Chapter

28 Liver Transplantation

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Three years following his Kasai procedure, a four-year-old male with biliary atresia (see Chapter 27) is posted for orthotopic liver transplantation for end-stage liver disease. He is currently intubated in the Pediatric ICU on dopamine and epinephrine infusions to maintain his blood pressure. Total parenteral nutrition and intralipids are infusing through a right subclavian line. Oxygen saturation on room air is 91%. His international normalized ratio (INR) is 5.6 and has required multiple transfusions of Elsewhere in book this is written as PRBCs. Make consistent to PRBCs, fresh frozen plasma (FFP), and platelets.

Hemoglobin: 8.0, Hematocrit: 23.8, Platelets: 60,000, PT: 49.6, INR: 5.6, PTT 88.3

Na: 129, K: 3.1, Cl: 105, HCO_3: 19, BUN: 30, Cr: 2.3, Glucose 65, Ca: 0.85, Mg: 1.9

Albumin: 2.5, Total Bilirubin 3.9.

What Are the Indications for and Underlying Diagnoses Associated with Pediatric Liver Transplantation?

The primary indications for liver transplantation are acute fulminant hepatic failure, chronic end-stage liver disease, and progressive primary liver disease refractory to maximal medical management and metabolic disease. Table 28.1 lists the common underlying diagnoses associated with liver transplantation.

What Is the PELD Score and How Is It Used in Pediatric Liver Transplantation?

The Pediatric End-Stage Liver Disease (PELD) score was implemented in 2002 to prioritize organ allocation to the sickest patients, rather than those who had been waiting the longest. It is used for children 12 years and younger. PELD uses the patient's values for serum bilirubin, serum albumin, the international normalized ratio for prothrombin time (INR), whether the patient is less than 1 year old, and whether the patient has growth failure (<2 standard deviation) to predict survival. It is calculated according to the following formula:

PELD = 4.80[Ln serum bilirubin (mg/dL)] + 18.57[Ln INR] − 6.87[Ln albumin (g/dL)] + 4.36(<1 year old) + 6.67(growth failure)

The PELD score is used to calculate a numerical value that is an accurate predictor of three-month mortality, independent of portal hypertension and etiology of the liver disease. A higher score correlates with a more critical condition. Thus, liver donations are usually allocated by United Network for Organ Sharing (UNOS) according to the PELD score to maximize the life-saving capability of each donated liver.

What Are the Common Pathophysiologic Derangements of End-Stage Liver Failure?

The pathophysiologic derangements common in patients undergoing liver transplantation are summarized in Table 28.2.

What Preoperative Workup Is Needed for Pediatric Liver Transplantation?

A liver transplant preoperative evaluation should include a standard history and physical exam to identify the primary cause of liver failure and identify the specific anatomic and physiologic derangements that need to be addressed. Standard preoperative workup includes past medical and surgical history, medication list, drug allergies, and NPO interval. Additional considerations include treating active infections, optimizing preexisting cardiac conditions, and completing the patient's immunization schedule.

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https://doi.org/10.1017/9781108668736.029 Published online by Cambridge University Press

Table 28.1 Relative frequency of the primary indications for liver transplantation in children. Data from Cote and Lerman, eds. *A Practice of Anesthesia for Infants and Children*. 5th Ed. Elsevier 2013

Diagnosis	Frequency (%)
Cholestatic liver disease	54
Biliary atresia	
Alagille syndrome	
Primary sclerosing cholangitis	
Intrahepatic cholestasis	
Biliary cirrhosis	
Fulminant hepatic failure	14
Acute liver failure	
Cirrhosis	
Autoimmune hepatitis	
Neonatal hepatitis cirrhosis	
Metabolic disease	14
Alpha 1 antitrypsin deficiency	
Urea cycle defects	
Cystic fibrosis	
Wilson's disease	
Tyrosinemia	
Primary hyperoxaluria	
Crigler-Najjar syndrome	
Glycogen storage disease	
Primary hepatic malignancy	6
Hepatoblastoma	
Other	
Other	6
Congenital hepatic fibrosis	
Budd–Chiari syndrome	

Based on the organ systems affected in liver disease, specific tests should be considered (Table 28.3).

How Can Liver Failure Be Treated Prior to Transplantation?

It is not uncommon for liver failure patients to wait months for a suitable organ to transplant. It is then

Table 28.2 Pathophysiologic derangements common in patients undergoing liver transplantation

Organ system	Common findings
Cardiovascular	Hyperdynamic circulation: ↑cardiac output, ↓systemic vascular resistance (SVR)
	Pericardial effusions
	Arteriovenous (AV) shunting Long term: cardiomyopathy, high output heart failure
Pulmonary	Hypoxemia due to V/Q mismatch
	Impaired hypoxic pulmonary vasoconstriction
	Intrapulmonary shunting
	↓ functional residual capacity (FRC) due to ascites
	Pulmonary hypertension
	Hepatopulmonary syndrome Pleural effusions
CNS	Encephalopathy
	Cerebral edema
Renal	Prerenal azotemia
	Hepatorenal syndrome
GI	Hepatic dysfunction: synthetic, metabolic and excretory
	Portal hypertension
	Delayed gastric emptying
Hematologic	Thrombocytopenia
	Coagulopathy
	Anemia
	Hypofibrinogenemia, dysfibrinogenemia Disseminated intravascular coagulopathy
Laboratory/ electrolyte anomalies	Metabolic acidosis
	Hypokalemia Hyponatremia
	Intravascular volume depletion

https://doi.org/10.1017/9781108668736.029 Published online by Cambridge University Press

Table 28.3 Specific preoperative evaluation tests for consideration prior to liver transplantation

Organ system	Exam	Rationale
CV	Echocardiography	Identify cardiomyopathy or congenital defects
	ECG	Identify arrhythmias and prolonged QT
Pulmonary	CXR	Identify pleural effusions
	ABG	Hepatopulmonary syndrome
Renal	Chemistry panel	BUN and creatinine levels for ARF
Hematologic	CBC	Assess anemia and thrombocytopenia
	PT/PTT/INR	Coagulopathy
	TEG	Coagulopathy
	Type and cross	Blood products needed for surgery
Laboratory/electrolyte anomalies	Chemistry panel	Hyponatremia, hypokalemia, hypocalcemia, glucose
	Liver panel	Albumin, AST, ALT

necessary to reduce the severity of the complications from liver failure. In a trans-jugular intrahepatic portosystemic shunt (TIPS), a stent connects the portal vein to the hepatic veins to bypass and decompress the hepatic circulation. The aim is to reduce portal hypertension and its sequelae, ascites, and esophageal varices.

Molecular adsorbent recirculating system (MARS) therapy is a liver dialysis of sorts. Similar to dialysis, it uses albumin with and without a traditional hemodialysis machine to cleanse the blood of toxins that would otherwise be cleared by the liver. While traditional hemodialysis removes water-soluble toxins, albumin is used to remove lipophilic toxins. MARS therapy is usually reserved as a short-term treatment for fulminant liver failure and as a bridge to transplantation. MARS requires insertion of a central hemodialysis catheter. It is associated with hypocalcemia, thrombocytopenia, and hypotension that must be treated aggressively. The patient described above, with two vasopressor therapy, would be the prototypical end-stage liver disease (ESLD) patient on MARS therapy as a bridge to transplant.

What Is the Etiology of the Hematologic Abnormalities of Liver Failure?

Hematologic abnormalities include decreased synthesis of coagulation factors, including fibrinogen and factors II, V, VII, IX, and X. In addition, decreased absorption of vitamin K results from decreased bile acid secretion, and leads to elevation of prothrombin time (PT) and partial thromboplastin time (PTT). Thromobocytopenia occurs secondary to hypersplenism. Production of the procoagulant factors, proteins S and C, and antithrombin III, are also decreased.

What Is the Etiology of the Electrolyte Abnormalities? How Will These Results Modify Your Perioperative Management?

Preoperative renal insufficiency exacerbates acid-base and electrolyte abnormalities whereas diuretic therapy may also cause electrolyte disturbances, such as hyponatremia, hypokalemia, and hypocalcemia. Hypoglycemia may also occur secondary to impaired gluconeogenesis and glycogenolysis with reduced glycogen stores.

What Monitors Are Needed for the Case?

In addition to standard ASA monitors, it is necessary to have an arterial line to help draw frequent labs needed throughout the case, and to guide strict control of blood pressure. A central venous line facilitates infusion of vasopressors and rapid administration of blood products. In addition, one to two large-bore peripheral IVs are placed in the upper extremity because the inferior vena cava (IVC) is clamped for

https://doi.org/10.1017/9781108668736.029 Published online by Cambridge University Press

a significant portion of the procedure. Fluid warmers, external warmers, and heat/moisture exchangers are used as well to keep the patient warm as hypothermia can exacerbate coagulopathy and alter drug metabolism.

How Does Liver Failure Affect Your Choice of Medications?

Since the liver is the primary organ for drug metabolism and plays a central role in both drug pharmacodynamics and pharmacokinetics, end-stage liver disease alters the expected pharmacokinetics and pharmacodynamics of drug administration. In the absence of dose alteration, one can expect to see extended drug duration of action and possible toxic levels for hepatically metabolized medications. This occurs due to impaired protein synthesis involving alpha-1-glycoprotein and albumin increasing the free fraction of drugs (i.e., opioids), potentially exaggerating their effects. Second, the biotransformation of drugs via cytochrome P450 is decreased, allowing the drug to persist far longer than expected. However, end-stage liver disease also affects volume of distribution, hepatic extraction and metabolism, and renal excretion, making broad recommendations for drug administration difficult.

As a result of this alteration in drug effect, medications should be titrated to effect. Long-acting medications need to be carefully selected as their duration of action may outlast their desired effects. In the case of muscle paralysis, it may not be an issue if extubation is not intended and pancuronium is administered. However, in the event of administration of morphine or vecuronium with the intent of extubation at the conclusion of the procedure, there might be accumulation of drug and residual narcosis and paralysis, respectively.

How Will You Proceed with Induction of Anesthesia?

There is no established standard induction for liver transplantation. If ascites is present, or there is recent food ingestion or delayed gastric emptying, a rapid sequence induction is indicated. Succinylcholine can be used in the absence of hyperkalemia associated with hepatorenal syndrome. Rocuronium, 1–1.2 mg/kg, provides muscle relaxation in a timeframe sufficient for rapid sequence induction. Fentanyl will not accumulate with renal disease and has minimal histamine release.

During the Preanhepatic Phase of Liver Transplantation, What Major Surgical Steps Occur and What Management Options Are Available?

The preanhepatic phase starts with induction of anesthesia and concludes with placement of clamp on the hepatic artery to effectively isolate the native liver. The superior vena cava (SVC), IVC, and portal vein are all clamped as well, and the bile duct is divided. The key issues encountered during this phase are hypotension secondary to any bleeding related to a preexisting coagulopathy, especially in patients who have had a prior Kasai procedure. Fresh frozen plasma and packed red blood cells are given to correct coagulopathy and bleeding respectively. Hypotension will occur when a large amount of ascites is drained on incision. Albumin is used to quickly expand the intravascular volume in anticipation of loss of venous return that accompanies the placement of the vena caval clamps. With the piggyback technique, only a partial cross clamp of the IVC is necessary which decreases the loss of cardiac preload. Metabolic issues with hyperkalemia, hypocalcemia, and acidosis can occur and need to be corrected. A previous Kasai procedure may make dissection of the native liver difficult secondary to scarring and adhesions as well as increase the risk for major bleeding.

A hemoglobin between 9 and 10 g/dL and an INR of 1.5 are appropriate if there is no hemodynamic instability. Thromboelastography (TEG) has been used successfully in pediatric liver transplantation, providing an indicator of clotting factor activity, platelet function, and fibrinolysis (see Chapter 9).

During the Anhepatic Phase of Liver Transplantation, What Major Surgical Steps Occur and What Management Options Are Available?

The anhepatic phase begins with en-bloc resection of the native, diseased liver and ends with release of the clamps and reperfusion of the new liver. Any hypotension resulting from the loss of preload with caval clamping should be treated with volume expansion and vasopressors to maintain blood pressure. However, aggressive fluid therapy can cause hepatic venous congestion after reperfusion. Dopamine and/or epinephrine may be needed to maintain mean arterial pressure

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(MAP) during this stage. In the absence of a functioning liver, anesthetic adjustments will be necessary as drug metabolism can be profoundly depressed. Excessive fluid administration should be avoided to prevent elevated right atrial pressure at reperfusion, which can cause graft congestion following reperfusion. Children often have normal urine output during this stage because of collateral vessels; therefore, urine output should not be used as a guide to fluid administration during the anhepatic phase. Because the portal vein is clamped during the anhepatic stage, portal venous hypertension develops with fluid translocation and bowel edema. Colloid administration may theoretically reduce the amount of bowel edema and potentially facilitate easier abdominal closure at the end of the procedure.

Metabolic abnormalities may occur following cross-clamping. Ionized calcium may decrease because the liver does not metabolize citrate, and metabolic acidosis may worsen because the liver does not metabolize lactate to bicarbonate. Metabolic acidosis also occurs secondary to impaired tissue perfusion. Hypoglycemia is further exacerbated with loss of gluconeogenesis and glycogenolysis. An infusion of 0.25–0.5 g/kg of glucose and 0.2 units/kg regular insulin may also be administered to reduce the serum K+ concentration.

Monitoring and correction of pH, electrolytes, calcium, and glucose are necessary. Calcium chloride and calcium gluconate are equally efficacious in improving ionized calcium concentrations. As a result of these metabolic challenges, serial ABGs are drawn to ensure correction of electrolyte and acid base disturbances.

Intraoperative administration of blood products, particularly fresh frozen plasma, further decreases ionized calcium and magnesium because citrate-based anticoagulant solutions used in blood collection and storage bind these ions. Significant bleeding may still occur from collateral vessels and previous scar tissue. An underbody forced air warmer should be used as patients become hypothermic when the new liver (previously on ice) is inserted. Body temperature should be increased to 36–37°C prior to reperfusion.

During the Reperfusion Phase of Liver Transplantation, What Major Surgical Steps Occur and What Management Options Are Available?

The reperfusion stage (also known as neohepatic phase) starts with release of all clamps with blood flow established to the new liver.

Reperfusion begins with the release of the suprahepatic IVC clamp followed by removal of the portal vein and infrahepatic IVC clamps. Inadequate fluid resuscitation, insufficient flushing of the cold preservative solution, and release of vasoactive substances into the central circulation may cause hemodynamic instability from elevated pulmonary vascular resistance, decreased cardiac output, and decreased systemic vascular resistance. The cold solution may directly decrease cardiac output, necessitating warm irrigating solution in the surgical field. Aggressive fluid resuscitation (central venous pressure (CVP) >10 mmHg) may cause graft engorgement and cause areas of the graft to become ischemic during this phase. Volume resuscitation should occur prior to clamp removal.

Within One Minute After the Vascular Clamps Are Removed, a Prolonged QT Interval, Peaked T Waves, Bradycardia, and Hypotension Occur. What Is This Reaction and How Is It Treated?

ECG changes are often caused by the rapid intravenous infusion of effluent from the transplanted liver. The transplant preservative fluid has a low pH and temperature and is high in potassium. In addition, infusion of air and/or microthrombi into the heart may precipitate acute pulmonary hypertensive crisis. Vigorous flushing of the liver (by the surgeon) with colloid solution followed by retrograde flushing with the recipient's blood prior to reperfusion reduces the potassium concentration and acid content of the effluent as the preservation fluid is very high in potassium (125 mmol/L in University of Wisconsin solution (UWS) solution). Preemptive treatment with sodium bicarbonate, calcium chloride as well as inotropic support can help maintain stability during this phase. At this point, any coagulopathy that needs correction will be treated, as well as restoration of circulating intravascular volume to maintain urine output and MAP sufficient to perfuse the liver. In addition, the biliary drainage system is constructed with either a Roux-en-Y in the case of biliary atresia or a direct biliary anastomosis.

Hepatic artery thrombosis may result from coagulation and hematologic disorders and/or technical factors during hepatic artery anastomosis. Intraoperative and postoperative Doppler ultrasound may be

https://doi.org/10.1017/9781108668736.029 Published online by Cambridge University Press

used to assess anastomosis patency. Hemoglobin concentrations should be maintained between 8 and 10 mg/dL to decrease blood viscosity while maintaining oxygen delivery. Aggressive fresh frozen plasma and platelet administration may also increase blood viscosity, increasing the risk of hepatic artery thrombosis. PT and PTT should be maintained no less than 1.5 times prolonged, and platelet counts of 50,000–100,000 are acceptable, if there are no signs of microvascular bleeding and hemodynamic instability. Furthermore, children are hypercoagulable following liver transplantation secondary to decreased protein C and antithrombin III, additionally increasing the risk of hepatic artery thrombosis.

What Intraoperative Clinical Findings Indicate a Well Functioning Graft?

Reduction in calcium supplementation requirements are consistent with adequate hepatic allograft function secondary to improved citrate metabolism. The development of metabolic alkalosis is also an indicator of adequate graft function secondary to lactate metabolism to bicarbonate. Hyperglycemia post reperfusion is an additional marker of adequate graft function with the restoration of gluconeogenesis and glycogenolysis.

What Are Immediate Postoperative Considerations?

It is common practice to leave patients intubated for the first 24–48 hours after liver transplant and transport to the ICU although early extubation is appropriate in uneventful and hemodynamically stable transplantations. Given the large subcostal incision, the child should be comfortable enough to adequately oxygenate and minimize atelectasis. If the patient remains intubated, PEEP is used to minimize atelectasis during positive pressure ventilation as ascites, pulmonary edema, and pleural effusions may occur. Third-spacing and blood loss will continue and may manifest as hypotension. IVF and albumin along with any necessary blood products should be considered in an effort to maintain euvolemia. Hepatic artery thrombosis is a very common vascular complication that occurs in pediatric liver transplantation. Some surgeons may request anticoagulation in the immediate postoperative period if risk of thrombosis is high. Bowel perforation is less likely, but also known to occur and requires returning to the operating room for laparotomy.

> The patient is extubated in the operating room and transported to the intensive care unit, where 12 hours later the patient has worsening coagulation studies, metabolic acidosis, and hypoglycemia.

What Is the Main Etiology of Graft Failure?

Patients may be started on a heparin or dopamine infusion to maintain hepatic artery patency as hepatic artery thrombosis (HAT) is the most common etiology for graft failure. HAT is directly related to the size of the vessels and thus is most likely in the smallest pediatric recipients. HAT is a serious postoperative complication that can result in bacteremia, biliary stricture, and hepatic necrosis with resultant loss of the graft. The incidence has been found to be as high as 25%, with children younger than three years at greatest risk. Transplant recipients with HAT have a 50% survival rate (and most undergo retransplant) compared to an 80% survival rate of those without HAT. Surgical factors that may play a role include technique of anastomosis, vessel size less than 3 mm, use of grafts, and donor anatomy. Medical factors include use of procoagulants and hyperviscosity from blood product administration. Bile leaks resulting from bile duct ischemia secondary to early HAT require retransplantation.

Suggested Reading

Cladis F, et al. Organ Transplantation. In Cote and Lerman, eds. *A Practice of Anesthesia for Infants and Children*. 5th Ed. Elsevier 2013.

https://doi.org/10.1017/9781108668736.029 Published online by Cambridge University Press