies, risk was increased in patients with primary sclerosing cholangitis (PSC) and alcoholic liver disease (ALD). The intensivist should be aware of the treatment for recurrent hepatocellular carcinoma or posttransplant lymphoproliferative disease since patients may return to the ICU due to failing graft function.

Hepatocellular Carcinoma

An increasing number of patients with hepatocellular carcinoma (HCC) undergo liver transplantation. This trend has occurred due to the UNOS organ allocation protocol, which allows exception to the MELD score for patients with HCC, giving them priority for liver transplantation beyond that determined by the degree of liver dysfunction [144, 145]. The rates of recurrence for patients with limited disease (with the Milan Criteria) are 10%, while patients with more aggressive disease demonstrate recurrence rates of 40–60% [146]. The risk of tumor recurrence in these patients is augmented by the use of immunosuppressants, and early discontinuation of calcineurin inhibitors may help to prevent disease recurrence. Uncontrolled pilot trials and retrospective analyses have suggested that sirolimus was associated with lower tumor recurrence and improved survival after liver transplantation [147]. These results have not been confirmed in an RCT and no recommendation can be made regarding use of mTOR inhibitors to reduce HCC recurrence outside of clinical trials.

Staging systems, such as the Milan Criteria or UCSF Criteria, can be used to predict the recurrence of HCC following liver transplant [148]. Risk factors for the development of recurrence include initial lesion size, number of lesions, and age of donor. AFP level, waiting time until transplant, and use of therapy to decrease disease burden prior to transplant did not affect the rate of recurrence [144]. While most disease recurs within the first 1–2 years following transplant, late disease recurrence is not uncommon [149]. Surveillance methods following transplant should include serial chest and abdominal imaging for 3 years following transplant. AFP levels may be trended as well. Once disease recurrence occurs, radiofrequency ablation or lesion resections are the treatments of choice. Liver retransplantation is not recommended for recurrent HCC [150].

Posttransplant Lymphoproliferative Disease

Posttransplant lymphoproliferative disease (PTLD) has an incidence of 2–5% following liver transplantation. Risk factors for the development of PTLD include Epstein-Barr virus (EBV) infection, young recipient age, cytomegalovirus (CMV) mismatch, and the use of thymoglobulin [151]. Early occurrence frequently occurs in the setting of EBV infection, while later occurrence is not associated with EBV. EBV status should be determined prior to transplantation in order to identify high-risk individuals. Patients with high viral loads should be considered for early preemptive therapy, including the use of antivirals or monoclonal B cell antibodies. The signs of PTLD development include lymphadenopathy, microcytic anemia, electrolyte disturbances, and abnormal liver or kidney function. The diagnosis relies on histopathology. Once PTLD has been diagnosed, a reduction or cessation of immunosuppression should be considered [151]. The anti CD20 antibody rituximab, chemotherapy, radiation

therapy, and surgical debulking are effective in the treatment of PTLD [152, 153]. Though not often seen in the ICU, some of these patients may be admitted due to complications from tumor growth or chemotherapy.

Conclusion

Post-liver transplant patients require ongoing medical management to both avoid and treat potential complications (Table 29.4). Optimal medical management encompasses all organ systems and requires close collaboration among the multidisciplinary physicians, nurses, and ancillary staff in the ICU. Many complications cannot be managed just medically, and will require relisting the patient or return to the operating room. Even after the immediate surgical period, many patients will require readmission to the ICU due to long-term complications. The intensivist must be knowledgeable about the immediate and long-term care related to liver transplantation.

Table 29.4 Common complications after OLT: their risk factors and treatment options

Post-op complication	Incidence	Risk factors	Treatment options
Poor Graft Function			
Primary nonfunction	4–8%	Ischemic time, donor age, graft size, retransplantation, graft steatosis	<ul style="list-style-type: none"> – Retransplantation – Temporizing measures: rescue hepatectomy, artificial liver support, iloprost
Initial poor function	20%	Graft quality, ischemic time, primary disease, operative techniques	<ul style="list-style-type: none"> – Supportive care
Vascular complications			
Hepatic artery	5%	Unmatched vessels, vascular damage, retransplantation, diabetes, hypercoagulable state, CMV mismatch, PSC, donor age	<ul style="list-style-type: none"> – Surgical reconstruction – Retransplantation
Portal vein	0.5–15%	Small size, pretransplant portal vein thrombosis, prior splenectomy, use of venous conduits	<ul style="list-style-type: none"> – Thrombectomy and reconstruction – Retransplantation
Hepatic vein	1–6%	Surgical technique, budd-chiari syndrome	<ul style="list-style-type: none"> – Angioplasty – Stenting
Biliary complications	5–20%	Vascular insufficiency, reperfusion injury, surgical technique	ERCP with dilation and stenting, percutaneous transhepatic biliary drainage, surgical reconstruction
Rejection			
Acute	36–75%	Prior steroid use, ABO incompatibility, recurrent rejection, low cyclosporine levels, elevated LFTs	<ul style="list-style-type: none"> – High-dose steroids – Anti-thymocyte antibodies
Chronic	3–5%	Poor monitoring, noncompliance with immunosuppressives, multiple episodes of rejection	<ul style="list-style-type: none"> – Retransplantation
Graft vs. host disease	1–2%	Alcoholic liver disease, HCC, diabetes	<ul style="list-style-type: none"> – High-dose steroids – Increased immunosuppression – Anti-T cell regimens
Recurrence of Disease			
HCC	10% (within Milan criteria)	Immunosuppression, number and size of lesions, donor age	<ul style="list-style-type: none"> – Radiofrequency ablation – Resection of recurrent lesion
HBV	20%	HBV DNA seropositivity, HBV associated cirrhosis	<ul style="list-style-type: none"> – HBIG – Antivirals
HCV	100% (30% develop cirrhosis in 5 years)	High doses of immunosuppression, donor age, ischemic time, reperfusion injury, graft steatosis, diabetes	<ul style="list-style-type: none"> – Pegylated interferon – Ribivarin – Direct acting antivirals

References

1. Glauser FL. Systemic hemodynamic and cardiac function changes in patients undergoing orthotopic liver transplantation. *Chest*. 1990;98(5):1210–5.
2. Feltracco P, Barbieri S, Galligioni H, Michieletto E, Carollo C, Ori C. Intensive care management of liver transplanted patients. *World J Hepatol*. 2011;3:61–71.
3. Schumann R. Intraoperative resource utilization in anesthesia for liver transplantation in the United States: a survey. *Anesth Analg*. 2003;97:21–8.
4. Connors Jr AF, Speroff T, Dawson NV, Thomas C, Harrell Jr FE, Wagner D, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. *JAMA*. 1996;276:889–97.
5. Wheeler AP, Bernard GR, Thompson BT, Schoenfeld D, Wiedemann HP, deBoisblanc B, et al. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med*. 2006;354:2213–24.
6. Gwak MS, Kim JA, Kim GS, Choi SJ, Ahn H, Lee JJ, et al. Incidence of severe ventricular arrhythmias during pulmonary artery catheterization in liver allograft recipients. *Liver Transpl*. 2007;13:1451–4.
7. Cannesson M, Aboy M, Hofer CK, Rehman M. Pulse pressure variation: where are we today? *J Clin Monit Comput*. 2011;25:45–56.
8. Natalini G, Rosano A, Franceschetti ME, Facchetti P, Bernardini A. Variations in arterial blood pressure and photoplethysmography during mechanical ventilation. *Anesth Analg*. 2006;103:1182–8.
9. Solus-Biguenet H, Fleyfel M, Tavernier B, Kipnis E, Onimus J, Robin E, et al. Non-invasive prediction of fluid responsiveness during major hepatic surgery. *Br J Anaesth*. 2006;97:808–16.
10. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med*. 2009;37:2642–7.
11. Rodriguez-Roisin R, Krowka MJ, Herve P, Fallon MB. Pulmonary-hepatic vascular disorders (PHD). *Eur Respir J*. 2004;24:861–80.
12. Colle IO, Moreau R, Godinho E, Belghiti J, Ettori F, Cohen-Solal A, et al. Diagnosis of portopulmonary hypertension in candidates for liver transplantation: a prospective study. *Hepatology*. 2003;37:401–9.
13. Krowka M. Hepatopulmonary syndrome and liver transplantation. *Liver Transpl*. 2000;6:113–5.
14. Krowka MJ, Mandell MS, Ramsay MA, Kawut SM, Fallon MB, Manzarbeitia C, et al. Hepatopulmonary syndrome and portopulmonary hypertension: a report of the multicenter liver transplant database. *Liver Transpl*. 2004;10:174–82.
15. Awdish RL, Cajigas HR. Early initiation of prostacyclin in portopulmonary hypertension: 10 years of a transplant center's experience. *Lung*. 2013;191:593–600.
16. Hong SK, Hwang S, Lee SG, Lee LS, Ahn CS, Kim KH, et al. Pulmonary complications following adult liver transplantation. *Transplant Proc*. 2006;38:2979–81.
17. Levesque E, Hoti E, Azoulay D, Honore I, Guignard B, Vibert E, et al. Pulmonary complications after elective liver transplantation: incidence, risk factors, and outcome. *Transplantation*. 2012;94:532–8.
18. Mandell MS, Lockrem J, Kelley SD. Immediate tracheal extubation after liver transplantation: experience of two transplant centers. *Anesth Analg*. 1997;84:249–53.
19. Mandell MS, Lezotte D, Kam I, Zamudio S. Reduced use of intensive care after liver transplantation: influence of early extubation. *Liver Transpl*. 2002;8:676–81.
20. Salizzoni M, Cerutti E, Romagnoli R, Lupo F, Franchello A, Zamboni F, et al. The first one thousand liver transplants in Turin: a single-center experience in Italy. *Transpl Int*. 2005;18:1328–35.
21. Biancofiore G, Romanelli AM, Bindi ML, Consani G, Boldrini A, Battistini M, et al. Very early tracheal extubation without predetermined criteria in a liver transplant recipient population. *Liver Transpl*. 2001;7:777–82.
22. Glanemann M, Busch T, Neuhaus P, Kaisers U. Fast tracking in liver transplantation. Immediate postoperative tracheal extubation: feasibility and clinical impact. *Swiss Med Wkly*. 2007;137:187–91.
23. Mandell MS, Stoner TJ, Barnett R, Shaked A, Bellamy M, Biancofiore G, et al. A multicenter evaluation of safety of early extubation in liver transplant recipients. *Liver Transpl*. 2007;13:1557–63.
24. Mandell MS, Hang Y. Pro: early extubation after liver transplantation. *J Cardiothorac Vasc Anesth*. 2007;21:752–5.
25. Steadman RH. Con: immediate extubation for liver transplantation. *J Cardiothorac Vasc Anesth*. 2007;21:756–7.
26. Musat AI, Pigott CM, Ellis TM, Agni RM, Levenson GE, Powell AJ, et al. Pretransplant donor-specific anti-HLA antibodies as predictors of early allograft rejection in ABO-compatible liver transplantation. *Liver Transpl*. 2013;19:1132–41.
27. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000;342:1301–8.
28. Futier E, Constantin JM, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med*. 2013;369:428–37.
29. Varpula T, Valta P, Niemi R, Takkunen O, Hynynen M, Pettila VV. Airway pressure release ventilation as a primary ventilatory mode in acute respiratory distress syndrome. *Acta Anaesthesiol Scand*. 2004;48:722–31.
30. Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, et al. High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med*. 2013;368:795–805.
31. Young D, Lamb SE, Shah S, MacKenzie I, Tunnicliffe W, Lall R, et al. High-frequency oscillation for acute respiratory distress syndrome. *N Engl J Med*. 2013;368:806–13.
32. Guerin C, Reigner J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013;368:2159–68.
33. Adhikari NK, Burns KE, Friedrich JO, Granton JT, Cook DJ, Meade MO. Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. *BMJ*. 2007;334:779.
34. Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010;363:1107–16.
35. Hodgson C, Keating JL, Holland AE, Davies AR, Smirneos L, Bradley SJ, et al. Recruitment manoeuvres for adults with acute lung injury receiving mechanical ventilation. *Cochrane Database Syst Rev*. 2009;CD006667.
36. Saner FH, Olde Damink SW, Pavlakovic G, van den Broek MA, Sotiropoulos GC, Radtke A, et al. Positive end-expiratory pressure induces liver congestion in living donor liver transplant patients: myth or fact. *Transplantation*. 2008;85:1863–6.
37. Arguedas MR, Abrams GA, Krowka MJ, Fallon MB. Prospective evaluation of outcomes and predictors of mortality in patients with hepatopulmonary syndrome undergoing liver transplantation. *Hepatology*. 2003;37:192–7.
38. Schiller O, Avitzur Y, Kadmon G, Nahum E, Steinberg RM, Nachmias V, et al. Nitric oxide for post-liver-transplantation

- hypoxemia in pediatric hepatopulmonary syndrome: case report and review. *Pediatr Transplant*. 2011;15:E130–4.
39. Gupta S, Castel H, Rao RV, Picard M, Lilly L, Faughnan ME, et al. Improved survival after liver transplantation in patients with hepatopulmonary syndrome. *Am J Transplant*. 2010;10:354–63.
40. Carson SS, Kress JP, Rodgers JE, Vinayak A, Campbell-Bright S, Levitt J, et al. A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. *Crit Care Med*. 2006;34:1326–32.
41. Fraser GL, Devlin JW, Worby CP, Alhazzani W, Barr J, Dasta JF, et al. Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials. *Crit Care Med*. 2013;41(9 Suppl 1):S30–8.
42. Terajima K, Takeda S, Taniai N, Tanaka K, Oda Y, Asada A, et al. Repeated dexmedetomidine infusions, a postoperative living-donor liver transplantation patient. *J Anesth*. 2006;20:234–6.
43. Enomoto Y, Kudo T, Saito T, Hori T, Kaneko M, Matsui A, et al. Prolonged use of dexmedetomidine in an infant with respiratory failure following living donor liver transplantation. *Paediatr Anaesth*. 2006;16:1285–8.
44. Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan Jr JA, Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis. *JAMA*. 2003;290:2455–63.
45. Janicic N, Verbalis JG. Evaluation and management of hyponatremia in hospitalized patients. *Endocrinol Metab Clin North Am*. 2003;32:459–81.
46. Biggins SW, Kim WR, Terrault NA, Saab S, Balan V, Schiano T, et al. Evidence-based incorporation of serum sodium concentration into MELD. *Gastroenterology*. 2006;130:1652–60.
47. Lee J, Kim DK, Lee JW, Oh KH, Oh YK, Na KY, et al. Rapid correction rate of hyponatremia as an independent risk factor for neurological complication following liver transplantation. *Tohoku J Exp Med*. 2013;229:97–105.
48. Nair S, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. *Hepatology*. 2002;35:1179–85.
49. Scheinin B, Orko R, Lalla ML, Hockerstedt K, Scheinin TM. Significance of ionized calcium during liver transplantation. *Acta Anaesthesiol Belg*. 1989;40:101–5.
50. Wallia A, Parikh ND, Molitch ME, Mahler E, Tian L, Huang JJ, et al. Posttransplant hyperglycemia is associated with increased risk of liver allograft rejection. *Transplantation*. 2010;89:222–6.
51. Park C, Hsu C, Neelakanta G, Nourmand H, Braunfeld M, Wray C, et al. Severe intraoperative hyperglycemia is independently associated with surgical site infection after liver transplantation. *Transplantation*. 2009;87:1031–6.
52. Ammori JB, Sigakis M, Englesbe MJ, O'Reilly M, Pelletier SJ. Effect of intraoperative hyperglycemia during liver transplantation. *J Surg Res*. 2007;140:227–33.
53. Marik PE, Preiser JC. Toward understanding tight glycemic control in the ICU: a systematic review and metaanalysis. *Chest*. 2010;137:544–51.
54. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283–97.
55. Yalavarthy R, Edelstein CL, Teitelbaum I. Acute renal failure and chronic kidney disease following liver transplantation. *Hemodial Int*. 2007;11 Suppl 3:S7–12.
56. Distant DA, Gonwa TA. The kidney in liver transplantation. *J Am Soc Nephrol*. 1993;4:129–36.
57. Kundakci A, Pirat A, Komurcu O, Torgay A, Karakayali H, Arslan G, et al. Rifle criteria for acute kidney dysfunction following liver transplantation: incidence and risk factors. *Transplant Proc*. 2010;42:4171–4.
58. Inoue Y, Soyama A, Takatsuki M, Hidaka M, Muraoka I, Kanematsu T, et al. Acute kidney injury following living donor liver transplantation. *Clin Transplant*. 2012;26:E530–5.
59. Lata J. Hepatorenal syndrome. *World J Gastroenterol*. 2012;18:4978–84.
60. Marik PE, Wood K, Starzl TE. The course of type 1 hepato-renal syndrome post liver transplantation. *Nephrol Dial Transplant*. 2006;21:478–82.
61. Lucey MR, Terrault N, Ojo L, Hay JE, Neuberger J, Blumberg E, et al. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Liver Transpl*. 2013;19:3–26.
62. Biancofiore G, Pucci L, Cerutti E, Penno G, Pardini E, Esposito M, et al. Cystatin C as a marker of renal function immediately after liver transplantation. *Liver Transpl*. 2006;12:285–91.
63. Beckebaum S, Cicinnati VR, Radtke A, Kabar I. Calcineurin inhibitors in liver transplantation—still champions or threatened by serious competitors? *Liver Int*. 2013;33:656–65.
64. Ziolkowski J, Paczek L, Senatorski G, Niewczas M, Oldakowska-Jedynak U, Wyzgal J, et al. Renal function after liver transplantation: calcineurin inhibitor nephrotoxicity. *Transplant Proc*. 2003;35:2307–9.
65. Penninga L, Wettergren A, Chan AW, Steinbruchel DA, Gluud C. Calcineurin inhibitor minimisation versus continuation of calcineurin inhibitor treatment for liver transplant recipients. *Cochrane Database Syst Rev*. 2012;3, CD008852.
66. Romero FA, Razonable RR. Infections in liver transplant recipients. *World J Hepatol*. 2011;3:83–92.
67. Razonable RR, Findlay JY, O'Riordan A, Burroughs SG, Ghobrial RM, Agarwal B, et al. Critical care issues in patients after liver transplantation. *Liver Transpl*. 2011;17:511–27.
68. Gurusamy KS, Kumar Y, Davidson BR. Methods of preventing bacterial sepsis and wound complications for liver transplantation. *Cochrane Database Syst Rev*. 2008;CD006660.
69. Bosch W, Heckman MG, Diehl NN, Shalev JA, Pungpapong S, Hellinger WC. Association of cytomegalovirus infection and disease with death and graft loss after liver transplant in high-risk recipients. *Am J Transplant*. 2011;11:2181–9.
70. Slifkin M, Ruthazer R, Freeman R, Bloom J, Fitzmaurice S, Fairchild R, et al. Impact of cytomegalovirus prophylaxis on rejection following orthotopic liver transplantation. *Liver Transpl*. 2005;11:1597–602.
71. Singh N, Husain S. Invasive aspergillosis in solid organ transplant recipients. *Am J Transplant*. 2009;9 Suppl 4:S180–91.
72. Pappas PG, Andes D, Schuster M, Hadley S, Rabkin J, Merion RM, et al. Invasive fungal infections in low-risk liver transplant recipients: a multi-center prospective observational study. *Am J Transplant*. 2006;6:386–91.
73. Napolitano LM, Kurek S, Luchette FA, Corwin HL, Barie PS, Tisherman SA, et al. Clinical practice guideline: red blood cell transfusion in adult trauma and critical care. *Crit Care Med*. 2009;37:3124–57.
74. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350:2247–56.
75. Barron ME, Wilkes MM, Navickis RJ. A systematic review of the comparative safety of colloids. *Arch Surg*. 2004;139:552–63.
76. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012;367:1901–11.
77. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, et al. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med*. 2005;352:777–85.
78. Boniatti MM, Filho EM, Cardoso PR, Vieira SR. Physicochemical evaluation of acid-base disorders after liver transplantation and the

- contribution from administered fluids. *Transplant Proc.* 2013;45:2283–7.
79. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA.* 2012;308:1566–72.
 80. Noritomi DT, Soriano FG, Kellum JA, Cappi SB, Biselli PJ, Liborio AB, et al. Metabolic acidosis in patients with severe sepsis and septic shock: a longitudinal quantitative study. *Crit Care Med.* 2009;37:2733–9.
 81. Northup PG. Hypercoagulation in liver disease. *Clin Liver Dis.* 2009;13:109–16.
 82. Massicotte L, Beaulieu D, Thibeault L, Roy JD, Marleau D, Lapointe R, et al. Coagulation defects do not predict blood product requirements during liver transplantation. *Transplantation.* 2008;85:956–62.
 83. Porte RJ. Coagulation and fibrinolysis in orthotopic liver transplantation: current views and insights. *Semin Thromb Hemost.* 1993;19:191–6.
 84. Pernambuco JR, Langley PG, Hughes RD, Izumi S, Williams R. Fibrinolytic abnormalities following liver transplantation in patients with fulminant hepatic failure. *Eur J Gastroenterol Hepatol.* 1995;7:155–9.
 85. Senzolo M, Cholongitas E, Thalheimer U, Riddell A, Agarwal S, Mallett S, et al. Heparin-like effect in liver disease and liver transplantation. *Clin Liver Dis.* 2009;13:43–53.
 86. Agarwal S, Senzolo M, Melikian C, Burroughs A, Mallett SV. The prevalence of a heparin-like effect shown on the thromboelastograph in patients undergoing liver transplantation. *Liver Transpl.* 2008;14:855–60.
 87. Bayly PJ, Thick M. Reversal of post-reperfusion coagulopathy by protamine sulphate in orthotopic liver transplantation. *Br J Anaesth.* 1994;73:840–2.
 88. Eissa LA, Gad LS, Rabie AM, El-Gayar AM. Thrombopoietin level in patients with chronic liver diseases. *Ann Hepatol.* 2008;7:235–44.
 89. Ingeberg S, Jacobsen P, Fischer E, Bentsen KD. Platelet aggregation and release of ATP in patients with hepatic cirrhosis. *Scand J Gastroenterol.* 1985;20:285–8.
 90. Gunduz E, Akay OM, Bal C, Gulbas Z. Can thrombelastography be a new tool to assess bleeding risk in patients with idiopathic thrombocytopenic purpura? *Platelets.* 2011;22:516–20.
 91. Yousef WI, Salazar F, Dasarathy S, Beddow T, Mullen KD. Role of fresh frozen plasma infusion in correction of coagulopathy of chronic liver disease: a dual phase study. *Am J Gastroenterol.* 2003;98:1391–4.
 92. Busani S, Semeraro G, Cantaroni C, Masetti M, Marietta M, Girardis M. Recombinant activated factor VII in critical bleeding after orthotopic liver transplantation. *Transplant Proc.* 2008;40:1989–90.
 93. Pillai AA, Levitsky J. Overview of immunosuppression in liver transplantation. *World J Gastroenterol.* 2009;15:4225–33.
 94. Zarrinpar A, Busuttill RW. Immunomodulating options for liver transplant patients. *Expert Rev Clin Immunol.* 2012;8:565–78.
 95. Klintmalm GB, Davis GL, Teperman L, Netto GJ, Washburn K, Rudich SM, et al. A randomized, multicenter study comparing steroid-free immunosuppression and standard immunosuppression for liver transplant recipients with chronic hepatitis C. *Liver Transpl.* 2011;17:1394–403.
 96. Shao ZY, Yan LN, Wang WT, Li B, Wen TF, Yang JY, et al. Prophylaxis of chronic kidney disease after liver transplantation—experience from west China. *World J Gastroenterol.* 2012;18:991–8.
 97. Kong Y, Wang D, Shang Y, Liang W, Ling X, Guo Z, et al. Calcineurin-inhibitor minimization in liver transplant patients with calcineurin-inhibitor-related renal dysfunction: a meta-analysis. *PLoS One.* 2011;6:e24387.
 98. Boudjema K, Camus C, Saliba F, Calmus Y, Salame E, Pageaux G, et al. Reduced-dose tacrolimus with mycophenolate mofetil vs. standard-dose tacrolimus in liver transplantation: a randomized study. *Am J Transplant.* 2011;11:965–76.
 99. Trotter JF. Sirolimus in liver transplantation. *Transplant Proc.* 2003;35(3 Suppl):193S–200.
 100. Fischer L, Klempnauer J, Beckebaum S, Metselaar HJ, Neuhaus P, Schemmer P, et al. A randomized, controlled study to assess the conversion from calcineurin-inhibitors to everolimus after liver transplantation—PROTECT. *Am J Transplant.* 2012;12:1855–65.
 101. Irish WD, Arcona S, Bowers D, Trotter JF. Cyclosporine versus tacrolimus treated liver transplant recipients with chronic hepatitis C: outcomes analysis of the UNOS/OPTN database. *Am J Transplant.* 2011;11:1676–85.
 102. Trotter JF. Hot-topic debate on hepatitis C virus: the type of immunosuppression matters. *Liver Transpl.* 2011;17 Suppl 3:S20–3.
 103. Chinnakotla S, Davis GL, Vasani S, Kim P, Tomiyama K, Sanchez E, et al. Impact of sirolimus on the recurrence of hepatocellular carcinoma after liver transplantation. *Liver Transpl.* 2009;15:1834–42.
 104. Monteiro I, McLoughlin LM, Fisher A, de la Torre AN, Koneru B. Rituximab with plasmapheresis and splenectomy in aboincompatible liver transplantation. *Transplantation.* 2003;76:1648–9.
 105. Andreu H, Rimola A, Bruguera M, Navasa M, Cirera I, Grande L, et al. Acute cellular rejection in liver transplant recipients under cyclosporine immunosuppression: predictive factors of response to antirejection therapy. *Transplantation.* 2002;73:1936–43.
 106. Akbulut S, Yilmaz M, Yilmaz S. Graft-versus-host disease after liver transplantation: a comprehensive literature review. *World J Gastroenterol.* 2012;18:5240–8.
 107. Thin L, Macquillan G, Adams L, Garas G, Seow C, Cannell P, et al. Acute graft-versus-host disease after liver transplant: novel use of etanercept and the role of tumor necrosis factor alpha inhibitors. *Liver Transpl.* 2009;15:421–6.
 108. Lock JF, Schwabauer E, Martus P, Videv N, Pratschke J, Malinowski M, et al. Early diagnosis of primary nonfunction and indication for reoperation after liver transplantation. *Liver Transpl.* 2010;16:172–80.
 109. Burton Jr JR, Rosen HR. Diagnosis and management of allograft failure. *Clin Liver Dis.* 2006;10:407–35.
 110. Uemura T, Randall HB, Sanchez EQ, Ikegami T, Narasimhan G, McKenna GJ, et al. Liver retransplantation for primary nonfunction: analysis of a 20-year single-center experience. *Liver Transpl.* 2007;13:227–33.
 111. Stahl JE, Kreke JE, Malek FA, Schaefer AJ, Vacanti J. Consequences of cold-ischemia time on primary nonfunction and patient and graft survival in liver transplantation: a meta-analysis. *PLoS One.* 2008;3(6):e2468.
 112. Arora H, Thekkekandam J, Tesche L, Sweeting R, Gerber DA, Hayashi PH, et al. Long-term survival after 67 hours of anhepatic state due to primary liver allograft nonfunction. *Liver Transpl.* 2010;16:1428–33.
 113. Barthel E, Rauchfuss F, Hoyer H, Breternitz M, Jandt K, Settmacher U. The PRAISE study: a prospective, multi-center, randomized, double blinded, placebo-controlled study for the evaluation of iloprost in the early postoperative period after liver transplantation (ISRCTN12622749). *BMC Surg.* 2013;13:1.
 114. Kjaergard LL, Liu J, Als-Nielsen B, Gluud C. Artificial and bioartificial support systems for acute and acute-on-chronic liver failure: a systematic review. *JAMA.* 2003;289:217–22.
 115. Zimmerman MA, Ghobrial RM. When shouldn't we retransplant? *Liver Transpl.* 2005;(11 Suppl 2):S14–20.
 116. Chen H, Peng CH, Shen BY, Deng XX, Shen C, Xie JJ, et al. Multi-factor analysis of initial poor graft function after orthotopic

- liver transplantation. *Hepatobiliary Pancreat Dis Int.* 2007;6:141–6.
117. Nanashima A, Pillay P, Verran DJ, Painter D, Nakasuji M, Crawford M, et al. Analysis of initial poor graft function after orthotopic liver transplantation: experience of an Australian single liver transplantation center. *Transplant Proc.* 2002;34:1231–5.
 118. Maring JK, Klompmaker IJ, Zwaveling JH, Kranenburg K, Ten Vergert EM, Slooff MJ. Poor initial graft function after orthotopic liver transplantation: can it be predicted and does it affect outcome? An analysis of 125 adult primary transplantations. *Clin Transplant.* 1997;11(5 Pt 1):373–9.
 119. Wu JF, Wu RY, Chen J, Ou-Yang B, Chen MY, Guan XD. Early lactate clearance as a reliable predictor of initial poor graft function after orthotopic liver transplantation. *Hepatobiliary Pancreat Dis Int.* 2011;10:587–92.
 120. Pareja E, Cortes M, Navarro R, Sanjuan F, Lopez R, Mir J. Vascular complications after orthotopic liver transplantation: hepatic artery thrombosis. *Transplant Proc.* 2010;42:2970–2.
 121. Stewart ZA, Locke JE, Segev DL, Dagher NN, Singer AL, Montgomery RA, et al. Increased risk of graft loss from hepatic artery thrombosis after liver transplantation with older donors. *Liver Transpl.* 2009;15:1688–95.
 122. Wu L, Zhang J, Guo Z, Tai Q, He X, Ju W, et al. Hepatic artery thrombosis after orthotopic liver transplant: a review of the same institute 5 years later. *Exp Clin Transplant.* 2011;9:191–6.
 123. Duffy JP, Hong JC, Farmer DG, Ghobrial RM, Yersiz H, Hiatt JR, et al. Vascular complications of orthotopic liver transplantation: experience in more than 4,200 patients. *J Am Coll Surg.* 2009;208:896–903.
 124. Darcy MD. Management of venous outflow complications after liver transplantation. *Tech Vasc Interv Radiol.* 2007;10:240–5.
 125. Porrett PM, Hsu J, Shaked A. Late surgical complications following liver transplantation. *Liver Transpl.* 2009;15 Suppl 2:S12–8.
 126. Balderramo D, Sendino O, Burrel M, Real MI, Blasi A, Martinez-Palli G, et al. Risk factors and outcomes of failed endoscopic retrograde cholangiopancreatography in liver transplant recipients with anastomotic biliary strictures: a case-control study. *Liver Transpl.* 2012;18:482–9.
 127. Ryu CH, Lee SK. Biliary strictures after liver transplantation. *Gut Liver.* 2011;5:133–42.
 128. Chan SC, Fan ST. Biliary complications in liver transplantation. *Hepatol Int.* 2008;2:399–404.
 129. Huang WD, Jiang JK, Lu YQ. Value of T-tube in biliary tract reconstruction during orthotopic liver transplantation: a meta-analysis. *J Zhejiang Univ Sci B.* 2011;12:357–64.
 130. Kiuchi T, Tanaka K, Ito T, Oike F, Ogura Y, Fujimoto Y, et al. Small-for-size graft in living donor liver transplantation: how far should we go? *Liver Transpl.* 2003;9:S29–35.
 131. Xiao L, Li F, Wei B, Li B, Tang CW. Small-for-size syndrome after living donor liver transplantation: successful treatment with a transjugular intrahepatic portosystemic shunt. *Liver Transpl.* 2012;18:1118–20.
 132. Gruttadauria S, Pagano D, Luca A, Gridelli B. Small-for-size syndrome in adult-to-adult living-related liver transplantation. *World J Gastroenterol.* 2010;16:5011–5.
 133. Samuel D, Muller R, Alexander G, Fassati L, Ducot B, Benhamou JP, et al. Liver transplantation in European patients with the hepatitis B surface antigen. *N Engl J Med.* 1993;329:1842–7.
 134. Rao W, Wu X, Xiu D. Lamivudine or lamivudine combined with hepatitis B immunoglobulin in prophylaxis of hepatitis B recurrence after liver transplantation: a meta-analysis. *Transpl Int.* 2009;22:387–94.
 135. Shouval D, Samuel D. Hepatitis B immune globulin to prevent hepatitis B virus graft reinfection following liver transplantation: a concise review. *Hepatology.* 2000;32:1189–95.
 136. Sawyer RG, McGory RW, Gaffey MJ, McCullough CC, Shephard BL, Houlgrave CW, et al. Improved clinical outcomes with liver transplantation for hepatitis B-induced chronic liver failure using passive immunization. *Ann Surg.* 1998;227:841–50.
 137. Laryea MA, Watt KD. Immunoprophylaxis against and prevention of recurrent viral hepatitis after liver transplantation. *Liver Transpl.* 2012;18:514–23.
 138. Papatheodoridis GV, Sevastianos V, Burroughs AK. Prevention of and treatment for hepatitis B virus infection after liver transplantation in the nucleoside analogues era. *Am J Transplant.* 2003;3:250–8.
 139. Wong TC, Fung JY, Lo CM. Prevention of recurrent hepatitis B infection after liver transplantation. *Hepatobiliary Pancreat Dis Int.* 2013;12:465–72.
 140. Ciria R, Pleguezuelo M, Khorsandi SE, Davila D, Suddle A, Vilca-Melendez H, et al. Strategies to reduce hepatitis C virus recurrence after liver transplantation. *World J Hepatol.* 2013;5:237–50.
 141. Roayaie S, Schiano TD, Thung SN, Emre SH, Fishbein TM, Miller CM, et al. Results of retransplantation for recurrent hepatitis C. *Hepatology.* 2003;38:1428–36.
 142. Jain A, Orloff M, Abt P, Kashyap R, Mohanka R, Lansing K, et al. Survival outcome after hepatic retransplantation for hepatitis C virus-positive and -negative recipients. *Transplant Proc.* 2005;37:3159–61.
 143. Jain A, Reyes J, Kashyap R, Dodson SF, Demetris AJ, Ruppert K, et al. Long-term survival after liver transplantation in 4,000 consecutive patients at a single center. *Ann Surg.* 2000;232:490–500.
 144. Sharma P, Welch K, Hussain H, Pelletier SJ, Fontana RJ, Marrero J, et al. Incidence and risk factors of hepatocellular carcinoma recurrence after liver transplantation in the MELD era. *Dig Dis Sci.* 2012;57:806–12.
 145. Nissen NN, Menon V, Bresee C, Tran TT, Annamalai A, Poordad F, et al. Recurrent hepatocellular carcinoma after liver transplant: identifying the high-risk patient. *HPB (Oxford).* 2011;13:626–32.
 146. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med.* 1996;334:693–9.
 147. Toso C, Merani S, Bigam DL, Shapiro AM, Kneteman NM. Sirolimus-based immunosuppression is associated with increased survival after liver transplantation for hepatocellular carcinoma. *Hepatology.* 2010;51:1237–43.
 148. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology.* 2001;33:1394–403.
 149. Chok KS, Chan SC, Cheung TT, Chan AC, Fan ST, Lo CM. Late recurrence of hepatocellular carcinoma after liver transplantation. *World J Surg.* 2011;35:2058–62.
 150. Clavien PA, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol.* 2012;13:e11–22.
 151. Allen U, Preiksaitis J. Epstein-barr virus and posttransplant lymphoproliferative disorder in solid organ transplant recipients. *Am J Transplant.* 2009;9 Suppl 4:S87–96.
 152. Oertel SH, Verschuuren E, Reinke P, Zeidler K, Papp-Vary M, Babel N, et al. Effect of anti-CD 20 antibody rituximab in patients with post-transplant lymphoproliferative disorder (PTLD). *Am J Transplant.* 2005;5:2901–6.
 153. Zimmermann H, Trappe RU. Therapeutic options in post-transplant lymphoproliferative disorders. *Ther Adv Hematol.* 2011;2:393–407.
 154. Glanemann M, Langrehr J, Kaisers U, Schenk R, Muller A, Stange B, et al. Postoperative tracheal extubation after orthotopic liver transplantation. *Acta Anaesthesiol Scand.* 2001;45(3):333–9.
 155. Biancofiore G, Bindi ML, Romanelli AM, Boldrini A, Bisa M, Esposito M, et al. Fast track in liver transplantation: 5 years' experience. *Eur J Anaesthesiol.* 2005;22:584–90.

156. Boylan JF, Klinck JR, Sandler AN, Arellano R, Greig PD, Nierenberg H, et al. Tranexamic acid reduces blood loss, transfusion requirements, and coagulation factor use in primary orthotopic liver transplantation. *Anesthesiology*. 1996;85:1043–8.
157. Kaspar M, Ramsay MA, Nguyen AT, Cogswell M, Hurst G, Ramsay KJ. Continuous small-dose tranexamic acid reduces fibrinolysis but not transfusion requirements during orthotopic liver transplantation. *Anesth Analg*. 1997;85:281–5.
158. Dalmau A, Sabate A, Acosta F, Garcia-Huete L, Koo M, Sansano T, et al. Tranexamic acid reduces red cell transfusion better than epsilon-aminocaproic acid or placebo in liver transplantation. *Anesth Analg*. 2000;91:29–34.
159. Dalmau A, Sabate A, Koo M, Bartolome C, Rafecas A, Figueras J, et al. The prophylactic use of tranexamic acid and aprotinin in orthotopic liver transplantation: a comparative study. *Liver Transpl*. 2004;10:279–84.
160. Ickx BE, van der Linden PJ, Melot C, Wijns W, de Pauw L, Vandestadt J, et al. Comparison of the effects of aprotinin and tranexamic acid on blood loss and red blood cell transfusion requirements during the late stages of liver transplantation. *Transfusion*. 2006;46:595–605.
161. Molenaar IQ, Warnaar N, Groen H, Tenvergert EM, Slooff MJ, Porte RJ. Efficacy and safety of antifibrinolytic drugs in liver transplantation: a systematic review and meta-analysis. *Am J Transplant*. 2007;7:185–94.
162. Gurusamy KS, Pissanou T, Pikhart H, Vaughan J, Burroughs AK, Davidson BR. Methods to decrease blood loss and transfusion requirements for liver transplantation. *Cochrane Database Syst Rev*. 2011;CD009052.