The Anatomy of a Pediatric Liver Transplant

Ira Landsman, MD
Kristalynne Godwin, MD

VANDERBILT CHILDREN’S HOSPITAL
VANDERBILT SCHOOL OF MEDICINE

Goals:

1. Discuss the etiology, symptomotology and treatment of biliary atresia
2. Discuss the etiology of portal hypertension and manifestations of liver failure that lead to indications for liver transplantation.
3. Formulate a differential diagnosis for acute renal failure in patients with liver failure and understand treatment options
4. Describe the intraoperative stages of liver transplantation
5. Discuss primary graft failure as a cause of liver transplant mortality.

Stem Case:

A 1 year old, 7 kg girl with biliary atresia treated with a hepatopancreaticoenterostomy at 3 months of age was admitted to the hospital for acute onset of abdominal pain, lethargy, nausea and vomiting.

What is biliary atresia?
How is it diagnosed?
What treatments are available?
How does timing of treatment effect the success of the Kasai procedure?

The patient was followed by hepatology for decline in hepatic function. The child’s abdominal girth has slowly increased along with the prominence of the umbilical vasculature. The patient was more jaundiced and experienced one episode of hematemesis.

What is causing these symptoms?
What is portal hypertension?
What are the known complications of portal hypertension?

Upon admission and further evaluation, the patient was diagnosed with worsening liver failure and placed on the liver transplant waiting list. Her PELD score was 25. The anesthesia team was called to evaluate the patient for possible liver transplantation. The chart is reviewed.

What is the PELD score?
How is it calculated?

While reviewing the labs, it became apparent that the patient had developed acute renal failure. Her creatinine had risen from 1.14, three weeks ago, to 3.42 upon admission. Her medications included furosemide and spironolactone. Paracentesis was performed 2 weeks prior to admission and peritoneal fluid was positive for Citrobacter freundii. Her mother reported that the patient’s urine output appeared normal.

What is your differential diagnosis of the acute renal failure?
How would one differentiate among these causes?
What treatment options are available?
The peritoneal infection was treated with Gentamicin. A gentamycin trough level of 20.5 was noted. Abdominal U/S and MRI revealed normal appearing kidneys, moderate ascites and possible portal vein thrombosis. The child was placed on dialysis for acute renal failure.

What other labs and/or tests would you deem necessary before taking this patient to the OR?
How does the fact that there is portal vein thrombosis change your anesthetic plan and expectations for the case?

Four weeks later, a compatible donor liver became available. The patient’s acute renal failure resolved. After discussing anesthetic concerns with the parents, you transport the child to the OR. She has a 22 gauge in her right saphenous vein.

Does she need a rapid sequence induction? How would you accomplish this?

The IV infiltrated after versed administration, but prior to induction.

How would you proceed?

Vital signs were stable after an uneventful tracheal intubation.

What other additional IV access and monitors do you require?
Would you consider a TEE?
What about a BIS monitor?

Monitors were placed. Peripheral IVs, central line and arterial line are inserted and the patient was positioned properly. The surgery team prepped and draped the patient.

At what point during the surgery does the Kasai procedure complicate surgery?
What other complications should you prepare for during the Pre-anhepatic stage? Anhepatic stage? Re-perfusion / neo-hepatic stage?
What serial lab tests should be monitored?
What special procedures might be performed because of the possible portal vein thrombosis?
Does this affect prognosis?

After 6 hours of surgery, the procedure nears completion. Hematocrit is 33. Platelets are 120k. Electrolytes (with the exception of BUN and creatinine) are within normal limits. INR is 1.2 and PTT is 33

How have you been treating this patient for post op pain?
Would you consider an epidural catheter placement at the end of this procedure?
What about a caudal epidural catheter?
If the patients labs were all within normal limits, would you have considered one prior to incision?

The patient was transported to the ICU at the conclusion of surgery. Report was given to the ICU team. 30 hours later, the patient was still supported by mechanical ventilation. LFT’s and coagulation studies had worsened since surgery. Also, the patient was in metabolic acidosis.

What is your differential diagnosis?
What other labs/studies would you request?

Hepatic vasculature ultrasonography showed patent vessels. Lab values of immunosuppressants were within desired levels.

How does this affect your differential diagnosis?
What is the definition of primary graft failure? What is the etiology?
Model Discussion:

Biliary Atresia (BA) is an inflammatory sclerosing cholangiopathy with an incidence between 1 in 8000 to 1 in 18,000 live births. It is a disease that typically presents within the neonatal period. It is important to diagnose this disease quickly since outcomes depend largely on timing of the appropriate intervention. BA progresses over time. At the onset, the child often appears normal. However, the infant soon develops clinical signs and laboratory abnormalities over the ensuing weeks. Pale stools, dark urine and icterus are apparent by the age of 4 to 6 weeks. Any neonatal jaundice beyond 2 weeks of life should raise the suspicion of this condition.

In addition to the clinical findings, abnormal laboratory values include moderate conjugated hyperbilirubinemia, elevated gamma-glutamyl transferase and mildly to moderately elevated serum transaminases. The conjugated bilirubin level is usually less than 7 mg/dl and is typically 50% to 80% of the total bilirubin.

It is difficult to differentiate patients with BA from those with intrahepatic disease with patent bile ducts. This is further complicated by the fact that BA needs to be diagnosed early. There are multiple algorithms used to diagnose BA. However, a relatively recent retrospective review of 9 centers in the United States showed that there was no standard approach to diagnosing BA, and the outcomes at age 2 were similar to other countries as long as the diagnosis of BA is made prior to 60 days of life.

**Diagnosis of Biliary Atresia**

Isolating the etiology of hyperbilirubinemia begins with a thorough history and physical. Prenatal testing and ultrasonography, stool and urine patterns and a complete family history is also reviewed. Laboratory tests should include CBC, BMP, LFT’s, coagulation studies, bacterial cultures, thyroid function test and screening for cystic fibrosis. Abdominal ultrasound and hepatobiliary scintigraphy or magnetic resonance cholangiopancreatography are radiological procedures used to help diagnose BA. If clinical concern persists after ultrasonography and hepatobiliary scintigraphy are performed, exploratory laparotomy with surgical cholangiography is recommended. This is performed by injecting contrast material through the gallbladder. If no communication is seen between the biliary tree and the gastrointestinal tract, biliary atresia is diagnosed. Finally, the gold standard remains the liver biopsy. However, if performed too early in the course of the disease, it may be indistinguishable from neonatal hepatitis. Findings on histology include: cholestasis, bile ductular proliferation, bile ductule cholestasis, extramedullary hematopoiesis, and giant cell transformation of hepatocytes. Insipissated concretions of bile within marginal bile ductules (bile ductular cholestasis) are a familiar pathologic entity in adults with sepsis, but during the neonatal period, this finding is most often associated with biliary atresia.

While diagnosing BA may be a challenge, its etiology is even more of an enigma. It appears that BA is a phenotype of two different pathologic processes. The first is perinatal or acquired form, which accounts for the majority of cases (80%) in Western countries. The second, is the embryonic or fetal form.

Neonates with perinatal BA are presumably born with a patent biliary system which undergoes progressive inflammation and fibro-obliteration initiated by a perinatal insult. The nature of this insult remains unclear and is probably multifactorial. Suspected causes include infectious (both viral and bacterial), toxic, vascular and immune mediators. Neonates with the embryonic form typically have other associated congenital anomalies. Their BA is due to defective morphogenesis caused by biliary developmental gene mutations. No one gene has been identified, but research continues.

**Kasai Procedure**

Once BA has been diagnosed, treatment is surgical. The surgery of choice is the hepatopportoenterostomy, or Kasai procedure, named after Dr. Kasai who first developed the technique in 1959. The procedure consists of mobilizing the extrahepatic biliary tree and anastomosing a jejunal Roux-en-Y loop to the liver hilum. Several other types of biliary conduits have been designed such as the Sawaguchi and the Suruga.
Both of these exteriorize the biliary drainage through a stoma so that it can be measured. However, none of these techniques have been shown to improve survival.

Regardless of the technique used for intrahepatic biliary tree drainage, the timing of the procedure is linked to success. Between 66 and 80% of neonates will have bile flow when operated on at less than 60 days of age. Establishment bile flow may take weeks to months. Even though results decrease with increasing age, most centers will recommend some type of hepatoportoenterostomy regardless of when BA is diagnosed.

Twenty to 30% of patients who undergo a Kasai will have long-term stability of their disease. The other two-thirds of children will eventually need liver transplantation. Although the Kasai failure rate is high, long term success is achievable. Low numbers of donor livers and the technical challenges of hepatic transplantation in children less than 1 years of age make hepatoportoenterostomy an accepted initial treatment of BA.

**Portal Hypertension**

Unfortunately, the majority of children with BA will ultimately go on to develop cirrhosis and portal hypertension. Portal hypertension (PH) is associated with comorbidities. Understanding the pathophysiology of PH will help in understanding its associated manifestations.

PH results from both an increased resistance to portal flow and an increased portal venous inflow. The increase in resistance is the result of architectural distortion of the liver secondary to fibrous tissue accumulation and regenerative nodules. There is also an apparent deficiency of nitric oxide contributing to portal vein venoconstriction. Portal venous pressures above 10-20 mmHg are required to be considered PH.

Bleeding from esophageal varices is the most common presentation of PH. Collateral vessels may form prominently in areas in which absorptive epithelium joins stratified epithelium, particularly in the esophagus or anorectal region. While increased pressure gradient leads to varice formation, it is the increased blood flow that causes variceal expansion and eventual rupture.

As the portal pressure increases, venous collaterals form. These collaterals should compensate for increased resistance in the liver and decrease portal pressure. However, the increased portal pressure is maintained by an increased splanchnic blood inflow secondary to vasodilatation. This splanchnic vasodilatation is the initiating event in the hyperdynamic circulatory state that aggravates many of the complication of cirrhosis. This vasodilatation is most likely triggered by increased levels of vasodilators.

**Hepatorenal Syndrome**

It is this intense systemic vasodilatation which can lead to hepatorenal syndrome (HRS). There are multiple causes of renal failure in patients with advanced liver disease such as volume depletion, shock, exposure to nephrotoxic drugs or intrinsic renal disease. Acute renal failure seen in HRS typically occurs in the absence of these factors. The common pathway for HRS is the splanchnic arterial vasodilatation which triggers compensatory vasoconstriction and activation of antinatriuretic systems in the kidneys. Renal perfusion cannot be maintained because of extreme arterial under-filling causing maximal activation of the renal vasoconstrictor systems.

There are no specific clinical findings in HRS. Any acute renal failure present in a cirrhotic patient needs to be evaluated. Renal failure in HRS is often associated with severe oliguria (<500 ml 24h), urinary sodium retention (urine Na <10 mEq/L) and dilutional hyponatremia (serum Na <130 mEq/l). Creatinine levels depend on which of the two types of HRS is present. Type 1 occurs rapidly with doubling of the creatinine within 2 weeks. Practically all patients die within 8-10 wks after onset of this renal failure. Type 2 has a more insidious course and is more benign. Patients’ median survival time is approximately 6 months. Unfortunately, HRS is a diagnosis of exclusion. There must be an absence of other renal disease etiologies such as shock, evidence of obstruction, ongoing bacterial infection or current/recent treatment with
nephrotoxic drugs. The child presented here was being treated with gentamicin and cefepime. The gentamicin trough was above safety limits.

**Aminoglycoside Nephrotoxicity**

The most common clinical presentation of aminoglycoside nephrotoxicity is nonoliguric acute renal failure. The onset of renal failure is usually slower and the daily rise in serum creatinine tends to be lower than that observed in acute renal failure from other causes. Recovery from aminoglycoside nephrotoxicity is usually slow, often requiring 4 to 6 weeks. The renal cortex stands alone in its ability to concentrate aminoglycosides several-fold greater than plasma. How this causes cell injury and death, though, is still not entirely known. Renal failure is generally reversible after discontinuation of the drug; however, supportive renal replacement therapy may be required.

**Pulmonary Hypertension**

The renal system is not the only organ affected by portal hypertension. The pulmonary system may also be affected. Both portopulmonary hypertension and hepatopulmonary syndrome (HPS) are caused by PH. In portopulmonary hypertension, high cardiac output and hyperdynamic circulation causes an increase in sheer stress on the pulmonary circulation. The pulmonary vascular bed responds by increasing pulmonary resistance eventually leading to pulmonary vascular remodeling and smooth muscle proliferation. In HPS, the same factors that cause splanchnic vasodilatation cause pulmonary vasculature dilatation. This leads to perfusion/ventilation mismatch and eventually hypoxemia.

**PELD SCORE**

There are a host of additional symptoms that accompany progressive liver failure. Ascites can become mechanically intrusive and increase the risk of spontaneous bacterial peritonitis. With worsening hepatic function, toxins accumulate. Hepatic encephalopathy is thought to be caused by increased ammonia levels. There are many temporizing treatments for these varied symptomatologies. As these treatment regiments fail, liver transplant becomes the only alternative to death. The Pediatric End-stage Liver Disease (PELD) score was developed to establish a scoring system to allow for appropriate allocation of donor grafts.

The PELD score is an objective tool used to prioritize children awaiting liver transplantation aged 12 years and younger. Higher PELD scores are associated with increased pre-liver transplant mortality. However, high PELD scores are not associated with worsening post-liver transplant outcome. This helps substantiate the currently adopted “sickest child first” allocation policy.

The PELD score uses the following calculations: Albumin (g/dl), bilirubin (mg/dl), INR, presence of growth failure and age at listing. The formula providing the actual PELD score number is the following:

$$\text{PELD Score} = 0.480 \times \log_{10}(\text{bilirubin})$$
$$+ 1.857 \times \log_{10}(\text{INR})$$
$$- 0.687 \times \log_{10}(\text{albumin})$$
$$+ 0.436 \text{ (if the patient is less than 1 year old)}$$
$$+ 0.667 \text{ (if the patient has growth failure <2 Stan. Dev.)}$$

This is then multiplied by 10 and is rounded to the closest whole number. The child is then placed on the transplant list in descending order of need.

Even before a child can be placed on the waiting list, criteria must be met. While the number of absolute contraindications to liver transplant has decreased, some contraindications remain. The inability to withstand the operative procedure, usually from a cardiovascular or pulmonary perspective, is an absolute contraindication. Recent intracranial hemorrhage is also a contraindication. Active substance abuse, as well as those patients that lack a social support system, are not candidates for transplantation.
Active sepsis and extrahepatic malignancy are contraindications. HIV infection is no longer an absolute contraindication. The development of highly effective anti-retroviral medications has allowed these patients to become recipients.

Pediatric patients only make up 10% of the liver transplant list. However, there are not enough livers to meet the demand. To address these needs, some centers offer reduced size or “cutdown” liver transplants. However, this technique has been complicated by both technical and ethical issues.

**Preoperative Evaluation**

Pediatric liver transplants require a multidisciplinary team approach to patient care. Teams are composed of surgeons, pediatricians, nutritionists, social services and pediatric anesthesiologists.

The evaluation of the patient in liver failure includes:

1. Neurological – Hepatic Encephalopathy; Cerebral edema/increased ICP
2. Cardiovascular – Hyperdynamic circulation; Congestive Heart Failure
3. Pulmonary – Restriction due to ascites; Multiple causes of hypoxemia
4. GI – Portal HTN, Delayed gastric emptying, Malnutrition
5. Renal – Acute or Chronic renal failure
6. Hematologic – Coagulopathy, DIC, Anemia, Thrombocytopenia
7. Immunologic – Decreased gammaglobulins
8. Electrolytes – Hyponatremia, hypo/hyperglycemia
9. Prior Surgical Procedures
10. Other associated pathologies especially those with known syndromes/

It is beyond the scope of this discussion to describe all of the anesthetic considerations attributed to the above pathologies. Rather, it serves to demonstrate how complex and challenging these cases are. After the anesthesiologist completes the chart review, a thorough history and physical is performed. It is important to remember that even though there are many complexities to the case, the basics (physical exam, airway classification, etc.) cannot be overlooked.

**Anesthesia Set Up For Pediatric Liver Transplant**

Prior to transporting the patient to the OR, it is the anesthesia team’s responsibility to insure proper preparation for their patient. Preparation may include:

1. Automated pump system with 4 channels; one of which is primed with NS and has a 4 gang stopcock
2. 3 Transducers (Art, CVP and ICP or 2nd Art for labs in children >25 kg)
3. 3 Fluid Warmers; 2 primed with NS with Y-tubing, one dry with Y-tubing
4. Central Line Kit and A-line Kit
5. 80 cc/kg of PRBC’s in cooler in OR
6. 80 cc/kg of FFP in cooler in OR
7. Recombinant Factor VIIa (FVIIa)
8. Platelets and Cryoprecipitate available upon request
9. Level 1 Primed with NS for patients <25 kg vs a Belmont rapid infuser for patients >25kg
10. 2 forced air warmers with room temperature elevated
11. Anesthesia machine check and emergency drug preparation

Pre-operative sedation is recommended for most patients who are hemodynamically stable, awake and oriented. Regardless of NPO status, full stomach precautions are justified. Intramuscular injections should be avoided if the patient is coagulopathic.
After adequate pre-oxygenation, modified or classic rapid sequence induction follows. Etomidate, propofol or sodium thiopental can be used as an induction agent. Both succinylcholine and rocuronium can be used for the initial paralysis. The patient’s volume of distribution is often increased, but their clearance is usually decreased. Pharmacodynamics and pharmacokinetics can, therefore, be unpredictable. Maintenance with a volatile agent is acceptable.

After tracheal intubation, line placement begins. Two large bore IV’s are placed above the diaphragm, if possible. A central for CVP monitoring and 1 or 2 arterial lines to monitor invasive blood pressure and blood sampling are inserted next. Orogastric tubes are favored over nasogastric tubes in anticipation of coagulation problems.

Three Stages of Liver Transplantation

Classically, the liver transplant is divided into three stages: Pre-anhepatic, Anhepatic and Neo-hepatic / Reperfusion. Each stage has its set of physiologic challenges and possible complications.

The pre-anhepatic stage begins with incision and ends with removal of the recipient’s liver. This stage can be complicated by previous abdominal surgical procedures (e.g. Kasai procedure). Previous abdominal surgery and portal hypertension increases blood loss. The anesthesiologist must replace ongoing blood loss and insensible losses that accompany large bilateral subcostal incisions. ABG’s, BMP’s and coagulation studies (INR/PT, PTT, thromboelastograms, are monitored at regular intervals and used as a guide for treatment. Most centers perform the piggy back procedure which obviates the need for cross clamping the IVC. In general, the piggy back technique causes less hemodynamic changes than IVC clamping and unclamping.

The anhepatic stage begins with the clamping of the hepatic vessels and ends with the reperfusion of the donor liver. Several key events occur during this phase. Fluid and electrolyte imbalances continue to fluctuate and must be monitored continuously. During this stage, fluid overload must be avoided since it can lead to liver congestion and graft dysfunction during the reperfusion phase. Without a liver, coagulopathy and fibrinolysis may worsen and hypothermia may occur if proper warming techniques are not utilized.

It is also during this stage that immunosuppressants are begun. The exact drugs used vary from center to center. In addition, the transplant surgeons prepare the hepatic bed for the donor liver.

At the completion of the vena cava anastomosis, the liver is flushed via the portal vein to remove air, preservation fluid and metabolites. The preservation fluid is typically very high in potassium (125 mmol/L in UW solution). The minimal amount of flush has been studied in adult transplants and is around 500 ml. This can be reduced in the pediatric population.

The neo-hepatic phase starts with the unclamping of the portal vein, hepatic artery and vena cava with reperfusion of the donor liver. It should be heralded by clear communication from the surgeon to the anesthesiologist. Even though the donor liver should be well flushed, there is danger of severe electrolyte imbalance during the reperfusion. It is critical to have emergency drugs organized and readily available. Cardiac arrest from massive, rapid hyperkalemia is a concern during reperfusion. Air and microthrombi from the graft/anastomosis can lead to pulmonary hypertension and possible paradoxical embolization. Reperfusion syndrome causes decreased heart rate, decreased blood pressure, heart conduction defects, decreased SVR and increased pulmonary pressure. Its exact cause is unknown; however, it is treated by supportive measures.

Lab values are continually monitored throughout this stage. Initially, acidosis and coagulopathy due to fibrinolysis continue to be a problem during this stage. Later, electrolytes usually normalize once the liver begins to function. Fluid balance continues to be of utmost importance. Fluid overload will cause graft congestion and should be avoided. Pulmonary edema may develop as part of the reperfusion syndrome. The patient’s temperature may also drop secondary to the perfusion of the cold organ which can worsen the
already ongoing coagulopathy. After surgery, the patient is transported to the ICU. Some centers are extubating their patients in the OR, but this is by no means the norm.

**Portal Vein Thrombosis**

Portal vein thrombosis, which occurs between 2.1% to 26%, is assessed during the anhepatic stage. The surgeons can perform a “simple” thrombectomy or, in more complex cases, perform a superior mesenteric venous conduit. Regardless of the technique used, both anhepatic phase time and blood loss is increased. Also, those with portal vein thrombosis will have a higher rate of re-thrombosis and re-exploration. However, 3-month and 4 year patient survival are no different in groups with and without portal vein thrombosis.

**Pain Control**

Pain control in these patients typically involves intravenous opioids. Anesthesiologists have avoided neuraxial analgesia secondary to the expected coagulopathies associated with the procedure. The first publication of a thoracic epidural catheter used for a pediatric liver transplant was reported in 2005. In that case report, the patient had normal coagulation studies at the time of catheter placement. However, after injection of the local anesthetic, the catheter was removed prior to surgery.

**Primary Graft Failure**

Patients are monitored in the ICU after surgery. Serial ABG’s, LFT’s and coagulation studies are followed serially. Most early complications of liver transplant involve technical issues concerning anastomosis of the biliary tree or hepatic vasculature. However, primary graft failure is a condition that happens without known physiologic insults and typically occurs within the first 24 to 72 hours after transplantation. Lab results show extremely elevated LFT’s and worsening coagulation studies. The etiology of this complication is unknown, but there are risk factors that have been identified:

**Donor:**

1. Age >65 years old
2. Steatosis in >30% of graft volume
3. Peak sodium >155 mEq/L
4. Use of high-dose multiple pressors
5. Prolonged intensive care unit stay
6. Prolonged interval between brain death and organ procurement

**Procurement:**

1. Cold ischemic time >12 hours
2. Non-heart beating donor

**Recipient**

1. Retransplantation
2. Severely ill, high MELD/PELD score
3. Use of high-dose or multiple pressors
4. Renal failure

Primary nonfunction (PNF) has important implications for patient survival because it always results in graft loss. Only 33% of the children who had PNF survive and we still lack understanding of the etiology. PNF occurs within the first 7 days and is usually accompanied by multi organ system failure. To survive the patient must be retransplanted.
Conclusion:

There are many challenges faced by the anesthesiologist who is anesthetizing the liver transplant child. Adequate preparation and thorough understanding of the patient’s pathophysiology is imperative. One must be able to anticipate and treat the problems associated with each stage of the transplant. It is clear that the pediatric anesthesiologist plays an important role in the team approach to pediatric liver transplant.

References:
Selected References:
