Cirrhosis and Portal Hypertension in the Pediatric Population

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KEYWORDS

• Cirrhosis • Portal hypertension • Esophageal varices • Ascites • Biliary atresia
• Children

KEY POINTS

- Cirrhosis is a complex diffuse process whereby the architecture of the liver has been replaced by structurally abnormal nodules due to fibrosis.
- Portal hypertension is characterized by a hepatic venous pressure gradient (HVPG) greater than 5 mm Hg with complications, such as ascites and varices, occurring at an HVPG greater than 10 mm Hg.
- Common causes of portal hypertension in children include extrahepatic portal vein obstruction, biliary atresia, alpha 1 antitrypsin deficiency, and autoimmune hepatitis, among others.
- Gastrointestinal bleeding secondary to esophageal or gastric varices may present as hematemesis or melena. Vasoactive drug therapy should be initiated as soon as possible before endoscopic treatment.
- Surgical shunt procedures or transjugular intrahepatic portosystemic shunt may be useful therapeutic options in patients with refractory portal hypertension.

INTRODUCTION

Cirrhosis is defined by the World Health Organization as a diffuse process whereby the architecture of the liver has been replaced by structurally abnormal nodules due to fibrosis.[1] Cirrhosis is a common outcome of a wide spectrum of disease processes (**Table 1**). The pathophysiology of cirrhosis is complex and involves a dynamic interplay between hepatocyte injury, cellular response to injury, and regeneration.[2] Fibrosis

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Table 1
Causes of cirrhosis and/or portal hypertension in children

Type	Disorders
Genetic-metabolic disorders	α1-Antitrypsin deficiency
	Amyloidosis
	Bile acid synthesis defects
	Cystic fibrosis
	Galactosemia
	Gaucher disease
	Glycogen storage disease type III and IV
	Hepatic porphyrias
	Hereditary fructose intolerance
	Hereditary hemochromatosis
	Indian childhood cirrhosis
	Langerhans cell histiocytosis
	Mitochondrial hepatopathies
	Niemann-Pick disease type C
	Sarcoidosis
	Tyrosinemia type I
	Wilson disease
	Wolman disease (lysosomal acid lipase deficiency)
Infectious diseases	Ascending cholangitis
	Chronic hepatitis B ± delta virus
	Chronic hepatitis C
	Cytomegalovirus
	Hepatitis E
	Herpes simplex virus
	Recurrent neonatal sepsis
	Rubella
	Schistosomiasis
	Tuberculosis
Inflammatory diseases	Autoimmune hepatitis
	Primary sclerosing cholangitis
Cholestatic diseases and biliary malformations	Alagille syndrome and nonsyndromic bile duct paucity
	Bile duct stenosis
	Biliary atresia
	Choledochal cyst
	Congenital hepatic fibrosis
	Caroli disease (intrahepatic cystic biliary dilatation)
	Progressive familial intrahepatic cholestasis
Vascular lesions	***Arteriovenous fistula***
	Budd-Chiari syndrome
	Congenital cardiomyopathy
	Congenital stenosis or extrinsic compression of the portal vein
	Congestive heart failure
	Constrictive pericarditis
	Nodular regenerative hyperplasia
	Portal vein thrombosis
	Sinusoidal obstructive syndrome
	Splenic vein thrombosis
	Venocaval web/inferior vena cava obstruction
Drugs and toxins	Hepatotoxic drugs (isoniazid, methotrexate)
	Hypervitaminosis A
	Natural toxins (eg, mushrooms)
	Organic solvents
	Peliosis hepatis (anabolic steroids, azathioprine)
	Total parenteral nutrition

(*continued on next page*)

Table 1
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Type	Disorders
Other	Fatty liver disease
	Hepatocellular carcinoma
	Idiopathic neonatal hepatitis
	Idiopathic or noncirrhotic portal hypertension
	Liver infiltration in hematologic diseases
	Zellweger (cerebrohepatorenal) syndrome

Disorders in bold/italic are causes of isolated portal hypertension.

is a common response to liver injury characterized by accumulation of extracellular matrix (ECM). Prolonged or sustained liver injury leads to chronic inflammation, excessive ECM deposition, and development of scar tissue. Alterations in sinusoidal structure and the formation of bands of connective tissue between portal areas results in poor blood flow and further injury with attempts at compensatory regeneration (nodule formation). Sinusoidal endothelial cells lose the ability to secrete and respond to vasodilators (such as nitric oxide), and levels of vasoconstrictors (such as endothelin-1) are increased.

Hepatic fibrosis may be staged by the degree of severity, from portal expansion to cirrhosis. METAVIR and Ishak are the most commonly used pathologic staging systems (Table 2).[3] More often cirrhosis is classified based on clinical outcomes. Patients with compensated cirrhosis have preserved liver synthetic function, with or without varices. Patients with decompensated cirrhosis on the other hand have loss of liver synthetic ability and development of jaundice or complications of portal hypertension including variceal hemorrhage, ascites, and hepatic encephalopathy. In adults the Child-Pugh classification has been widely used to assess the degree of hepatic dysfunction and the relative risk of mortality among patients with cirrhosis.[4] Similarly, the model for end-stage liver disease and pediatric end-stage liver disease scores, including age less than 1 year, serum albumin, serum bilirubin, international normalized ratio, and growth failure, can be used to predict short-term survival for adults and children with chronic liver disease.[5]

Portal hypertension occurs when there is an increase in portal blood flow, an increase in portal resistance to blood flow, or both. A basic paradigm of the pathophysiology of portal hypertension is in Fig. 1. Normally the portal venous system

Table 2
METAVIR fibrosis and activity score

Fibrosis Score		Activity Score	
No fibrosis	F0	No activity	A0
Portal fibrosis without septa	F1	Mild activity	A1
Portal fibrosis with few septa	F2	Moderate activity	A2
Portal fibrosis with numerous septa without cirrhosis	F3	Severe activity	A3
Cirrhosis	F4	—	—

From Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. The French METAVIR Cooperative Study Group. Hepatology 1994;20(1 Pt 1):15–20; with permission.

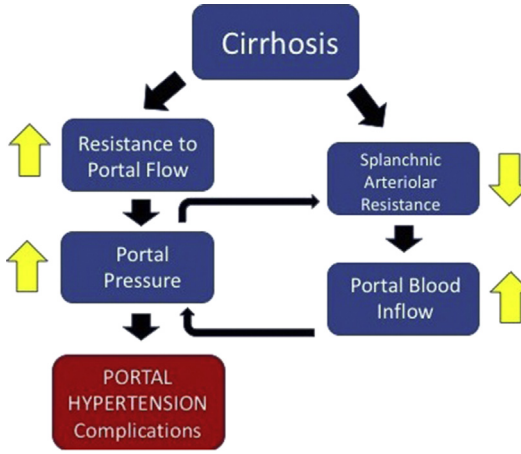

Fig. 1. Pathophysiology of development of portal hypertension.

has a low pressure with a hepatic venous pressure gradient (HVPG) of 1 to 4 mm Hg (the difference between the wedged hepatic venous pressure and the free hepatic venous pressure). Portal hypertension is defined as HVPG greater than 5 mm Hg. An HVPG greater than 10 mm Hg is associated with the development of esophageal varices, and greater than 12 mm Hg is associated with variceal bleeding and ascites. Decreased portal blood flow leads to an increase in systemic vascular resistance and marked splanchnic arterial vasodilation. This increase results in several systemic hemodynamic alterations. A state of low effective circulating blood volume activates the renin-angiotensin-aldosterone system, with a subsequent increase in antidiuretic hormone and sodium and free water retention. Low effective circulating blood volume leads to splanchnic vasodilation and the development of a hyperdynamic circulatory state with increased cardiac output and heart rate. Excess sodium and water retention leads to increased portal blood flow, increased portal pressure, and further exacerbates portosystemic shunting.

Portal hypertension can result from several disorders, including but not exclusive to conditions that also may lead to cirrhosis (see **Table 1**). In children, extrahepatic portal vein thrombosis (EHPVO) is the most common cause of portal hypertension, followed by biliary atresia (BA).[6]

Clinical and Physical Examination Findings and Evaluation

The clinical and physical examination manifestations of cirrhosis and portal hypertension vary depending on the underlying cause and degree of hepatocellular dysfunction and fibrosis (**Table 3**). Signs of portal hypertension include splenomegaly, ascites, and thrombocytopenia. Children frequently exhibit nonspecific signs of systemic illness, including fatigue, muscle weakness, anorexia, nausea, vomiting, and growth failure. Evaluation of patients with suspected cirrhosis and/or portal hypertension should focus on determining the cause of the liver dysfunction, the stage of fibrosis, and the presence and severity of extrahepatic complications. Some of the many diagnostic tests that may be considered are listed in **Table 4**. In addition, all patients should have an abdominal ultrasound with Doppler to evaluate the hepatic echotexture and determine the presence of any structural or vascular anomalies.

Table 3
Findings on clinical history and physical examination that may be seen in patients with cirrhosis and/or portal hypertension

General	Fatigue, anorexia, poor growth, malnutrition, decreased exercise tolerance, fever, nausea
HEENT	Easy bruising or bleeding (nose, gums)
Skin and extremities	Jaundice, pruritus, digital clubbing, cyanosis, flushing or pallor, palmar erythema, spider angiomata, xanthoma, telangiectasia
Msk	Muscle wasting, bone pain or fractures, peripheral edema
Abdomen	Caput medusa, ascites, abdominal distention, abdominal pain, hepatomegaly or a firm small nodular liver, splenomegaly, rectal varices
GU	Delayed puberty, testicular atrophy, gynecomastia
CNS	Asterixis, positive Babinski reflex, hyperreflexia, mental status changes, reversal of sleep-wake cycle, emotional lability

Abbreviations: CNS, central nervous system; GU, genitourinary; HEENT, head, eyes, ears, nose, throat; Msk, Musculoskeletal.

Complications of Portal Hypertension

Ascites

Ascites frequently develops in pediatric patients with cirrhosis and portal hypertension. Ascites occurs when osmotic and hydrostatic pressure within hepatic and mesenteric capillaries exceeds the drainage capacity of lymphatics and excess fluid

Table 4
Diagnostic tests in cirrhosis and/or portal hypertension

Disorder	Diagnostic Tests
Hepatitis B	Hepatitis B surface antigen
Hepatitis C	Hepatitis C antibody
Cytomegalovirus	Serology and/or viral DNA with PCR
Epstein-Barr virus	Serology and/or viral DNA with PCR
Autoimmune hepatitis	Antinuclear antibodies, anti–smooth muscle antibody, anti–liver-kidney-microsomal antibody, and total IgG level
α1-Antitrypsin deficiency	Serum α1-antitrypsin level and α1-antitrypsin phenotype
Glycogen storage disease	Lactic acid, fasting lipid panel, fasting glucose level, uric acid, genetic testing
Galactosemia	Urinary reducing substances, red blood cell galactose-1-phosphate uridyltransferase level
Tyrosinemia	Urine succinylacetone, serum amino acids
Gestational alloimmune liver disease; neonatal hemochromatosis	Buccal biopsy, MRI pancreas, ferritin, alpha-fetoprotein
Cystic fibrosis	Newborn screen, sweat chloride test, genetic testing
Wilson disease	Serum ceruloplasmin, urine 24-h copper, slit-lamp examination, liver copper quantification, genetic testing

Abbreviations: IgG, immunoglobulin G; PCR, polymerase chain reaction.

accumulates in the peritoneal space.[7] Clinically, this may manifest as weight gain, abdominal distention, a fluid wave, ballotable spleen, or shifting dullness on physical examination. Hypoalbuminemia worsens ascites formation, as albumin helps to retain fluid in the capillary lumen. Performance of a diagnostic paracentesis and calculation of the serum-to-ascites albumin gradient (SAAG) helps to differentiate ascites due to portal hypertension (SAAG $\geq$1.1 g/dL) from ascites due to other causes.[8,9] Initial treatment of ascites includes sodium restriction ($\leq$2 mEq/kg/d) as well as diuretic therapy. Fluid restriction is recommended in the setting of severe hyponatremia with serum sodium levels less than 125 mEq/L.[10] Spironolactone, which targets the hyperaldosteronism of portal hypertension, is typically the first-line diuretic, with hydrochlorothiazide and furosemide used as secondary agents. Intermittent therapeutic paracentesis can be performed for symptomatic ascites (abdominal discomfort or respiratory compromise), and in severe cases transjugular intrahepatic portosystemic shunt (TIPS) may be considered.[11] Any patient with ascites who presents with fever and abdominal pain should have a diagnostic paracentesis performed to evaluate for spontaneous bacterial peritonitis (SBP), which is defined as a positive ascitic fluid culture or absolute polymorphonuclear cell count greater than 250 cells per microliter. SBP is usually monomicrobial secondary to gram-negative enteric organisms, most commonly *Escherichia coli*, *Klebsiella pneumoniae*, and *Streptococcal pneumoniae*.[12] Cefotaxime or a similar third-generation cephalosporin is the initial treatment of choice for a 5- to 10-day course.[13] As the risk of recurrence is high, secondary antibiotic prophylaxis with oral norfloxacin, ciprofloxacin, or trimethoprim/sulfamethoxazole is typically recommended.[14,15]

Gastrointestinal bleeding

Gastrointestinal (GI) bleeding secondary to esophageal or gastric varices, presenting as hematemesis and melena, may be the initial manifestation of portal hypertension. Variceal bleeding is associated with an HVPG of greater than 12 mm Hg. There are several grading systems looking at the size of varices; however, few of them have been validated for interobserver reliability[16,17] (**Box 1**). Describing esophageal varices as small or large may be more reproducible among different endoscopists and better correspond to treatment and surveillance recommendations based on variceal size.[18,19] Gastric varices are typically supplied by the short gastric veins and develop in 4 basic patterns. Primary gastric varices generally refer to the presence of gastric varices at initial examination in someone who has never had treatment of esophageal varices. Secondary gastric varices refer to the development of gastric varices after

Box 1
Classification of esophageal and gastric varices

Esophageal varices, designed from the Japanese Research Society for Portal Hypertension.[16,17]
- Grade I varices are flattened by insufflation.
- Grade II varices are not flattened by insufflation and are separated by areas of healthy mucosa.
- Grade III varices are confluent and not flattened by insufflation.

Sarin classification of gastric varices
- GOV1 extend 2 to 5 cm below gastroesophageal junction and are in continuity with esophageal veins.
- GOV2 are in cardia/fundus and in continuity with esophageal varices.
- IGV1 are varices that occur in fundus in absence of esophageal varices.
- IGV2 are varices that occur in gastric body, antrum or pylorus.

endoscopic therapy for esophageal varices. Gastric varices in continuity with esophageal varices may regress following treatment of esophageal varices. Additionally, varices may be noted in the small intestine[20] or gall bladder[21] or may present as symptomatic hemorrhoids in the rectum.[22]

Portal hypertensive gastropathy (PHG) is characterized by dilation of the mucosal and submucosal vessels of the stomach and visually appears as discrete cherry-red spots in a lacy mosaic pattern. Bleeding from PHG is usually chronic and should be suspected in cirrhotic patients with persistent iron-deficiency anemia. A high rate of PHG has been demonstrated in pediatric patients with end-stage liver disease.[23] In addition, patients with portal hypertension are at an increased risk of bleeding from other lesions not secondary to portal hypertension, such as gastric or duodenal ulcers and gastritis.

The incidence of gastroesophageal varices in children is disease dependent, as is the risk of bleeding. Large varices, elevated prothrombin time, ascites, increased total bilirubin, the presence of variceal red markings, and the presence of gastric varices are associated with an increased risk of bleeding.[24,25] One long-term study of children with BA demonstrated that the risk of bleeding is 27%.[26] A cross-sectional study of children with BA demonstrated 19% had experienced GI bleeding with 7% having had multiple episodes.[27] In a single-center study evaluating liver transplant in alpha 1 antitrypsin deficiency, 35% of patients presented with liver failure with variceal bleeding.[28] Most patients with cystic fibrosis–related liver disease (CFLD) have splenomegaly and varices,[29] and 10-year cumulative variceal bleeding has been demonstrated to be 6.6%.[30] Age at bleeding also depends on the underlying cause of cirrhosis, with patients who have surgically corrected but progressive BA bleeding for the first time at a mean age of 3 years and those with cystic fibrosis at a mean age of 11.5 years.[31]

Prophylaxis of variceal hemorrhage

Prevention of variceal hemorrhage is categorized by strategy. *Primary prophylaxis* refers to approaches to prevent the first episode of bleeding from established varices and *secondary prophylaxis* targets varices that have already bled.

Primary prophylaxis

In adults with cirrhosis and esophageal varices, the 1-year risk of a variceal hemorrhage is approximately 12%[32]; primary prophylaxis to prevent bleeding is recommended. Although there are no clear pediatric guidelines, surveillance of varices may identify children with cirrhosis and portal hypertension who have an increased risk of bleeding.

Surveillance approaches Most gastroenterologists use clinical features that suggest a child is likely to have varices to decide which patients should undergo primary prophylaxis surveillance. Although more prospective studies are needed to determine the full utility of noninvasive parameters, the clinical predictive rule, albumin level, platelet count, and spleen size may be used for triaging children for endoscopic evaluation.[17,33,34] Less invasive modalities that may be used to screen for varices include esophageal capsule endoscopy, transnasal endoscopy, and small bowel capsule endoscopy. In patients with BA and CFLD, measuring liver stiffness by transient elastography has also been used to screen for varices.[35–37] A pilot study found that measurement of liver and spleen stiffness by acoustic radiation force impulse identified children with high-risk varices.[38]

Most centers perform primary prophylaxis[39] as studies have shown that there is an increased risk of morbidity and mortality even with a first variceal bleed.[40,41] A recent

study of screening endoscopy in children with BA and portal hypertension found that 28% of patients who had endoscopy before 2 years of age had grade II and III varices. GI bleeding occurred in 20% of patients, with 6% having a bleeding episode that preceded the first endoscopy.[24] Serial endoscopy in patients who initially have small varices reveals an increase in size over time.[42] However, the utility of primary prophylaxis in the pediatric population remains in question.[43] In the current era with widespread use of vasoactive drugs, such as octreotide, and with liver transplantation options, such as living donation, it is unclear if there is a true mortality risk. The Baveno VI pediatric conference on portal hypertension was unable to come to a conclusion about the benefit of primary prophylaxis in the pediatric population.[44] At this time, decisions regarding primary prophylaxis in children are considered on an individual basis and take into account the specific circumstances of patients, including their proximity to adequate medical care.

Beta-blockade

Beta-blockers reduce portal venous flow by unopposed α-receptor–mediated splanchnic vasoconstriction, thus, decreasing portal pressure. Beta-blockade also decreases cardiac output and reduces the norepinephrine-induced constriction of intrahepatic myofibroblasts, activated stellate cells, and vascular smooth muscle cells.[32,45] Meta-analysis of nonselective beta-blockade (NSBB) as the primary prophylaxis in adults with cirrhosis demonstrated a decrease in the rate of first variceal bleed and mortality over a median 2-year follow-up.[46] The beta-blocker dose is titrated to achieve a reduction in the heart rate of 25% or the maximally tolerated dose.

Potential side effects of NSBB, which may impact the pediatric population, include a lack of response to bronchodilators in patients with reactive airway disease or asthma, exacerbation of peripheral artery disease, blunted response to hypoglycemia, depression, fatigue, and weight gain. Beta-blockade may also inhibit the ability to mount a compensatory increase in heart rate in the setting of hypovolemia, thereby worsening the outcome from a variceal bleed, especially in young infants.[45,47] This concern has limited the use of NSBB in younger children. Although, some clinicians use NSBB as the primary prophylaxis in older children, based on results from adult trials, clear recommendations for this approach await additional evidence.[17]

In children, both endoscopic variceal ligation (EVL) and sclerotherapy have been studied for primary prophylaxis. Duche and colleagues[48] used both techniques for primary prophylaxis in children with BA and major endoscopic risk factors for variceal bleeding and found that 11% went on to have a GI bleed. Approaches for primary prophylaxis of gastric varices in both adults and children are based on bleeding risk, and surgical options or TIPS should be considered.[49]

Secondary prophylaxis

Because of the high recurrence rate of variceal hemorrhage once a first bleed has occurred, secondary prophylaxis is indicated.[17] In children, esophageal variceal obliteration by either EVL or sclerotherapy is recommended to decrease the risk of rebleeding. Treatment sessions should occur every 2 to 4 weeks until varices are eradicated.[18]

Therapy for acute variceal hemorrhage

GI bleeding is the major cause of morbidity in patients with portal hypertension. However, as previously discussed, the risk of mortality has improved over the last few decades with improved medical management[32,50]; mortality rates in children are lower than in adults.

The treatment of patients with portal hypertension and an acute GI hemorrhage is summarized in **Box 2**. The first steps to be taken include protecting the airway, assuring that patients are breathing, and maintaining circulation. A nasogastric tube should be placed to monitor ongoing bleed and remove blood from the GI tract, which can predispose patients with cirrhosis to encephalopathy. Prophylactic antibiotics are recommended in the setting of acute esophageal variceal hemorrhage; all patients should have vasoactive drug therapy, such as octreotide, initiated as soon as possible.[17,51] These drugs work by decreasing splanchnic blood flow, reducing portal venous inflow, and reducing portal pressure. Octreotide can be given as a bolus (1 μg/kg) followed by continuous infusion (1–5 μg/kg/h) or as subcutaneous injections 3 times daily and has been shown to safely slow the rate of GI bleeding in children with varices.[52]

Endoscopy should be performed as soon as possible once patients are stable to determine the source of bleeding. Recent guidelines recommend the administration of erythromycin 3 mg/kg intravenously over 30 minutes before endoscopy to enhance emptying of the stomach and improve visualization on endoscopy.[53,54] Patients failing to respond to fluids, vasoactive medications, and correction of coagulopathy may require emergent endoscopy and rarely placement of a balloon tamponade device, emergent surgical intervention, or TIPS.[17] Endoscopic variceal ligation has largely supplanted endoscopic sclerotherapy for treatment of esophageal varices in both adults and children with good success.[48,55] In pediatrics, sclerotherapy is currently used only in infants and small children (<10 kg) in whom the band ligation device is too large to pass through the upper esophageal sphincter. When sclerotherapy is performed, injections may be either intravariceal, inducing thrombus formation within the vessel, or paravariceal, causing local inflammation that compresses the vessel. Sclerotherapy is effective in the treatment of variceal bleeding but is associated with a higher rate of complications than EVL, including aspiration pneumonia and esophageal stricture.[56] EVL causes thrombosis of the varix and the band and varix subsequently slough off together in about 5 to 7 days. Long-term administration of proton pump inhibitors should be considered to reduce the risk of treatment failure after EVL.[57]

Box 2
Therapy for acute variceal hemorrhage

- Secure the airway
- Intravenous placement with volume resuscitation with blood, crystalloid, or colloid to achieve hemodynamic stability
- Nasogastric tube placement to evaluate ongoing bleed and remove blood from the stomach
- Blood transfuse to a goal of approximately 7 to 8 g/dL
- Octreotide 1 mcg/kg bolus plus 1 mcg/kg/h infusion
- Measurement of platelets and prothrombin time/international normalized ratio
- Vitamin K administration
- Antibiotics: ceftriaxone or norfloxacin
- Consider urgent/emergent endoscopy if ongoing bleeding or hemodynamic instability
- Urgent elective endoscopy if controlled with octreotide and volume expansion

From Shneider BL, Bosch J, de Franchis R, et al. Portal hypertension in children: expert pediatric opinion on the report of the Baveno v consensus workshop on methodology of diagnosis and therapy in portal hypertension. Pediatr Transplant 2012;16(5):426–37; with permission.

The approach to bleeding gastric varices is similar to that of esophageal varices, including initiation of medical therapy with vasoactive agents. Some gastric varices may regress following thrombosis of associated esophageal varices. Injection of varices with tissue adhesives, such as *n*-butyl-2-cyanoacrylate, has been successful in halting gastric variceal bleeding in children[58,59]; but complications, including pyrexia and abdominal pain, have been described.[60] Balloon-occluded retrograde transvenous obliteration (BRTO) is an interventional radiology technique that obliterates gastric fundal varices[61] and has been used safely in children.[62] Although both BRTO and cyanoacrylate injection may be considered in children with gastric varices, TIPS or portosystemic shunting may be associated with better long-term resolution and outcome.[17]

Surgical therapy and transjugular intrahepatic portosystemic shunt

In patients who fail endoscopic therapy or in whom there are additional problems, such as refractory ascites, shunt surgery, or TIPS, may be considered. In many cases, children with progressive liver disease who fail endoscopic therapies are best treated with liver transplantation. In patients with stable liver disease who are not likely to progress to transplantation soon, surgical shunting may be an excellent option.

Surgical shunting is used to treat complications resulting from noncirrhotic portal hypertension, including idiopathic portal hypertension, congenital hepatic fibrosis, and EHPVO. In the long-term, surgical shunts control bleeding from esophageal or gastric varices in more than 90% of patients[63] and overall outcomes are very good.[64–66] The type of shunt selected depends on the underlying etiology and the vascular anatomy. Meso rex shunt is the recommended option for patients with EHPVO[44] but requires normal liver architecture to ensure long-term patency. The distal splenorenal shunt selectively decompresses esophageal and gastric varices through the splenic vein to the left renal vein.

Creation of a TIPS effectively reduces portal pressure by creating a communication between the hepatic and portal vein. The shunt can be placed by an interventional radiologist and is technically feasible in children.[67] Indications for TIPS in pediatric patients with portal hypertension include recurrent variceal bleeding not responsive to more conservative therapy, hypersplenism, refractory ascites, hepatorenal syndrome, and hepatopulmonary syndrome.[68] Complications include portal vein leakage, encephalopathy, perforation, hemolysis, infection, and restenosis; but overall mortality from the procedure is low.[69] Studies of children with severe portal hypertensive and refractory variceal bleeding or ascites demonstrate a high degree of resolution of symptoms with TIPS.[70,71]

Extrahepatic Manifestations of Portal Hypertension

Cardiopulmonary

Patients with cirrhosis are at an increased risk of cardiopulmonary complications. Hepatopulmonary syndrome (HPS) and portopulmonary hypertension (POPH) are associated with increased mortality.[72] HPS is due to intrapulmonary vasodilation and the development of arteriovenous shunting with resultant hypoxemia. Increased circulating levels of endothelin-1 and nitric oxide as well as pulmonary vascular angiogenesis are thought to play a role.[73] The disorder typically manifests as dyspnea on exertion, but patients may also have digital clubbing, cough, decreased oxygen saturation, and shortness of breath or hypoxemia that worsens with sitting up (platypnea and orthodeoxia, respectively).[74] Liver transplantation is the preferred treatment of HPS with a significant improvement in 5-year survival.[75] POPH is due to increased pulmonary vascular resistance resulting in elevated mean pulmonary artery pressure and

is diagnosed by right heart catheterization. POPH typically responds to vasodilators and may improve with liver transplantation but carries a higher risk of cardiopulmonary mortality. Patients with cirrhosis and portal hypertension may also develop cirrhotic cardiomyopathy, which is characterized by impaired contractile response to stress, diastolic dysfunction, and electromechanical abnormalities.[76]

Endocrine and hematologic

Endocrine abnormalities including increased circulating levels of estrogen and other sex hormones may lead to gynecomastia, testicular atrophy, spider angiomata, palmar erythema, and delayed puberty.[77] Hyperinsulinemia or diabetes mellitus and hypothyroidism are also more common in cirrhosis, and patients with end-stage liver disease have relative adrenal insufficiency.[78] Patients with cirrhosis and portal hypertension frequently have anemia, which is multifactorial due to GI blood loss, hemolysis from hypersplenism, micronutrient deficiency secondary to malabsorption and malnutrition, and a dilutional effect from sodium and water retention. Decreased synthesis of liver-derived clotting factors (prothrombin, factor VII and IX) and increased consumption of clotting factors through fibrinolysis and disseminated intravascular coagulation contributes to coagulopathy in cirrhosis, which may be exacerbated by vitamin K deficiency. As anticoagulant and procoagulant factors are decreased to a similar degree, cirrhotic patients are often in a state of homeostasis.[79] However, with any perturbation in this balance, they are at an increased risk of both bleeding and thrombosis. Thrombocytopenia due to splenic sequestration from portal hypertension is common. In addition, patients with cirrhosis are immunocompromised and at an increased risk of infection, most commonly from SBP, urinary tract infections, and pneumonia.[80]

Renal

Hepatorenal syndrome (HRS) is a condition that occurs in patients with cirrhosis and portal hypertension and is associated with increased mortality. Renal vasoconstriction leads to poor renal perfusion, decreased glomerular filtration rate, and a decreased ability to excrete sodium and free water.[81] Type 1 HRS is characterized by the rapid onset of progressive kidney failure and a high mortality versus type 2 HRS, which is more slowly progressive and has a better prognosis.[82] In adults, albumin infusion has been shown to prevent HRS in the setting of SBP.[83,84] Management includes the treatment of reversible causes of renal failure, including hypovolemia, discontinuation of diuretics, and avoidance of nephrotoxic drugs. Vasoconstrictor therapy with terlipressin, octreotide and midodrine, or norepinephrine, with or without albumin, has been shown to be effective in adults and reduce mortality.[85] Renal replacement therapy is often used in patients with azotemia, fluid overload, or electrolyte abnormalities. Liver transplantation can be a treatment of HRS, but some patients continue to require hemodialysis for some interval after transplant.

Growth and nutrition

Malnutrition is a common problem in cirrhosis because of anorexia and inadequate intake, increased metabolic demand, malabsorption, steatorrhea, and fat-soluble vitamin deficiency. Most children with cirrhosis will require fat-soluble vitamin supplementation as well as an increase in total fat and calories. If unable to meet these requirements orally, there should be a low threshold to initiate nasogastric tube feedings; if this fails, begin parenteral nutrition. Stunting secondary to chronic malnutrition is often seen in children with cirrhosis and is associated with poor outcomes.[86] Because of vitamin D deficiency and other factors, cirrhotic patients often have liver-associated bone disease putting them at an increased risk of fractures, which should be screened for with dual energy x-ray absorptiometry scans.[87]

Neurologic

Hepatic encephalopathy (HE) encompasses several reversible neuropsychiatric abnormalities that can be seen in patients with cirrhosis and/or portosystemic shunting. Effects are thought to be secondary to increased levels of potentially neurotoxic substances, such as ammonia, in the systemic circulation and crossing the blood-brain barrier. Manifestations range from mild to severe and are grouped into stages (**Table 5**).[88] In children, HE is associated with cerebral atrophy and impaired cognitive function that may persist even after liver transplantation.[89] Patients with HE are at risk of cerebral edema secondary to astrocyte swelling from ammonia metabolism. However, in patients with cirrhosis who have chronically elevated ammonia levels, brain osmoregulatory mechanisms are often able to compensate.[90] Minimal HE (MHE) is the mildest form of HE in which patients have no overt symptoms but may have subtle motor and cognitive defects and impairment on neuropsychological tests. Studies suggest that up to 50% of children with chronic liver disease have MHE, which negatively impacts brain function and school performance.[91,92] In most patients, HE is triggered by some precipitating event, such as infection, GI bleeding, or renal failure; initial treatment should focus on identifying and treating these complications. More

Table 5
Stages of hepatic encephalopathy

Stage	Clinical Manifestations	Asterixis/ Reflexes	Neurologic Signs	EEG Changes
Subclinical	None	Absent/normal	Abnormalities on psychometric testing and proton magnetic spectroscopy in older patients	Usually absent
I	Confused, mood changes, altered sleep habits, loss of spatial orientation, forgetfulness	Absent/normal	Tremor, apraxia, impaired handwriting	May be absent or diffuse, slowing to theta rhythm, triphasic waves
II	Drowsy, inappropriate behavior, decreased inhibitions	Present/ hyperreflexive	Dysarthria, ataxia	Abnormal, generalized slowing, triphasic waves
III	Child is stuporous but obeys simple commands; infant is sleeping but arousable	Present/ hyperreflexive with positive Babinski sign	Muscle rigidity	Abnormal, generalized slowing, triphasic waves
IV	Child is comatose but arousable by painful stimuli (IVa) or does not respond to stimuli (IVb)	Absent	Decerebrate or decorticate	Abnormal, very slow delta activity

Abbreviation: EEC, electroencephalography.

Data from Rogers EL. Hepatic encephalopathy. Crit Care Clin 1985;1(2):313–25; and Devictor D, Tahiri C, Lanchier C, et al. Flumazenil in the treatment of hepatic encephalopathy in children with fulminant liver failure. Intensive Care Med 1995;21(3):253–6.

long-term therapeutic options include nonabsorbable disaccharides (such as lactulose or lactitol) that acidify the stool and trap ammonia as the less absorbable ammonium and nonabsorbable antibiotics (such as rifaximin), which decrease ammonia production from gut bacteria.[93]

SUMMARY

Portal hypertension remains a significant cause of morbidity and mortality in pediatric patients with cirrhosis. The natural history of portal hypertension in pediatrics still requires further elucidation. As we develop a better understanding of the underlying mechanisms of this disease, more treatment options for portal hypertension may arise.

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