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Complication of Cirrhosis Portal Hypertension: A Review

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Abstract

Portal hypertension is responsible for most of the complications that mark the transition from compensated to decompensated cirrhosis, namely variceal hemorrhage, ascites and hepatic encephalopathy. Gastroesophageal varices result almost solely from portal hypertension, although the hyperdynamic circulation contributes to variceal growth and rupture. Ascites results from sinusoidal hypertension (portal hypertension) and sodium retention, which is, in turn, secondary to vasodilatation and activation of neurohumoral systems. The hepatorenal syndrome results from extreme vasodilatation with extreme decrease in effective blood volume and maximal activation of vaso constrictive systems, renal vasoconstriction and renal failure, which is probably an indirect effect of the changes in splanchnic circulation. Spontaneous bacterial peritonitis, a frequent precipitant of the hepatorenal syndrome, most probably results from deficient immunity, resulting in pathological gut bacterial translocation. Hepatic encephalopathy results from portosystemic shunting and hepatic insufficiency leading to accumulation of neurotoxins, mainly ammonia, in the brain. As for any illness, prediction of death in cirrhosis is essential in its management; and the development of portal hypertension and its complications have important prognostic value.

Keywords: Endopeptidase; Glucagon; Natriuretic peptide; Liver; Isoenzymes

Introduction

Portal hypertension is a frequent complication of liver cirrhosis, which develops in many patients and plays a role in the development of other complications of the disease. Portal hypertension results in the development of esophago-gastric varices which often bleed; and plays a role in the development of ascites, hepatorenal syndrome and hepatic encephalopathy. Portal hypertension and resulting portosystemic collaterals may also be responsible for the cardiopulmonary complications like porto-pulmonary hypertension and hepato-pulmonary síndrome [2].

Clinically significant portal hypertension is defined as an HVPG (Hepatic Venous Pressure Gradient) of at least 10 mmHg [3]. HVPG measurement is not routinely performed, but HVPG is an important tool for the management of patients with cirrhosis and portal hypertension. HVPG of >20 mmHg identifies variceal bleeders who are unlikely to respond to conventional therapy. HVPG monitoring is also useful in tailoring therapy in patients with esophageal varices that have bled and perhaps may be used to assess the effects of antiviral therapy on patients with advanced fibrosis and cirrosis [3,4]. HVPG, Model for End-Stage Liver Disease (MELD) score, and serum albumin levels are independent predictors of hepatic decompensation in cirrhotics [3].

Assessment of degree of portal hypertension

A low platelet count may be a reliable method for diagnosing portal hypertension and esophageal varices. However, recently the Portal Hypertension Collaborative Group showed that the measurement of platelets was inadequate as a noninvasive method for diagnosing esophageal varices. But if the platelet count was higher than 105 in patients with mild portal hypertension, then the risk of developing varices is low [3].

Transient elastography has been extensively studied in the assessment of the degree of liver fibrosis; however, its role in identifying patients with portal hypertension and varices is controversial. Also known as fibroscan, it is a noninvasive tool in the armamentarium of the clinician in measuring the degree of tissue stiffness. Though it is effective in assessing the extent of fibrosis, its effectiveness in assessing the degree of portal hypertension still needs large scale studies to precisely define the role of fibroscan in the assessment of portal hypertension [3,4].

Till newer developments take place, HVPG remains the gold standard for the diagnosis and quantification of cirrhotic (sinusoidal) portal hypertension.

Pathogenesis and pathology of cirrhotic portal hypertension

Portal venous pressure is directly related to the volume of portal blood flow as well as the vascular resistance to portal flow.

PVP~VR

PVP – Portal Venous Pressure.

V – Volume of portal blood flow.

R – Venous resistance.

In cirrhotic portal hypertension, the portal blood flow as well as the intrahepatic vascular resistance is increased.

The increased intrahepatic vascular resistance has two components, a fixed components and a functional component. The fixed component is secondary to sinusoidal fibrosis and compression by regenerative nodules and relative obstruction to the terminal portal venules. This resistance at the level of the hepatic microcirculation (sinusoidal portal

hypertension) results from architectural distortion of the liver due to fibrous tissue, regenerative nodules, and collagen deposition in the space of Disse [3,4].

A functional component also exists due to vasoconstriction secondary to a deficiency in intrahepatic NO and enhanced activity of vasoconstrictors [3,4]. This dynamic component results from active contraction of portal/septal myofibroblasts, activated hepatic stellate cells, and vascular smooth muscle cells in portal vasculature. The increased intrahepatic vascular tone is mediated by the increased activity of endogenous vasoconstrictors, viz endothelin, alpha-adrenergic activity, leukotrienes, thromboxane A_2, angiotensin II, etc [3,4]. The vascular tone is reduced by nitric oxide, prostacyclin and by various drugs (nitrates, adrenolytic agents, and calcium channel blockers). In cirrhotics with portal hypertension, the hepatic vascular resistance is increased because of an imbalance between vasodilatory and vasoconstrictor stimuli [3]. Hydrogen sulphide (H_2S), a gas neurotransmitter with vasodilator activity, was found to be altered in cirrhosis, and there is abrogation of the relaxation produced by l-cysteine thru H_2S production [3].

Neutral endopeptidase, in cirrhotics, degrades atrial natriuretic peptide and bradykinin and generates endothelin-1, which contributes to increased intrahepatic resistance [5].

The increase in portal blood flow is caused by splanchnic arteriolar vasodilatation. Splanchnic vasodilatation and hyperdynamic circulation may be the eventual result of bacterial translocation from the gut, which results in an increase in circulating levels of tumor necrosis factor and NO [5]. VEGF mediated angiogenesis may play a role in the increased splanchnic arterial flow as well as in the development of porto-systemic collaterals [5].

Earlier research focused on circulating vasodilator substances of splanchnic origin such as glucagon, vasoactive intestinal peptide, bile salts, platelet-activating factor, substance P, calcitonin gene-related peptide, atrial natriuretic peptide, etc., since these agents accumulate in liver disease due to reduced hepatic metabolism and/or increased portosystemic shunting [3].

Glucagon excess accounts for 30-40% of the splanchnic vasodilation in cirrhotic portal hypertension, and thus somatostatin may be useful in the treatment of variceal bleeding [6]. The major enzymatic source of the vascular NO overproduction is be eNOS [6].

Impaired activation of eNOS (endothelial NO synthetase) found in cirrhotic livers may be due to multiple defects in several interconnected signaling cascades that regulate intrahepatic eNOS activity [6], and also leads to down regulation of specific receptors for adrenomedullin, atrial natriuretic peptide and VEGF. Thus there is resultant vasoconstriction in the intrahepatic portal vasculature. An important role in the up regulation of eNOS has been attributed to a chronic increase in the shear stress in endothelial cells as a result of the increased portal blood flow and hyperdynamic circulationon [6]. The pathogenetic relationship between shear stress and arterial vasodilation has been further reinforced in other animal experiments.

In addition, other factors like vascular endothelial growth factor [6] and pro-inflammatory cytokines have been associated with enhanced eNOS activity. CO has also been suggested to participate in the mesenteric arterial vasodilatation of portal hypertensive rats through the activity of heme oxygenase isoenzymes [6].

Complications of portal hypertension

Chronic portal hypertension leads to multiple effects as a result of congestion and venous obstruction in the organs drained by the portal vein and the development of multiple porto-systemic collaterals.

The most significant among these is the development of esophageal varices i.e. grossly dilated sub-mucosal veins in the esophagus and stomach as a result of increased portal venous pressure and opening up of the porto-systemic connections within the esophagus. Similar changes may lead to the development of varices in other parts of the gut, like duodenal varices and rectal varices, which may manifest as hemorrhoids. Ectopic varices account for between 1% and 5% of variceal bleeding [3]. Such collateral vessels may also be seen as caput medusa around the umbilicus, peri-stomal varices which may bleed, or may be seen in and around the bile duct manifesting as portal biliopathy. Although ectopic varices can occur at several sites, they are most commonly found in the duodenum and at sites of previous bowel surgery including stomas. In a review of 169 cases of bleeding ectopic varices, 17% occurred in the duodenum, 17% in the jejunum or ileum, 14% in the colon, 8% in the rectum, and 9% in the peritoneum [6,7]. In the review, 26% bled from peri-stomal varices and a few from infrequent sites such as the ovary and vagina.

Dilatation of veins in the peri-choledochal plexus of Petren and para-choledochal plexus of Saint may give rise to portal biliopathy in patients with cirrhosis, though this is far more commonly seen in patients with EHPVO and non-cirrhotic causes of PHT [7].

Congestion in the organs having portal drainage leads to splenomegaly with hypersplenism (usually manifest as thrombocytopenia), portal gastropathy, portal hypertensive enteropathy and portal colopathy. Gut congestion may also reflect in the reduced delivery of hepatotrophic factors to the liver, and relative growth hormone insensitivity may also be seen. Cirrhosis is associated with low IGF-1 levels and an attenuated response to exogenous GH. These findings correlate better with the extent of hepatic dysfunction, though the presence of portal hypertension or malnutrition is also required [7].

Portal hypertension leads to the development of porto-systemic collaterals and diversion of portal flow from the gut to the systemic circulation. The delivery of venous blood from the intestines to the systemic circulation has its attendant effects with the development of porto-systemic encephalopathy. With the development of portal hypertension, most cirrhotics will go on to develop a hyperdynamic circulation with increased cardiac output. Shear stress in the portal circulation results in the upregulation of eNOS in systemic circulation resulting in increased vascular capacitance and a hyperdynamic circulation. Portal hypertension seems to be the common denominator in the circulatory disturbances seen in cirrhotics [7], and the resulting relative hypovolemia plays a significant role in renin-angiotensin activation and water retention. States of homeostasis and anti-natriuresis are activated, which results in sodium and water retention. In addition, a combination of portal hypertension and splanchnic arterial vasodilation alters splanchnic microcirculation and intestinal permeability, facilitating the leakage of fluid into the abdominal cavity and hence ascites. Sodium retention and ascites develop and decreased free water excretion leads to dilutional hyponatremia and eventually to impaired renal perfusion and hepatorenal syndrome. Thus portal hypertension effectively plays a role in the development of ascites and the hepatorenal síndrome [7].

Portal hypertension also seems to be pathogenetically closely linked to the development of pulmonary complications seen in liver disease: hepatopulmonary syndrome and portopulmonary hypertension. Although commonly seen in Childs C cirrhotics, both have been described in isolated portal hypertension without cirrosis [2,7,8]. A hyperdynamic circulation has been a common denominator in both the conditions, though the exact mechanism hasn't been completely understood as yet.

The Management of Portal Hypertension

Varices and Variceal Bleeding

The natural history and prognosis is quite different in patients who have never bled, patients having acute variceal bleed, and patients who have survived a bleeding episode. The efficacy of available treatments in controlling or preventing bleeding is inversely proportional to invasiveness and the adverse effects.

Variceal stage	Aim of therapy	Nomenclature
No varices	To prevent development of varices	Preprimary prophylaxis
Small varices (≤ 5 mm)	To prevent: (a) Enlargement of varices from small to large or (b) Variceal bleed	Early primary prophylaxis
Large varices (>5 mm) prophylaxis	To prevent bleed	Primary prophylaxis
Varices that have bled	To prevent rebleed.	Secondary prophylaxis

Table 1: Varices and Variceal Bleeding.

Screening for varices

Upper Gastrointestinal Endoscopy (UGIE) is indicated once the diagnosis of cirrhosis is established and is the gold standard for the diagnosis of esophageal varices according to the APASL (Asia pacific Association for study of the Liver) guidelines. The predictive value of noninvasive methods such as fibroscan, spleen size, portal vein diameter, and transient elastography in the diagnosis of esophageal varices remains to be established [7].

The size and variceal wall thickness, the presence of endoscopic stigmata such as red signs (an area where the variceal wall is thin and weakened), the severity of the liver disease, and the portal pressure are determinants of risk of variceal bleeding [7,8]. The APASL 2008 established criteria for diagnosing high risk and low risk varices. High-risk varices were identified as large (>5 mm) varices with at least one of the following red signs: cherry-red spots, hematocystic spots, or red wale markings. Small (≤5 mm) varices without red signs were classified as low risk varices.

Varices form at an HVPG>10 mm Hg and bleed only when the HVPG >12 mm Hg [7]. Not all patients who have a HVPG greater than 12 mm Hg bleed. Other local factors that increase variceal wall tension and cause mucosal injury play a role.

The wall tension is defined by Frank's modification of Laplace's law:

T = (P varices-P esophageal lumen) × (radius of varix)/wall thickness.

Surveillance endoscopy may be repeated every two years in patients without varices. In those with small varices and a high risk factor like alcoholic cirrhosis, decompensated cirrhosis or those with red signs at baseline endoscopy may warrant yearly endoscopic surveillance.

The APASL guidelines for primary prophylaxis of screening and surveillance of varices are as follows:

Endoscopic screening should be carried out on all cirrhotic patients at diagnosis.

Patients with no varices should have an endoscopic surveillance every 2 years. The frequency of endoscopic surveillance depends on the severity of liver disease.

Varices may progress in size from small to large in 5–12% of cirrhotic patients per year, but is highly dependent on the severity of liver disease.

Patients with compensated cirrhosis and small varices (≤5 mm) at initial endoscopy should undergo endoscopic surveillance at 1-year intervals.

Prophylactic VBL to prevent variceal bleeding should be used in patients with high-risk varices at the time of initial screening.

Preprimary prophylaxis

There is no effective treatment to prevent development of varices (preprimary prophylaxis) and available prophylactic measures have been disappointing with unacceptable adverse effects and limited efficacy [7].

Early primary prophylaxis

Small varices enlarge and get converted to large varices at a relatively uniform rate of 12% by 1 year and 31% at three years [7]. Merkel et al. [7] showed that nadolol resulted in slower progression to large varices (11% at 3 years) as compared to placebo (37% at 3 years), however there was no differences in survival. A large number of patients taking nadolol withdrew due to adverse effects as compared to placebo, (11% v/s 1%, P<0.05). Cales et al [7] found that more patients taking propranolol (31%) showed large varices at 2 years as compared to placebo (14%).

Patients with small varices having red signs or small varices with decompensated liver disease should be offered β-blocker therapy.

There does not seem to be any role for endoscopic therapy in early primary prophylaxis as yet.

Primary prophylaxis

Increase in Intra-Abdominal Pressure (IAP) markedly increases the azygous blood flow (an index of gastro-esophageal collateral blood flow) and variceal pressure and tensión [7]. It may be therefore wise to advise patients to avoid activities that cause increase in the IAP. Total volume paracentesis may decrease variceal pressure and may improve

portal hemodynamics by reducing the intra-abdominal pressure [7]. Beta blockers may help protect against the effect of moderate physical exercise at the expense of reducing blood flow to the liver [7].

Acute alcohol ingestion [7], post-prandial hyperemia, and NSAID's and aspirin [7] might predispose to variceal bleeding. Post prandial hyperemia is reduced by octreotide [2] and isosorbide mononitrate, whereas propranolol only reduces basal HVPG.

The APASL Recommendations Therefore Include Patients with Esophageal Varices should Avoid Activities that Cause Increase in IAP

Total volume paracentesis may decrease variceal pressure and improve portal hemodynamics. Propranolol may protect against the effects of a moderate physical exercise on portal hemodynamics. Postprandial hyperemia might be blunted by octreotide and ISMN. Propranolol decreases only the baseline HVPG. Acute ethanol consumption may cause variceal bleeding. It is wise to abstain from alcohol.

Primary prophylaxis for large varices

Options available for primary prophylaxis of bleeding from large varices include beta-blockers, Variceal Band Ligation (VBL) and Endoscopic Sclerotherapy (EST).

Nonselective beta-blockers reduce the rate of variceal bleeding and also bleeding related mortality. The incidence of bleeding in patients with large or medium-sized varices or in those with varices and HVPG >12 mm Hg [8] is lower when treated with beta-blockers. Studies comparing β-blocker therapy with placebo have shown that nonselective beta-blockers reduce the incidence of initial bleeding by approximately 50% (bleeding rate 30% in controls v/s 14% in β-blocker-treated patients). A decrease in HVPG to <12 mm Hg or at least 20% reduction in baseline values seems to be the best predictor of efficacy of drug therapy for primary prophylaxis [8]. The efficacy of beta-blockers is clinically monitored by a decrease in the resting heart rate >25% but not <55 beats/min. Only 20% to 30% of subjects achieve these endpoints, and 15% to 20% of subjects cannot tolerate therapy and require discontinuation.

EST is effective in preventing variceal bleeding, but has been superseded by VBL due to a better safety profile. VBL is effective primary prophylaxis with a very low incidence of adverse effects and significantly reduces the risk of first variceal bleed. A meta-analysis concluded that VBL reduces first variceal bleed, bleeding related mortality and overall mortality [8]. Simple measures like proton pump inhibitors and sucralfate reduce esophageal ulceration [8]. Other measures like using multi-banders and increasing the interval between banding sessions [8] may improve the results of VBL and increase its safety and efficacy compared with those of beta-blockers.

Nitrates, short-acting (nitroglycerin) or long-acting (isosorbide mononitrates) reduce portal blood flow, but the effect on intrahepatic resistance is not impressive, and nitrates are no longer recommended for primary prophylaxis due to discrepant results of clinical trials [8]. Combination therapy with beta blockers and nitrates cannot be recommended yet for primary prophylaxis, due to limited and conflicting evidence.

Two trials in the last decade showed that beta-blockers with VBL was better than VBL alone in primary prophylaxis [8,9], suggesting that treatment with VBL alone should be restricted to patients with contraindications to beta-adrenergic blockers. However, Sarin et al. in two separate studies were able to show that VBL plus propranolol and VBL alone, both are equally effective in primary prophylaxis of variceal bleeding. Addition of propranolol alone or along with ISMN did not decrease the probability of first bleed or death in patients on VBL. However, the recurrence of varices seems to be lower if propranolol is added to VBL [8,9].

TIPS (transjugular intrahepatic portosystemic shunt) may be more effective in reducing portal pressure and primary variceal bleeding that endoscopic or pharmacotherapy. However, it does not prolong survival and has its own disadvantages of cost and encephalopathy.

Endothelin receptor blockers and liver-selective NO donors that target intrahepatic vascular resistance are promising investigational therapies.

APASL recommendations

Beta-blockers and VBL, both reduce the risk of primary variceal hemorrhage and bleeding-related mortality compared with no treatment.

VBL reduces the risk of initial bleeding episodes compared with β-blockers, but there is no survival advantage.

The addition of β-blockers to VBL does not further reduce the risk of primary bleeding, but it does reduce variceal recurrence rates.

ISMN monotherapy has no role in primary prophylaxis, alone or in combination.

Patients with large varices should be treated with nonselective β-blockers, preferably with monitoring of HVPG or VBL to prevent initial variceal bleeding.

Patients with large varices who are intolerant to or nonresponsive to β-blockers should be offered VBL.

Management of Acute Variceal Bleeding

The management of acute variceal bleeding includes hemodynamic resuscitation, general treatments, prevention of complications, and achievement of hemostasis. Transfusion of packed RBC to replace the blood loss is indicated, but over-transfusion can cause a rebound increase in portal pressure and should be avoided [8]. Transfusion of FFP and platelets is commonly used to correct the coagulopathy. However the usual amounts of FFP and platelets used may be inadequate in correcting the coagulopathy and cause volume overload and rebound portal hypertension [9]. Antibiotic prophylaxis is indicated as it significantly reduces episodes of infective complications, which are common and gravely affect prognosis [8].

Pharmacotherapy

Terlipressin is the only drug shown to improve survival in patients with acute variceal bleeding and therefore should be the drug of choice [8]. Somatostatin, octreotide, and vapreotide are the next option [8,9]. If these drugs are not available, then vasopressin with transdermal nitroglycerin may be used.

Terlipressin is usually initiated at a dose of 2mg/4hr for the first 48 hours and then may be continued upto 5 days at a dose of 1mg/4hr to prevent re-bleeding. Terlipressin results in splanchnic vasoconstriction resulting in reduction in portal inflow and thereby reducing portal and variceal pressure. Terlipressin is the only drug that has been shown to

have a beneficial on control of bleeding and survival. It is probably as effective as other therapies like EST and VBL, it protects against renal failure that may develop after a variceal bleed [8] and is safer than vasopressin with nitroprusside.

Somatostatin has been compared to terlipressin in efficacy, and no differences were found for failure to control bleeding, rebleeding, and mortality [8]. In a landmark article published by Bosch et al two decades ago, they showed that somatostatin reduced WHVP and estimated hepatic blood flow in cirrhotic patients. WHVP decreased by 28.4% after 250 μg bolus injection. During continuous infusion of somatostatin, wedged hepatic venous pressure and estimated hepatic blood flow decreased by, respectively, 17.0% and 17.4% [8]. Usually used at a dose of 250 mcg bolus followed by 250 mcg/h infusion, it has recently been found that higher doses i.e. 500 mcg bolus may have a better efficacy.

Whereas somatostatin induced long-lasting effects on portal pressure, the results of octreotide were far more inconsistent. Although bolus octreotide markedly reduced portal pressure, continuous infusion or repeated injections of octreotide seem to have shorter and insignificant effects compared with the first bolus injection [8]. On the other hand, octreotide consistently prevented postprandial splanchnic hyperemia in patients with portal hypertension. Usually given as an initial bolus of 50 mcg, followed by an infusion of 25 or 50 mcg/h, therapy can be maintained for 5 days to prevent early rebleeding.

Endoscopic therapy

Both EST (Endoscopic sclerotherapy) and VBL (variceal band ligation) are effective in controlling acute variceal bleeding. A meta-analysis by de Franchis et al. showed that VBL was better than sclerotherapy in the initial control of bleeding, was associated with fewer adverse events and improved mortality [8]. Additionally, sclerotherapy, but not band ligation, may induce an increase in portal pressure [8]. Emergency endoscopic therapy can be done at the time of diagnostic endoscopy, soon after admission. If there is no active bleeding and the patient is stable, however, endoscopic treatment can be delayed.

Current recommendations include combination of the two approaches, as early administration of a vasoactive drug facilitates endoscopy and improves control of bleeding and 5-day rebleeding [8,9]. Early vasoactive drug therapy seems to improve the results of endoscopic treatment, and endoscopic therapy may improve the efficacy of vasoactive treatment.

Rescue therapy

Balloon tamponade, TIPS, and porto-systemic shunt surgery may be used for variceal bleeding refractory to endoscopic and pharmacotherapy. Balloon tamponade is effective in the majority, but must be used in only massive bleeding and for a short duration only (<24 hrs).

Both TIPS and shunt surgery are very effective in controlling variceal bleeding, but invasiveness and high incidence of adverse effects (mainly encephalopathy and worsening liver function) are the main drawbacks.

Secondary Prophylaxis

Once a patient has had a variceal bleed, the rate of recurrence without further treatment is >60%. Endoscopic eradication of the varices may lower the rate to 25-30% at one year, and beta blocker therapy has been shown to reduce rebleeding rates to 44% [4]. The Baveno IV consensus concluded that combination of VBL and medication is likely best treatment. A recent meta-analysis showed that pharmacotherapy by itself, may be as effective as endoscopic therapy in reducing rebleeding rates and all-cause mortality, but pharmacotherapy plus endoscopic intervention is more effective than endoscopic intervention alone [9].

Gastric Varices

Gastric varices develop in about 20% of patients with portal hypertension, and account for about 10-15% of upper GI bleeding in cirrhotics. Gastric varices are less likely to bleed, but bleeding form gastric varices, especially fundal varices tends to more severe, has higher transfusion requirements and carries a higher mortality [9]. Similar to esophageal varices larger varices, decompensated liver disease and red signs are high risk factors for bleeding from gastric varices. Gastric varices were classified by Sarin et al. [9] into 4 different types which define the bleeding risk and the treatment of these varices.

There has been no randomized trial assessing the efficacy of beta blockers in the primary prophylaxis of gastric variceal bleed, but the reduction in HVPG seems likely to reduce the chances of gastric variceal bleeding. Endoscopic therapy for gastric varices is successful in the control of bleeding, especially with the use of cyanoacrylate glue injection [4], but there is a tendency to bleed from the injection site or rebleeding from the rupture site. Embolization of the glue may occur during cyanoacrylate injection of gastric varices [10].

Regarding VBL of gastric varices, the main concern is the adverse effect on portal hypertensive gastropathy and gastric mucosal hemodynamics [10]. The exacerbation of portal hypertensive gastropathy after variceal ligation is related to increased vascular congestion of the gastric mucosa. While treatment with VBL or snares effectively achieves hemostasis and eradication of varices, there was a high rate of recurrence of previously eradicated varices. Also the technical complexity of snaring precludes it from being a widely accepted treatment modality [4]. It has recently been shown that cyanoacrylate glue injection may be superior to and more effective than beta-blocker treatment for the prevention of gastric variceal rebleeding and improving survival [11].

Balloon-occluded retrograde transvenous obliteration (B-RTO) is a relatively novel technique described by Japanese physicians, which aims at obliteration of gastric varices through a previously identified gastro-renal shunt. It has been shown to be effective and safe in obliterating gastric fundal varices, with a success rate in about 90% of cases and a variceal recurrence rate of less than 7% [11]. Portal blood flow and serum albumin parameters are transiently increased after B-RTO, but liver function is unchanged after B-RTO [11].

In acute variceal bleeding from gastric varices, most authorities recommend starting therapy with vasoactive drugs, to be augmented with endoscopic therapy and injection with cyanoacrylate glue. In cases with massive bleeding or in case of failure to control bleeding by other measures, TIPS may be inserted.

Ascites

Ascites occurs in cases of advanced cirrhosis and severe portal hypertension, and may become refractory, or develop spontaneous bacterial peritonitis and may contribute to hepatorenal syndrome.

All patients with ascites should undergo an evaluation of ascitic fluid content to rule out SBP, and should include cell count, bacterial culture in blood culture medium, fluid protein concentration and cytology [11]. Leukocyte reagent strips have been recently proposed for the early detection of leukocytes in ascites and SBP [11].

Reduction in daily sodium intake (90 mmol/d) is recommended once ascitis is diagnosed. Dietary sodium restriction (90 mmol/d) should be imposed [11]. Spironolactone is the drug of choice at the onset of treatment because it promotes better natriuresis than loop diuretics. The initial dose is about 100–200 mg/d. In edematous patients, treatment with furosemide (20-40 mg/d) may be added for a few days to increase natriuresis. Amiloride (5-10 mg/d) may be used when spironolactone is contraindicated or poorly tolerated.

Diuretic therapy should be monitored with the patient's weight, serum electrolytes, and renal function tests. Maximum weight loss should not exceed 500 g/d in patients without peripheral edema and 1000 g/d in those with edema.

If the therapeutic effect is insufficient, urinary sodium excretion should be determined to identify nonresponsive patients as well as patients non-compliant with salt restriction. In some patients, free-water excretion is impaired and severe hyponatremia may develop. Frequently, large-volume paracentesis needs to be done. Paracentesis should be routinely combined with plasma volume expansion with colloids/ albumin.

Refractory ascitis responds only to liver transplantation, and till then therapeutic strategies can involve repeated large-volume or TIPS. TIPS improve renal function, sodium excretion and are more effective than paracentesis.

SBP occurs in 10%–30% of patients with ascites. All cases in which the neutrophil count is at least 250 × 106/L in ascitic fluid should be treated empirically, since ascites culture yields negative results in about 40% of patients with symptoms suggestive of spontaneous bacterial peritonitis.

Therapy with a third generation cephalosporin is the treatment of choice (cefotaxime 2-4 g/d, intravenously, for 5 days). Alternative treatments include combination therapy with amoxicillin and clavulinic acid (1 g and 0.125 g respectively, given intravenously or orally 3 times daily) or norfloxacin (400 mg/d, orally) for 7 days [11,12]. Antibiotic therapy should be used in conjunction with albumin infusion to protect against renal dysfunction. Treatment efficacy should be assessed by means of evaluating clinical symptoms and determining the neutrophil count in ascitic fluid after 48 hours. Primary prophylaxis of spontaneous bacterial peritonitis with continuous oral norfloxacin therapy (400 mg/d) in hospital patients with cirrhosis who have a low ascitic protein concentration (<10 g/L) is still debated.

Hepatorenal Syndrome

HRS probably results from the reflex intense renal vasoconstriction resulting from an activation of systemic vasoconstrictor mechanisms in response to systemic and splanchnic and systemic vasodilatation. This results in reduced renal perfusion and further accentuation of the renin angiotensin system and antinatriuretic mechanisms. Three important and easily recognized risk factors are low mean arterial blood pressure (80 mm Hg), dilutional hyponatremia, and severe urinary sodium retention (urine sodium 5 mEq/L). Interestingly, patients with advanced liver disease, defined by a high Child-Pugh score or worsening liver function tests do not seem to be at higher risk of developing HRS [11].

HRS may be acute worsening of renal function in the presence of a precipitating event, like an infection and is then called as type 1 HRS; or it may be more chronic with the worsening of renal function over more than 2 weeks. Development of HRS is associated with a significantly poor prognosis.

The ideal treatment for HRS is liver transplantation. Besides transplantation, vasoactive drug therapy in combination with albumin (20-40 g/d for 5-15 days) is useful in the management of HRS. The efficiency of terlipressin (0.5-1 mg intravenously every 4-12 hours) has been reported in several uncontrolled trials [11]. Therapy with norepinephrine (0.5-3.0 mg/h intravenously) [12] or midodrine (7.5-12.5 mg orally 3 times daily) in association with octreotide (100-200 mcg subcutaneously 3 times daily) [11] has been shown to improve hepatorenal syndrome. TIPS has been found to be effective in the management of hepatorenal syndrome, since it may result in relieving portal hypertension and correction of the systemic hypovolemia and improving renal perfusion [11].

Portopulmonary hypertension and hepatopulmonary syndrome

Portopulmonary Hypertension (PPHT) occurs in 2-8% of the patients with cirrhosis. Imbalance between vasodilating (decreased pulmonary eNOS and prostacyclin I2) and vasoconstrictive agents (increased ET-1 and angiotensin 1) may be responsible for misguided angiogenesis and pulmonary hypertension. The diagnosis is made by echocardiography and a right heart catheterisation when pulmonary artery pressure is higher than 30 mmHg on echocardiography.

A minority of patients have portal hypertension secondary to non-hepatic causes [4]. This suggests that portal hypertension, and not cirrhosis, is the primary instigator of pulmonary hypertension. The non-hepatic causes of portal hypertension leading to pulmonary hypertension are diverse and include biliary atresia [12] extrahepatic portal vein obstruction [12], noncirrhotic portal fibrosis [4], and idiopathic portal hypertension. Surgical portosystemic shunts can also be complicated by pulmonary hypertension [13]. A retrospective study in patients with surgical portosystemic shunts found a similar rate of occurrence [13].

Susceptible patients with portal hypertension may develop portopulmonary hypertension in response to increased vascular wall shear stress due to the increased blood flow through the lungs. The amount of blood shunted from portal circulation along with an increased genetic susceptibility, a humoral mediator, or an environmental insult maybe all involved in the pathogenesis. The presence of portosystemic shunting may allow substances normally cleared by the liver to gain access to the pulmonary circulation. Several vasoactive mediators, cytokines, or growth factors have been demonstrated in patients with portal hypertension [13].

Among these mediators, serotonin (5-hydroxytryptamine) [13] and IL-1 have been identified. Serotonin causes pulmonary vasoconstriction and pulmonary artery smooth muscle proliferation.

Bosentan is probably the therapy of choice for patients with PPHT because it decreases pulmonary but can also diminish portal hypertension. Sildenafil, a phosphodiesterase-5 inhibitor is used for idiopathic pulmonary hypertension; however, it should be used

cautiously in patients with portal hypertension as it may increase portal hypertension by splanchnic vasodilation.

Hepatopulmonary syndrome (HPS) is found in 4-47% of patients with cirrosis [13] and is characterized by intrapulmonary vascular dilatations especially in the basal parts of the lung. Liver injury and/or portal hypertension trigger the release of endothelin-1, TNF-a, cytokines and mediate vascular shear stress and release of nitric oxide and carbon monoxide, all contributing to intrapulmonary vasodilation. Microvascular dilatation impairs ventilation-perfusion matching and can produce anatomical and functional shunt physiology, leading to hypoxemia.

The diagnosis is made by calculating the alveolar-arterial oxygen gradient and by performing a contrast echocardiography. Medical therapy fails and the only long-term treatment available is liver transplantation. More than 85% experience significant improvement or complete resolution in hypoxaemia, but this may take more than 1 year.

Conclusion

Thus portal hypertension in patients with Cirrhosis accounts for significant morbidity and contributes to the development of sinister complications. Portal hypertension contributes to and along with porto-systemic collaterals is responsible for most of the life threatening complications. Identification and individualized therapy of these is thus important in bridging the patient to liver transplantation. The degree of portal hypertension reflects the severity of liver fibrosis, which can be modulated by treatment of the primary disease. The degree of portal hypertension probably contributes to the degree of splenomegaly and hypersplenism. After liver transplantation, the degree of portal flow to the graft size mismatch is responsible for the development of the Small for Size Syndrome (SFSS). This may be especially important in the Asian sub-continent, where living donor transplantation limits the graft size and predisposes to SFSS. The degree of hypersplenism and blood counts may also dictate the timing of interferon therapy in HCV recurrence. Therefore the therapy of portal hypertension needs to be individualized to attain maximum benefit and appropriate utilization of scarce resources. A thorough understanding of the pathogenesis is therefore important in the management of these patients.

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