Seminars in Pediatric Surgery (2012) 21, 211-218

ELSEVIER

SEMINARS IN PEDIATRIC SURGERY

Medical management of esophageal varices and portal hypertension in children

Lorenzo D'Antiga, MD, FEBS

From the Paediatric Hepatology, Gastroenterology, and Transplantation, Ospedali Riuniti di Bergamo, Bergamo, Italy.

KEYWORDS
Portal hypertension;
Esophageal varices;
Propranolol;
Endoscopy;
TIPS;
Shunt surgery

Portal hypertension (PH) is a common complication of chronic liver disease in children and represents a cause of morbidity and, rarely, mortality in this group of patients. Although often self-limiting, gastrointestinal bleeding in this setting is regarded as a frightening event by patients and carers, giving the impression of impending death. Therefore, it is important to raise the awareness on the natural history of PH in children, the utility of tools that help preventing and managing acute bleeding, and the signs predicting a poor outcome, thus indicating surgery. There is lack of data on the ability of endoscopy screening, endoscopic treatment of varices, and use of nonselective β-blockers to alter the outcome of PH in children; major efforts should be made to avoid such treatments empirically and promote multicenter trials instead. Nevertheless, such approach should be balanced against the need of offering the best care to children with PH. In this review, we discuss the advances made in the management of PH in children and compare it with the larger adult experience. A rational approach to acute gastrointestinal bleeding is proposed along with an algorithm suggesting a stepwise protocol to manage children with esophageal varices in the long-term, with some hints on possible future studies.

Portal hypertension (PH) is the commonest complication of chronic liver disease in children and requires a multidisciplinary medical, endoscopic, and surgical approach.[1] Those with PH are at risk of severe complications and even death. Parents of children with PH may be frightened by gastrointestinal hemorrhage, often referred to as a terrifying experience and giving the impression of impending death.

There are very few robust data despite many children with PH having been managed in the past few decades.[2] Conversely, in adults, many treatments have been challenged and a plethora of studies have been conducted yearly and summarized periodically in the Baveno Consensus Conference.[3] There is also a panel of experts who periodically provide a pediatric opinion in the Baveno Conference that attempts to translate the experience in adults to children.[4]

Therefore, most children are treated according to what has been shown to be effective in adults by simply extrapolating the data and applying the same protocols to this age-group with modification according to body size.[5,6] Nevertheless, there are at least 2 important differences between PH in children and adults. The first is the early onset and rapid progression of pediatric liver disease together with a relatively larger availability of split organ donations that allows us to solve most of the severe pediatric cases of cirrhotic PH by organ replacement. Consequently, the length of the follow-up of children with severe cirrhotic PH is short. Secondly, a large proportion of children with PH have presinusoidal disease, which has different implications as far as management and outcome are concerned.[7] These points explain why most of the children with large varices and bleeding that we manage in the long-term usually have

Address reprint requests and correspondence: Lorenzo D'Antiga, MD, FEBS, Paediatric Hepatology, Gastroenterology, and Transplantation, Ospedali Riuniti di Bergamo, Largo Barozzi 1, 24128 Bergamo, Italy.
E-mail: ldantiga@ospedaliriuniti.bergamo.it.

1055-8586/$ -see front matter
http://dx.doi.org/10.1053/j.sempedsurg.2012.05.004

noncirrhotic PH—clearly a scenario different to that in adult practice.

There is little evidence on the efficacy of nonselective β-blockers (NSBBs), endoscopic treatment of varices, effectiveness of portosystemic shunts in children with PH, and even less in noncirrhotic PH.[2,8,9]

We will review the information available in this field so far and compare it with the larger experience in adults in which different factors, such as the complications of the hyperdynamic circulation and the occurrence of hepatic encephalopathy, play a role in response to treatment, morbidity, and mortality.[3]

Distinctiveness of PH in children: noncirrhotic PH

Many children with long-standing PH have a noncirrhotic cause, such as extrahepatic portal vein obstruction (EHPVO) and conditions characterized by the wide spectrum of the liver ductal plate malformation.[10] Most children with noncirrhotic EHPVO develop severe bleeding episodes and hypersplenism but do not progress to end-stage liver disease,[11] and therefore show no indication for liver transplantation (LT).

EHPVO is commonly considered a less severe form of PH, especially because mortality from bleeding appeared to be negligible in this group of patients[12] and the major complications of the hyperdynamic circulation of cirrhosis (high cardiac output, hepatorenal syndrome, spontaneous bacterial peritonitis) are not seen. Nevertheless, children with EHPVO have much morbidity affecting their quality of life, such as frequent bleeding episodes, huge splenomegaly and hypersplenism, growth retardation, and neurocognitive impairment.[13-16]

We reviewed our institutional series of 65 children with EHPVO and found that most were born preterm and had had insertion of an umbilical venous catheter. The median age at diagnosis was 3.5 years, and half of them presented with a gastrointestinal bleed. Overall, 40 children (61%) had had at least 1 episode of gastrointestinal bleeding at a median age of 4 (range, 0.5-17.5) years during a follow-up period of 10.2 (0.6-19.4) years; 23 (35%) had more than 1 episode (up to 6 episodes). Overall, 254 endoscopies were carried out in this cohort. No one died of a bleeding episode. By the age of 10 years, 60% of children had varices that were not controlled by medical/endoscopic treatment. Thirty-four patients (53%) had a complicated course and were considered for further intervention; of 34 patients, 13 (38%) underwent a proximal splenorenal shunt, 13 (38%) a meso-portal bypass (MPB), 3 a meso-caval shunt, 2 a transjugular intrahepatic portosystemic shunt (TIPS), 2 a distal splenorenal shunt, and 1 a LT because of hepatopulmonary syndrome. Overall, the management of patients requiring surgical or radiological interventions was successful in 28 of 34 (82%), with a high rate of patency of shunts and bypass (27/33, 82%). At the last follow-up, control of bleeding by medical and surgical means was achieved in 93% of the group.[17]

It is clear that most of the efforts spent on PH in children are directed at a population whose features and management are different from the adult population. Therefore, it seems obvious that the experience gained in adults cannot be translated directly to the pediatric setting.

Definition and clinical features of PH in children

PH is commonly defined as a condition in which portal pressure is higher than 10 mm Hg. In adults, hepatic venous pressure gradient (HVPG; normal values, 1-6 mm Hg) is widely used to measure the portal pressure and to diagnose PH, and in this setting a gradient >10 mm Hg has been shown to predict the formation of esophageal varices and bleeding.[18,19] In children, this simple tool is considered to be technically demanding and invasive, making it impractical. Besides, many children have presinusoidal PH that cannot be unmasked by HVPG. Therefore, PH is diagnosed on the basis of indirect signs such as splenomegaly, hypersplenism, and esophageal varices. Recent studies have shown that a clinical prediction rule can predict the presence of esophageal varices in children,[20] with the best predictor being platelet/spleen size z score ratio.[21] Such clinical indices may allow triaging children with chronic liver disease to undergo an invasive procedure such as upper gastrointestinal endoscopy. The value of such predictors of formation of varices, however, should be considered on the basis of a definite intention to perform some sort of prophylaxis of bleeding. Currently, there are no data supporting the role of preprimary prophylaxis (prevention of the formation of varices) or primary prophylaxis (prevention of first bleeding) in children[2]; nevertheless, many clinicians would consider a cirrhotic child with large varices at risk of mortality from the first bleed, and therefore a definite candidate for primary prophylaxis.[5,22] A reasonable, and somehow evidence-based, consensus on indication to perform endoscopic secondary prophylaxis (prevention of rebleeding) in cirrhotic children appears to be wide.[4]

The common practice: a survey on management of PH in children

During the year 2007, a group of 27 pediatric experts working in tertiary care European and American centers carried out a survey on their practice in the management of PH (Figure 1A-H). According to the survey, the overall number of children followed by the experts was approximately 600, of whom 350 had EHPVO. Most centers were looking after 10-50 children with PH; the majority evaluated a child with

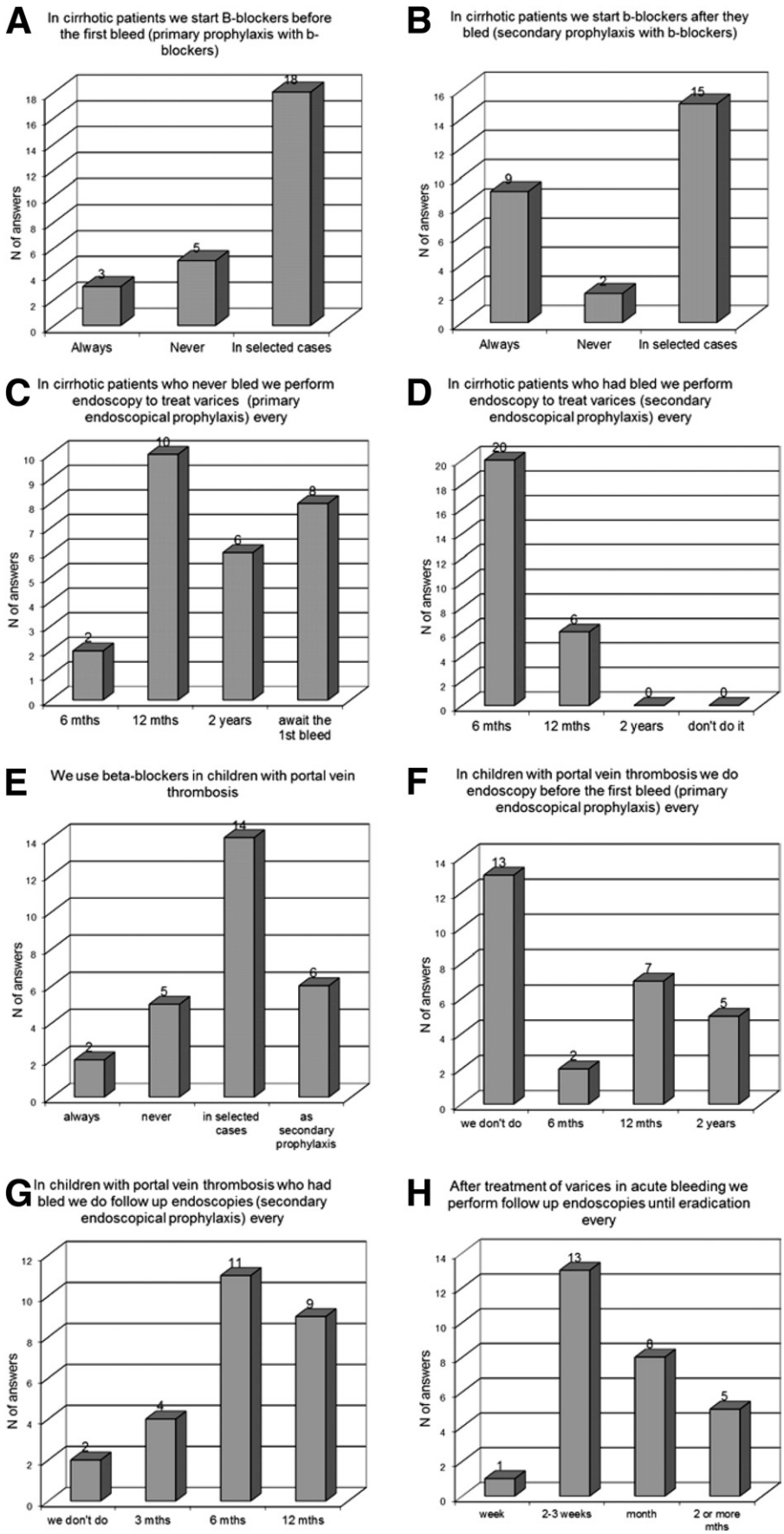

Figure 1 (A-H) Results of a multicenter survey on the current practice in the management of portal hypertension in children.

clinical signs of PH by performing a diagnostic endoscopy followed by a yearly monitoring, whereas a minority would not perform any investigation before the first bleeding episode, especially in children with noncirrhotic PH (Figure 1A-G). Primary prophylaxis by endoscopic treatment of varices was carried out in 60% of the centers but only for cirrhotic PH (Figure 1C, 1F), whereas secondary prophylaxis was performed in nearly all cirrhotic and noncirrhotic patients with a 6-monthly surveillance protocol (Figure 1D, 1G). Eradication of varices after an episode of bleeding was carried out within a month from the event (Figure 1H). NSBBs were started as primary prophylaxis only in selected cases regardless of the pathophysiology of PH, whereas about half of the centers introduced NSBBs as secondary prophylaxis (Figure 1A, 1B, 1E). In many centers, endoscopic treatment of varices was carried out in the operating theater with intubation under general anesthesia. Most of the centers used octreotide during a bleeding episode and would perform an abdominal tap to rule out spontaneous bacterial peritonitis in case of signs of infection in ascitic children.

Management of acute variceal bleeding

The main goal of the management of a child with acute esophageal bleeding is blood volume restitution. It is therefore mandatory to monitor vital signs, obtain venous access to perform blood tests (full blood count, International Normalized Ratio, liver function and electrolytes, C-reactive protein, and a blood crossmatch) and start blood volume correction.[23] Packed red blood cells (PRC) should be provided with the aim to maintain the hemoglobin >7 g/dl, carefully avoiding a rebound overload of fluids that favor rebleeding. In the presence of coagulopathy, it might be wise to support the patient with plasma, also in view of the fact that esophageal bleeding implies loss of whole blood that, if large, will not be efficiently replaced by PRC. Children with upper gastrointestinal bleeding may benefit from nasogastric tube placement, with the primary goal being to monitor persistence of active bleeding. Vasoactive drugs, such as octreotide, are effective in stopping bleeding from varices and should be started immediately to bridge the child to endoscopy, and continued thereafter for a total of 4-5 days.[24] In adults, it has been proven that infectious complications commonly follow an episode of variceal bleeding in cirrhotic patients.[25] Although in children there is no such evidence so far, it is recommended to monitor them for any sign of infection and, if present, to start antibiotic treatment promptly, especially in cirrhotic children with advanced disease.

After the initial step, the child should be managed according to hemodynamic stability and the control of bleeding. If unstable, the child should be managed in an intensive care setting, possibly with a central venous catheter providing information on circulating blood volume and preload.

Figure 2 Proposed algorithm for the approach to the child with acute variceal bleeding. NGT, nasogastric tube; INR, international normalized ratio; CRP, C-reactive protein; ICU, intensive care unit; PRC, packed red blood cells; FFP, fresh frozen plasma; TIPS, transjugular intrahepatic portosystemic shunt.

Usually bleeding stops spontaneously after the ruptured varix empties. After cessation, it is usually acceptable to schedule an elective endoscopy in the following 24-72 hours because rebleeding is uncommon during this time frame. If bleeding does not stop despite appropriate fluid load and correction of coagulopathy, the child may require urgent endoscopy, and rarely, the placement of a Sengstaken balloon as a bridge to TIPS or urgent shunt surgery (Figure 2).[4] Endoscopic sclerotherapy (EST) around the vessel may be the only option to treat an acutely bleeding varix that is underfilled, and therefore difficult to be strangulated by a rubber band placed by endoscopic variceal ligation (EVL) devices.

Endoscopy for screening and management of esophageal varices

There are few reports on the prevalence of varices in children with PH, and it is therefore difficult to predict how many children would benefit from endoscopic screening. Besides, the uncertainty regarding the impact of any prophylaxis in this setting makes endoscopic screening questionable. Despite this, the mortality of cirrhotic children at the time of first bleeding episode has been reported to be as high as 5%-15%[26] and supports screening endoscopy in all children with advanced liver disease and clinical signs of PH.

There are scant data on diagnosis and grading of esophageal varices in children. Scoring systems adopted in adults have been neither validated nor standardized in children, and there is little knowledge of their reproducibility.[21,27] Such information is mandatory to determine the effectiveness of prophylaxis of variceal bleeding by either NSBBs or endoscopic treatment. However, studies

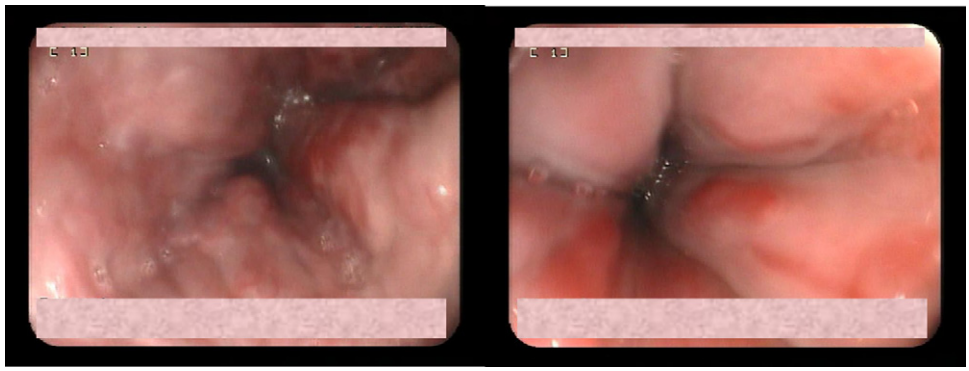

Figure 3 Large esophageal varices with red marks in a child with portal hypertension. (Color version of figure is available online.)

on the interobserver agreement on pediatric varices scoring are underway, and the preliminary results suggest that accordance in the recognition of large varices is satisfactory.[28]

Endoscopic obliteration of varices in the past was done with sclerotherapy using sclerosing agents (such as ethanolamine or polidocanol) injected inside or around the varix. In the last decade or so, variceal band ligation (EVL) has become more popular and has been shown to be superior to EST as far as efficacy, safety, and degree of standardization are concerned, even in children.[29] Nevertheless, EVL is not feasible in infants because the devices available on the market cannot be used with small pediatric endoscopes. In these patients, EST remains the only option to obliterate large varices.

A real challenge in this setting is the presence of large gastric varices; there are no published data on experience of management of gastric varices in children, and probably most centers would treat this scenario according to the experience in adults.[3,4] Large gastric varices are a threat because they are difficult to obliterate prophylactically, and even more so if actively bleeding; in this situation, balloon tamponade is often ineffective and the only option is to perform EST with tissue glue (such as *N*-butyl-cyanoacrylate). In general, a child with large gastric varices should be considered for TIPS, shunt surgery, or LT based on the degree of liver disease.

A major issue to be solved is how to grade varices in this setting. Historically, varices have been defined into 3 degrees according to the size, and red marks have been shown to predict bleeding. More recently, the classification has been simplified, and the proposed description of small or large varices, with or without red marks, appears to be more practical.[30] The point is establishing what picture predicts bleeding; probably large varices, varices of any size but with red marks, and gastric varices are at higher risk of bleeding in the short-term (Figure 3).[31]

Thus, it appears that endoscopy in children with PH is definitely indicated only for the treatment of acute bleeding and in the secondary prophylaxis of further bleeding episodes. The usefulness of diagnostic endoscopy and primary prophylaxis of bleeding by endoscopic obliteration is still unproven, and its impact on the outcome should be a matter of structured investigational trials.

Nonselective β-blockers

PH in cirrhotic subjects results from distorted liver architecture, small vessel portal thrombosis, increased vascular tone, all leading to an increase in portal vascular resistance.[32] Splanchnic arteriolar vasodilation caused by vasoactive substances released in cirrhotic patients also leads to increasing portal venous flow, exacerbating PH. The rationale of NSBBs, such as propranolol, stands on its ability to decrease the portal flow by reduction of cardiac output (via β1-receptor antagonism) and to diminish the intrahepatic and splanchnic vasoconstriction (via β2-receptor antagonism).[33] Studies in adults have shown that a dose reducing the heart rate by 25% (or the HVPG by 20%) does decrease the bleeding rate in cirrhosis.[34]

There are no randomized trials assessing the efficacy of propranolol as prophylaxis of variceal bleeding in children, and the few cohort studies carried out did not include the measurement of HVPG before and after treatment start.[5,35-39] Moreover, these studies showed that in children the evaluation of heart rate at rest is problematic and the range of drug dosage required to reduce it by 25% is very wide, making achievement of adequate NSBBs dosage impractical and time-consuming. Whether pediatric patients with presinusoidal PH, having no classical features of the hyperdynamic circulation, may benefit from treatment with NSBBs has yet to be demonstrated.[40]

A further difficulty in carrying out trials with NSBBs in this setting is that in Europe propranolol is not licensed for use in children. Although the drug has been prescribed extensively in cardiac and liver pediatric patients for years, no studies on safety and tolerability are available, and therefore it will be very difficult to get approval from European Medical Agency and/or local ethic committee for such a trial. Despite these difficulties, and although the official recommendation is that lack of evidence should lead to avoid the empirical use of available treatments, many clinicians taking care of children with severe PH use NSBBs

as prophylaxis of bleeding (Figure 1B, 1C). From their experience as well as from the previously published studies, it appears that propranolol is safe for children, even at high doses.[41]

Surgical procedures (see also "Surgical Management of Portal Hypertension in Children," in this issue)

When medical and endoscopic treatment of bleeding varices fails, the only option is to consider decompression of the portal system by a shunt or a bypass.[42]

Children with EHPVO can be managed effectively by MPB[43]; however, in our experience of children who had an umbilical venous catheter placed at birth, only about half had a patent Rex recessus at retrograde portogram.[17] If the MPB is not feasible, these can usually be treated by other forms of shunt surgery.[9] One recently suggested approach is to perform the MPB preemptively, regardless of complications of PH, in view of its beneficial effects on growth and neurocognitive outcome.[44] Other patients with presinusoidal PH, but not amenable to a MPB, can be managed by TIPS or by shunt surgery.[45] In the aforementioned survey, less than half of participants would propose a preemptive MPB in children with EHPVO, whereas there was agreement on the possible use of TIPS in children with compensated cirrhosis and severe PH (Figure 1H).

Cirrhotic children with PH usually have a rapidly progressive biliary type of cirrhosis (such as biliary atresia, intrahepatic cholestasis, and Alagille syndrome), are young, and have a short transplant-free survival. In our institution, we have performed 480 pediatric transplants in 15 years, and the median age at transplantation is 1.4 years. Therefore, shunt surgery is rarely indicated in this cohort of patients in whom PH is usually accompanied by liver decompensation and is an indication for LT. However, cirrhotic children with a compensated long-standing noncholestatic liver disease complicated by severe PH may occasionally be considered for shunt surgery.[45]

Transjugular intrahepatic porto-systemic shunt

TIPS is a well-established tool to manage severe complications of PH in adults, but its experience in children is limited. We have recently reported our series of 13 children affected by PH unresponsive to NSBBs and endoscopic treatment who were considered candidate for TIPS. Eleven underwent a successful expanded-polytetrafluoroethylene-covered stent placement, including 3 who had had a split LT. The shunt led to significant decrease of the portosystemic gradient and to the resolution of PH complications in all but one. No patient developed overt hepatic encephalopathy. All shunts were patent at the last follow-up (median of 20 months) or transplantation.[46] TIPS appears to be feasible and effective in children as it is in adults and should become part of the armamentarium used to manage PH complications in pediatric patients.

What is the best protocol for screening, prophylaxis and treatment of esophageal varices?

Large sample sizes, difficulties in recruiting patients into multicenter studies, and the lack of official approval and knowledge on drug dosing make it quite unlikely that there will be robust data on the use of NSBBs in children with PH in the next years. The same applies to endoscopy because there is no single center able to recruit enough patients to answer questions regarding screening and primary prophylaxis of varices, and multicenter trials require diagnosis and treatment standardization. Besides, such studies can probably only be carried out in noncirrhotic children having sufficient follow-up time to test the given hypothesis. Alternatively, many centers are already using these tools empirically (Figure 1) both in cirrhotic and noncirrhotic children, with uncertain and inconsistently measurable results. Is it then possible to gather more information on the utility of NSBBs and endoscopic treatment of varices in children?

A proper trial on this matter should be randomized and have variceal bleeding as the primary end point; however, many clinicians and families would consider permitting a gastrointestinal bleed as unacceptable to test the hypothesis of effectiveness of NSBBs or endoscopic treatment. One possibility to overcome this could come from considering the development of large varices as the end point because children with large varices or red marks have failed treatment and will eventually bleed. At least 2 studies have shown that most children with cirrhosis or portal vein

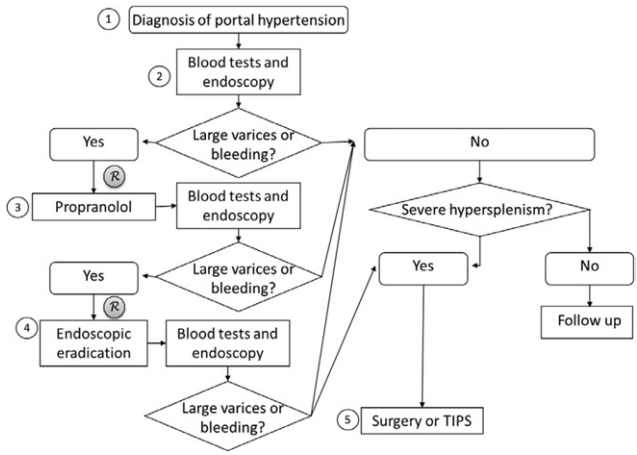

Figure 4 Proposed algorithm for the approach to the child with portal hypertension. TIPS, transjugular intrahepatic portosystemic shunt. The circled "R" represents a step for possible randomization in a clinical trial.

thrombosis and grade 2-3 varices will bleed within a few years of follow-up.[47,48]

Therefore, it is possible to hypothesize a randomized, nonblinded multicenter trial of development of large varices in children and their response to treatment. Because of the large sample size needed, such study would first require a solid proof that there is sufficient agreement among endoscopists to recognize large varices in different pediatric centers. Figure 4 illustrates an algorithm of a stepwise approach to manage esophageal varices, which considers the formation of large varices as the end point and could offer the chance to test the hypothesis that NSBBs and endoscopy can improve the outcome of children with PH, avoiding the risk of not offering the best of practice currently available. Pediatric societies and their working groups are the natural setting to test new hypothesis and organize well-structured multicenter trials in this field. However, an extraordinary effort will be required to produce such evidence on the correct management of PH in children.

References

1. Alonso EM, Hackworth C, Whitington PF. Portal hypertension in children. Clin Liver Dis 1997;1:201-22, xiii.
2. Ling SC, Walters T, McKiernan PJ, et al. Primary prophylaxis of variceal hemorrhage in children with portal hypertension: A framework for future research. J Pediatr Gastroenterol Nutr 2011;52:254-61.
3. de Franchis R, Baveno V Faculty. Revising consensus in portal hypertension: Report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. J Hepatol 2010;53:762-8.
4. Shneider BL, Bosch J, de Franchis R, et al. Portal hypertension in children: Expert pediatric opinion on the report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. Pediatr Transplant 2012 March 13 [Epub ahead of print].
5. Shashidhar H, Langhans N, Grand RJ. Propranolol in prevention of portal hypertensive hemorrhage in children: A pilot study. J Pediatr Gastroenterol Nutr 1999;29:12-7.
6. Howard ER, Stringer MD, Mowat AP. Assessment of injection sclerotherapy in the management of 152 children with oesophageal varices. Br J Surg 1988;75:404-8.
7. Abd El-Hamid N, Taylor RM, Marinello D, et al. Aetiology and management of extrahepatic portal vein obstruction in children: King's College Hospital experience. J Pediatr Gastroenterol Nutr 2008;47:630-4.
8. Ling SC. Should children with esophageal varices receive beta-blockers for the primary prevention of variceal hemorrhage? Can J Gastroenterol 2005;19:661-6.
9. Lillegard JB, Hanna AM, McKenzie TJ, et al. A single-institution review of portosystemic shunts in children: An ongoing discussion. HPB Surg 2010;2010:964597.
10. Gunay-Aygun M. Liver and kidney disease in ciliopathies. Am J Med Genet C Semin Med Genet 2009;151C:296-306.
11. Maksoud-Filho JG, Gonçalves ME, Cardoso SR, et al. Long-term follow-up of children with extrahepatic portal vein obstruction: Impact of an endoscopic sclerotherapy program on bleeding episodes, hepatic function, hypersplenism, and mortality. J Pediatr Surg 2009;44:1877-83.
12. Orloff MJ, Orloff MS, Girard B, et al. Bleeding esophagogastric varices from extrahepatic portal hypertension: 40 years' experience with portal-systemic shunt. J Am Coll Surg 2002;194:717-28.
13. Sharma P, Sharma BC, Puri V, et al. Minimal hepatic encephalopathy in patients with extrahepatic portal vein obstruction. Am J Gastroenterol 2008;103:1406-12.
14. Krishna YR, Yachha SK, Srivastava A, et al. Quality of life in children managed for extrahepatic portal venous obstruction. J Pediatr Gastroenterol Nutr 2010;50:531-6.
15. Lautz TB, Sundaram SS, Whitington PF, et al. Growth impairment in children with extrahepatic portal vein obstruction is improved by mesenterico-left portal vein bypass. J Pediatr Surg 2009;44:2067-70.
16. Mack CL, Zelko FA, Lokar J, et al. Surgically restoring portal blood flow to the liver in children with primary extrahepatic portal vein thrombosis improves fluid neurocognitive ability. Pediatrics 2006;117:e405-412.
17. Alberti D, Cheli M, Stroppa P, et al. Stepwise approach to extra hepatic portal vein obstruction in children. J Pediatr Gastroenterol Nutr 2010;50(suppl 7):E214.
18. Garcia-Tsao G, Groszmann RJ, Fisher RL, et al. Portal pressure, presence of gastroesophageal varices and variceal bleeding. Hepatology 1985;5:419-24.
19. Groszmann RJ, Wongcharatrawee S. The hepatic venous pressure gradient: Anything worth doing should be done right. Hepatology 2004;39:280-2.
20. Gana JC, Turner D, Roberts EA, et al. Derivation of a clinical prediction rule for the noninvasive diagnosis of varices in children. J Pediatr Gastroenterol Nutr 2010;50:188-93.
21. Gana JC, Turner D, Mieli-Vergani G, et al. A clinical prediction rule and platelet count predict esophageal varices in children. Gastroenterology 2011;141:2009-16.
22. Yachha SK, Sharma BC, Kumar M, et al. Endoscopic sclerotherapy for esophageal varices in children with extrahepatic portal venous obstruction: A follow-up study. J Pediatr Gastroenterol Nutr 1997;24:49-52.
23. Lacroix J, Hébert PC, Hutchison JS, et al. Transfusion strategies for patients in pediatric intensive care units. N Engl J Med 2007;356:1609-19.
24. Eroglu Y, Emerick KM, Whitingon PF, et al. Octreotide therapy for control of acute gastrointestinal bleeding in children. J Pediatr Gastroenterol Nutr 2004;38:41-7.
25. Goulis J, Armonis A, Patch D, et al. Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage. Hepatology 1998;27:1207-12.
26. van Heurn LW, Saing H, Tam PK. Portoenterostomy for biliary atresia: Long-term survival and prognosis after esophageal variceal bleeding. J Pediatr Surg 2004;39:6-9.
27. Bendtsen F, Skovgaard LT, Sørensen TI, et al. Agreement among multiple observers on endoscopic diagnosis of esophageal varices before bleeding. Hepatology 1990;11:341-7.
28. D'Antiga L BP, Dall'Oglio L, Davenport M, et al. Interobserver agreement on endoscopic classification of oesophageal varices in children: A multicenter study. J Pediatr Gastroenterol Nutr 2011;52(suppl 2):E72.
29. Zargar SA, Javid G, Khan BA, et al. Endoscopic ligation compared with sclerotherapy for bleeding esophageal varices in children with extrahepatic portal venous obstruction. Hepatology 2002;36:666-72.
30. Garcia-Tsao G, Bosch J, Groszmann RJ. Portal hypertension and variceal bleeding—unresolved issues. Summary of an AASLD and EASL: Single-topic conference. Hepatology 2008;47:1764-72.
31. Duché M, Ducot B, Tournay E, et al. Prognostic value of endoscopy in children with biliary atresia at risk for early development of varices and bleeding. Gastroenterology 2010;139:1952-60.
32. Garcia-Tsao G, Sanyal AJ, Grace ND, et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology 2007;46:922-38.
33. Lebrec D. Pharmacological treatment of portal hypertension: Hemodynamic effects and prevention of bleeding. Pharmacol Ther 1994;61:65-107.
34. Turnes J, Garcia-Pagan JC, Abraldes JG, et al. Pharmacological reduction of portal pressure and long-term risk of first variceal bleeding in patients with cirrhosis. Am J Gastroenterol 2006;101:506-12.

35. de Kolster CC, Rapa de Higuera M, Carvajal A, et al. [Propranolol in children and adolescents with portal hypertension: its dosage and the clinical, cardiovascular and biochemical effects]. G E N 1992;46:199-207.
36. Erkan T, Cullu F, Kutlu T, et al. Management of portal hypertension in children: A retrospective study with long-term follow-up. Acta Gastroenterol Belg 2003;66:213-7.
37. Ozsoylu S, Koçak N, Demir H, et al. Propranolol for primary and secondary prophylaxis of variceal bleeding in children with cirrhosis. Turk J Pediatr 2000;42:31-3.
38. Ozsoylu S, Koçak N, Yüce A. Propranolol therapy for portal hypertension in children. J Pediatr 1985;106:317-21.
39. Sökücü S, Süoglu OD, Elkabes B, et al. Long-term outcome after sclerotherapy with or without a beta-blocker for variceal bleeding in children. Pediatr Int 2003;45:388-94.
40. Braillon A, Moreau R, Hadengue A, et al. Hyperkinetic circulatory syndrome in patients with presinusoidal portal hypertension. Effect of propranolol. J Hepatol 1989;9:312-8.
41. Ostman-Smith I, Wettrell G, Riesenfeld T. A cohort study of childhood hypertrophic cardiomyopathy: Improved survival following high-dose beta-adrenoceptor antagonist treatment. J Am Coll Cardiol 1999;34:1813-22.
42. Botha JF, Campos BD, Grant WJ, et al. Portosystemic shunts in children: A 15-year experience. J Am Coll Surg 2004;199:179-85.
43. de Ville de Goyet J, Alberti D, Clapuyt P, et al. Direct bypassing of extrahepatic portal venous obstruction in children: A new technique for combined hepatic portal revascularization and treatment of extrahepatic portal hypertension. J Pediatr Surg 1998;33:597-601.
44. Sharif K, McKiernan P, de Ville de Goyet J. Mesoportal bypass for extrahepatic portal vein obstruction in children: Close to a cure for most! J Pediatr Surg 2010;45:272-6.
45. Evans S, Stovroff M, Heiss K, et al. Selective distal splenorenal shunts for intractable variceal bleeding in pediatric portal hypertension. J Pediatr Surg 1995;30:1115-8.
46. Di Giorgio A, Agazzi R, Alberti D, et al. Feasibility and efficacy of transjugular intrahepatic portosystemic shunt (TIPS) in children. J Pediatr Gastroenterol Nutr 2012;54:594-600.
47. Gonçalves ME, Cardoso SR, Maksoud JG. Prophylactic sclerotherapy in children with esophageal varices: Long-term results of a controlled prospective randomized trial. J Pediatr Surg 2000;35:401-5.
48. Lykavieris P, Gauthier F, Hadchouel P, et al. Risk of gastrointestinal bleeding during adolescence and early adulthood in children with portal vein obstruction. J Pediatr 2000;136:805-8.