Management of Portal Hypertension in Children: A Focus on Variceal Bleeding

Mortada H.F. El-Shabrawi, Mona Isa, Naglaa M. Kamal

ABSTRACT

Treatment of the primary cause of many chronic liver diseases (CLDs) may not be possible and serious complications like portal hypertension (PH) must be prevented or controlled enabling the child with CLD to live with a good quality of life. Early detection of PH is achieved by history taking, examination, imaging techniques as well as esophagastroduodenoscopy (EGD). Primary prevention of first episode of variceal hemorrhage involves use of non-selective β-blocker (NSBB) and rubber band endoscopic variceal ligation (EVl). Management of acute variceal bleeding includes effective resuscitation, prompt diagnosis, control of bleeding and prevention of complications. Prevention of secondary variceal hemorrhage is through a combination of EVl plus pharmacological therapy, other therapies include surgical porto-systemic shunt (PSS) and Meso-Rex bypass. The goal of this review is to highlight the pediatrician role in management of variceal bleeding in children with PH in order to improve their survival and avoid its life-threatening complications.

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Key words: Chronic liver disease; Portal Hypertension

INTRODUCTION

Portal hypertension (PH) is characterized by prolonged elevation of the portal venous pressure [PVP] the normal \(= 2-5 \text{ mm Hg}\]. Minor elevations of the PVP (6-10 mm Hg) do not result in esophageal varices, but higher pressures may. Variceal hemorrhage may occur when PVP exceeds 12 mm Hg\(^6\). PH associated with chronic liver disease (CLD) poses distinctive risks, including luminal gut bleeding, ascites and hepatic encephalopathy. PH can also be present in the absence of CLD in the setting of portal vein obstruction (PVO). A major cause of cirrhosis-related morbidity and mortality is the development of variceal hemorrhage, a direct consequence of portal hypertension. Variceal hemorrhage may be lethal, although effective interventions have resulted in a threefold decrease in mortality over the past three decades. In one study mortality between 1980 and 2000 decreased from 9% to 0% in Child-Turcotte-Pugh (CTP) class A patients, from 46% to 0% in CTP B patients and from 70% to 30% in CTP C patients\(^7\). Much of this improvement has resulted from more effective interventions before, during and after a bleeding episode\(^8\).

CLASSIFICATION AND ETIOLOGY OF PH

PH is classified based on the anatomical location into extrahepatic, infrahepatic and posthepatic (Table 1). Extrahepatic PH is caused by increased resistance in the extrahepatic portal vein, and is associated with mural or intraluminal obstruction (e.g., congenital atresia or fibrosis, thrombosis, neoplasia) or extraluminal compression\(^9\). Intrahepatic PH is caused by increased resistance in the microscopic portal vein tributaries, sinusoids, or small hepatic veins. Intrahepatic PH is further classified by hepatic anatomical level into presinusoidal, sinusoidal, and postsinusoidal PH (Table 1)\(^10\). Presinusoidal PH occurs because of increased resistance in the terminal intrahepatic portal vein tributaries, while sinusoidal intrahepatic PH is most often the result of fibrotic hepatopathies\(^9\). Postsinusoidal intrahepatic PH is associated with veno-occlusive disease (also called sinusoidal obstruction syndrome). Veno-occlusive disease is caused by damage to the sinusoidal endothelium and hepatocytes in the centrallobular region, resulting in obliteration of the small terminal hepatic veins and central veins by fibrosis. Posthepatic obstruction is seen in Budd-Chiari syndrome, right heart failure and cardiac tamponade. The Budd-Chiari syndrome occurs with obstruction to the sublobular and big hepatic veins anywhere between the efferent hepatic veins and the entry of the inferior vena cava into the right atrium\(^11\).

PATHOGENESIS OF PH

Vasoreactivity such as vasoconstriction in hepatic circulation and vasodilation in systemic circulation plays a major role in pathophysiology of PH\(^10\). Vascular structural changes including...
vascular remodeling and angiogenesis have been identified as additional important compensatory processes for maintaining and aggravating portal hypertension\textsuperscript{10}. Vascular remodeling is an adaptive response of the vessel wall that occurs in response to chronic changes in the environment such as shear stress\textsuperscript{10}. Angiogenesis promoted through both proliferation of endothelial and smooth muscle cells also occurs as response to increased pressure and flow.

Table I Classification and Etiology of Portal Hypertension.

<table>
<thead>
<tr>
<th>Extrahepatic (Prehepatic or Infrahepatic)</th>
<th>Intrahepatic</th>
<th>Posthepatic (Suprahepatic)</th>
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<tbody>
<tr>
<td>-Portal vein obstruction (atresia, agenesis, stenosis)</td>
<td>- Presinusoidal</td>
<td>-Budd-Chiari syndrome</td>
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<td>-Portal vein thrombosis</td>
<td>Congenital hepatic fibrosis</td>
<td>-Right sided heart failure</td>
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<td>-Spleenic vein thrombosis</td>
<td>Schistosomiasis</td>
<td>-Cardiac tamponade</td>
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<td>-Increased portal flow</td>
<td>Acute and chronic hepatitis</td>
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<td>-Arteriovenous fistula</td>
<td>- Sinusoidal Cirrhosis</td>
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**COMPLICATIONS OF PH**

**Collateral circulation**

The development of portosystemic shunts and collateral circulation is a compensatory response to decompress the portal circulation and reduce the PH, but unfortunately contributes to significant morbidity and mortality. Vasodilation of pre-existing collateral vessels results in increased collateral blood flow and volume. They are mainly found in the lower esophagus causing varices, rectal mucosa causing hemorrhoids, and anterior abdominal wall causing caput medusa (Figure 1). The mechanism of collateral vessel regulation still remains unclear. The control of collateral circulation could be a key in managing complications of PH, therefore, extensive experimental studies are performed in this field\textsuperscript{11}.

![Figure 1 Caput medusa in a 6-year old boy with portal hypertension due to congenital hepatic fibrosis.](image)

**Ascites**

Ascites occurs as a consequence of imbalances in Starling’s law so that the forces keeping fluid in the vascular space are less than the forces moving fluid out of the vascular space\textsuperscript{12}. In PH, increased PVP drives fluid into the interstitial space. When the capacity of the regional lymphatics is overwhelmed, ascites develops. The development of ascites is perpetuated by the splanchnic vasodilatation that accompanies PH. This vasodilatation results in pooling of blood in the abdomen, which leads to a decrease in effective systemic blood volume. Initially, increased cardiac output is compensatory, establishing the hyperdynamic circulation of hepatic disease marked by high cardiac output and low systemic vascular resistance\textsuperscript{13}. As liver disease progresses, vasodilators that escape hepatic degradation accumulate in the systemic circulation and systemic arteriolar vasodilatation worsens.

Eventually, inotropic and chronotropic compensation fails, and systemic hypotension ensues. This results in activation of the endogenous vasopressor system, including the renin-angiotensin-aldosterone system, sympathetic neurons, and the nonosmotic release of antidiuretic hormone (ADH). Resultant volume expansion further increases hydrostatic pressure in the portal vasculature causing increased lymph formation\textsuperscript{13}. Concurrent hypoalbuminemia secondary to hepatic synthetic failure lowers vascular colloid osmotic pressure that furthers aggravates ascites formation\textsuperscript{13}.

**Spontaneous Bacterial Peritonitis**

Spontaneous bacterial peritonitis is infection of ascitic fluid without a detectable nidus\textsuperscript{14}. It occurs in 8-30% of hospitalized cirrhotic human patients with ascites, with an associated mortality of 20-40% if untreated\textsuperscript{14}. Many patients are asymptomatic, but clinical signs can include abdominal pain, fever, and diarrhea. A neutrophil count 250 cells/mm\textsuperscript{3} in the ascitic fluid is diagnostic, regardless of whether or not organisms are visible cytologically\textsuperscript{15}.

**Hepatorenal syndrome**

Another consequence of the hyperdynamic circulatory derangements associated with PH is hepatorenal syndrome. This syndrome, a form of reversible renal failure, occurs as a consequence of profound renal vasoconstriction secondary to the release of angiotensin, norepinephrine, and ADH in response to splanchnic vasodilatation\textsuperscript{15}. The syndrome is always accompanied by a state of refractory ascites and end-stage liver failure\textsuperscript{17}.

**Hepatopulmonary syndrome, portopulmonary hypertension, and hepatic hydrothorax**

Hepatopulmonary syndrome, portopulmonary hypertension, and hepatic hydrothorax are pulmonary complications of PH\textsuperscript{18}. Hepatopulmonary syndrome occurs because of microvascular pulmonary arterial dilatation (most likely because of nitric oxide overproduction in the lung) leading to ventilation-perfusion mismatch\textsuperscript{19}. Portopulmonary hypertension is likely mediated by humoral substances that enter the systemic circulation through multiple acquired portosystemic shunts (MAPSS)\textsuperscript{19}. Initially, these substances cause vasoconstriction, but subsequent thrombosis leads
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TREATMENT OF VARICEAL HEMORRHAGE

Primary prophylaxis of variceal hemorrhage

Since varices per se cause no symptoms, strategies to detect them are required. It is well accepted that almost all cirrhotics should be screened for the presence of esophageal varices at the time of diagnosis and at intervals afterwards. Those with severe liver impairment and endoscopic stigmata such as red wale signs should undergo yearly surveillance. EGD remains the most reliable way of detecting varices and affords the possibility of management at the time of diagnosis. Newer techniques for looking at the esophageal varices such as trans-nasal and capsule endoscopy may have a future role.

The availability of measuring liver stiffness either by ultrasound or magnetic resonance imaging technology holds a promise in excluding a significant number of cirrhotics from the need for endoscopy, as lower liver stiffness correlates quite well with a hepatic venous pressure gradient (HVPG) < 10 mm Hg[26].

To date, primary prevention of varices in cirrhosis remains elusive. Limited evidence fails to demonstrate a role for non-selective β-blocker (NSBB) therapy in preventing the formation of esophageal varices in cirrhotics[28]. Other innovative strategies remain to be developed. Two therapies are currently accepted in the primary prevention of the first episode of variceal hemorrhage, namely NSBBs and rubber band endoscopic variceal ligation (EVL), other modalities as endoscopic injection sclerotherapy and various porto-systemic shunt (PSS) procedures are more controversial as primary prophylactic modalities[29]: (1) NSBBs as propranolol (and to a lesser extent nadolol) may act by lowering the cardiac output and portal perfusion by both reduction of the cardiac output (β-blockade) and reduction of the portal blood flow through splanchnic vasoconstriction (β-blockade)[30]. Selective β-blockers as atenolol and metoprolol are less effective and are not recommended for the primary prophylaxis of variceal hemorrhage[29, 30]. Propranolol significantly reduces the incidence of the first variceal hemorrhage from 15% to 25% in a median follow-up of 24 months. The effect is more evident in patients with medium or large sized varices[31]. The incidence of first variceal hemorrhage in patients with small varices, although low, is reduced with β-blockers from 7% to 2 % over a period of 2 years. In patients with small varices that are not at a high risk of hemorrhage, NSBBs have been effective in delaying variceal growth, and thereby preventing variceal hemorrhage[29]. NSBBs significantly lower mortality[32]. They are contraindicated in asthma, Raynaud's syndrome, heart failure, and heart block; and the dose is adjusted with renal dysfunction[33-35], and should be used with caution in obstructive lung disease, diabetes mellitus or decompensated hepatic disease[36].

Intravenous use of NSBBs should be avoided with calcium channel blockers; as it may increase their effect[37]. Propranolol has a wide dosing range (0.6-8.0 mg/kg body weight divided into two to four doses per day) that has been required in children in order to observe a “therapeutic effect”[16,37]. Propranolol side effects may include hypoglycemia, systemic hypotension, nausea, vomiting, depression, weakness, bronchospasm, heart block as well as cutaneous reactions, including Stevens-Johnson syndrome, exfoliative dermatitis, erythema multiforme, and urticaria[38]. Bronchospasm, bradycardia and heart failure may also occur[37]. Carvedilol is a vasodilating β-blocker which combines non selective β-blockade with α-1 receptor antagonism[38,39]. It is a potent acute portal hypertensive agent which does not...
appear to compromise renal perfusion. However, patients with ascites are at greater risk of its systemic hypotensive action[39]. Carvedilol is more powerful than propranolol in decreasing hepatic venous pressure gradient[40]. The initial dose is 0.08 mg/kg, to be gradually increased over 2-3 months, based on response reaching a maximum of 0.5 mg/kg/24 h divided q 12 h[39]. Carvedilol may cause atrioventricular block, arrhythmias, bradycardia, or worsen asthma or heart failure and may cause excessive hypotension when used with other antihypertensives[39]. Evidence in adult patients shows that β-blockers may reduce the incidence of variceal hemorrhage and improve long-term survival. In patients without varices, treatment is not recommended given the lack of efficacy of NSBBs in preventing the development of varices and a higher rate of side effects[41]. A therapeutic effect is thought to result when the pulse rate is reduced by at least 25%. There is limited published experience with the use of this therapy in children[42]; (2) EVL during EGD is achieved by placing rubber bands around varices until their obliteration. EVL has been compared with NSBBs in several randomized trials. Two early meta-analysis showed that EVL is associated with a small but significantly lower incidence of first variceal hemorrhage without differences in mortality[43,44]. However, another recent meta-analysis showed that this effect may be biased and was associated with the duration of follow-up: the shorter the follow-up, the more positive the estimated effect of EVL[45] and that both therapies seemed equally effective. NSBBs have other advantages, such as prevention of bleeding from other portal hypertension sources (portal hypertensive gastropathy and gastric varices) and a possible reduction in the incidence of spontaneous bacterial peritonitis[46]. The role of a combination of a NSBB and EVL in the prevention of the first variceal hemorrhage is uncertain and cannot be currently recommended[46]. (3) Endoscopic sclerotherapy as a primary prophylaxis has yielded controversial results. Early studies showed promising results; whereas later studies showed no benefit in decreasing the first episode of variceal hemorrhage and/or mortality from variceal bleeding[46,47]. Therefore, sclerotherapy is not generally recommended to be used for the primary prevention of variceal hemorrhage. N.B: Nitrates [such as isosorbide mononitrate (ISMN)] are ineffective in preventing the first variceal hemorrhage[48,49]. The combination of an NSBB and ISMN is not recommended for primary prophylaxis[50,51]. The results of a randomized controlled trial comparing carvedilol with EVL in the primary prophylaxis of variceal hemorrhage showed that carvedilol was associated with a significantly lower rate of first variceal hemorrhage (9%) compared with EVL (21%) with a tendency for higher rate of adverse events with carvedilol[52]. Before the details of this study were published, carvedilol was not recommended[49]. However, after completing the study, the researchers concluded that carvedilol is effective in preventing the first variceal bleeding and recommended it as an option for primary prophylaxis in patients with high-risk esophageal varices[52]; (4) Surgical PSS procedures and radiological procedures in which a stent is placed via the internal jugular vein between the portal vein and the hepatic vein called percutaneous transjugular intrahepatic portosystemic shunt (TIPS), although very effective in preventing the first variceal hemorrhage, yet they end up with shunting blood away from the liver accompanied by more frequent HE and higher mortality[40]. They should not be used in the primary prevention of variceal hemorrhage[29].

Management of acute variceal hemorrhage

Acute variceal hemorrhage is associated with a mortality rate of 15-20%. Management should be aimed at providing simultaneous and coordinated attention to effective resuscitation, prompt diagnosis, control of bleeding, and prevention of complications[9].

**General measures:** The blood volume should be expanded to maintain a systolic blood pressure of 90-100 mm Hg and a heart rate below 100 beats per minute[39]. Colloids are more effective than crystalloids and packed red blood cells in reaching optimal hemodynamics[41]. Transfusion goals are required to maintain a hemoglobin of around 8 grams/deciliter[44] as total blood restitution is associated with increases in portal pressure[39] and higher rates of re-bleeding and mortality[45]. Endotracheal intubation should be performed before EGD in patients with massive bleeding and decreased consciousness level[39]. One of the main complications associated with variceal hemorrhage is bacterial infection. Short-term antibiotic prophylaxis not only decreases the rate of bacterial infections, but also decreases variceal re-bleeding[17] and increases survival[46,47]. Therefore, antibiotic prophylaxis is considered a standard practice[46]. Recently, it is suggested to use intravenous ceftriaxone[45]. Transfusion of fresh frozen plasma and platelets can be considered in patients with significant coagulopathy and thrombocytopenia. A multicenter placebo-controlled trial of recombinant factor VIIa in cirrhotic patients with gastro-intestinal hemorrhage failed to show a beneficial effect over standard therapy[48]; therefore, recombinant factor VIIa is not routinely recommended. Once the patient is hemodynamically stable, EGD should be performed as soon as possible particularly in patients with more severe bleeding[29].

**Specific measures to control acute hemorrhage and prevent early recurrence:** The most accepted approach consists of combination of pharmacological and endoscopic therapy. Pharmacological therapy has the advantage of being generally easy-applicable, with a low rate of adverse events. It includes somatostatin or its analogs (octreotide or vapreotide)[29] and arginine vasopressin[43]. Somatostatin or its analogs can be initiated as soon as a diagnosis of variceal hemorrhage is suspected, before diagnostic EGD[56]. Continuous infusion of 1–5 μg/kg/h of octreotide appears to be effective, but may need to be initiated by the administration of a bolus of 1 hour’s worth of the infusion[56]. Optimal duration has not been well established, but considering that ~50 % of early recurrent hemorrhage occurs within the first 5 days[48], continuing vasoactive drugs for 5 days seems rational[40]. Shorter duration is acceptable, particularly in patients with a low risk of re-bleeding (e.g., CTP class A)[29]. Randomized controlled trials comparing different pharmacological agents (somatostatin, octreotide, vapreotide, vasopressin and terlipressin), show no differences among them regarding control of hemorrhage and early re-bleeding, although vasopressin is associated with more adverse events[31]. Arginine vasopressin is a naturally occurring peptide[39]. It acts as a vasoconstrictor through V1 receptors or an aquagenic agent allowing free water retention through V2 receptors in the kidney[47]. Splanchnic vasoconstriction thereby decreases the portal blood pressure[39]. It is given as a 0.33 U/kg bolus over 20 minutes followed by a continuous infusion of the same amount hourly or a continuous infusion of 0.2 U/1.73 m² surface area/min[64,66]. The continuous infusion may be increased up to three times its initial rate[32]. Vasopressin has a half-life of 30 minutes[31].

**Other therapies:** Regarding endoscopic therapy, EVL is more effective than endoscopic variceal sclerotherapy with greater control of hemorrhage, less re-bleeding, lower rates of adverse events, but without differences in mortality[47,67]. Sclerotherapy is reserved for cases in which EVL cannot be performed[29]. Despite urgent endoscopic (with or without pharmacological) therapy, variceal bleeding can not be controlled or recurs early in approximately 10-20% of patients and other therapies have to be implemented[48,69]. Shunt...
surgery and TIPS have proven clinical efficacy as salvage therapy in these patients[26,27]. Balloon tamponade is very effective in controlling bleeding temporarily with immediate control of hemorrhage in >80% of patients[28]. However, re-bleeding after the balloons are deflated is high and its use is associated with potentially lethal complications, such as aspiration, migration, and necrosis/perforation of the esophagus with mortality rates as high as 20%. Therefore, it should be restricted to patients with uncontrollable bleeding for whom a more definitive therapy (e.g. TIPS) is planned within 24 h of placement. Airway protection is strongly recommended when balloon tamponade is used. Linton tube which has a larger gastric balloon (and no esophageal balloon) is preferred for uncontrollable bleeding from fundal gastric varices. The use of self-expandable metallic stents to arrest uncontrollable acute variceal bleeding has been reported in a pilot study of 20 patients to be associated with bleeding cessation in all patients, and without complications after its removal 2 to 14 days later[29]. Compared with endoscopic variceal sclerosis or EVL, endoscopic variceal obturation with tissue adhesives, such as N-butyl-cyanoacrylate is more effective in treating acute fundal gastric variceal bleeding with better control of initial hemorrhage, as well as lower rates of re-bleeding[30,31]. In an uncontrolled pilot study, 2-ocetyl cyanoacrylate, an agent approved for skin closure in the United States, has been described to be effective in achieving initial hemostasis and in preventing re-bleeding from fundal varices[32].

**Therapies under investigation:** TIPS is considered to be a salvage therapy in the control of acute hemorrhage which if used early (within 24 h of hemorrhage) is associated with significantly improved survival in high-risk patients, especially when acute variceal hemorrhage is not controlled with pharmacological and endoscopic means[26,27]. However, this cannot be recommended until more data are available[29]. No method has been shown to be more effective than TIPS in controlling bleeding from either esophageal or gastric variceal hemorrhage and preventing subsequent bleeding episodes. The two major drawbacks of the TIPS procedure are that its high technology character limits its availability, and that the shunt has a propensity to result in HE.

**Prevention of recurrent variceal hemorrhage (secondary prophylaxis)**

Patients who survive an episode of acute variceal hemorrhage have a very high risk of re-bleeding (~60% within 1-2 years) with a mortality rate of 33%[33]. Therefore, it is essential to start these patients on therapy to reduce the risk of hemorrhage recurrence, before discharging them from the hospital. Patients who required shunt surgery/TIPS to control the acute episode do not require further preventive measures[29]. The most accepted approach is a combination of EVL plus pharmacological therapy, because NSBBs will protect against re-bleeding before variceal obliteration and will delay variceal recurrence. Several meta-analysis studies showed that this combination reduces variceal re-bleeding more than either therapy alone[34,35]. If a patient is not a candidate for EVL, one would try to maximize portal pressure reduction by giving combination pharmacological therapy (propranolol plus ISMN)[36]. Surgical PSS procedures are numerous, but they are beyond the scope of this review. PSS are very effective in preventing re-bleeding; however, their role has changed in the past few years because of the acceptance of liver transplantation and endoscopic hemostasis[37]. Development of physiologic shunts as the mesenterico-left portal vein (or meso-Rex) bypass and successful liver transplant has changed the paradigm of portal hypertension surgery[38]. Meso-Rex bypass has proven to be an effective method of resolving portal hypertension caused by PVO including thrombosis after living donor transplantation. This shunt is preferable to other surgical procedures because it eliminates portal hypertension and its sequelae by restoring normal portal flow to the liver[39].

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