

Beyond Varices: Complications of Cirrhotic Portal Hypertension in Pediatrics

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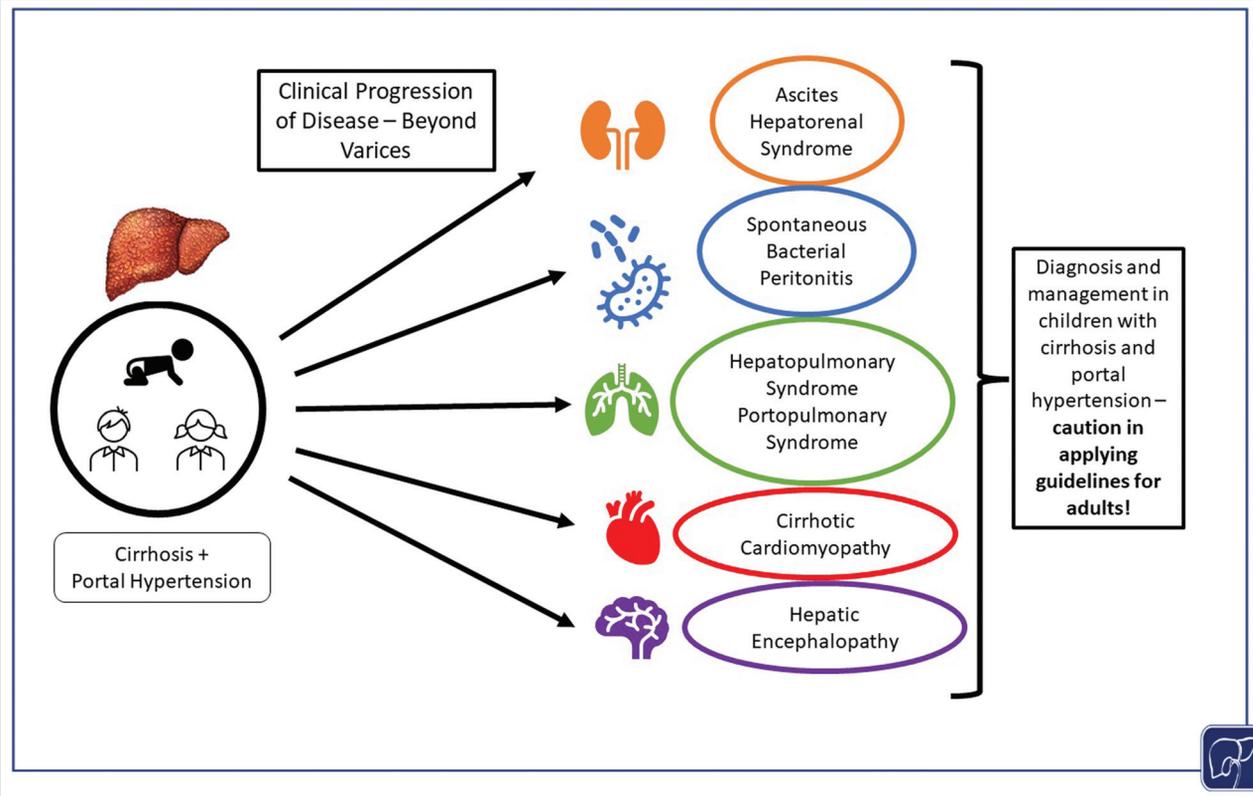
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Graphical Abstract



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Abstract

Complications of cirrhotic portal hypertension (PHTN) in children are broad and include clinical manifestations ranging from variceal hemorrhage, hepatic encephalopathy (HE), ascites, spontaneous bacterial peritonitis (SBP), and hepatorenal syndrome (HRS) to less common conditions such as hepatopulmonary syndrome, portopulmonary hypertension, and cirrhotic cardiomyopathy. The approaches to the diagnosis and management of these complications have become standard of practice in adults with cirrhosis with many guidance statements available. However, there is limited literature on the diagnosis and management of these complications of PHTN in children with much of the current guidance available focused on variceal hemorrhage. The aim of this review is to summarize the current literature in adults who experience these complications of cirrhotic PHTN beyond variceal hemorrhage and present the available literature in children, with a focus on diagnosis, management, and liver transplant decision making in children with cirrhosis who develop ascites, SBP, HRS, HE, and cardiopulmonary complications.

Keywords

- ▶ cirrhosis
- ▶ complications of portal hypertension
- ▶ children
- ▶ ascites
- ▶ transplant

Liver disease in children develops from a variety of etiologies ranging from cholestasis, inflammatory conditions, to genetic/metabolic diseases. Progression to cirrhosis occurs in many and is characterized by the replacement of the liver architecture by structurally abnormal nodules due to fibrosis.¹ Compensated cirrhosis is typically manifest by features of portal hypertension (PHTN) (splenomegaly and/or thrombocytopenia) and characterized by preserved liver synthetic function. Hallmarks of decompensated cirrhosis include ascites, hepatic encephalopathy (HE), variceal hemorrhage, hepatopulmonary syndrome (HPS), and portopulmonary hypertension (POPH), cirrhotic cardiomyopathy (CCM), as well as markers of hepatic synthetic dysfunction.^{1,2} As disease progresses, advanced manifestations such as refractory ascites with hyponatremia and hepatorenal syndrome (HRS) may develop. Children with cirrhosis who begin to develop complications of PHTN should be considered for liver transplantation (LT), although these complications are not always an indication for immediate LT.³

The approaches to diagnosis and management of these complications have become standard of practice for adults with cirrhosis with numerous recommendations published over the years.^{4–7} Guidelines on the diagnosis and management of variceal hemorrhage in children with cirrhosis, while controversial, have been the subject of numerous reviews and will not be reviewed here; we refer readers to the references provided for additional information on this topic.^{8–13} However, there is a paucity of literature on approaches to the diagnosis and management of other complications of PHTN in children with cirrhosis. The aim of this review is to summarize the current guidelines on the diagnosis and management of complications of cirrhotic PHTN in adults and present the most recent data in pediatrics.

Diagnosis of Portal Hypertension in Children

PHTN is by definition a pathological increase in portal venous blood pressure. The portal venous system originates in capillar-

ies which drain from the spleen and mesentery ending in hepatic capillaries—in healthy patients, a normal direct measurement of portal pressure is 5 to 10 mm Hg.¹⁴ In adults, the diagnosis of PHTN can be made through indirect quantitative measurements of portal pressures, typically using the hepatic venous pressure gradient (HVPG).^{2,15} HVPG measurements are useful for predicting risk of PHTN complications, as a gradient of 10 mm Hg or higher is defined as clinically significant PHTN, signified by risk of esophageal varices development, and correlated with histologic evidence of cirrhosis. In addition, complications of variceal hemorrhage and ascites, as well as a fivefold increase in mortality risk, have been associated with HVPG of over 12 mm Hg and over 20 mm Hg, respectively.^{2,16,17}

Unfortunately, the utility of HVPG in children remains limited, mainly due to its invasive nature typically requiring general anesthesia (GA).^{18–21} In adults, HVPG is measured in the setting of “light” sedation, and GA required in children is expected to alter measurements and their prognosis, though in poorly defined ways. Given the preponderance for pre-sinusoidal lesions in children (i.e., biliary atresia [BA]), HVPG may grossly underestimate pressures as it ideally assesses sinusoidal disease.²² Furthermore, intrahepatic veno-venous collaterals in children with BA may also lead to an underestimation of PHTN using HVPG.¹⁸ As such, HVPG has historically not been incorporated routinely into chronic liver disease workup in children.²²

In 2019, an a priori definition for clinically evident PHTN (CEPH) in children was advanced and denotes clinical findings and manifestations of elevated portal pressures for the diagnosis of intrahepatic PHTN (▶ Fig. 1). CEPH has value as its variables are easily assessed and provide a consistent method for diagnosis in children. However, CEPH is not a surrogate measurement of portal pressures, as elevation of such pressures in PHTN clearly precedes CEPH. As such, CEPH reflects a stage of PHTN in children with chronic liver disease. Difficulties in assessing splenomegaly and thresholds for thrombocytopenia may limit the utility of CEPH in infants and very young children. Variability in the practice of endoscopic screening for varices in pediatrics impacts

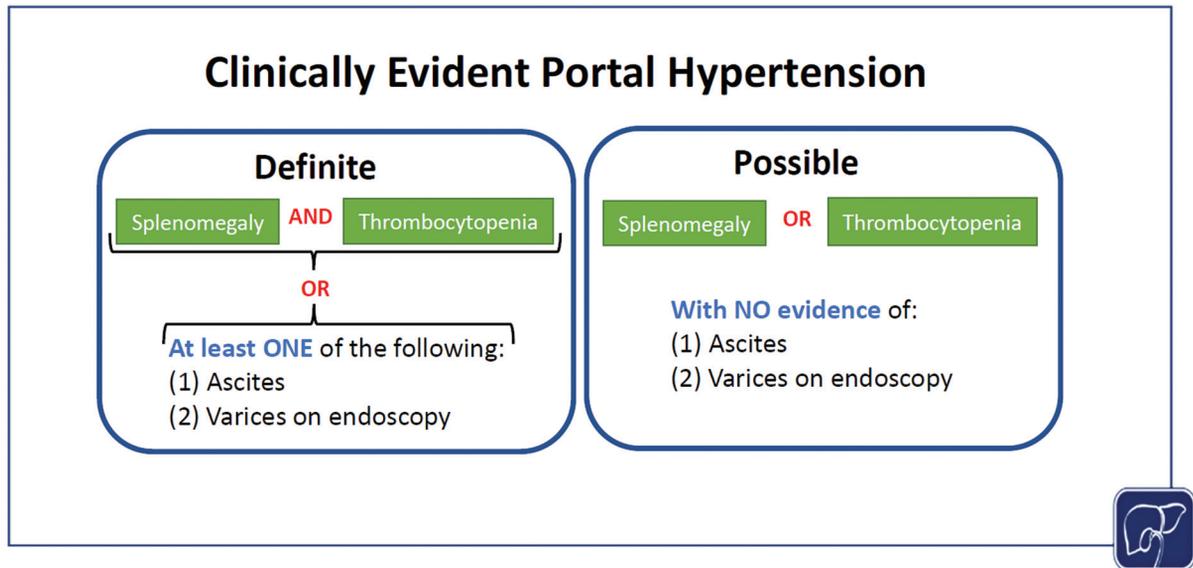


Fig. 1 Definition of clinically significant and clinically evident portal hypertension in children. Splenomegaly is defined as spleen tip palpable > 2 cm below costal margin. Thrombocytopenia is defined as platelet count $< 150 \times 10^9/L$. Ascites in this definition requires the use of chronic diuretic therapy.

identification of varices, which serve as an important defining clinical manifestation of CEPH.²

Ongoing research focuses on noninvasive testing as surrogate predictors for progression of PHTN in children. Elastographic or magnetic resonance assessment of liver and/or spleen stiffness is emerging noninvasive modalities that may predict PHTN in children.^{23–25} Calculated scores such as the aspartate-to-platelet ratio index (APRI), GGT-to-platelet ratio, and fibrosis-4 (Fib-4) require only standard laboratory values.^{26–30}

Ascites, Spontaneous Bacterial Peritonitis, and Hepatorenal Syndrome in Children

Pathophysiology of Ascites, SBP, and HRS

Multiple forces contribute to the development of ascites in cirrhosis. Hydrostatic forces related to dense fibrosis and nodules in cirrhosis drive hepatic lymph formation due to permeability of the sinusoidal membrane.^{31,32} PHTN is associated with splanchnic vasodilation, diminished effective circulating volume, and subsequent activation of compensatory mechanisms including renal vasoconstriction, activation of the renin–angiotensin–aldosterone system (RAAS), and increased antidiuretic hormone (ADH) secretion.^{33–35} Together, this leads to sodium and associated water retention, plasma volume expansion, increased cardiac output, and a hyperdynamic circulation which further exacerbates portal pressures and ascites formation.^{33–35} Systemic inflammation in the setting of increased bacterial translocation may also contribute to the development of ascites.^{34,36,37}

Renal blood flow autoregulation, which normally acts to increase renal perfusion in the setting of hypoperfusion, is altered in cirrhosis due to sympathetic overactivity.³⁸ Early in ascites, cortical renal blood flow is preserved.

However, with progression to diuretic-refractory ascites, there is a significant reduction in renal cortical blood flow, leading to cortical ischemia, renal dysfunction, and HRS.^{39,40}

The risk of bacterial infections in patients with cirrhosis is an interplay of gut dysbiosis, cirrhosis-associated immune dysfunction, and increased bacterial translocation. Patients with cirrhosis have higher levels of proinflammatory cytokines, alterations in innate immunity leading to impaired pathogen surveillance, increased bacterial translocation leading to systemic endotoxemia, and a state of chronic inflammation with decreased effectiveness to respond to and clear pathogenic insults.^{41–44} All of these factors increase the risk of infection including SBP.^{36,45,46}

Diagnosis of Ascites

The clinical diagnosis of new-onset ascites in children is often based on physical examination findings, which can be difficult especially in young children and infants. Rapid, inappropriate weight gain may be the most objective sign of the development of ascites. Less specific findings may include abdominal distention or bulging flanks.³² Sonographic confirmation of the presence of ascites in children is sensible and the relevance of trace ascites is unclear.^{32,47,48} Adult guidelines recommend diagnostic paracentesis for all patients with new-onset ascites as well as those hospitalized for worsening ascites.^{5,7} This recommendation may not be applicable to all children with new-onset ascites since, unlike adults, it is less important to exclude malignancy-related or other noncirrhotic conditions as the cause of ascites in children. However, any child with new-onset ascites with any clinical suspicion for infection should undergo diagnostic paracentesis (– **Table 1**).

Multiple studies in children have shown that the presence of ascites is associated with worsening prognosis.^{49–51} The

Table 1 Diagnosis and management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome

	Adult recommendations	Pediatric recommendations
Ascites		
Diagnosis	<ul style="list-style-type: none"> • Diagnostic paracentesis in all adult patients with new-onset ascites that is accessible for sampling or patients hospitalized with worsening ascites^{5,7} • Initial fluid analysis to include ascitic neutrophil (PMN) count, total protein, albumin so that the provider can calculate the SAAG, with SAAG ≥ 1.1 g/dL diagnostic of ascites due to portal hypertension⁵ 	<ul style="list-style-type: none"> • Evidence of rapid, inappropriate weight gain • Diagnostic paracentesis may <i>not</i> be warranted in all children with new-onset ascites—sonographic confirmation of ascites is generally indicated • Diagnostic paracentesis should be performed in any child with new-onset ascites and any clinical suspicion for infection • Initial fluid analysis to include ascitic neutrophil (PMN) count, total protein, albumin so that the provider can calculate of the SAAG, with SAAG ≥ 1.1 g/dL diagnostic of ascites due to portal hypertension⁵
Management	<ul style="list-style-type: none"> • Sodium restriction to 1–2 g/d to avoid excess salt intake to achieve negative sodium balance and fluid loss^{5,7} • Avoid fluid restriction unless concomitant hyponatremia and Na ≤ 125 mmol/L • Diuretic therapy^{5,7}: <ul style="list-style-type: none"> ◦ Spironolactone 100 mg/d \rightarrow increase every 72 h to max 400 mg/d ◦ Add furosemide 40 mg/d (max 160 mg/d) ◦ Maintain ratio of spironolactone 2.5:1 to ensure adequate effect of each diuretic and balanced effect on K ◦ Goal weight loss ~ 0.5 kg/d to suggest appropriate response ◦ Closely monitor electrolytes for hyperkalemic acidosis with spironolactone and hypokalemic alkalosis with furosemide • Large-volume paracentesis (defined as removal of > 5 L of fluid) should be performed as first-line therapy for refractory ascites^{5,7} <ul style="list-style-type: none"> ◦ Administer 6–8 g of IV albumin per L of ascitic fluid removed to avoid post-paracentesis circulatory dysfunction ◦ For example, after 5 L removed, ~ 40 g of albumin should be infused, and after 8 L removal, the amount of albumin given should be ~ 64 g • Careful patient selection is the key to the success of TIPS in the management of refractory ascites • Early referral for liver transplantation 	<ul style="list-style-type: none"> • Consider sodium restriction to 2 mEq/kg/d to avoid excess salt intake to achieve negative sodium balance and fluid loss (careful monitoring for diminished nutritional intake is warranted with Na restriction) • Avoid fluid restriction unless concomitant hyponatremia and Na ≤ 125 mmol/L • Diuretic therapy²⁹: <ul style="list-style-type: none"> ◦ Spironolactone 2–3 mg/kg/d once daily (max 4–6 mg/kg/d) ◦ Add furosemide 1 mg/kg/d (max 3 mg/kg/d) if inadequate response to spironolactone ◦ Maintain ratio of spironolactone 2.5:1 to ensure adequate effect of each diuretic and balanced effect on K ◦ Closely monitor electrolytes for hyperkalemic acidosis with spironolactone and hypokalemic alkalosis with furosemide • Large-volume paracentesis may be considered in children with refractory ascites (reported volumes of 50–150 mL/kg) <ul style="list-style-type: none"> ◦ Administer IV albumin 0.5–1.0 g/kg or 6–8 g per L of ascites removed to avoid post-paracentesis circulatory dysfunction ◦ <i>Example</i>: 20 kg child has removal of 2 L (100 mL/kg) of ascitic fluid \rightarrow administer 15 g of IV albumin (0.5 g/kg or 7.5 g/L removed) • Active listing for liver transplantation
SBP		
Diagnosis	<ul style="list-style-type: none"> • Diagnostic paracentesis to evaluate for SBP in any adult hospitalized with cirrhosis + ascites^{5,7} • Patients with ascites due to cirrhosis emergently admitted to the hospital should undergo a diagnostic abdominal paracentesis to rule out SBP even in the absence of symptoms/signs of infection^{5,7} • Patients with ascites who develop signs, symptoms, or laboratory abnormalities suggestive of infection should undergo workup for infection plus a diagnostic abdominal paracentesis^{5,7} • SBP is diagnosed in presence of ascitic fluid absolute neutrophil count $> 250/\text{mm}^3$ • Ascitic fluid should be cultured at the bedside in both aerobic and anaerobic bottles before initiation of antibiotics with at least 10 mL of ascitic fluid to increase the sensitivity of culture to $> 90\%$⁵⁷ 	<ul style="list-style-type: none"> • Diagnostic paracentesis should be performed in any child with ascites and fever or other symptom to suggest SBP (abdominal pain, peritonitis) • SBP is diagnosed in presence of ascitic fluid absolute neutrophil count $> 250/\text{mm}^3$ • Ascitic fluid should be cultured at the bedside in both aerobic and anaerobic bottles with at least 10 mL of ascitic fluid to increase the sensitivity of culture to $> 90\%$⁵⁷
Management	<ul style="list-style-type: none"> • Empiric antibiotic therapy after diagnosis of SBP based on diagnostic paracentesis^{5,7} <ul style="list-style-type: none"> ◦ First-line empirical antibiotic therapy for community-acquired SBP/SBE is IV third-generation cephalosporin 	<ul style="list-style-type: none"> • Empiric antibiotic therapy after diagnosis of SBP based on diagnostic paracentesis: <ul style="list-style-type: none"> ◦ First-line agent: cefotaxime or ceftriaxone $\times 5$–7 d

(Continued)

Table 1 (Continued)

	Adult recommendations	Pediatric recommendations
	<ul style="list-style-type: none"> o Narrow antibiotics once culture results return • Response to empirical antibiotic therapy may be assessed by repeating diagnostic paracentesis 2 d after antibiotic initiation^{5,7} o A decrease in fluid PMN < 25% from baseline indicates lack of response and should lead to broadening of antibiotic coverage and further evaluation to rule out secondary bacterial peritonitis • Primary prophylaxis^{5,7}: <ul style="list-style-type: none"> o Norfloxacin reduced 1-year probability of first SBP compared with placebo (60 vs. 7%) in patients with low protein ascites and advanced liver failure (Child–Turcotte–Pugh score > 9 points with serum bilirubin level > 3 mg/dL) or impaired renal function (serum creatinine level > 1.2 mg/dL, blood urea nitrogen level > 25 mg/dL, or serum sodium level < 130 mEq/L) o IV ceftriaxone as prophylaxis in patients with cirrhosis and upper GI hemorrhage for max 7 d • Secondary prophylaxis: Norfloxacin after first episode of SBP and should be considered long-term; ciprofloxacin is also an alternative • Early referral for liver transplantation after 1st episode of SBP 	<ul style="list-style-type: none"> o Concern for MDRO: piperacillin/tazobactam and/or vancomycin o Narrow antibiotics once culture results return • No data to support recommendations for primary or secondary prophylaxis; however, given high mortality in children with first episode of SBP, secondary prophylaxis may be warranted • Prioritization for liver transplantation after 1st episode of SBP
HRS		
Diagnosis	<ul style="list-style-type: none"> • Presence of cirrhosis with ascites and a diagnosis of AKI according to the International Club of Ascites-Acute Kidney Injury Criteria (one of the following)⁷⁸: <ul style="list-style-type: none"> o Increase in serum creatinine ≥ 0.3 mg/dL from baseline within 48 h o A percent increase in serum creatinine of $\geq 50\%$ which is known or presumed to have occurred within the preceding 7 d • No response in serum creatinine after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin infusion (1 g/kg per day) • Absence of shock • No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, contrast agents) • No signs of structural kidney injury (proteinuria > 500 mg per day, microhematuria > 50 RBC per high-power field, abnormal renal ultrasound) 	<ul style="list-style-type: none"> • No pediatric-specific AKI-HRS criteria
Management	<ul style="list-style-type: none"> • The treatment of choice for HRS-AKI is vasoconstrictor drugs in combination with albumin <ul style="list-style-type: none"> o Terlipressin—preferred agent, administered either as IV bolus or continuous IV infusion o Norepinephrine—in settings where terlipressin is not available o Oral midodrine—consider when neither terlipressin or norepinephrine can be administered (5–15 mg PO every 8 h) in combination with octreotide (100–200 μg every 8 h or 50 μg/h IV), but the efficacy is low⁸⁴ • Consider CRRT as bridge to LT: <ul style="list-style-type: none"> o Common indications for CRRT include worsening renal function, fluid overload, electrolyte abnormalities • Early referral for liver transplantation 	<ul style="list-style-type: none"> • No specific recommendations for medical management for AKI-HRS • Single-center studies found use of terlipressin (as available) as continuous infusion with albumin showed improvement or stabilization in renal function^{87,88} • Prioritization for urgent liver transplantation

Abbreviations: CRRT, continuous renal replacement therapy; HRS, hepatorenal syndrome; NSAIDs, nonsteroidal anti-inflammatory drugs; RBC, red blood cell; SAAG, serum-ascitic albumin gradient; SBP, spontaneous bacterial peritonitis.

presence of ascites at the time of transplant listing is associated with enhanced waitlist mortality.^{49,50,52} Children with BA and grade 3 ascites had 1-year survival of only 13.6% (HR: 17.3, $p < 0.01$) as compared with 97.1% in children without any ascites ($p < 0.001$).⁵⁰ This is even higher than previously reported HR of 2.59 (95% CI: 1.44–4.64, $p = 0.001$) of ascites leading to increased mortality risk at 90 days after LT listing.⁴⁹ These findings support timely LT referral and evaluation in children who develop ascites.⁵

There are limited high-quality data on the utility of diagnostic paracentesis in children. Out of 207 children with significant ascites at a single center, only 9.6% (20 patients; 6 with cirrhosis) had a diagnostic paracentesis performed.⁵³ Given its invasive nature, diagnostic paracentesis in children may require sedation and has poorly defined guidelines and performance parameters. In adults, the risk of complications from diagnostic paracentesis is very low³² with only 1.6% of adults with cirrhosis experiencing major complications (bleeding, infection).⁵⁴ Similar safety data in children are generally lacking, although it is presumed to be relatively safe children.^{55,56}

Diagnosis of SBP

The use of diagnostic paracentesis is critical in the diagnosis of SBP. Clinical presentation of SBP may include fever, worsening jaundice, abdominal pain, and tenderness to palpation, although 10% may be asymptomatic.^{5,32} Adult guidelines suggest any patient emergently hospitalized with cirrhosis and ascites undergo diagnostic paracentesis to evaluate for SBP, even in the absence of symptoms to suggest infection. Paracentesis should ideally be performed prior to the initiation of antibiotics and the ascites fluid should be cultured at the bedside in aerobic and anaerobic bottles to increase sensitivity of culture to over 90% (► **Table 1**).^{5,7,57}

There are limited data on the incidence and characteristics of SBP in children with cirrhosis. The incidence of SBP ranges from 17 to 38% in children with chronic liver disease from single-center experiences,^{58–63} with only 50% of patients showing symptoms to suggest SBP in one study.⁶³ In adults, gram-negative organisms such as *Escherichia coli* and *Klebsiella pneumoniae* account for up to approximately 60% of positive ascitic fluid cultures; in contrast, gram-positive organisms, such as *Streptococcus pneumoniae*, have been more commonly isolated in children.^{5,59,64,65} More recently, there has been a shift toward multidrug-resistant organisms (MDROs) with a recent study in children finding that up to 83% of gram-negative bacilli that were isolated in ascitic fluid were extended-spectrum β -lactamase producers.^{5,62,66}

Children with ascites and fever or other symptoms consistent with infection should undergo diagnostic paracentesis focused on identification of SBP (► **Table 1**).^{5,7} A single-center study found that only 11% of children survived with their native liver 6 months after their first episode of SBP and in-hospital mortality was as high as 39%.⁶⁷ Thus, prompt and accurate diagnosis of SBP in children not only guides management but may also aid clinicians in prioritizing urgency for LT.

Diagnosis of HRS

HRS is a type of AKI that occurs in patients with cirrhosis and has distinct pathophysiology (as described earlier) with recently updated nomenclature from Type 1/Type 2 HRS to AKI-HRS.^{68,69} Diagnosis of AKI-HRS in adults is based on specific consensus criteria requiring absence of both shock and structural kidney injury in addition to specific changes in serum creatinine with diuretic withdrawal and volume expansion (► **Table 1**).^{5,7,68} Prevalence of AKI-HRS in adults with cirrhosis varies depending on diagnostic criteria used and prevalence ranges of 10 to 17%.³⁹

There are currently no diagnostic criteria for AKI-HRS specific for children as very limited data published on AKI-HRS in pediatrics exist.^{70,71} One study identified a prevalence of HRS in 4.1% of all pediatric patients evaluated for LT and 5.3% of all patients listed at a single center.⁷² Up to 32% of children who developed AKI in the setting of acute-on-chronic liver failure met adult criteria for AKI-HRS in a recent study.⁷³ Direct application of this adult definition to pediatrics should be used with caution as children have lower baseline creatinine values and certain pediatric chronic liver disease diagnoses may have associated renal involvement, all of which may potentially lead to overdiagnosis of AKI-HRS.

Management of Ascites

The mainstay for the early management of ascites in adults depends on establishing negative sodium balance through dietary sodium restriction and use of diuretics (► **Table 1**).^{5,7} Evidence-based recommendations for sodium restriction are lacking for children, although sodium restriction to 2 mEq/kg/day is employed by some pediatric hepatologists.³² Low-sodium diets are often not palatable and clinicians need to weigh the risks of worsening failure to thrive associated with diminished nutritional intake.

Diuretic therapy is almost always required to manage significant ascites. Aldosterone antagonists (i.e., spironolactone) are the mainstay of initial diuretic therapy, acting at the main site of perturbation in the kidneys in PHTN.^{5,7} Guidelines in adults exist for dosing and dose escalation as well as addition of loop diuretics, such as furosemide (► **Table 1**).^{5,7} Many pediatric hepatologists begin with single-agent spironolactone and the addition of furosemide may be necessary, with a ratio of spironolactone to furosemide of 2.5:1 (► **Table 1**).^{5,32,74,75} Though cumbersome, obtaining urinary sodium excretion coupled with careful assessment of sodium intake can confirm negative sodium balance. Low urinary sodium may indicate nonadherence to diuretics. Typically, serum sodium levels are only modestly reduced in the setting these therapies for ascites. Significant hyponatremia (e.g., $\text{Na} < 130$ or 125 mmol/L) is a feature of very advanced liver disease and reflects free water overload requiring fluid restriction.

Intravenous (IV) albumin infusion may be used to augment diuretics in the setting of hypoalbuminemia (e.g., serum albumin < 2.5 g/dL).³² A recent meta-analysis in adults showed that coadministration of furosemide with albumin enhances diuresis and natriuresis effects, with advantage seen when albumin is less than 2.5 g/dL.⁷⁶

Albumin administration was associated with shorter hospital stays, enhanced outpatient ascites management, and decreased hospital readmission.⁷⁷ Although there are no studies confirming these findings in children, supplemental albumin is often used in combination with loop diuretics when serum albumin is less than 2.5 g/dL (► **Table 1**).⁷⁵

Refractory ascites, which develops in approximately 5 to 10% of adults,⁵ is defined by ascites that persists despite sodium restriction and maximal doses of diuretics, intolerance of maximal diuretics, or that recurs after large-volume paracentesis (LVP). Sodium restriction and diuretic therapy are difficult and clinicians should confirm adherence to medical recommendations, prior to diagnosing refractory ascites. Adult guidelines recommend the use of LVP as the first-line therapy for refractory ascites (► **Table 1**).^{5,7} Rates of refractory ascites in children are unknown and there are very limited studies on the use of LVP in children.^{55,56} In a single-center study, a mean of approximately 120 mL/kg of ascitic fluid was removed per LVP session in children with tense ascites and this was associated with very low complications.⁵⁵ Access to timely LT has diminished the incidence of refractory ascites in children with chronic liver disease.

Patients undergoing LVP are at risk for post-paracentesis circulatory dysfunction (PPCD) due to pronounced reactivation of the RAAS and increased plasma renin activity.^{78,79} In adults, PPCD has been associated with the development of recurrent ascites, acute kidney injury (AKI) and HRS, worsening hyponatremia, and decreased survival.^{78–80} Infusions of 6 to 8 g of albumin per liter of ascites removed have been shown to reduce the incidence of PPCD as well as other complications.^{5,7,80} The incidence of PPCD was as high as 67% in children who did not receive IV albumin after LVP in one study.⁵⁶ Additionally, children with PPCD showed higher rates of recurrent ascites, readmission, and mortality at 3 months.⁵⁶ Given these data, administration of IV albumin at 0.5 to 1 g/kg in children who receive LVP should be strongly considered.^{5,55,56} Other management strategies for refractory ascites in adults include the use of transjugular intrahepatic portosystemic shunts (TIPS), peritoneal pumps, and LT.^{5,7} The experience with TIPS in children with refractory ascites is very limited and with varying ranges of use (1.5–38.5%) in single-center experiences.^{81–83}

Management of SBP

Adult guidelines recommend empiric antibiotics immediately after a diagnosis of SBP on diagnostic paracentesis and before obtaining culture results (► **Table 1**).^{5,7} Antibiotic therapy should be narrowed once culture results return to minimize the future threat of MDRO. In adults with SBP, the development of AKI is the main predictor of in-hospital mortality and studies have shown that volume expansion with IV albumin improves survival in patients with cirrhosis and SBP.⁸⁴

Current recommendations for primary prophylaxis (no prior history of SBP) in adults include the use of norfloxacin, as studies have shown this regimen to significantly decrease the 1-year probability of first SBP as compared with placebo (7 vs. 60%).^{85,86} In addition, adult guidelines recommend the

use of daily norfloxacin (ciprofloxacin) as secondary SBP prophylaxis as risk of recurrence is quite high, up to 70% within 1 year.^{5,7} As patients with SBP have poor long-term survival, patients who recover should be considered for LT.

Specific antibiotic recommendations and prophylactic regimens have not been systematically studied in children with SBP and current antibiotic practices are often based on adult guidelines.³² Very few of the published studies in children with infected ascites present data on antimicrobial agents used or antibiotic sensitivity of the bacteria on positive cultures.^{58–61,64,67} Published studies suggest isolated bacteria in ascitic fluid cultures were sensitive to commonly used antibiotics (cefotaxime, ceftriaxone, ciprofloxacin).^{65,67} The use of primary or secondary prophylaxis or the use of IV albumin for SBP has not been reported in children. It is difficult to determine which children might benefit from primary prophylaxis of SBP. Given the poor prognosis after a first episode of SBP in children, secondary prophylaxis may be warranted.

Unfortunately, in-hospital mortality in children with first episode of SBP is as high as 38.9 to 50% and native-liver survival only 11% at 6 months.^{63,67} These pediatric findings appear similar to adults, where SBP remains an indicator of poor prognosis and these patients should be considered for LT early during their clinical course.

Management of HRS

In adults, the mainstay of therapy for AKI-HRS is the use of vasoconstrictors such as terlipressin and norepinephrine in conjunction with albumin to help improve renal perfusion and reverse the functional renal failure that characterizes AKI-HRS (► **Table 1**).^{5,7,68} Studies in adults have shown improvement in kidney function with variable response rates ranging from 20 to 80%.^{5,7,68} As AKI-HRS progresses, patients may require renal replacement therapy (RRT) as a bridge to LT, especially in those with worsening renal function, fluid overload, and electrolyte abnormalities.^{5,7} Given the poor prognosis associated with AKI-HRS, urgent LT evaluation should be considered in all adults with cirrhosis and AKI.^{5,7}

Two single-center experiences present data on the use of terlipressin in children with HRS.^{87,88} In one study, four children with varying etiologies of cirrhosis who presented with HRS received terlipressin as a continuous infusion with albumin. All four responded with improvement or stabilization of renal function without any reported adverse effects.⁸⁸ Another study assessed the use of terlipressin in critically ill children with liver disease admitted to the ICU.⁸⁷ Improvement was seen in children with AKI-HRS, but this was not significantly different when compared with children who received terlipressin for non-HRS indications.⁸⁷ Existing data on the use of RRT in children with AKI-HRS are incredibly scarce. In one single-center study, only 6% of patients received RRT prior to LT for HRS (median of 21 days prior to LT) and those who received LT recovered renal function within 1 month.⁸⁹ Similar to adult recommendations, children who experience AKI-HRS should be considered early for LT, as this is the only management strategy that can lead to reversal of AKI-HRS.

Table 2 Diagnosis and management of cardiopulmonary complications of cirrhotic portal hypertension

HPS		
Diagnosis	<ul style="list-style-type: none"> • Screening pulse oximetry should be performed in all LT candidates⁸⁹ • Presence of chronic liver disease or portal hypertension (ascites, varices, splenomegaly, or thrombocytopenia) • No clinically significant underlying primary pulmonary disease • A shunt identified either by contrast-enhanced echocardiography or macro-albumin aggregated scan <ul style="list-style-type: none"> ◦ Positive contrast-enhanced transthoracic echocardiography^{7,89} <ul style="list-style-type: none"> ■ Microbubbles in the left heart ≥ 3 cardiac cycles after right heart microbubbles following 10 mL agitated saline injection in a peripheral arm vein • Abnormal arterial oxygenation defined by: <ul style="list-style-type: none"> ◦ Blood samples obtained via ABG ◦ $AaO_2 \geq 15$ mm Hg (> 20 mm Hg if age > 64) ◦ Calculation of A-a gradient: <ul style="list-style-type: none"> ■ AaO_2 mm Hg = P alveolar O_2 - P arterial $O_2 = (FIO_2 [Patm - PH_2O] - PaCO_2/0.8) - PaO_2$, where FIO_2, inspiratory oxygen fraction; $Patm$, atmosphere pressure; PH_2O, water vapor partial pressure; $PaCO_2$, arterial carbon dioxide pressure; and PaO_2, partial pressure of oxygen 	<ul style="list-style-type: none"> • No pediatric-specific criteria to define HPS in children • Screening pulse oximetry in all pediatric LT candidates; however, some patients may have normal pulse oximetry despite evidence of shunting on TTE⁹⁴ • Contrast-enhanced transthoracic echocardiography should be performed to assess for HPS in children • Consider use of macro-albumin aggregated scan to quantify degree of shunting • Use of arterial blood gas measurements may be limited in children due to associated abnormal breathing in young children (i.e., screaming, crying, etc.), supine positioning, as well as concerns for hematoma formation and arteriospasm⁸⁹
Management	<ul style="list-style-type: none"> • Supplemental oxygen and supportive care⁸⁹ • TIPS and coil embolization has shown uncertain benefit^{7,89} • Early referral for liver transplantation 	<ul style="list-style-type: none"> • Supplemental oxygen and supportive care • Early referral for liver transplantation
Portopulmonary hypertension		
Diagnosis	<ul style="list-style-type: none"> • Screening echocardiography should be performed in all LT candidates⁸⁹ • Diagnosis of portal hypertension • Findings suggestive of elevated R-sided heart strain on echo should prompt RHC <ul style="list-style-type: none"> ◦ Right ventricle systolic pressure > 50 mm Hg ◦ Right ventricular hypertrophy or dysfunction • Diagnostic criteria based on RHC⁸⁹: <ul style="list-style-type: none"> ◦ mPAP > 35 mm Hg ◦ PVR > 3 wood units (240 dynes/s per cm^{-5}) ◦ Values must be from the same test date ◦ Other causes of pulmonary hypertension have been assessed and determined not to be a significant contributing factor 	<ul style="list-style-type: none"> • No pediatric-specific criteria to define POPH in children • Screen echocardiography should be performed in all pediatric LT candidates • Right heart catheterization should be considered if findings concerning for elevated R-heart pressures on echo (tricuspid regurgitant jet consistent with increased pressure or bowed intraventricular membrane)
Management	<ul style="list-style-type: none"> • Use of prostacyclin analogs, endothelin receptor antagonists, prostaglandin inhibitors • Consider therapy in patients with mPAP ≥ 35 mm Hg with goal to lower mPAP to < 35 mm Hg and PVR to < 3 WU before LT^{7,88,89} • Consider liver transplantation in select patients who demonstrate improvement in mPAP < 35 mm Hg and have preserved RV function with another hepatic indication for LT⁸⁹ • Patients with mPAP ≥ 45 mm Hg should be considered absolute contraindication to LT due to 100% of perioperative mortality^{7,89,95} 	<ul style="list-style-type: none"> • Limited data in children on medical therapy for POPH • Liver transplantation considerations should be patient-specific
Cirrhotic cardiomyopathy		
Diagnosis	<ul style="list-style-type: none"> • Diagnostic criteria for systolic dysfunction¹⁰⁸: <ul style="list-style-type: none"> ◦ LV ejection fraction $\leq 50\%$ ◦ Absolute GLS $< 18\%$ • Diagnostic criteria for diastolic dysfunction¹⁰⁸: 	<ul style="list-style-type: none"> • No pediatric-specific criteria to define cirrhotic cardiomyopathy • Abnormalities in LV geometry (increased LVMI, increased LV mass, increased wall thickness, and

(Continued)

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Table 2 (Continued)

HPS		
	<ul style="list-style-type: none"> o ≥ 3 of the following <ul style="list-style-type: none"> • Septal e' velocity < 7 cm/s • E/e' ratio ≥ 15 • LAVI > 34 mL/m² • TR velocity > 2.8 m/s • Routine echo at 6-mo intervals in pre-LT period • Routine echo at 6, 12, 24 mo post-LT with any patient with pre-LT systolic or diastolic dysfunction¹⁰² 	increased LV internal diameter) on TTE have been detected in children with CCM ^{115,116,121}
Management	<ul style="list-style-type: none"> • Consider traditional heart failure management^{7,108} <ul style="list-style-type: none"> o Diuretics to reduce volume and hyperdynamic load o Beta-adrenergic agents to improve QT interval abnormalities o ACE inhibitors to reduce cardiac remodeling o Aldosterone antagonists to decrease aldosterone-induced myocardial fibrosis and sympathetic activation 	<ul style="list-style-type: none"> • No pediatric-specific management recommendations

Abbreviations: AaO₂, alveolar-arterial oxygen gradient; ABG, arterial blood gas; ACE, angiotensin-converting enzyme; CCM, cirrhotic cardiomyopathy; GLS, global longitudinal strain; HRS, hepatorenal syndrome; LAVI, left atrial volume index; LT, liver transplantation; LV, left ventricle; LVMI, LV mass index; mPAP, mean pulmonary arterial pressure; POPH, portopulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; TIPS, transjugular intrahepatic portosystemic shunts; TR, tricuspid regurgitation; TTE, transthoracic echocardiography.

Hepatopulmonary Syndrome and Portopulmonary Hypertension in Children

Pathophysiology of HPS and POPH

Pulmonary manifestation including HPS and POPH often develops as severity of PHTN progresses. While these complications are commonly related to portosystemic shunting which develop in the setting of PHTN, they can also occur with congenital portosystemic shunts, where PHTN is typically absent. Experimental models have shown a variety of mediators including nitric oxide (NO), endothelin-1, and vascular endothelial growth factor which accumulate in the lungs and play a role in the development of dilation of the capillary and precapillary vessels that characterize HPS as well as angiogenesis of the pulmonary vasculature.^{90,91} These changes manifest as hypoxemia due to the development of ventilation/perfusion mismatch, shunting, and diffusion limitation.^{90,91} POPH is characterized by obstruction of arterial blood flow in the pulmonary arterial bed due to a combination of vasoconstriction, endothelial and smooth muscle proliferation, and platelet aggregation and involves a variety of mediators such as endothelin-1 and deficiency of prostacyclin synthase in pulmonary endothelial cells.^{90–92}

Diagnosis of HPS

HPS diagnosis requires the presence of portosystemic shunting, most frequently related to PHTN, and the presence of intrapulmonary vascular dilatation leading to impaired gas exchange and hypoxemia with specific diagnostic criteria (– **Table 2**).^{91,92} Patients are often asymptomatic early in the disease process, but as the disease progresses, dyspnea on exertion or fatigue often develops. Platypnea (dyspnea on standing) and orthodeoxia (hypoxemia exacerbated in the upright position) are characteristic features of HPS. Digital clubbing and cyanosis may be present.⁹¹

Current adult guidelines recommend pulse oximetry screening as initial step; however, arterial blood gas (ABG) to determine oxygenation is necessary to diagnose HPS.^{7,92} Contrast-enhanced transthoracic echocardiography (CE-TTE) using agitated saline identifies the characteristic intrapulmonary shunting and is recommended as the optimal screening study in adults with low pulse oximetry.^{7,92} Macro-aggregated albumin scanning is useful to quantify shunting in HPS.⁷

HPS is estimated to occur in 3 to 20% of pediatric patients with PHTN.^{92–96} However, due to the lack of standardized clinical definitions of HPS, differences in diagnostic modalities, and variability of screening in pediatrics, the true prevalence in children is unknown. In a recent study, all patients at a single center with biopsy-proven cirrhosis were screened for HPS, with 40% demonstrating evidence of intrapulmonary shunting on CE-TTE.⁹⁷ Interestingly, all of these patients had normal pulse oximetry values of greater than 98%.⁹⁷ Although the authors conclude that pulse oximetry may not be an ideal screening tool, it is possible that CE-TTE may be identifying shunting that is not physiologically relevant and subsequently not resulting in lower SpO₂ or hypoxemia. ABG sampling is required to document PaO₂ and more accurately document hypoxemia, but this procedure is often limited in children due to hematoma formation and arteriospasm.⁹² In addition, ABGs in children are often associated with very abnormal breathing (i.e., screaming, crying, etc.) and a supine position, which are not ideal for documentation of hypoxia in HPS. In practice, many pediatric hepatologists use pulse oximetry in the outpatient clinic setting as a screening test for HPS.⁹³ CE-TTE can confirm that hypoxia is related to shunting, which can be quantified using an MAA scan. Difficulties with ABGs in children make application of rigorous adult criteria difficult.

Diagnosis of POPH

Adult guidelines recommend the use of TTE as a screening tool for POPH.^{7,92} Findings on TTE allow for estimation of right ventricular (RV) systolic pressure using the peak tricuspid regurgitant jet velocity in the presence of tricuspid regurgitation.⁹⁸ Different centers use varying cut-off values for RV systolic pressure (30–50 mm Hg in the presence of other signs of RV dysfunction) to recommend right heart catheterization (RHC) and RHC indices are used to define POPH and its severity (► **Table 2**).^{7,92,99}

Overall prevalence is 5 to 10% in adults,⁹² but its prevalence in pediatrics is unknown with only single-center studies and case series describing POPH in children.^{91,96,100–103} Prevalence of POPH in children with chronic liver disease based on the above RHC criteria was only 0.9% in a single-center study,¹⁰¹ but as high as approximately 5% when diagnosed per autopsy findings.¹⁰⁴ TTE can be used as a screening tool for children being evaluated for LT. RV systolic pressures can be estimated with low threshold to consider RHC in children with concerns for elevated R-sided pressures.

Management of HPS

No established pharmacologic therapies have demonstrated a proven benefit in treating HPS. Adult guidelines recommend the use of supplemental oxygen in addition to rest, exercise, and sleep.^{7,92} As hypoxemia worsens, referral for LT is recommended, as LT is the only proven treatment for HPS.^{7,92} Complete resolution of HPS symptoms is expected in most patients who undergo LT and typically resolves within 6 to 12 months.⁹⁹

Supplemental oxygen is the mainstay of medical intervention for pediatric patients with HPS and chronic hypoxemia to maintain SpO₂ at greater than 88%.^{91,92} Evaluation for LT for children with HPS should be performed. Case series have shown excellent outcomes post-LT with complete resolution of HPS in many of these children.^{94,105–108} In single-center studies, children with very severe HPS (PaO₂ < 50 mm Hg) had longer need for supplementation oxygen, mechanical ventilator, and ICU stay as compared with children with less severe degrees of hypoxemia.^{93,109} Additional management strategies in children with HPS and persistent hypoxemia have been reported including the use of inhaled NO and high-flow nasal cannula and even in these children, eventual resolution of HPS is achieved.^{110,111}

Management of POPH

The goal of POPH therapy is to reduce pulmonary artery pressure. Pharmacologic agents that target vasodilation (i.e., prostacyclin analogs), blockade of pulmonary vasoconstriction (i.e., endothelin receptor antagonists), and reduction of pulmonary vascular resistance (i.e., prostaglandin inhibitors) are commonly used to treat pulmonary hypertension. These agents have also been used in POPH and may be useful to improve hemodynamics and exercise capacities in patients (► **Table 2**).^{7,91,92} Single-center experiences using these agents in children with POPH have shown varying results.^{100–103,112,113} In a single center from Europe, five children with POPH (two with underlying cirrhosis) were

treated with pulmonary artery hypertension therapy and showed improvement in hemodynamics with several of these patients proceeding to successful LT.¹⁰³ On the contrary, in a separate single-center study, three out of five children with POPH died prior to LT despite medical management.¹⁰⁰

Survival after LT in adults with POPH is variable and dependent on the severity of the POPH; thus, the diagnosis of POPH in a patient with cirrhosis is not a definitive indication for LT.^{91,92,99} A mean pulmonary artery pressure of 45 mm Hg or higher should be considered a strong contraindication for LT due to the very poor outcomes with a 100% risk of perioperative mortality.^{7,92,99} Data on LT outcomes in children with POPH are sparse with conflicting results in several studies where some children with POPH do not survive to LT,^{100,113} whereas several other patients received successful LT after medical intervention for POPH.¹⁰³ As specific RHC criteria for POPH in children do not exist, many centers apply current adult POPH criteria for considerations for LT in children with POPH.

Pathophysiology, Diagnosis, and Management of Cirrhotic Cardiomyopathy in Children

Pathophysiology of CCM

Cirrhosis accompanied by PHTN creates a hyperdynamic circulatory state that impairs normal cardiac function, known as CCM.^{114–116} CCM is defined as a chronic cardiac dysfunction characterized by impaired cardiac contractility (systole) in response to stress (induced by catecholamine/exercise/surgical) and altered diastolic relaxation with electrophysiological abnormalities in patients with cirrhosis and no known inherent heart disease. This consensus definition previously established in 2005 has been further refined in adults to include recent advances in cardiac scanning modalities (► **Table 2**).¹¹⁴ A variety of pathophysiological events occur and have been reviewed in detail elsewhere.^{117,118} In addition to autonomic dysfunction, excessive cytokine exposure, and elevated growth factors contributing to the development of fibrosis, recent studies have also implicated serum bile acids as well as other circulating metabolites inherent to cirrhotic liver failure and PHTN that are cardio-depressants and implicated in the pathophysiology of CCM.^{118–120}

Diagnosis of CCM

CCM is often silent and masked by the hyperdynamic state of cirrhosis. The symptoms of heart failure due to CCM do not become apparent until later stages of the disease, in the setting of a significant stressor, or after LT when afterload increases toward normal. An estimated 50% of adult patients undergoing LT have evidence of cardiac dysfunction.¹¹⁷ There are very limited studies on CCM children with only retrospective studies published,^{121,122} and the lack of universally accepted criteria create diagnostic challenges.

Specific criteria to define CCM based on TTE and EKG findings have been proposed and define CCM based on

systolic dysfunction, diastolic dysfunction, and electrophysiologic abnormalities (► **Table 2**).^{7,114,117} Studies in children with cirrhosis have identified abnormalities in left ventricle (LV) geometry on ECHO. One study found children with cirrhosis had significantly higher LV end-diastolic diameter z score, LV mass z score, and LV mass index (LVMI) as compared with noncirrhotic children, with similar findings in children with BA.^{116,121,122} Another study found higher markers to suggest diastolic dysfunction as well as B-natriuretic peptide in children with cirrhosis.^{116,121,122} The true incidence of CCM in children is unknown, as pediatric studies are limited by smaller sample sizes and lack of universal a priori definitions. In single-center experiences, up to 20% of children with PHTN met criteria for CCM and in one study, up to 50% of children with BA listed for LT met modified criteria for CCM.^{115,123,124} Future studies are needed in this area in children to further characterize and define CCM.

Management of CCM

Although no established treatment exists for CCM, an estimated 7 to 21% of adult LT recipients die due to complications of heart failure and most medical management is similar to traditional heart failure management strategies.^{7,114,117} Data on CCM and its association with pre- and post-LT survival in children are scarce. Two studies have found contrasting findings with one showing that CCM does not significantly impact pre- or post-LT survival, whereas another showed increased pre- and post-LT mortality in children with BA and CCM.^{115,121} A recent study, interestingly, identified CCM early in the course of BA and found the ratio of LVMI to its upper limit of normal was a predictor of post-Kasai outcome.¹²⁵ Despite these differences in survival, studies found CCM is associated with higher ICU length of stay as well as multiorgan dysfunction, mechanical ventilation, and the need for pressor support prior to LT.^{115,116,121,124} Adult guidelines recommend routine TTE at regular intervals before and after LT (► **Table 2**).¹¹⁷ Approaches to surveillance for and monitoring of CCM in children are not well defined.

Pathophysiology, Diagnosis, and Management of Hepatic Encephalopathy in Children

Pathogenesis of HE

The exact underlying pathogenesis of HE is not fully elucidated. Ammonia, a common biomarker for HE, is thought to be one of the substances implicated in the development of HE; however, other neurotoxins such as mercaptans, short and medium chain fatty acids, as well as phenols have been under investigation.^{126,127} In response to these potential neurotoxins, astrocytes undergo changes in function which can also influence neuronal function and contribute to the clinical manifestation of HE.¹²⁶ Benzodiazepine receptors as well as γ -aminobutyric acid (GABA) type A receptors have also been implicated in the development of HE and higher levels of endogenous benzodiazepines and GABA tone have been demonstrated in patients with HE.¹²⁷ Despite the

implication of ammonia in HE, ammonia levels do not correlate tightly with the severity/grade of HE.^{128,129}

Diagnosis of HE

HE is defined as “brain dysfunction caused by liver insufficiency and/or portosystemic shunting, and manifests as a wide spectrum of neurologic/psychiatric abnormalities ranging from subclinical alterations to coma.”⁶ HE can be classified based on underlying etiology, clinical severity, time course, as well as associated precipitating factors (i.e., infection, GI bleeding, electrolyte disturbances).^{4,6,130} The West Haven criteria to grade HE based on severity of clinical symptoms is used in adults and older children (► **Table 3**).^{6,130} Determining degree of HE in younger children and infants is difficult and subtle changes such as inconsolability and excessive crying can be seen early in grades I–II HE (► **Table 3**).¹³¹

Prevalence of overt HE in adults ranges from 10 to 14% at the time of diagnosis of cirrhosis to as high as 30 to 40% during the subsequent clinical course.⁶ In adults, minimal HE (MHE) occurs in 20 to 80% and has been shown to impact quality of life as well as ability to perform complex tasks.^{6,130} Overt HE in children with chronic liver disease is uncommon; however, MHE may be more common than appreciated with reports showing that up to 50% of children with cirrhosis have MHE on neuropsychological testing.^{132,133} In adults, the presence of MHE has been associated with reduction in 5-year survival rates,¹³⁴ but there are no data in children on the impact of MHE on survival or common functional activities. One would surmise that MHE has a deleterious impact on school performance.

Management of HE

Adult guidelines have outlined specific treatment recommendations for HE (► **Table 3**).^{4,6} Medications are the cornerstone of overt HE management and include lactulose as the first-line agent for episodic overt HE, which acts to acidify the intestinal lumen and limit absorption of ammonia.⁶ The addition of a nonabsorbable antibiotic such as rifaximin to lactulose is often considered as an adjunct.^{4,135,136} Protein restriction may be considered; however, many cirrhotic patients are malnourished and protein restriction may worsen malnutrition. Recommended daily protein intake should be 1.2 to 1.5 g/kg/day and specific guidelines for nutritional management in patients with HE have been published.¹³⁷

There is a paucity of data on the treatment of HE in children with cirrhosis. A retrospective review presented data on the use of lactulose in children admitted with HE at a single center and assessed response to lactulose, defined as complete resolution of HE symptoms.¹³⁸ Of the 22 children admitted with HE, a precipitating factor was not identified in 32% and all patients received lactulose at a dose to achieve two stools per day. A complete response to lactulose therapy was seen in 73%, whereas 27% did not respond to therapy.¹³⁵ Despite limited data, lactulose is commonly used by pediatric hepatologists in children with hyperammonemia and HE (► **Table 3**). Specific nutrition recommendations for children with HE do not exist; however, pediatric guidelines for

Table 3 Diagnosis and management of hepatic encephalopathy (HE)

HE		
Diagnosis	<ul style="list-style-type: none"> West Haven Criteria for diagnosis as below^{4,6,117} Rule out other conditions that might mimic HE Covert HE includes: <ul style="list-style-type: none"> Minimal HE: identified only on psychometric/neuropsychological testing, no clinical evidence of mental changes Grade I: unawareness (mild), euphoria or anxiety, shortened attention span, impairment of addition/subtraction, altered sleep rhythm Overt HE includes: <ul style="list-style-type: none"> Grade II: lethargy or apathy, disorientation for time, obvious personality change, inappropriate behavior, dyspraxia, asterixis Grade III: somnolence to semi-stupor, responsive to stimuli, confused, gross disorientation, bizarre behavior Grade IV: coma 	<ul style="list-style-type: none"> West Haven Criteria for diagnosis in older children and adolescents^{4,6,117} Criteria to be considered in younger children and infants as below¹¹⁸ <ul style="list-style-type: none"> Grade I-II: inconsolability, crying, sleep reversal Grade III: somnolence, combativeness Grade IV: coma Unclear value of screening for minimal HE
Management	<ul style="list-style-type: none"> Identification and management of precipitating factors as nearly 90% of patients can be treated by addressing precipitating factors⁶ Medical management of acute overt HE⁶: <ul style="list-style-type: none"> Lactulose 25 mL every 1–2 h until at least 2 soft or loose bowel movements per day Rifaximin should be considered as an adjunct to lactulose Consider other therapies such as oral branch-chain amino acids, IV L-ornithine L-aspartate, and other antibiotics in patients nonresponsive to conventional therapies Prevention of recurrence HE as risk of recurrence is high (~ 40%)⁶: <ul style="list-style-type: none"> Lactulose and/or rifaximin, which are often continued indefinitely Treatment of minimal or covert HE should be patient-specific and is not routinely recommended Recommended protein intake 1.2–1.5 g/kg/d and specific nutritional management guidelines for HE should be followed¹²⁴ Consider LT evaluation in patients with HE and evidence of poor liver function 	<ul style="list-style-type: none"> Medical management of acute overt HE: <ul style="list-style-type: none"> Lactulose 0.3–0.4 mL/kg/dose 2–3 times daily to achieve 2–3 soft stools/day Consider additional of rifaximin if no response Pediatric guidelines for management of nutrition in chronic liver disease should be followed¹²⁶ and protein-restriction should be avoided due to risk of malnutrition

nutrition support in children with chronic liver disease have been published which recommend avoiding protein restriction and ensuring protein requirements are met based on patient’s dietary reference intake for age.¹³⁹

LT is considered in patients with HE, but without associated poor liver function, HE alone is not an indication for LT in adults.⁶ HE will often improve after LT; however, studies have found that some patients may still experience mild cognitive impairment, smaller brain volume, and differences in white matter integrity.^{140,141} There are limited data on neurodevelopmental outcomes in children with chronic liver disease, with much of the available data limited to children with BA.^{142–144} However, these studies do not present data on the presence/absence of HE in this population. A recent systematic review assessed neurodevelopmental outcomes in all children with liver disease before and after transplant and found that up to two-thirds of studies demonstrated neurodevelopmental deficits in these children before and after LT.¹⁴⁵ However, one of the major limitations is the inclusion

of noncirrhotic children as well as the absence of data on the presence of HE.

Indications for LT Children with Cirrhotic Portal Hypertension

Early referral for LT evaluation for children with cirrhotic PHTN should be considered. From 2018 through 2020, BA remained the leading indication for LT (33.2%) followed by other/unknown diagnoses (21.6%) and other cholestatic conditions (13.1%).¹⁴⁶ However, these data do not report on the presence of complications of PHTN in these patients. Practice guidelines for LT evaluation in children exist and recommend evaluation in children with chronic liver disease and “evidence of deteriorating liver function characterized by poor weight gain, growth failure, variceal hemorrhage, intractable ascites, recurrent cholangitis, or episodes of spontaneous bacterial peritonitis, pruritus, advancing encephalopathy, and/or uncorrectable coagulopathy.”³ These guidelines,

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however, do not make specific recommendations on the timing of LT in these patients.

Children who develop complications of cirrhotic portal HTN should be evaluated in a timely manner for LT, especially as many of these complications lead to worsening prognosis as previously presented. In many children with cirrhotic PHTN, failure to thrive and malnutrition is common due to significant malabsorption and a hypermetabolic state.^{3,139} Aggressive nutritional support is often needed in these patients; LT should be strongly considered in those refractory to nutritional interventions.^{3,139} Society guidelines exist in the nutritional management and rehabilitation of children with cirrhosis awaiting LT and multidisciplinary care with dietitians who have experience managing children with chronic liver disease should be pursued.^{139,147} Although outside the scope of this review, it is important to mention that children who experience variceal hemorrhage should be considered for LT evaluation. However, the management of variceal hemorrhage with secondary prophylaxis and serial endoscopy may control variceal bleeding and some children may be candidates for surgical shunts, leading to control of varices for years.^{8,9,11} Thus, variceal hemorrhage in certain patients may not necessitate urgent LT.^{8,9} The presence of chronic and significant ascites is associated with decreased 1-year survival in children and thus becomes a strong indication for LT, especially when there is associated significant hyponatremia.^{49,50} Progression to AKI-HRS in the setting of ascites, given its reversibility with LT, necessitates prioritization for urgent LT.¹⁴⁷ Finally, as SBP has been associated with high mortality in children and poor survival with native-liver, proceeding with LT in any child after a first episode of SBP is warranted.^{63,67}

As there are limited data in children on the role of LT in HPS, POPH, CCM, and HE, appropriate timing of LT is complicated. As LT is the only treatment for HPS, any child who has evidence of HPS and hypoxemia should be considered for LT. Children with mild HPS, in the absence of other complications of PHTN, may be followed up and may not necessitate urgent LT. Even in adults, POPH as a sole indication for LT is challenging; however, children who have evidence of mild POPH should be considered for LT before there is disease progression and R-sided pressures become too elevated, which would preclude LT in these children. Children who experience HE may also manifest other clinical signs of PHTN, and thus, proceeding with LT is appropriate. As there are extremely limited data in children with cirrhosis on the prevalence of CCM, it is difficult to determine appropriate timing of LT in these patients. Despite these limitations, many of these children will also likely experience other complications of chronic liver disease that are common indications for LT evaluation, and, thus, should be considered on a patient-specific basis.

Conclusion

In summary, children with chronic liver disease and PHTN will often have progression of disease and develop complications including ascites, SBP, AKI-HRS, HE, HPS, POPH, or

CCM. Although future studies are needed to better characterize the impact of these complications on prognosis, pre-LT quality of life, mortality, and post-LT outcomes, currently available data suggest that, similar to adults, children who experience these complications should at minimum undergo LT evaluation and, in some, even proceed with urgent LT.

Pediatric recommendations for the diagnosis and management of these complications need refinement. Thus, future multicenter, collaborative research networks should be developed to systematically define and study many of the areas that are lacking quality data. Specifically, there is urgent need to develop criteria for AKI-HRS, further understand the differences that occur in children, and determine whether adult management strategies for AKI-HRS are applicable to children. Additional studies are also needed to further characterize prognosis of HPS in children and optimal timing of LT based on HPS severity in addition to exploring the role of pulmonary hypertension management in POPH in children and its impact on post-LT outcomes. As there is more interest in CCM and its prevalence in pediatric chronic liver disease, further understanding of its prognosis, the role and frequency of TTE monitoring prior to LT, and data on rates of resolution of cardiac changes post-LT in children with CCM is needed. Finally, characterization of HE in children with chronic liver disease, understanding its impact on quality of life and development, and further understanding the clinical relevance of MHE will be important to explore further. Multicenter collaborations in all of these areas will aid clinicians to better define these clinical entities in children and their impact on quality of life, pre-LT mortality, and post-LT outcomes.

Lay Summary

Children who develop worsening of liver disease and cirrhosis can experience other complications including the development of fluid and/or infection of this fluid in the abdomen, abnormalities in kidney function, and changes in the lungs and heart. There are many recommendations in adults for physicians to help treat these conditions; however, there is very limited information in children. The goal of this article is to provide an overview of how physicians diagnose and manage these complications in adults and provide the current data available in children who experience these complications.

Conflict of Interest

The authors report no conflict of interest.

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