

# 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

Shneider BL, Bosch J, de Franchis R, Emre SH, Groszmann RJ, Ling SC, Lorenz JM, Squires RH, Superina RA, Thompson AE, Mazariegos GV. 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.

**Abstract:** Complications of portal hypertension in children lead to significant morbidity and are a leading indication for consideration of liver transplantation. Approaches to the management of sequelae of portal hypertension are well described for adults and evidence-based approaches have been summarized in numerous meta-analyses and conferences. In contrast, there is a paucity of data to guide the management of complications of portal hypertension in children. An international panel of experts was convened on April 8, 2011 at The Children's Hospital of Pittsburgh of UPMC to review and adapt the recent report of the Baveno V Consensus Workshop on the Methodology of Diagnosis and Therapy in Portal Hypertension to the care of children. The opinions of that expert panel are reported.

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Portal hypertension and its attendant complications remain a cause of significant morbidity and mortality. There has been continuous advancement in the understanding of the pathophysiology and optimal means for the management of portal hypertension in adults. These advances have been captured in the publications derived from the Baveno meetings, the most recent of

which took place in May 2010 (1). The Baveno statements have been primarily focused on adults. Limits in the scope of evidence-based approaches to the management of portal hypertension in children have precluded the development of similarly rigorous guidelines for pediatrics. In light of this limitation, expert commentary had been prepared based upon the Baveno IV statements (2, 3). On April 8, 2011, at The Children's Hospital of Pittsburgh of UPMC, a group of experts reviewed and revised the Baveno V statement and developed a pediatric-specific commentary (Reprinted from *The Journal of Hepatology*. Volume 53 pages 762-768, 2011 with permission from Elsevier). A reference list at the

Abbreviations: EHPVO, extrahepatic portal vein obstruction; EST, endoscopic sclerotherapy; EVL, endoscopic variceal ligation; HVPG, hepatic venous pressure gradient; NSBB, nonselective beta blockers; PTFE, polytetrafluorethylene; TIPS, transjugular intrahepatic portosystemic shunting.

end of this article provides key recent publications to the issues addressed in these guidelines. Given the very limited number of randomized trials in pediatric liver disease, these guidelines are not graded on the basis of type of evidence. Most of the statements are expert opinion or are derived from case series or cohorts.

### Preamble

The following revisions pertain primarily to prepubescent children, where physiologic parameters are most distinct from those found in adults. For adolescents, clinicians should use their judgment in applying these revised guidelines or guidelines that have been derived primarily for adults.

### Definition of key events regarding the bleeding episode

Baveno V definitions and criteria for failure to control bleeding

- These definitions have rarely been utilized in the pediatric literature; it would be valuable to employ them in future clinical descriptions of acute variceal hemorrhage.
- The time frame for the acute bleeding episode should be 120 h (five days).
- Failure to control the acute bleeding episode is defined as death (from any cause) or need to change therapy defined by one of the following criteria:
  - Fresh hematemesis or nasogastric aspiration of  $\geq 2$  mL/kg or 100 mL of fresh blood  $\geq 2$  h after the start of specific drug treatment or therapeutic endoscopy.
  - Development of hypovolemic shock.
  - Three gram drop in Hgb (9% drop of Hct) within any 24 h period after the initial resuscitation if no transfusion is administered. This time frame needs to be further validated.
- The potential value of an index of blood transfusion requires prospective validation and characterization in pediatrics based upon prospective analysis of changes in blood indices in response to standard transfusion practices.

Baveno V definitions and criteria for failure of secondary prophylaxis:

- Failure to prevent rebleeding is defined as a single episode of clinically significant rebleeding from portal hypertensive sources after day 5.
- Clinically significant rebleeding is defined as: recurrent melena or hematemesis resulting in any of the following:

- Hospital admission.
- Blood transfusion.
- Three gram drop in Hgb.
- Death (from any cause) within six wk.
- Death from variceal hemorrhage in children is defined as any death occurring within six wk of variceal hemorrhage independent of the specific immediate cause – it does not need to be directly related to exsanguination.

### Therapeutic options in patients with portal hypertension

Preprimary prophylaxis (prevention of the formation of varices)

#### Background

- Prevention of the development of complications of portal hypertension is an important area of research in adults, and similar studies in children should await further information from adults.
- Hepatic venous pressure gradient (HVPG)  $\geq 10$  mmHg is predictive of varices formation and decompensation of cirrhosis in adults. Published data on HVPG measurement in children are very limited, but suggest that there may be similar pressure thresholds for the development of complications in the pediatric population (4).

#### Recommendations for management

- Children with clinical evidence of portal hypertension should only be screened by surveillance endoscopy if they are candidates for primary prophylaxis or for specific counseling related to lifestyle (see below).
- Those children who are likely to have portal hypertension and to be at risk of esophageal varices usually have thrombocytopenia and splenomegaly. If considering surveillance endoscopy, these variables (or a clinical prediction rule that includes spleen size, platelet count, and albumin) help to determine the likelihood of varices and to triage for endoscopy (5).
- Treatment for underlying liver disease may reduce portal hypertension and prevent its clinical complications.
- There is no indication, at this time, to use beta-blockers to prevent the formation of varices.

#### Areas requiring further study

- Basic mechanisms in the development and progression of portal hypertension.

- Careful prospective natural history data for the complications of portal hypertension.
- Non-invasive tests and clinical rules should be investigated as a means to help triage children for endoscopy to screen for esophageal varices.
- The impact of treating the underlying chronic liver disease in the development of varices and other portal hypertensive-related complications.

#### Prevention of the first bleeding episode

- The risk of bleeding and the efficacy of primary prophylactic therapy for children with varices have been inadequately quantified, and therefore, no overall recommendation for prophylactic treatment of children can be provided.
- Systems for endoscopic grading of varices in children have not been extensively validated, although inter-observer agreement for one system when used in children ( $\kappa = 0.65$ ) was similar to levels achieved in studies of adults (6).
- Little published data from children are available to determine the ability of endoscopic appearance of varices to predict future variceal bleeding. The risk of bleeding among children with biliary atresia is greater in the presence of Grade II or III esophageal varices, red marks on the varices, or gastric varices, although similar data for children with other liver diseases are lacking (7). Grading of varices in this analysis was defined according to Japanese Research Society for Portal Hypertension (8). Grade I was flattened by insufflation, while Grade II and III varices were not flattened by insufflation. Confluency differentiated Grade II from III, with Grade III being confluent around the circumference of the esophagus.
- Prophylactic therapy with non-selective beta-blockers (NSBB) or endoscopic variceal ligation (EVL) can be considered within the context of defined research protocols.
- Prophylactic therapy with EVL may be considered in selected children within defined clinical circumstances with ongoing evaluation of outcomes. Those clinical circumstances include conditions where the clinician feels the risk of mortality from first variceal hemorrhage is greater than that for children in general (e.g., when a child is not in reasonable proximity to medical care that can provide life-saving treatments for variceal hemorrhage).
- In general, primary prophylactic therapy with NSBB should be avoided in children while

evidence is awaited concerning appropriate dosing, efficacy, and safety.

- As a result of the unfavorable adverse effect profile of endoscopic sclerotherapy (EST), it is not indicated for primary prophylaxis.

#### Role of HVPG measurement

- HVPG measurements are feasible in pediatric patients. Measurements should be performed using similar guidelines as for adult patients – in particular, these studies should only be performed by individuals with a complete understanding of the specific elements required for accurate measurements.
- Available data on HVPG measurements in the pediatric population are limited, but suggest that the pressure thresholds for the formation of varices and decompensation (development of ascites or/and variceal bleeding) in pediatric patients with cirrhosis are similar as for the adult population. Ongoing prospective analyses of the relationship of HVPG measurements in children and complications of portal hypertension are warranted.
- The panel was undecided as to whether HVPG measurements in children are sufficiently well characterized to support their use as part of specialized clinical practice or should still be considered as a research tool.
- In children with chronic liver disease, who require a liver biopsy for clinical indications, HVPG measurement can be completed at the same time and may provide important additional information as to prognosis of the underlying liver disease. In some circumstances (e.g., with severe coagulopathy or ascites), a transvenous approach to liver biopsy is safer than a percutaneous approach.
- The use of HVPG measurements in patients with biliary atresia may be limited by the frequent presence of veno-venous communications, which may lead to an underestimation of portal pressure (4).

#### Treatment for acute bleeding from varices

##### *Blood volume restitution*

- The goal of resuscitation is to preserve tissue perfusion. Volume restitution should be initiated to restore and maintain hemodynamic stability. Particular attention should be given to persistent tachycardia as an indicator of

compensated shock. Central venous oxygen saturation and venous lactate can be useful markers of adequate tissue perfusion.

- Packed red blood cell transfusion should be provided conservatively with a target hemoglobin level between 7 and 8 g/dL (9), although transfusion policy in individual patients should also consider other factors such as comorbidities (particularly underlying lung disease or cyanotic congenital heart disease), age, hemodynamic status, and ongoing bleeding.
- Comprehensive recommendations regarding the management of coagulopathy and thrombocytopenia cannot be made on the basis of currently available data. However, the following recommendations do apply:
  - PT/INR is not a reliable indicator of the coagulation status/bleeding risk in patients with cirrhosis.
  - Evidence to support the correction of PT/INR in acute variceal hemorrhage is lacking. During an acute, hemodynamically significant hemorrhage, both red cells and plasma are lost. Providing plasma/clotting factor support in the setting of an acute hemorrhage is advised in the context of general supportive care. However, the goal should not be to “normalize” or “correct” the clotting abnormality as the risk of fluid overload with its associated consequences (brain edema, pulmonary edema, recurrent variceal bleeding) is great.
  - Vitamin K deficiency, related in particular to cholestatic liver disease, should be corrected if present.
  - Administration of platelet concentrates should be considered in cases of profound thrombocytopenia (i.e., < 20 000).
  - Use of recombinant Factor VIIa has not been shown to be effective in treatment for adults with variceal hemorrhage (10) and cannot be recommended for use in children with acute variceal hemorrhage.
- These recommendations apply to the management of hemorrhage from varices and not to the management of children with advanced liver disease undergoing invasive therapeutic procedures.

#### *Antibiotic prophylaxis*

- The frequency of known or suspected bacterial infections in children with cirrhosis presenting with upper gastrointestinal bleeding is unknown.

- Retrospective and/or prospective analyses of the prevalence of bacterial infection in children with variceal hemorrhage need to be performed to determine whether empiric antibiotic therapy is warranted in children.
- A high index of suspicion for bacterial infection in acute variceal hemorrhage should be maintained, thereby permitting timely institution of antibacterial therapies.

#### *Prevention of hepatic encephalopathy*

- Recommendations regarding prevention of encephalopathy that may follow upper GI bleeding beyond those used in children with cirrhosis cannot be made on the basis of currently available data.

#### *Assessment of prognosis*

- Research studies are required to define factors that predict treatment failure and mortality following variceal hemorrhage in children.

#### *Timing of endoscopy*

- Patients with GI bleeding and features suggesting portal hypertension should have upper endoscopy as soon as possible after admission (within 24 h) and after the child is hemodynamically stable (as documented above).

#### *Pharmacological treatment*

- In suspected variceal bleeding, vasoactive drugs should be started as soon as possible and before endoscopy is performed.
- Vasoactive drugs (terlipressin, somatostatin, octreotide, vapreotide, vasopressin ± nitroglycerine) should be used in combination with endoscopic therapy and continued for up to five days.

#### *Endoscopic treatment*

- Endoscopic therapy is recommended in any patient who presents with documented upper GI bleeding and in whom esophageal varices are the cause of bleeding.
- EVL is the recommended form of endoscopic therapy for acute esophageal variceal bleeding.



- EST is the recommended form of endoscopic therapy for acute esophageal variceal bleeding for infants and in children in whom ligation is technically difficult.

#### *Use of balloon tamponade*

- Balloon tamponade is very rarely indicated and should only be used in massive bleeding as a temporary “bridge” until definitive treatment can be instituted (for a maximum of 24 h, preferably in an intensive care facility by trained physicians and nurses).

#### *Management of treatment failures*

- Rebleeding during the first five days may be managed by a second attempt at endoscopic therapy.
- Persistent bleeding despite combined pharmacological and endoscopic therapy is best managed by transjugular intrahepatic portosystemic shunting (TIPS) with polytetrafluoroethylene (PTFE)-covered stents.
- In infants and small children, uncovered rather than PTFE-covered stents may be the only size-appropriate equipment available for TIPS, despite the fact that concerns exist about the long-term maintenance of TIPS patency.
- Failure of TIPS or lack of local expertise in TIPS in small children necessitates consideration of emergent portosystemic shunting.

#### *Management of gastric variceal bleeding*

- Evidence for the management of gastric variceal bleeding in children is limited to case reports and uncontrolled case series, and it is therefore not possible to make evidence-based recommendations. These case reports and clinical experience suggest that the following interventions may be appropriate:
  - Endoscopic therapy with tissue adhesive (e.g., N-butyl-cyanoacrylate or N-butyl-2-cyanoacrylate plus methacyloxysulfonate) may be considered for acute bleeding from isolated gastric varices and for gastroesophageal varices type 2.
  - Balloon-occluded retrograde transvenous obliteration has been used for isolated gastric fundal varices, although evidence is lacking for its efficacy and safety in children.

- TIPS and/or portosystemic shunt therapy may be considered as an alternative approach to treating bleeding gastric varices.

#### *Areas requiring further study*

- Comprehensive studies of acute variceal hemorrhage are urgently needed in pediatrics. Areas for either prospective or careful retrospective investigation include:
  - Clinical course including hemodynamic, biochemical, and hematologic parameters.
  - Analysis of responses to various forms of vasoactive therapy.
  - Determination of prognostic markers that would identify high risk bleeding episodes where early TIPS might be advantageous.
  - Prospective analysis of infectious risks and potential role of antibiotic prophylaxis.
  - Prospective investigation of responses to standardized transfusion practices with target goals for transfusion at 7–8 g/dL of Hgb.
  - Definition and characterization of a transfusion index (e.g., ABRI) in children with variceal hemorrhage with a particular focus on expected responses to transfusions with a determined policy of transfusion.

#### *Prevention of rebleeding*

##### *Patients with cirrhosis*

- EVL is the preferred therapy for secondary prophylaxis of esophageal variceal bleeding in children with cirrhosis (11). There are insufficient data on the use of NSBB in children after variceal bleeding to recommend its use as either monotherapy or as an adjunct to EVL.
- EVL should be performed every two to four wk for up to five sessions to eradicate varices after a first variceal bleed. Failure to eradicate varices should lead to consideration of an alternative therapeutic approach.
- There is a need to investigate hemodynamic response to NSBB or other drug therapies in children to determine whether these drugs affect rebleeding risk and survival.

##### *Patients with cirrhosis who cannot be treated with EVL*

- EST is recommended for secondary prophylaxis of esophageal variceal bleeding in infants

and small children in whom EVL is not possible.

- In children unable or unwilling to be treated with EVL or EST, the use of NSBB may be considered, although evidence for appropriate dosing is lacking. There are no data that show that NSBB reduce HVP in children with cirrhosis. The safety of treating infants and young children with NSBB has not been adequately studied, especially with regard to their greater reliance on tachycardia to compensate for hypovolemia during a major bleeding episode.
- If NSBB are felt to be necessary, confirmation of therapeutic response by HVP measurement is desirable.
- There is inadequate evidence to recommend the use of isosorbide mononitrate in children after variceal hemorrhage.

#### *Patients who fail endoscopic treatment for the prevention of rebleeding*

- Surgical portosystemic shunting is effective, and the preferred option in a child who is predicted to have a good overall prognosis in the ensuing five yr (e.g., a child with biliary atresia and a total serum bilirubin level < 4 mg/dL).
- TIPS may be a long-term alternative in children with a good overall prognosis when surgical shunting is not feasible or when there are medical complications that increase the risk of surgical shunting. In these cases, all efforts should be undertaken to use PTFE-covered stents. TIPS may be used in children with a poorer near-term prognosis as a bridge to transplantation.
- Liver transplantation provides good long-term outcomes in appropriate candidates and should be considered for some children with variceal hemorrhage that is unresponsive to endoscopic therapy, especially those with decompensated liver disease.
- Liver transplantation may be considered as primary therapy in patients with variceal bleeding with coexisting indications for transplant (i.e., hepatopulmonary syndrome, hepatopulmonary hypertension, concern for coexisting hepatic malignancy) or a liver disease with a particularly unpredictable clinical course where near-term decompensation has a high likelihood.

Extrahepatic portal vein obstruction (EHPVO)

#### *Preamble*

The prior discussion of the management of portal hypertension is primarily relevant to children

with liver disease that results in cirrhosis and subsequent portal hypertension. Some but not all of these concepts are applicable to EHPVO. In particular, the approaches to secondary prophylaxis of variceal hemorrhage may differ for EHPVO and are delineated in subsequent sections of this expert opinion.

#### *Definition and etiology*

- EHPVO is defined by the obstruction of the extrahepatic portal vein with or without the involvement of the intrahepatic portal veins and does not include isolated thrombosis of the splenic vein.
- EHPVO may include occlusion of the splenic, superior mesenteric, and coronary veins.
- The term EHPVO implies chronicity and refers primarily to a long-standing condition characterized by the replacement of the normal portal vein with cavernous transformation.
- Recent thrombosis of the portal vein may be referred to as acute portal vein thrombosis.
- EHPVO in children is generally considered to be a form of non-cirrhotic non-malignant portal hypertension. If either cirrhosis and/or malignancy is a complicating factor, there are important implications for treatment, which may be distinct from the following guidelines.
- EHPVO is a heterogeneous entity with regard to causes and pathogenesis.
- Hypercoagulable conditions may play an important role in the etiology and should be excluded using assays that are not impacted by diminished portal perfusion of the liver (e.g., genetic testing is preferred over functional assays based upon proteins synthesized in the liver).

#### *Diagnosis*

- EHPVO is diagnosed by Doppler US, CT, or MRI, which demonstrate portal vein obstruction, presence of intraluminal material, or portal vein cavernoma.
- The state of the other abdominal veins can also be determined by CT or MRI, thus facilitating planning for any future intervention. The patency of the intrahepatic portal vein may be demonstrated in this way, but when uncertainty persists, the gold standard test of transjugular retrograde or percutaneous transhepatic portal venography should be undertaken.
- Diagnosis of underlying conditions:
  - Full hypercoagulability panel including genetic factors

- Liver biopsy is absolutely necessary if there is a suggestion of intrinsic liver disease
- Echocardiography may be useful to rule out congenital heart disease and to look for evidence of associated hepatopulmonary syndrome or portopulmonary hypertension
- Acute portal vein thrombosis can be assumed when patients present with symptoms such as abdominal pain, ascites, or fever in the absence of portal cavernoma and portosystemic collaterals. Patients also can be asymptomatic.

#### *Natural history*

- The incidence and natural history of chronic EHPVO are incompletely characterized
- Most children develop hypersplenism that triggers a more detailed medical assessment.
- One-third to one half of children present with sudden onset of upper gastrointestinal bleeding with no prior history of GI disorders or hypersplenism and the age of the onset of symptoms varies greatly.
- In the great majority of patients, some morbidity can eventually be expected, some of it severe (12).
- Morbidity is mainly related to variceal bleeding, hypersplenism, limitations of quality of life (e.g., limited ability to participate in sports owing to extreme thrombocytopenia and/or splenomegaly), recurrent thrombosis, growth retardation, neurocognitive impairment, and symptomatic portal biliopathy.

#### *Treatment: chronic EHPVO: anticoagulation*

- Anticoagulation therapy can be considered for patients with a well-documented prothrombotic state.
- In most patients with idiopathic chronic EHPVO, where there is no well-documented prothrombotic state, there is no role for anticoagulant therapy.
- There is insufficient evidence in favor of interventional therapy such as local thrombolysis.

#### *Treatment for chronic EHPVO: use of the meso-Rex bypass procedure*

- The meso-Rex bypass procedure should only be performed by individuals with significant experience with hepatobiliary surgery in children.
- Successful application of the meso-Rex bypass procedure represents a physiologic repair of EHPVO, with the expectation of prevention of

all of the known complications of EHPVO (13).

- It is surgically feasible in most children with EHPVO even with poor or non-visualization of the intrahepatic portal vein on routine pre-operative CT or MR angiography.
- Available data suggest that the restoration of appropriate portal venous flow to the liver after meso-Rex bypass is inversely related to the age of the patient, implying that early utilization may be advantageous (13).
- Controversy exists as to the appropriateness of utilization of this procedure in an asymptomatic child, including those who have not yet had a variceal bleed. One approach would suggest the assessment of the feasibility of surgery in all children with a cavernoma and features of portal hypertension. This approach could be pre-emptive for the development of complications. Another approach would defer surgery until there was clear and significant disease associated with EHPVO (see approaches to specific complications listed below).

#### *Treatment for chronic EHPVO: bleeding*

- For primary prophylaxis of variceal bleeding, there is insufficient evidence to support a clear recommendation for either NSBB or endoscopic therapy.
- Surveillance endoscopy is indicated to assist in decision making regarding prophylactic use of the meso-Rex bypass.
- Children with Grade II or III varices should be assessed as potential candidates for the meso-Rex bypass procedure. If meso-Rex bypass is not felt to be feasible, EVL is preferred in children who are at high risk of mortality from initial variceal hemorrhage. Primary prophylaxis with NSBB is not recommended owing to limited information as to efficacy and appropriate dosing regimens.
- For the control of acute variceal bleeding, endoscopic therapy is effective.
- Meso-Rex bypass is the preferred method for subsequent secondary prophylaxis of bleeding from gastroesophageal varices and portal gastropathy.
- When the meso-Rex bypass procedure is not feasible, secondary prophylaxis with EVL is safe and effective. There is a lack of data on the role of NSBB for secondary prophylaxis.
- Distal splenorenal shunting can be highly efficacious in the management of variceal hemorrhage from EHPVO. It is an alternative to meso-Rex bypass that should only be

implemented if a meso-Rex bypass is clearly shown to not be feasible, either owing to anatomic issues or the finding of no useable portal vein at the time of surgical exploration of the Rex recessus. Careful investigation for the complications of portosystemic shunting (e.g., hepatopulmonary syndrome, portopulmonary hypertension, and hepatic encephalopathy) is warranted prior to this surgical procedure. Presence of these complications may suggest the need for consideration of an alternative intervention, including liver transplantation.

- TIPS, while technically feasible in EHPVO, is rarely if ever indicated as a means of secondary prophylaxis for variceal hemorrhage from EHPVO. Placement of TIPS stents can prevent future successful meso-Rex bypass by permanently blocking access to the intrahepatic portal vein if it is open. If necessary, TIPS should include a detailed consideration of approaches to minimize the risk of negatively impacting upon the intrahepatic portal vein.

#### *Portal biliopathy – diagnosis*

- Portal biliopathy is the effect of EHPVO on the appearance of the intra- and extrahepatic bile ducts resulting in irregular dilatation of portions of the biliary tree.
- Portal biliopathy is present in a proportion of patients with EHPVO (14). In the majority, it is asymptomatic and demonstrated only on imaging. In some patients, portal biliopathy may cause cholestasis, biliary obstruction, or progressive biliary cirrhosis.
- CT scanning and MRCP are the first line of investigation.

#### *Portal biliopathy – treatment*

- Asymptomatic: No interventional or direct surgical treatment is recommended. Theoretically, reversal of the portal hypertension through the meso-Rex bypass should lead to the resolution of the portal biliopathy and prevent cholestasis and silent progression of fibrosis. Therefore, asymptomatic portal biliopathy is a potential indication for meso-Rex bypass.
- Symptomatic:
  - Decompressive portal hypertension surgery should be considered.
  - Children with EHPVO have a higher than normal incidence of cholelithiasis and cholecystitis.

- Symptomatic gallstones should be treated with cholecystectomy.
- Asymptomatic stones present at the time of any portal hypertension surgery should be removed to prevent future complications including meso-Rex thrombosis.
- Asymptomatic stones that develop after surgery should be observed and treated only if symptoms develop.
- Bile duct stones may be treated with endoscopic therapy.
- Common bile duct stricture: Endoscopic or percutaneous stenting can be considered. Portosystemic shunt surgery should be considered whenever possible. Hepaticojejunostomy could be considered if endoscopic measures are unsuccessful; however, it should not be attempted without decompressive shunt surgery.

#### *Hypersplenism – treatment*

- Hypersplenism with platelets  $< 50\,000$  is a strong indication for meso-Rex bypass.
- Significant restrictions in physical activity imposed on a child because of the perceived increased risk of splenic rupture in conjunction with platelets of  $< 100\,000$  is a strong indication for meso-Rex bypass.
- Splenectomy is not indicated, because it will not diminish probability of hemorrhage from varices and may remove the option of a distal splenorenal shunt as a future intervention. The only exception may be in the circumstance of coincident splenic vein thrombosis, where splenectomy may effectively treat left-sided portal hypertension.

#### *Neurocognitive impairment suggestive of hepatic encephalopathy*

- Neurocognitive testing suggestive of hepatic encephalopathy and increased blood ammonia levels are relative indications for meso-Rex bypass.

#### *Growth impairment*

- Somatic growth is dependent on intact hepatic function, which may be disrupted by EHPVO.
- Restoration of portal blood flow to the liver results in improved growth in children who demonstrate growth retardation.



- Therefore, growth retardation is a relative indication for meso-Rex bypass.

#### *Portopulmonary hypertension and hepatopulmonary syndrome*

- Periodic monitoring of upright transcutaneous oxygen saturation is indicated in routine follow-up of children with EHPVO, values persistently <97% should lead to further diagnostic testing (15).
- Hepatopulmonary syndrome can be diagnosed and quantified by agitated saline echocardiography and macroaggregated albumin nuclear scintigraphy (16).
- Portopulmonary hypertension is best characterized by cardiac catheterization.
- Portopulmonary hypertension and hepatopulmonary syndrome are absolute indication for the consideration of the meso-Rex bypass.
- Restoration of portal blood flow to the liver usually results in the reversal of these complications of portosystemic shunting.

#### *Unresolved issues and future studies*

- Prospective registry data on outcomes after meso-Rex bypass.
- Prospective data on the frequency and clinical profile of acute and chronic EHPVO.
- Natural history of EHPVO in children vs. adults.
- Case-control studies on frequency of prothrombotic states in EHPVO.

#### **Concluding comments**

The management of portal hypertension in children is challenging and requires careful assessment of risks and benefits of interventions often in the absence of evidence-based approaches. Extrapolation of approaches used in the care of adults may not be optimal for children. Nowhere is this difference more notable than in the management of EHPVO, where pre-emptive intervention with meso-Rex bypass may be a physiologic “cure” for portal hypertension. Important examples of differences in the approach to portal hypertension stemming from cirrhosis in children that evolved from this conference include (i) no general recommendation for surveillance endoscopy for varices or primary prophylaxis of variceal hemorrhage, (ii) reliance on endoscopic and not pharmacologic means of secondary prophylaxis of variceal hemorrhage, and (iii) increased potential utilization of portosystemic shunting in compensated cirrhosis. The future of evolving recommendations would be

enhanced by ongoing research into the pathophysiology, natural history, and management of portal hypertension in children.

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