Portal hypertension

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Purpose of review

Report on significant advances in the pathophysiology, diagnosis, and management of the complications of portal hypertension that have occurred in the last year.

Recent findings

The specific areas reviewed refer to experimental studies aimed at modifying the factors that lead to portal hypertension (increased intrahepatic vascular resistance and splanchnic vasodilatation) and recent advances in the diagnosis and management of the complications of portal hypertension. The specific complications reviewed in this paper are varices and variceal bleeding (primary prophylaxis, treatment of the acute episode, and secondary prophylaxis), ascites and some of its complications (hyponatremia, hepatic hydrothorax), hepatorenal syndrome, spontaneous bacterial peritonitis, and hepatic encephalopathy.

Summary

Important studies, mostly prospective, regarding the management of the complications of portal hypertension are reviewed, including trials that demonstrate the value of the hepatic venous pressure gradient in predicting these complications, a trial of β-blockers in patients with small varices, a randomized trial of transjugular intrahepatic portosystemic shunt using covered stents and another pilot study using this shunt in the treatment of hepatorenal syndrome, a trial of antibiotic prophylaxis in preventing early variceal rebleeding, and a trial of synbiotic therapy in hepatic encephalopathy. These trials will contribute to advancing the practice of hepatology and defining future research areas.

Keywords

ascites, encephalopathy, portal hypertension, spontaneous bacterial peritonitis, variceal hemorrhage

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Abbreviations

AASLD	American Association for the Study of Liver Diseases
bDNA	bacterial DNA
HVPG	hepatic venous pressure gradient
LBP	LPS-binding protein;
LPS	lipopolysaccharide
LVP	large-volume paracentesis
LVP+A	large-volume paracentesis plus albumin
MELD	model for end-stage liver disease
MHE	minimal hepatic encephalopathy
MRS	magnetic resonance spectroscopy
NO	nitric oxide
PHG	portal hypertensive gastropathy
PTFE	polytetrafluoroethylene
rFVIIa	recombinant coagulation factor VIIa
SBP	spontaneous bacterial peritonitis
TIPS	transjugular intrahepatic portosystemic shunt
VBL	variceal band ligation

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Introduction

Portal hypertension is the main consequence of cirrhosis and is responsible for its most common complications. Portal pressure increases initially as a result of an increased intrahepatic resistance, but once collaterals have formed, high portal pressure is maintained by an increased splanchnic blood inflow secondary to vasodilatation. Splanchnic and systemic vasodilatation, and the subsequent development of the hyperdynamic circulatory state, lead to a worsening of all complications of cirrhosis. Although the increased portal pressure gradient *per se* leads to the formation of gastroesophageal varices, it is the increased flow through them, a result of the hyperdynamic splanchnic circulation, that leads to their growth and eventual rupture. Another frequent complication of cirrhosis, ascites, results not only from an increased sinusoidal pressure but also from sodium retention that in turns results from vasodilatation and activation of neurohumoral systems. The hepatorenal syndrome results from severe peripheral vasodilatation that leads to renal vasoconstriction. Spontaneous bacterial peritonitis and hepatic encephalopathy are a consequence of portal hypertension and liver insufficiency.

Pathophysiology

Cirrhosis is the end stage of any chronic liver disease. Portal hypertension is the main consequence of cirrhosis and is responsible for most its complications. Portal hypertension results from both an increased resistance to portal flow and an increased portal venous inflow.

Increased intrahepatic vascular resistance

Portal pressure increases initially as a consequence of an increased resistance to portal flow. This is mostly a result of an architectural distortion of the liver secondary to fibrous tissue and regenerative nodules, but a recently reviewed landmark study in 1985 showed that there is a component of primary intrahepatic vasoconstriction [1] that appears to be caused at least in part by a deficiency

in nitric oxide (NO) and is amenable to pharmacological manipulation.

Simvastatin, which enhances Akt-dependent endothelial NO synthase phosphorylation, may increase hepatic NO release and decrease intrahepatic resistance and thereby portal pressure. The oral administration of 40 mg simvastatin to 13 patients with cirrhosis led to an increase in NO in hepatic venous blood, a 14% decrease in hepatic sinusoidal resistance, and an increase in hepatic blood flow, but had no effect on portal pressure [2]. In a placebo-controlled hemodynamic study, simvastatin pretreatment (40 mg, 24 hours and 1 hour before the study) significantly attenuated the postprandial increase in hepatic venous pressure gradient, which increased by 10% in patients on simvastatin compared with 21% in patients on placebo [2]. These somewhat encouraging results deserve further investigation.

Increased portal venous inflow

Once porto-systemic collaterals have formed, high portal pressure is maintained by an increased splanchnic blood inflow secondary to vasodilatation. Splanchnic vasodilatation is the initiating event in the hyperdynamic circulatory state that aggravates many of the complications of cirrhosis. As recently reviewed, gut bacterial translocation appears to play a role in the pathogenesis of both splanchnic vasodilatation and the hyperdynamic circulatory state of cirrhosis, and measures that prevent or reduce bacterial translocation appear to ameliorate these hemodynamic abnormalities [3••].

Splanchnic and peripheral vasodilatation in cirrhosis is most likely triggered by increased levels of vasodilators, mainly NO. Sildenafil, a selective inhibitor of the cGMP-specific phosphodiesterase type V (PDE) in the corpus cavernosum, potentiates the effects of NO. Because PDE is also present in the mesenteric artery, sildenafil may further decrease mesenteric vascular tone and increase portal venous blood flow. In rats with cirrhosis induced by bile duct ligation, both the intramesenteric and the intravenous administration of large supratherapeutic doses of sildenafil significantly decreased mean arterial pressure and increased mesenteric blood flow and portal pressure in a dose-dependent way [4]. These hemodynamic changes were more marked in sham-operated rats, suggesting vascular hyporesponsiveness to sildenafil in cirrhosis. The effect of orally administered PDE inhibitors at therapeutic doses in patients with cirrhosis remains to be determined.

Complications of portal hypertension and portal pressure

Transition from a compensated to a decompensated stage of cirrhosis is marked by the development of the complications of portal hypertension. In a recent study performed in a cohort of 200 consecutive patients with cirrhosis secondary to hepatitis C, ascites was the most frequent decompensating event (48%), followed by portal hypertensive gastrointestinal bleeding (32%), severe bacterial infection (14%), and hepatic encephalopathy (5%) [5]. The risk of developing these complications can be reduced by decreasing portal pressure, as demonstrated in studies in which portal pressure is assessed by the hepatic venous pressure gradient (HVPG). HVPG responders (defined as patients in whom HVPG decreases $\geq$20% from baseline or to $<$12 mmHg) had a significantly lower rate of variceal rebleeding, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatic encephalopathy, and death than nonresponders [6]. These findings were confirmed in another study in which 64 of 132 (50%) patients on pharmacological therapy were HVPG responders (determined 1–3 months after starting therapy). Compared with nonresponders, they had a significantly lower probability of developing ascites and encephalopathy, a greater improvement of Child–Pugh score, and a lower likelihood of requiring liver transplantation and of death [7]. Long-term maintenance of HVPG response was observed in 55 of 68 (81%) patients who had a third HVPG measurement 12–18 months after starting therapy [7•].

The technique for measuring HVPG is easy, but as recently described, certain guidelines should be followed to obtain accurate and reproducible measurements [8••]. Its invasive nature has prevented its widespread use, leading to the search for noninvasive methods to assess portal pressure. In a recent study, HVPG was correlated to dynamic gadolinium-enhanced magnetic resonance and Doppler ultrasonography parameters in 46 patients (three normal, 12 chronic hepatitis, 31 cirrhosis). While ultrasonography parameters correlated poorly (if at all) with HVPG, most of the magnetic resonance parameters, particularly the portal fraction of liver perfusion and the mean transit time, correlated well with HVPG (r = 0.77 and 0.73, respectively) [9]. Of note, the portal fraction was the parameter that best identified patients with an HVPG greater than 10 mmHg (clinically significant portal hypertension), because all 13 patients with a portal fraction below 30% had an HVPG greater than 10 mmHg. Additionally, most magnetic resonance parameters correlated with Child–Pugh score in patients with cirrhosis. The value of magnetic resonance parameters in assessing HVPG (and changes in HVPG) requires further validation.

Varices and variceal bleeding

Current guidelines recommend endoscopic screening for patients with cirrhosis and, in those with medium to large varices, primary prophylaxis with a nonselective β-blocker. Predicting the presence of esophageal varices through nonendoscopic methods is of importance, since half the patients do not have esophageal varices on screening endoscopy. In a retrospective study performed in 255 patients with primary sclerosing cholangitis, platelet

count (<150,000/dl), albumin level, and advanced histologic disease were independent predictors of esophageal varices [10]. An accompanying editorial summarizes existing studies on predictors of esophageal varices and identifies problems with these studies, mainly diverse disease spectra, concluding that reliable noninvasive markers of esophageal varices that would be acceptable for use in clinical practice are yet to be identified and that until large prospective studies of noninvasive markers are performed, endoscopic screening is still the main means of assessing esophageal varices [11].

Three main aspects need to be considered in the management of variceal hemorrhage: primary prophylaxis, treatment of active hemorrhage, and prevention of rebleeding.

Prevention of first variceal hemorrhage

Nonselective β-blockers are the gold standard in the prevention of first variceal hemorrhage. The 2-year risk of first bleeding in patients with large varices is reduced from 30% (in untreated patients) to 14% in patients on β-blockers.

The efficacy of variceal band ligation (VBL) in preventing the first episode of variceal bleeding has not been fully evaluated. Two studies compared a nonselective β-blocker with VBL; one used nadolol and included 100 patients (50 in each group) [12], and the other, the largest study so far, used propranolol and included 152 patients (75 propranolol, 77 VBL) [13•]. Both studies showed similar rates of first variceal bleeding and mortality between the β-blocker and VBL. However, in the larger study, two fatal bleeding episodes were related to the ligation procedure itself [13•]. Therefore, VBL should be offered to patients with large varices who are not candidates for long-term treatment with nonselective β-blockers.

So far, prophylaxis is not recommended in patients with small varices since the risk of hemorrhage is low and numbers are too small to detect a significant reduction in first hemorrhage with β-blockers. A study aimed at determining whether β-blockers can delay the growth of small varices randomized patients with cirrhosis and small esophageal varices to nadolol (n = 83) or to placebo (n = 78) [14•]. In a mean follow-up of 36 months, varices increased in size in significantly fewer patients randomized to nadolol (n = 9 or 11%) compared with those in the placebo group (n = 29 or 37%). Variceal bleeding was also lower in patients randomized to nadolol, but there were no differences in survival. This suggests that patients with small varices should also be started on β-blockers; however, further studies are necessary before this approach can be widely recommended.

A cost-effectiveness analysis compared HVPG monitoring with no monitoring in patients with large varices who have never bled. The assumptions were that patients intolerant to β-blockers would undergo VBL, whereas HVPG nonresponders to β-blocker therapy would have nitrates added before VBL was considered. Compared with the current standard of no monitoring, measuring the HVPG response to primary pharmacologic prophylaxis substantially reduced the number of bleeding episodes and was cost-effective or cost-saving over a wide range of sensitivity analyses [15]. These results would require prospective validation, particularly since the combination of β-blockers plus nitrates has not been shown to be superior to β-blockers alone in randomized trials.

Treatment of acute variceal hemorrhage

Over the past 2 decades, new therapies have been introduced for the management of variceal bleeding. A retrospective single center study assessed the outcome of 319 episodes of variceal hemorrhage in 295 patients admitted to a liver intensive care unit over a 20-year period. While balloon tamponade was first-line treatment in 1980, patients treated in 2000 received a vasoactive agent, endoscopic treatment, and antibiotic prophylaxis in more than 90% of cases [16]. The in-hospital mortality rate steadily decreased over the study period: 43%, 30%, 25%, 16%, and 14% in 1980, 1985, 1990, 1995, and 2000, respectively. This improved survival was associated with a decrease in rebleeding rates (from 47% in 1980 to 13% in 2000) and bacterial infection rates (from 38% to 14%). On multivariable analysis, endoscopic therapy, and antibiotic prophylaxis were independent predictors of survival [16].

Bacterial infection in this setting has been associated with recurrent variceal hemorrhage. In a study aimed at determining whether antibiotic prophylaxis could prevent variceal rebleeding, patients with acute variceal hemorrhage were randomized to prophylactic antibiotics (ofloxacin 200 mg intravenously every 12 hours for 2 days followed by oral ofloxacin 200 mg every 12 hours for 5 days; n = 59) or to receive antibiotics only in the presence of infection (n = 61) [17•]. Antibiotic prophylaxis significantly decreased rates of infection (3% compared with 26%) and early variceal rebleeding (7% compared with 34%). This study underlines the importance of short-term antibiotic prophylaxis in the setting of acute variceal hemorrhage, a practice that is currently considered standard of care.

Emergency endoscopic therapy is still used as first-line therapy for controlling variceal bleeding in cirrhosis. Endoscopic sclerotherapy and VBL have been used indistinctly in this setting; however, a study in which HVPG was measured before and after endoscopic sclerotherapy or VBL demonstrated that while HVPG increased significantly immediately after both therapies, HVPG in the VBL group returned to baseline values within 48 hours, and in the endoscopic sclerotherapy group, it remained high

during the 120-hour study period [18]. Importantly, the rebleeding rate was significantly lower in the VBL group than in the endoscopic sclerotherapy group [18]. This would suggest that VBL should be preferred over endoscopic sclerotherapy in the control of acute variceal hemorrhage.

Vasoactive substances are used as adjuncts to endoscopic therapy in acute variceal bleeding. Another pharmacological strategy is the use of agents that correct coagulopathy such as recombinant coagulation factor VIIa (rFVIIa). In a placebo-controlled trial, 245 patients with cirrhosis with upper gastrointestinal hemorrhage were randomized to receive eight doses of 100 μg/kg rFVIIa or placebo in addition to vasoactive and endoscopic treatment. While rFVIIa showed no advantage over standard treatment in the whole study population, post-hoc analysis revealed that rFVIIa significantly decreased the number of treatment failures in the subgroup of Child–Pugh B and C variceal bleeders [19]. Further studies are needed to verify these findings before this expensive therapy can be recommended.

The transjugular intrahepatic portosystemic shunt (TIPS) is currently recommended for patients who rebleed despite endoscopic and pharmacologic therapy. The efficacy of early TIPS placement in high-risk patients with acute variceal hemorrhage was recently explored in a prospective trial in which 52 patients with an HVPG greater than 20 mmHg (measured within 24 hours from admission for variceal hemorrhage) were randomized to early TIPS (within 24 hours of admission) compared with standard therapy [20]. Early TIPS placement significantly reduced not only treatment failure (failure to control acute variceal bleeding and/or early rebleeding) but also in-hospital and 1-year mortality. Studies in a larger number of patients followed for a longer period are required to confirm these compelling results.

Prevention of recurrent variceal hemorrhage

In a recent summary of randomized controlled trials of secondary prophylaxis of variceal hemorrhage, 1-year rebleeding rates of 55–67% (interquartile ranges) were reported in untreated patients, while they were lower with the currently recommended therapies, namely VBL (20–43%) and combined pharmacological therapy with β-blockers plus nitrates (30–42%). Although even lower rebleeding rates were reported with TIPS (12–22%) and with the distal splenorenal shunt (11–31%), the lowest rebleeding rates (7–13%) were reported in patients on pharmacological therapy who were HVPG responders [21••].

Two cost-effectiveness analyses of different strategies for the prevention of recurrent variceal hemorrhage included a strategy of HVPG monitoring. One of them concluded that combination medical therapy guided by HVPG monitoring is more effective and only marginally more expensive than VBL [22]. The other study concluded that the cost-effectiveness of HVPG monitoring to guide secondary prophylaxis of recurrent variceal bleeding is highly dependent on local HVPG costs, life expectancy, and rebleeding rates [23]. Cost-effectiveness analyses depend on assumptions that may be affected by several factors, including biases in the studies on which they are based.

Transjugular intrahepatic portosystemic shunt

Hepatic encephalopathy and a high dysfunction rate are the main drawbacks of TIPS. A strategy to delay the increase in portal pressure after TIPS and to reduce the need for reintervention is the use of β-blockers, since these have been shown to decrease portal pressure gradient in patients with TIPS dysfunction [24]. Another alternative is to combine VBL and TIPS (without angiographic surveillance), since this combination was shown to be as effective as TIPS (with angiographic surveillance) in preventing rebleeding and was accompanied by a lower rate of encephalopathy [25].

Preliminary studies suggested that the use of stents covered with polytetrafluoroethylene (PTFE) could decrease the risk of TIPS dysfunction. In a prospective trial in which 80 patients with cirrhosis and uncontrolled bleeding ($n = 23$), recurrent bleeding ($n = 25$), or refractory ascites ($n = 32$) were randomized to be treated by TIPS with either PTFE-covered stent ($n = 39$) or a standard, uncovered stent ($n = 41$), the 10-month rate of shunt dysfunction (defined as a >50% reduction of the lumen of the shunt at angiography or a portosystemic pressure gradient >12 mmHg) was significantly lower in the covered-stent group (13% compared with 44%) [26••]. Interestingly, there were tendencies for a lower development of encephalopathy and lower 2-year mortality in the covered stent group. In fact, a separate case-control study showed that patients undergoing PTFE stent placement had significantly higher 2-year survival rates compared with patients with bare stents [27]. In light of these findings, studies of TIPS in portal hypertension will need to be revisited.

Prognostic scores identify patients with a poor prognosis after TIPS. Most studies have recommended excluding patients with a Child–Pugh score greater than 11. The model for end-stage liver disease (MELD) score was developed to better predict mortality after TIPS. A large study compared the predictive power of these scores and showed that they are equivalent [28]. A Child–Pugh score threshold of greater than 11 for high-risk patients (median survival of 3 months or less) was confirmed. The threshold MELD score was found to be lower (>14) than the originally described threshold (>18), one that was confirmed in another study [29]. Given these discrepancies, the Child–Pugh score would

appear to be an easy and more than adequate score for the selection of patients undergoing TIPS.

Portal hypertensive gastropathy

In a natural history study, 222 patients with cirrhosis and no or small varices at entry, 48 of whom had portal hypertensive gastropathy (PHG), were followed with upper endoscopy every 12 months. The incidence of PHG was 3% at 1 year and 24% at 3 years, while the progression was 3% at 1 year and 14% at 3 years. The presence of varices and Child–Pugh class B or C were predictive of the development of PHG, while only Child–Pugh class B or C correlated with its progression from mild to severe. During a mean follow-up of 47 months, 16 patients bled from PHG (nine acutely and seven chronically), and one of them exsanguinated. Therefore, the natural history of PHG is significantly influenced by the severity of liver disease, and although acute bleeding is infrequent, it may be severe [30].

Ascites

In the past year, the American Association for the Study of Liver Diseases (AASLD) updated its recommendations for the therapy of cirrhotic ascites [31•]. Although most patients with ascites respond to therapy with salt restriction and spironolactone-based diuretics, about 10–20% of patients have diuretic-refractory ascites. Approved therapy consists of large-volume paracentesis plus albumin (LVP+A). Large-volume paracentesis (LVP) does not act on the mechanisms that lead to the formation of ascites, and therefore, recurrence is the rule. TIPS relieves sinusoidal pressure and increases urinary sodium excretion, and as shown in a Cochrane meta-analysis of four randomized clinical trials that included 264 patients, TIPS is more effective than LVP in reducing ascites reaccumulation [32]. The meta-analysis showed that mortality did not differ significantly between TIPS and LVP; however, hepatic encephalopathy occurred significantly more often in the TIPS group. This meta-analysis did not include a fifth multicenter, prospective clinical trial performed in 66 patients with cirrhosis and refractory or recidivant ascites randomized to TIPS (n = 33) or LVP+A (n = 33). Unlike other trials, survival was significantly greater in patients randomized to TIPS, although episodes of severe encephalopathy occurred more frequently in the TIPS group [33]. Reasons for the better survival are uncertain but may be related to having included patients with less severe liver disease. Until these results can be confirmed, particularly in trials using PTFE-covered stents, LVP+A will continue to be first-line therapy for refractory ascites.

Large-volume paracentesis has traditionally been performed by physicians; however, it was shown that, with proper training, LVP can be performed safely as an outpatient procedure by trained gastrointestinal endoscopy assistants; 10 supervised paracenteses were optimal for this training [34]. Additionally, in this series, which included more than 1000 LVPs, there were no significant bleeding complications, even in patients with marked thrombocytopenia or prothrombin time prolongation [34], thereby supporting the AASLD recommendation that correction of coagulopathy is not required when performing LVP.

Water retention and dilutional hyponatremia, mainly attributable to an impairment of free water excretion through the nonosmotic release of vasopressin, are well-documented complications in patients with cirrhosis and ascites. In a study performed in United States veterans, persistent ascites and low serum sodium identified patients with cirrhosis with high mortality risk despite low MELD scores and suggested that these parameters merit further prospective study as prognostic indicators in patients awaiting liver transplantation [35].

Hepatic hydrothorax is another complication related to ascites that occurs in 5–10% of patients with cirrhosis. As mentioned in a recent review, its pathophysiology involves the direct movement of ascitic fluid from the peritoneal cavity into the pleural space through diaphragmatic defects [36]. Therapy is similar to that of portal hypertensive ascites and includes sodium restriction and diuretics. Refractory hydrothorax can be managed with TIPS in selected cases, and pleurodesis is not routinely recommended [36]. As reported in a retrospective study of 59 patients, chest tube placement is associated with high morbidity and mortality, with 80% of patients developing renal dysfunction, electrolyte abnormalities, and/or infection and with a 33% mortality rate [37]. Therefore, chest tube placement should be proscribed in hepatic hydrothorax.

Hepatorenal syndrome

Hepatorenal syndrome is a common complication of advanced cirrhosis, characterized by renal failure and major disturbances in circulatory function. As recently reviewed, hepatorenal syndrome is a severe reduction of renal function caused by renal vasoconstriction secondary to an impairment in systemic hemodynamics and activation of the renin-angiotensin and sympathetic nervous systems [38]. The diagnosis of hepatorenal syndrome is based on the exclusion of other causes of renal failure. One of such causes is the use of nonsteroidal anti-inflammatory drugs. It has been suggested that selective cyclooxygenase-2 (COX-2) inhibitors do not impair renal function; however, significant reductions in glomerular filtration rate were observed in four of nine patients with cirrhosis and ascites who received a 4-day course of celecoxib [39]. Therefore, the use of COX-2 inhibitors should be avoided in patients with cirrhosis until more clinical data are available.

Another potential cause of renal dysfunction in patients with cirrhosis is the use of radiologic contrast media.

In a prospective study, however, the administration of contrast media was not associated with significant changes in renal function tests, sodium, and free water excretion either in the whole group of patients or in patients with ascites or renal failure [40]. Although cirrhosis *per se* does not appear to be a risk factor for contrast-induced nephrotoxicity, the same precautions observed in patients without cirrhosis should apply to patients with cirrhosis.

The treatment of choice in type 1 hepatorenal syndrome is the combination of vasoconstrictors (to reduce arterial vasodilation) and plasma volume expansion with albumin (to increase cardiac preload). In a recent study, TIPS placement in five patients with hepatorenal syndrome, whose renal function had improved on octreotide plus midodrine plus albumin, led to further improvement in renal function and sodium excretion, so that by 12 months after TIPS, glomerular filtration rate, urinary sodium, and plasma renin activity had normalized [41•]. The five patients in this study were derived from a total of 14 patients with hepatorenal syndrome, 10 of whom had responded to vasoconstrictors plus albumin, but five of whom were not candidates for TIPS. Although this strategy would appear to be an option in only a minority of patients with hepatorenal syndrome, results are very encouraging and require further study.

To determine the impact of vasoconstrictor therapy for hepatorenal syndrome on the outcome of liver transplant, a case control study of nine patients treated with vasopressin analogues before transplant was compared with that of a contemporary control group of 27 patients without hepatorenal syndrome matched by age, severity of liver failure, and type of immunosuppression. Patients with hepatorenal syndrome treated with vasopressin analogues before transplant had an outcome after transplant similar to that of patients transplanted with normal renal function [42].

Spontaneous bacterial peritonitis and other bacterial infections

Spontaneous bacterial peritonitis (SBP), the most common infection in cirrhosis, is a complication that was first defined in 1963–1964 [43]. As recently reviewed, gut bacterial translocation appears to play a role in the pathogenesis of SBP and other bacterial infections in cirrhosis, and measures that prevent or reduce bacterial translocation appear to prevent infection [3••].

Studies on bacterial translocation in humans have been hampered by technical issues, mainly the need to obtain mesenteric lymph nodes and the lack of a noninvasive reliable surrogate marker. Serum LPS-binding protein (LBP), a protein that is synthesized in the liver in response to endotoxin, has been proposed as a surrogate marker of bacterial translocation. In support of this contention, a study showed that patients with cirrhosis, ascites, and a high LBP ($n = 34$) were four times more likely to develop bacterial infections (32% compared with 8%) than patients with normal LBP ($n = 50$) [44]. Another proposed marker is the identification of bacterial DNA (bDNA) by polymerase chain reaction in blood of uninfected patients. The dynamic nature of blood and ascites bDNA was shown in a study of seven patients with advanced cirrhosis in which bDNA (a single species) persisted in the blood for a minimum of 24 hours and was reported to last as long as 72 hours in some patients. In addition, different patterns of bDNA appearance and clearance from the blood were identified [45]. Peritoneal macrophages obtained from patients with cirrhosis and positive blood bDNA are markedly activated, as evidenced by an increase in NO synthesizing ability and enhanced cytokine production [46]. This study suggests that bDNA may be a good surrogate marker of bacterial translocation in humans; however, the experimental association between bacterial translocation and worsening of the hyperdynamic circulatory state and development of infections must be confirmed with bDNA before it can be widely adopted.

Renal dysfunction is the most important predictor of death in SBP. Hemodynamic abnormalities induced by cytokines and vasodilating substances play an important role in the genesis of this renal dysfunction. Ascitic fluid NO levels have recently been found to be independent predictors of renal dysfunction in SBP, suggesting that NO is an important vasodilator in this setting [47].

Albumin administration prevents renal failure and improves survival in SBP. In an uncontrolled study in which all patients with SBP received albumin, infection resolution was associated with a significant improvement in systemic hemodynamics and renal function, as indicated by a significant increase in mean arterial pressure (+8%), a fall in heart rate (−10%), suppression of plasma renin activity (−67%), and a decrease in creatinine levels. These changes were related to both significant increases in cardiac work (stroke work index: +18%) and in peripheral vascular resistance (+14%), indicating that the beneficial effects of albumin are related to both an improvement in cardiac function and a decrease in the degree of arterial vasodilation [48].

The search has continued for nonantibiotic measures to prevent bacterial translocation that could be used in the prophylaxis of bacterial infections. In a model of hemorrhagic shock in noncirrhotic rats, high-fat enteral nutrition led to a significant decrease in endotoxemia and bacterial translocation [49]. A high-fat diet led to increased plasma triacylglycerol and apolipoprotein B levels, and it is proposed that endotoxin is bound and neutralized by triacylglycerol-rich lipoproteins, with a decrease in the inflammatory response and a subsequent preservation of

gut barrier function. In another study in the same experimental model, a high-fat diet led to a significant decrease in endotoxin and tumor necrosis factor levels, prevention of loss of tight junction structure, and a significant reduction in intestinal permeability to horseradish peroxidase, with a 10-fold reduction of bacterial translocation early after hemorrhagic shock [50]. In a study performed in rats with carbon-tetrachloride–induced cirrhosis and ascites, pretreatment with high-density lipoprotein ameliorated the decrease in mean arterial pressure induced by the administration of endotoxin (decrease of 12% compared with a 25% decrease in animals pretreated with saline) [51]. The effect of a high-fat diet on bacterial translocation in cirrhosis requires further investigation.

Hepatic encephalopathy

Hepatic encephalopathy is a reversible neuropsychiatric complication of cirrhosis characterized neuropathologically by astrocyte edema. Ammonia plays a central role in the pathogenesis of hepatic encephalopathy. Regional differences in cerebral ammonia metabolism have been detected in patients with cirrhosis and hepatic encephalopathy by magnetic resonance spectroscopy (MRS) and positron emission tomography, demonstrating highest ammonia extraction fractions in the thalamus, lenticular nucleus, and cerebellum, corresponding to the distribution of histopathological changes in the brain of patients with cirrhosis [52].

The ammonia/glutamate/brain swelling hypothesis of hepatic encephalopathy suggests that the accumulation of glutamine in the astrocytes induced by hyperammonemia produces an osmotic stress and causes astrocytes to swell and dysfunction. A study using MRS suggests that, rather than the degree of hyperammonemia, it is the ability of the brain to buffer ammonia-induced increases in glutamine by losing osmolytes like myo-inositol that leads to hepatic encephalopathy. In this study, eight patients whose memory test deteriorated after amino acid–induced hyperammonemia were compared with seven patients who did not deteriorate, revealing equivalent ammonia levels but lower baseline myo-inositol–creatine ratio and a higher glutamate/glutamine-to-creatine ratio in patients whose memory test deteriorated [53].

Hyponatremia, a finding common in advanced cirrhosis, appears to aggravate the reduction in brain concentration of myo-inositol as a result of hypo-osmolality of the extracellular fluid. In a study using MRS, patients with hyponatremia were found to have remarkably lower levels of myo-inositol compared with values in patients without hyponatremia and healthy people. Serum sodium was the only independent predictor of low brain myo-inositol levels. Hyponatremia may thereby be a factor that aggravates hepatic encephalopathy [54].

Mediators of the systemic inflammatory response syndrome, such as nitric oxide and proinflammatory cytokines, may also exacerbate the neuropsychological effects of hyperammonemia in cirrhosis. In a study performed in 10 patients with cirrhosis and bacterial infection, there was a significant deterioration of neuropsychological test scores following amino acid–induced hyperammonemia during the inflammatory state, but not after the resolution of infection [55•]. The mechanisms by which inflammation and infection exert a synergistic effect with ammonia are discussed in an accompanying editorial [56].

Ammonia is generated in both the small bowel (from the effects of glutaminase on glutamine) and the large intestine (from urease activity of the colonic flora). Evidence suggests that ammonia produced by the small intestine is a more important contributor to the pathogenesis of hepatic encephalopathy, including a study in which the intestinal (duodenal) activity of enterocyte phosphate-activated glutaminase was found to be higher in cirrhotic patients than in controls, particularly in those with minimal hepatic encephalopathy (MHE), and was highest in patients with both MHE and an abnormal oral glutamine challenge test. A significant correlation was observed between phosphate-activated glutaminase activity and intracerebral glutamine plus glutamate/creatine ratio ($r = 0.7$) [57].

Congenital portosystemic shunts can cause neurologic symptoms, probably as a result of the effects of intestinal ammonia that is shunted into the systemic circulation and the brain. In fact, abnormalities of neuropsychological tests, MRS findings and response to oral glutamine challenge in three patients with congenital portosystemic shunting were similar to those observed in six patients with cirrhosis and prior episodes of hepatic encephalopathy [58].

Patients with cirrhosis and early hepatic encephalopathy (MHE and grade I hepatic encephalopathy) score lower than controls in memory tasks, predominantly because of deficits in attention and visual perception [59]. These deficits may explain the impairment in fitness to drive a car observed in patients with MHE when subjected to a standardized on-road driving test designed for patients with brain impairment. This study demonstrated that the total driving score was significantly lower in patients with cirrhosis with MHE than either patients with cirrhosis without MHE or controls [60]. The instructor had to intervene in the driving of five of the 14 MHE patients to avoid an accident, significantly more than in patients with cirrhosis without MHE.

The effect of liver transplantation on MHE is controversial. A study that excluded patients with an alcoholic etiology showed that liver transplantation improved cognitive functions in patients with cirrhosis and MHE.

The improvement was not generalized but appeared prominent in attention and memory and occurred at different times after liver transplantation [61]. A study evaluating visuo-motor and visuo-constructive performance in patients with MHE before and (11–33 months) after liver transplantation revealed that while half the patients had an improvement in these neuropsychological parameters after liver transplantation, half had no improvement or even a worsening, suggesting that there may be neurodegenerative processes underlying the cerebral pathophysiology of MHE [62]. In an accompanying editorial, it is postulated that the nonreversibility of MHE can also occur because of pre-existing pathology, since some of the patients had an alcoholic etiology of cirrhosis, hypoxemic brain injury during liver transplantation, or even because of the effect of immunosuppressants [63]. More detailed and uniform neuropsychological and radiologic assessments will be needed before the issue of the reversibility of MHE is resolved.

Lactulose appears to be of benefit in MHE. Lactulose acts by acidifying the gut lumen and creating a gut environment hostile to urease-producing gut flora. Synbiotics (probiotics and fermentable fiber) also modulate the gut flora and acidify the lumen and could be as useful as lactulose. In a randomized pilot study, 55 patients with MHE were randomized to receive a synbiotic preparation ($n = 20$), fermentable fiber alone ($n = 20$), or placebo ($n = 15$) for 30 days. Both synbiotic and fiber treatments were associated with a significant reduction in blood ammonia and endotoxin levels and reversal of MHE (assessed by number connection test and auditory evoked potentials) in 50% of patients. Interestingly, Child–Pugh class improved in almost half the patients on synbiotic therapy [64•]. This stimulating work needs corroboration in larger studies.

Of note, a Cochrane meta-analysis to assess the effects of nonabsorbable disaccharides (lactulose and lactitol) in patients with hepatic encephalopathy concluded that there is insufficient evidence to support or refute the use of nonabsorbable disaccharides for hepatic encephalopathy and that nonabsorbable disaccharides should not serve as a comparator in randomized trials on hepatic encephalopathy [65].

Protein-restricted diets are usually prescribed for patients with cirrhosis with overt episodic hepatic encephalopathy; however, protein restriction may worsen the nutritional status and may have no effect on hepatic encephalopathy. Despite difficulties in the design of studies in patients with episodic hepatic encephalopathy, a randomized trial performed in patients with cirrhosis admitted to the hospital because of an episode of acute encephalopathy ($n = 30$) randomized patients to receive a low-protein diet with progressive increments or a normal protein diet for 14 days, in addition to standard measures to treat hepatic encephalopathy. The outcome of hepatic encephalopathy was not significantly different between study groups. Protein synthesis was similar for a low-protein and normal-protein diet, but those of the low-protein diet group showed higher protein breakdown [66•]. As mentioned in an accompanying editorial, the rationale for a low protein diet in the short and long-term management of hepatic encephalopathy seems questionable, because it is of no benefit and could be detrimental [67].

Conclusion

This review summarizes exciting developments in the area of the complications of portal hypertension published in the last year, mostly derived from prospective trials. These studies will contribute to advancing the practice of hepatology and defining future research areas.

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