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Chapter

Pediatric Portal Hypertension

Reda A. Zbaida

Abstract

Portal hypertension is increased intravascular pressure of the portal vein. The prevalence of causes in children is different from adults ones. The commonest cause of pediatric portal hypertension is the extra-hepatic portal hypertension, comparing with an adult where liver cirrhosis is the comments cause. Also, taking into consideration, the fundamental physiological differences between the two age groups. These elements are making the attempt to extrapolate the adult guidelines to the pediatric age group unpractical. On the other hand, the limitation of well-designed studies in the pediatric age group makes reaching a consensus about the safety and efficiency of primary prophylaxis of variceal bleeding difficult. In contrast, there were enough data to recommend the secondary prophylaxis of variceal bleeding and the safety and efficiency of Meso-Rex shunt for portal hypertension have been confirmed. These indicate the necessity of further studies to reach a complete algorithm of guidelines for pediatric portal hypertension.

Keywords: portal hypertension, children, esophageal varices, variceal bleeding, selective shunts, non-selective shunts

1. Introduction

The portal hypertension is caused by an increased resistance to venous flow in portal vein. Which leads to an increase to pressure in the portal circulation. It is a result of chronic liver disease, obstruction of portal vein, or portosystemic shunt, which leads to hyperdynamic circulation.

The normal hepatic venous pressure gradient (HVPG) correlates with normal portal pressure which is 1–4 mm Hg. A pressure gradient of more than 10 mm Hg links to esophageal varices. The pressure 12 mm Hg predicts the risk of active bleeding. [1]

The most common complication of pediatric portal hypertension is acute variceal bleeding. The grading system of the Japanese Research Society for Portal Hypertension of esophageal varices is as follows: grade 1: flattened by insufflation, grade 2: not flattened by insufflation but is not circumferential, grade 3: not flattened and is circumferential. [2]

2. Embryology

The three main venous embryo systems will be recognizable by the end of the 3rd week of gestation.

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They include (1) the 2 cardinal veins which drain the embryo blood (intra-embryonic system). To the sinus venosus (primitive atrium). The other two are extraembryonic systems, one of them transports the blood from the yolk sac to the heart (sinus venosus) which is called (2) the vitelline veins (two pairs). Finally, (3) the 2 umbilical veins transport the oxygenated blood from the placenta to the embryo's heart. [3]

The hepatic bud starts branching off from the caudal end of the foregut, which expands into the transversum septum (Mesenchymal tissue in the pericardiac area). The cephalic part of the hepatic bud will eventually form the liver. And the caudal part will form the biliary tree and the gall bladder. During liver development, the primitive liver tissue in the transversum septum is in close contact with the two extraembryonic venous systems (**Figure 1**).

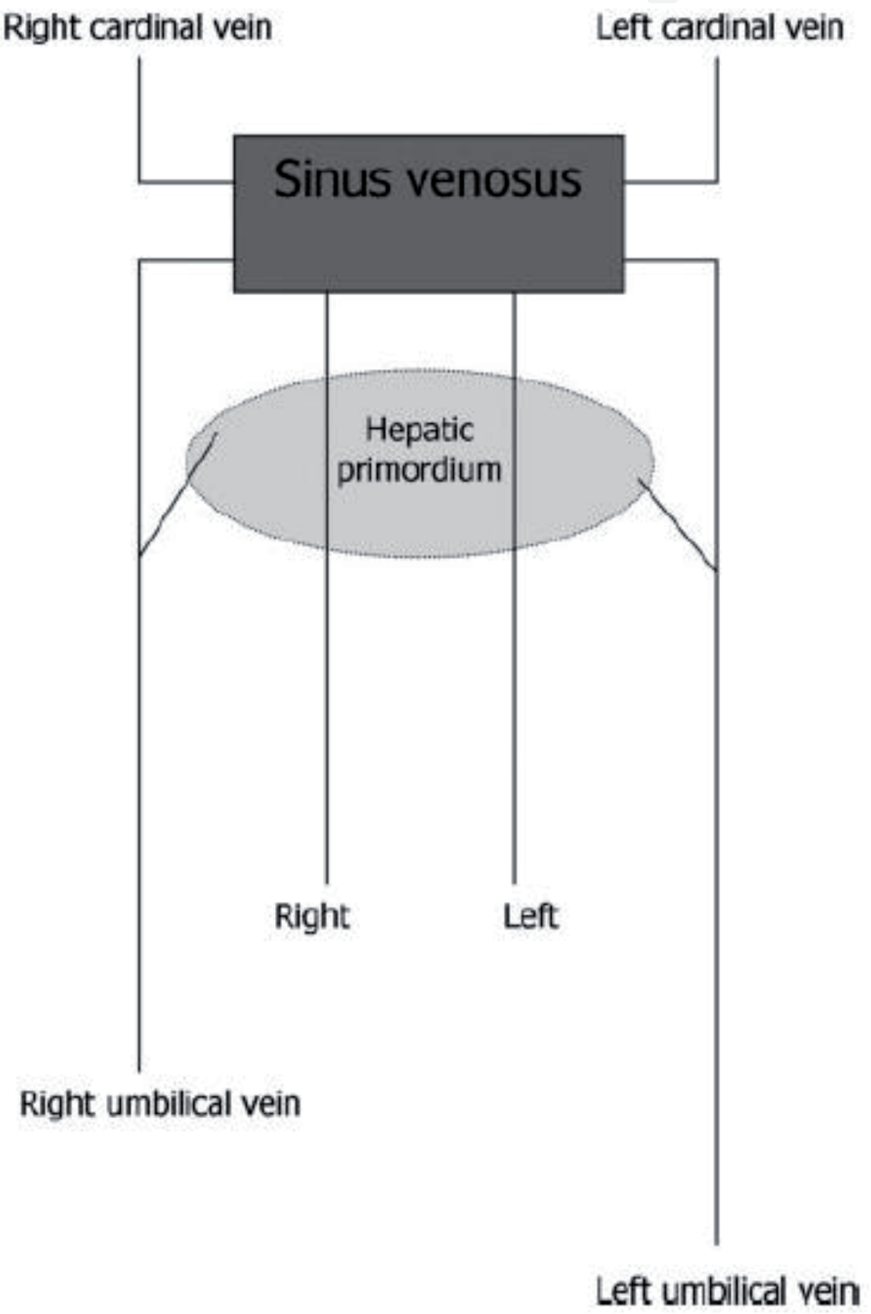


Figure 1.
Schematic drawing represents the relation between the primitive hepatic bud and the major fetal venous systems. (Courtesy of Collardeau-Frachon and Scoazec et al. [4]. All the rights reserved).

The portal circulation of the liver develops between the 4th and 6th weeks, which is the result of a complex interaction between a primitive liver and a pair of vitelline veins and umbilical veins.

Initially, the vitelline veins form 4 sites of anastomoses between each other in their way to the sinus venosus, which are the caudal-ventral anastomosis, middle dorsal (they named according to their relation to the foregut), subhepatic, and finally the subdiaphragmatic anastomosis.

A net of smaller anastomoses between the right and the left vitelline veins extend in the area between the subdiaphragmatic and the subhepatic anastomoses in the same site where the hepatic bud will proliferate and develop to form the liver (the caudal part of the septum transversum). Synchronously, the umbilical veins in their way to the sinus venosus each vein are divided into 2 branches. One runs in parallel to the primitive liver and the other one ends in the liver parenchyma. The right umbilical vein and its branches atrophy in the 4th week. Also, the direct branch to the sinus venosus disappears in the same period. But the left branch of the umbilical vein to the liver parenchyma persists. It increases in size gradually inside liver parenchyma till communicates with the left end of the subhepatic anastomosis of the vitelline veins. That is known as a portal sinus. So, all the oxygenated blood is conveyed to the liver via the left umbilical vein. Due to massive blood influx to the liver, one of the anastomosing veins between the subhepatic and subdiaphragmatic anastomoses increases in size tremendously (Ductus venosus) to accommodate the oxygenated blood from the portal sinus to sinus venosus via a subdiaphragmatic anastomosis. [4]

The future portal vein is formed of the inferior section of the left vitelline vein, middle dorsal anastomosis, and the superior section of the right vitelline vein. By end of this process in the 6th week, the S-shape portal vein starts to appear. By this, the definitive fetal portal circulation is formed. [4]

The next major event happens at birth when the umbilical blood flow ceases. Subsequently, intravascular pressure in the umbilical vein and the ductus venosus drop and obliterating of these veins start within minutes after birth, which usually takes 15–20 days for complete closure. [3]

3. Anatomy and collateral circulation

The portal vein is formed by the union of the superior mesenteric and the splenic veins behind the neck of the pancreas. It passes behind the first part of the duodenum, then it runs in the free edge of the lesser momentum posterior to the common bile duct (on the right side) and hepatic artery proper (on the left side) up to the porta hepatis where it divides into right and the left portal veins. Both main branches continue breaking down up to the sinusoids.

There is a specific pattern of the breakdown of the portal vein, the biliary duct, and hepatic arteries within the liver parenchyma, which does not correlate with the liver surface anatomy.

The Cantlie's line extends from the inferior vena cava to the fundus of the gall bladder, which divides the liver into right and left lobes. Cantlie's line represents the true surgical division of the liver into right and left lobes. [5]

The description of further portal triad breakdowns and its correlation with hepatic veins is delineated by a French surgeon and anatomist "Claude Couinaud", depending on his framework that every half further divides into sectors, and a hepatic sector according to Couinaud system (**Figure 2**) is a region bounded by 2 hepatic veins or a hepatic vein and the hepatic edge. And the segment in the region

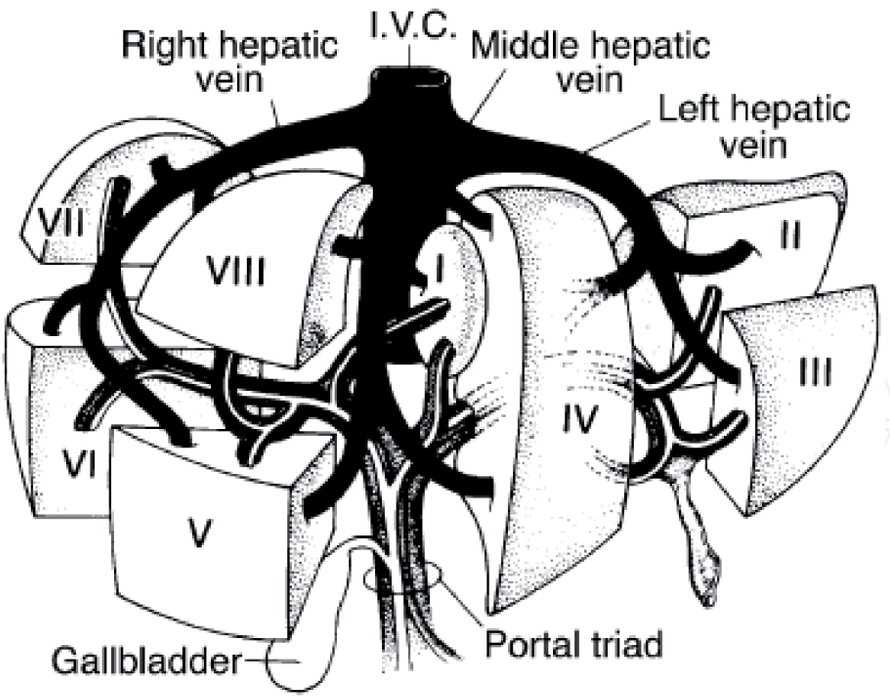


Figure 2.
Drawing represents the Couinaud system and the relation of left portal vein to ligamentous teres in the umbilical fissure. (Courtesy of John E. Skandalakis et al. [6], All rights reserved).

of the liver that has an independent portal triad (separate branches from the portal vein, the hepatic artery, and the biliary duct) supplies it. These anatomical facts guide the hepatobiliary surgeons to execute the hepatectomy (right or left) and segmentectomy precisely. [7]

The location of the Rex recess has an important surgical application in pediatric portal hypertension. That is where a branch from the left portal branch lies in the porto-umbilical fissure between the left lateral sector (segments II, III) and the left medial sector (segment IV). In intrauterine life, the left portal branch in the recess of Rex was communicating with the left umbilical vein. The fibrous remnant of the left umbilical postnatally known as ligamentous teres can be used as a reliable anatomical landmark for the recess of the Rex, which is surgically accessible and connecting it to the mesenteric vessel (superior mesenteric vein) via graft to bypass the portal occlusion and avoid the cavernoma, which is a net of collaterals formed after the portal obstruction in the area of porta hepatis. A portal vein occlusion is the commonest cause of portal hypertension in the pediatric age group.

Another important anatomical aspect of portal hypertension is the collateral anastomoses [8] between the portal and systemic circulations. Under normal circumstances, the mesenteric vein returns to the liver via the portal vein, then to the inferior vena cava (systemic circulation) via the hepatic veins to reach finally, the right atrium of the heart. This normal pathway would be interrupted in portal hypertension where the resistance to blood flow in the portal circulation is increased. This forces the blood to use the porto-systemic anastomoses as alternative pathways to reach the systemic circulation, which are negligible in normal situations. But in portal hypertension, these anastomoses increase in size with the increased potentiality of hemorrhage (ex: esophageal varices).

These anastomoses are as follows:

- The esophageal branches of the left gastric vein (a tributary of the portal circulation) anastomose with esophageal branches of hemiazygos vein (systemic circulation).

- The anastomosis between the superior rectal vein (portal circulation) with the middle and inferior rectal veins (systemic circulation) in the anal canal.

- Paraumbilical anastomoses (caput medusa) are the communication between tributaries of portal vein which run in the falciform with the superficial veins of the anterior abdominal wall.

- The communications between veins of ascending colon, descending colon, and duodenum (portal circulation) with the left renal vein (systemic circulation).

- The veins of Retzius connect retroperitoneally between tributaries of inferior vena cava and tributaries of the superior and inferior mesenteric veins.

- The accessory portal system of sappey is a set of diaphragmatic veins connecting the portal system to the systemic system.

4. Causes

The spectrum of causes is arranged in the pre-hepatic, the hepatic, and the post-hepatic lesions.

- *Pre-hepatic lesions:* Extra-hepatic portal vein obstruction is the commonest cause of portal hypertension. The underlying cause of portal thrombosis is unidentifiable in most cases. [9] But it links to the predisposing factors. They are an injury to the portal vein in the cannulation of the umbilical vein, dehydration, abdominal sepsis, omphalitis, and hypercoagulable state. Another factor is the extra-mural compression like enlarged lymph node due to inflammation or malignancy. [10]

  The portosystemic shunt is another cause of portal hypertension which can be surgical or iatrogenic cause or congenital shunts. Lautz et al. proposed a classification for congenital portosystemic shunts which divide them into 2 types. Type I with no intrahepatic portal venous flow. Type II with some intrahepatic portal venous flow. [11]

- *Hepatic lesions:* Hepatic cellular injury of any cause (e.g. Biliary atresia, Schistosomiasis) stimulates collagen deposition via activated stellate cells, which leads to an increase resistance to venous outflow. [12]

- *Post-hepatic lesions:* They include the hepatic veno-occlusive disease. [13] Busulfan containing regimes use for a bone marrow ablation in the bone marrow transplant considered are risk factors for hepatic veno-occlusive disease, because of hepatic and endothelial cellular injuries, which cause hepatic venules obstruction leading to venous congestion and eventually, to portal hypertension. Budd-Chiari syndrome is another cause of post-hepatic obstruction. Although it is uncommon in the pediatric age group, Budd-Chiari syndrome does occur in children. The level of obstruction can be at any level from the hepatic veins up to the level of the aortocaval junction. The most underlying cause of Budd-Chiari syndrome in children is the hypercoagulable state (Protein C, S deficiency, antithrombin III deficiency). [14]

5. Clinical presentations

How the pediatric patient with portal hypertension is presented depends on 2 essential factors: (1) the site of the obstruction (2) whether the patient has liver cirrhosis or not.

- *Upper GI bleeding:* It is a frightening and common presenting symptom of portal hypertension in the pediatric age group. About 70% of the extra-hepatic portal hypertension cases present with upper GI bleeding, which is the common cause of pediatric portal hypertension presented. [10] But since the liver parenchyma and functions are preserved for decades in the extra-hepatic portal hypertension at the time of the presentation almost all the patients have a normal liver function. For this reason, most of these patients recovered without serious complications with a low mortality rate. This is true for all patients with compensated liver function presented with upper GI bleeding. Unfortunately, this is not the case for patients with decompensated liver disease (cirrhosis). Mathieu Duche et al. in their study reported that 1/5 of patients with cirrhosis developed life-threatening complications after upper GI bleeds. [15]

- *Portal hypertensive gastropathy:* It is gastric lesions related to portal hypertensive disease. It ranges from erythema to diffuse gastritis. It is an occasional cause of upper GI bleeding. But it most commonly causes iron deficiency anemia due to chronic blood loss, which also may manifest as melena. [16]

- *Splenomegaly and hypersplenism:* Splenomegaly alone could be the presenting symptom in the extra-hepatic portal hypertension, in this scenario usually there are no other hepatic signs and symptoms, which necessitates excluding hematologic causes. If the patient has cirrhosis, the signs, and symptoms of liver disease (e.g. spider naevi, jaundice, ascites) will be presented with *splenomegaly*. *Splenomegaly* imposes a significant risk in adolescent patients due to the type of sports and activities involved in this age group. It may lead to a spleen rupture and catastrophic bleeding. Splenectomy may be the only option in these patients, who do not complaint about avoiding contact sports. Also, these patients may develop hypersplenism (*splenomegaly,* with thrombocytopenia and leukopenia). [17] Although the *hepatomegaly* is not common in pediatric portal hypertension. But it could be associated with Budd-Chiari syndrome and congenital hepatic fibrosis. [14, 18]

- *Encephalopathy:* It is a known complication of liver cirrhosis. But it can be associated with normal liver function in the extra-hepatic portal hypertension patients caused by port-systemic shunts, whether it is congenital or systemic shunts. It could be manifested as learning difficulties and behavior abnormalities. [19]

- *Pulmonary related disorders: Pulmonary hypertension* is associated with portal hypertension with or without liver disease. [20] It is caused by increased vascular resistance due to pulmonary vasoconstriction as a result of shunting vasoactive substance to the systemic circulation whether is due to prehepatic shunting or inability of the liver to process the proteins (liver cirrhosis). And the *hepatopulmonary syndrome* is the contrast to *pulmonary hypertension,* which present with dyspnea and hypoxia resulting from pulmonary arteriovenous shunting and partial oxygenation of the blood due to massive capillary dilation as a response to vasodilators proteins bypassed to the systemic circulation. [21]

Patients with portal hypertension may present with signs of liver disease if the underlying cause of portal hypertension is the damage of liver parenchyma. For example, *Ascites* develops due to 2 important factors: (1) protein synthesis failure in the liver which impairs the intravascular oncotic pressure (2) dilated abdominal vascular capillaries and lymphatic microcirculation as a result of the increased portal hydrostatic pressure. [22] *Jaundice* is another sign of decompensated liver function. It happens due to the inability of the liver to process the bilirubin as one product of hemoglobin breakdown. [23]

6. Work up

- *Blood investigation:*

- *Complete blood count (CBC):* It is useful to identify the presence of and type of anemia. Also, it is essential in the management of acute variceal bleeding. The presence of thrombocytopenia and leukopenia in portal hypertension investigation usually indicate hypersplenism.

- *Liver function test:* It assesses the functionality of the liver. That will help to point toward the underlying cause of portal hypertension with help of other investigation modalities (see later). Low protein level (albumin) and prolonged coagulation profile indicate the impaired synthetic ability of the liver. The increased bilirubin level and hepatic enzymes indicate hepatocellular damage.

- *Renal function test:* It assesses dehydration especially in acute variceal bleeding, and impaired renal function test associated with liver diseases, like congenital hepatic fibrosis which linked to polycystic kidney disease.

Other investigations are requested according to the clinical status of the patients. Blood glucose will be low in decompensated liver cirrhosis and it is low in glycogen storage disease. Also, the ammonia level is indicated to confirm the diagnosis of encephalopathy. The coagulation screen in liver cirrhosis is prolonged. But in the extra-hepatic portal thrombosis, the coagulation profile shows secondary hypercoagulable abnormalities. [24] It will be reversed after the obstruction is overcomed.

- *Endoscopy:* It is an essential tool in portal hypertension management. It confirms the presence of varices in the esophagus and the stomach and identifies the cause of the upper GI bleeding whether from varices or other origins like hemorrhagic gastritis or Mallory-Weiss syndrome. Also, in cases of acute upper GI bleeding are not responsive to medical management, endoscopy offers an important therapeutic option to control the variceal bleeding whether via variceal banding or sclerotherapy. [25]

- *Radiological modalities:* The first radiological modality in use as part of the diagnosis armamentarium is an abdominal ultrasound with Doppler. It provides a lot of important and useful information, which include the size, echogenicity of the liver, and presence of the cysts or nodules. It also delineates the status of the intra and extra biliary tree, the patency of the portal vein, and the presence of the cavernoma in the porta hepatis. The size and echogenicity of the spleen are demonstrated in the abdominal ultrasound. And by assessing the vascularity of the abdomen it can provide valuable information for the surgical team

such as the patency of the superior mesenteric, renal, and splenic veins. The neck Doppler ultrasound plays an important role in planning for surgical intervention, by confirming the patency of Jugular veins. This allows using one of them as an autologous graft provided both veins are patent. [26] Furthermore, the distance between the veins can assess the possibility of shunting between them like the distance between the renal and the spleen veins to assess the possibility of the splenorenal shunting. It may also pick up the portosystemic shunting. But the computed tomography angiography and magnetic resonance angiography are more accurate to pick up such anomalies. The later radiological modalities are usually the second step in the work up to delineate the anatomy more accurately. Invasive radiological investigations are required in specific cases. For example, the wedged hepatic venography is required in the congenital porto-systemic shunts [27] and to check the patency of the left portal vein tributary in the Rex recess to assess the possibility of Rex shunt.

7. Management of acute variceal bleeding

The upper GI bleeding can be the first presenting symptom of pediatric portal hypertension, especially when the extra-hepatic portal vein thrombosis is the underlying cause of portal hypertension. The mortality risk from the first variceal bleeding is less than 1% in pediatric portal hypertension. [28] This is due to 2 facts. First, portal hypertension in children develops early in course of the pathology, which leads subsequently to early variceal formation in children who have well-compensated liver function. Thus, the ability of the children's recover is better comparing with adults (adult mortality rate ranging from 7 to 15%). Secondly, improved medical management reduce the mortality rate in all age groups. [12]

The management of acute variceal bleeding should start with securing the airway. Insertion 2 large cannulas withdraw the blood simultaneously for urgent investigations, which should include complete blood count, blood crossmatch, urea and electrolytes, liver function test, and blood clotting profile. The other blood tests as the medical situation are mandatory. [12]

The volume replacement should start as soon as possible with crystalloids and packed red blood cells aiming to maintain the hemoglobin at or above 7 g/dL. [25] This strategy prevents tissue hypoxia which reduces lactic acid accumulation in the tissues and blood. Therefore, blood acidosis becomes less likely. Eventually, the impairment of clotting factors (proteins) function also becomes less likely. This strategy hinders the slipping towards deleterious complications of disseminated intravascular coagulopathy. The insertion of the nasogastric tube is also beneficial in observing the continuity of the bleeding and evacuating the blood of the stomach. Evacuation of the blood from the stomach has significant importance in cirrhotic patients to prevent encephalopathy. The octreotide is a synthetic analogue of somatostatin, which reduces the portal venous inflow by constriction of the splanchnic arterioles via a direct effect on the arteriole smooth muscles. It is started as a bolus dose (1 mcg/kg) followed by infusion (1 mcg/kg/H) usually for 4–5 days, which is often followed endoscopy after controlling the bleeding. [29] The only accepted situations to use endoscopic sclerotherapy in children should be acute bleeding not responding to the medical management with technical difficulty to apply band and infant's cases where there is no banding device available for them. There is a randomized trial showing the administration of erythromycin intravenously by 30 minutes before the endoscopy improves visibility and reduces the time of the procedure. [30] In a situation where medical management (including the endoscopy) fails to stop the bleeding, urgent shunt surgery or trans-jugular

intrahepatic portosystemic shunt (TIPS) should be performed. The optimal environment for the management of these patients is the intensive care unit, where all the vital signs are monitored closely.

8. Primary prophylaxis

The primary prophylaxis aims to prevent the first variceal bleeding. The efficiency of the primary prophylaxis is well established in adult by screening the portal hypertension patients and identify the high-risk elements for variceal bleeding like the large size of varices (Grade 2,3), presence of the red wale on varices' surface, and the severity of the liver disease. [31] Using the endoscopic banding and/or non-selective beta-blockers which act by decreasing the portal pressure via un-opposed action of alfa-receptor on the splanchnic arterioles and decreasing the cardiac output. Sclerotherapy is not recommended for primary prophylaxis because of increased mortality in one randomized study which is forced the discontinuity of this study. [32] Regarding the children, there is no consensus about the primary prophylaxis in the pediatric age group because there is no substantial data to decide which patients need screening and what are the predictive factors for variceal presence. [28] Some studies indicate that the presence of varices in children should be related to low albumin levels, increased size of the spleen, and thrombocytopenia. But there is a need for larger, well designed randomized studies to standardize these predictive factors for children. Also, the necessity for general anesthesia for endoscopic sessions in children is another worrying point. The deleterious effect of general anesthesia on the neurodevelopment of children is well documented. [33] And the recurrence of esophageal varices after eradication is common if the underlying cause of portal hypertension is not treated. There is increased incidence of gastric varices and portal hypertensive gastropathy after eradication of esophageal varices. The same is true regarding the non-selective beta-blocker. There is no properly designed randomized study to assess the therapeutic doses and the safety of the drug in children [34]. Taking into account the mortality rate due to the first variceal bleeding is exceedingly low (1%). All these points together came against standardizing the primary prophylaxis in children. But in special circumstances, the primary prophylaxis in children is justifiable like the child living away from the medical facilities which may necessitate primary prophylaxis.

9. Secondary prophylaxis

The secondary prophylaxis is the prevention of recurrence of variceal bleeding after the first variceal bleeding. Secondary prophylaxis is recommended in children due to the high recurrence rate after the first bleeding and enough data supporting the efficiency and safety of endoscopic banding and superior to endoscopic sclerotherapy therapy. As in the primary prophylaxis, no enough data support the safety and efficiency of non-selective beat-blockers. [28, 35]

10. Radiological intervention

TIPS refers to an establishment of intrahepatic portosystemic by inserting a stent (a communication) between the portal and hepatic veins. [36] It can be used in acute variceal bleeding uncontrolled by other means. Also, it is considered a good option for bridging to liver transplant for patients who have cirrhosis to improve the

severe symptoms (e.g. Massive ascites). In this scenario, TIPS is considered an ideal option by avoiding abdominal operation with subsequent adhesions and fibrosis, which makes the liver transplant operation much easier. [26]

This technique is considered as a non-selective shunt where most of the portal blood diverted to the systemic circulation which participates in encephalopathy. Also, TIPS has potential complications, which are shunt stenosis/thrombosis, bleeding, and dislodge of the stent to the right atrium. [26, 34]

11. Surgical shunts

The type of surgery depends on the level of obstruction (pre-hepatic, hepatic. Post-hepatic).

Pre-hepatic portal vein thrombosis with suitable anatomy means a patent left portal vein in the umbilical fissure and the patent superior mesenteric vein. They connect via graft whether synthetic or autologous, but as a rule in pediatric surgery, the use of autologous graft is always preferred whenever it is possible due to the fact the graft grows with the child. The most used autologous graft is one of the internal jugular veins after making sure the contralateral one patent pre-operatively by doppler ultrasound. After the anastomosis has been established, the porto-systemic circulation is re-established. Another important point that the liver parenchyma in the extrahepatic portal thrombosis is preserved for a long time. Based on this fact the functionality of the liver is expected to recover after re-establishing the porto-systemic circulation. Fortunately, the data of the surgical outcome confirms this concept. The secondary coagulation abnormalities, hepatopulmonary syndrome, liver adenomas, encephalopathy, and neurocognitive all will be reverted after successful Rex shunt. [37] And for the congenital portosystemic shunt the surgical ligation of the shunt when it is technically feasible. [27]

When the cause of portal hypertension is liver cirrhosis in the modern era the suitable option is a liver transplant. [38]

There are other surgical options for portal hypertension which are considered palliative rather than therapeutic: (1) Selective shunt: the technique is known as distal splenorenal shunt (Warren shunt). The principle of this technique is diverting part of the portal circulation to the systemic circulation by dividing the splenic vein and anastomosing the distal end to the left renal vein. It helps to reduce gastro-esophageal variceal pressure subsequently reducing the bleeding potentials. Also, hypersplenism and encephalopathy are improved. But the issue with this shunt is that with time the selective shunt becomes non-selective due to the formation of collaterals. [26]

(2) Non-selective shunt: its principle is based on diverting the whole portal circulation to systemic circulation by mobilization of the superior mesenteric vein and creation of side to side anastomosis with inferior vena cava or by used graft to connect the 2 veins whether synthetic or autologous grafts. This technique is not preferred in children because of the high-risk encephalopathy and deleterious effect on the cognitive ability of the children. [38]

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Author details

Reda A. Zbaida
Pediatric Surgery Department, Stellenbosch University, Cape Town, South Africa

*Address all correspondence to: redazbida@yahoo.co.uk

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