Portal hypertension
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Portal hypertension, the main complication of cirrhosis, is responsible for its most common complications: variceal hemorrhage, ascites, and portosystemic encephalopathy. Portal hypertension is the result of increased intrahepatic resistance and increased portal venous inflow. Vasodilatation (splanchnic and systemic) and the hyperdynamic circulation are hemodynamic abnormalities typical of cirrhosis and portal hypertension. Gastroesophageal varices result almost solely from portal hypertension, although the hyperdynamic circulation contributes to variceal growth and hemorrhage. Ascites results from sinusoidal hypertension and sodium retention, which, in turn, is secondary to vasodilatation and activation of neurohumoral systems. The hepatorenal syndrome represents the result of extreme vasodilatation, with an extreme decrease in effective blood volume that leads to maximal activation of vasoconstrictive systems, renal vasoconstriction, and renal failure. Spontaneous bacterial peritonitis is a potentially lethal infection of ascites that occurs in the absence of a local source of infection. Portosystemic encephalopathy is a consequence of both portal hypertension (shunting of blood through portosystemic collaterals) and hepatic insufficiency that result in the accumulation of neurotoxins in the brain. This review covers the recent advances in the pathophysiology and management of the complications of portal hypertension.

Pathophysiology
Cirrhosis represents the end stage of any chronic liver disease. Portal hypertension, the main consequence of cirrhosis, is responsible for its complications: variceal hemorrhage, ascites, and portosystemic encephalopathy.

Increased intrahepatic vascular resistance
Portal pressure increases initially as a consequence of an increased resistance to portal flow. This is mostly caused by an architectural distortion of the liver secondary to fibrous tissue and regenerative nodules. However, in addition to this structural resistance to blood flow, a primary increase is seen in intrahepatic vascular tone. The vascular, reversible component of the increased intrahepatic resistance is mainly the result of a deficit of the vasodilator nitric oxide (NO) in the liver microcirculation. This has led to the use of NO donors to decrease intrahepatic resistance and thereby portal pressure. In this regard, recombinant adenovirus carrying the endothelial NO synthase (NOS 3) gene was injected intraportally into rats with cirrhosis induced by carbon tetrachloride [1]. Contrary to what has been shown by other investigators, a decrease in NOS 3 protein immunoreactivity in sinusoidal cells of cirrhotic animals not transfected was observed, which was partially reversed by NOS 3 transfection. Importantly, portal pressure of NOS 3-transfected cirrhotic animals, measured 5 days after transfection, was significantly lower (7.8 mm Hg) than that of cirrhotic animals not transfected (11.4 mm Hg). However, the duration of the effect and the toxicity of adenoviral transfection require further investigation. As has been raised by other similar studies, a concern is that the 38% lower portal pressure observed in transfected animals is significantly greater than the fall in perfusion resistance observed in studies in which cirrhotic livers are perfused directly with NO donors (22% to 28%) [2].

A recent study suggests, however, that cirrhotic livers may have a lower vasorelaxant response to NO donors. In this study, the vascular relaxation induced by either nitroglycerin, from which NO is liberated enzymatically, or the spontaneous NO donor, 5-nitroso-N-acetylpenicillamine (SNAP), which liberates NO nonenzymatically, was investigated using in situ perfusion of normal and cirrhotic rat livers [3]. Compared with normal livers, cirrhotic livers exhibited lower vasorelaxant response to both nitroglycerin and SNAP, indicating an inability of the cirrhotic vasculature to respond to NO. In addition, nitroglycerin induced less vasorelaxation than SNAP, indicating impaired liver metabolization of nitroglycerin to NO.
An increase in production of endogenous vasoconstrictors (eg, angiotensin and norepinephrine) has also been proposed to occur in the intrahepatic circulation. Cysteinyi-leukotrienes are also vasoconstrictors that can contribute to an increased intravascular resistance in cirrhosis. The production of cysteinyi-leukotrienes was increased in cirrhotic perfused livers and blockade of cysteinyi-leukotrienes synthesis by 5-lipoxygenase inhibition caused a greater reduction in perfusion pressure in cirrhotic than in control livers [4]. Unexpectedly, specific LT$_{1}$ and LT$_{2}$ receptor blockade was unable to reproduce these findings, and this issue requires further investigation.

**Increased portal venous inflow**

Cirrhosis is associated with mesenteric arteriolar vasodilation that contributes to portal hypertension by increasing portal venous inflow. This vasodilation is not confined to the splanchnic circulation but also occurs in the systemic circulation and is the initiating event in the development of the hyperdynamic circulation in the patient who is cirrhotic. This vasodilation is most likely triggered by increased levels of vasodilators. Studies in experimental animals indicate that NO is the most important of these vasodilators. This is further confirmed in a study performed in nine patients with cirrhosis in whom samples of hepatic artery were obtained at the time of liver transplantation [5]. NOS activity was significantly higher in hepatic artery of patients who were cirrhotic, particularly in those with ascites, compared with controls and correlated significantly ($r^2 = 0.69$) with cardiac output.

Although a deficit of NO plays a role in the increased intrahepatic resistance, increased NO appears to play a major role in the vasodilatory state of cirrhosis. The complex interactions of NO in cirrhosis and portal hypertension were reviewed [6••] and, as noted in this review, evidence indicates that the increase in NO in the peripheral and splanchnic circulation results from an increase in endothelial NO synthase (eNOS). This was further confirmed in a study performed in rats with biliary cirrhosis that showed that aortic eNOS protein was 3.0 and 1.7 times higher than in control and portal veinstenosed rats, respectively [7].

Nitric oxide blockers, by producing mesenteric vasoconstriction and decreasing portal venous inflow, could lead to a reduction in portal pressure. The acute systemic, hepatic, and renal hemodynamic effects of N(G)-monomethyl-L-arginine (1-NMMA) were examined in 10 patients with decompenated cirrhosis [8] at a dose sufficient (3 or 9 mg/kg) to increase mean arterial pressure by 10 mm Hg. Acute NOS inhibition increased systemic vascular resistance and decreased cardiac output, without causing changes in the hepatic venous pressure gradient (HVPG). Administration of NO blockers did not result in a reduction in portal pressure probably because the reduction in portal venous inflow induced by NO blockers was offset by an increase in intrahepatic and portocollateral resistance.

Unexpectedly, a study performed in mice lacking eNOS and in mice lacking both eNOS and iNOS genes demonstrated that, after portal vein ligation, all these animals develop vasodilatation and hyperdynamic circulation to the same degree as wild-type mice [9]. This indicates that, in these experimental models, compensatory vasodilator molecule(s), other than NO, are upregulated in the systemic and splanchnic circulation in portal hypertensive animals.

Neural factors (eg, sympathetic over-reactivity) have been postulated to be involved in the genesis of the disturbed cardiovascular function in liver disease. In rats with portal vein ligation, brain immunostaining for Fos (protein product of c-fos gene) was significantly increased in brain nuclei involved in cardiovascular regulation and preceded the development of the hyperdynamic circulation, suggesting that activation of central nuclei, through a c-fos-dependent pathway, is necessary for the development of the hyperdynamic circulatory state [10].

**Complications of portal hypertension**

**Pharmacologic manipulation of portal pressure**

Postprandial increases in portal pressure can influence esophageal variceal rupture. In a randomized, placebo-controlled trial, the effects of the addition of a single dose of octreotide (100 or 200 µg, subcutaneously) on postprandial HVPG was evaluated in 36 patients with cirrhosis who had been on propranolol for more than a month [11•]. Although the HVPG in patients on propranolol was significantly lower than HVPG before initiation of propranolol, the acute administration of placebo did not blunt the postprandial increase in portal pressure, whereas octreotide (100 µg) partially ameliorated postprandial increase in portal pressure and octreotide (200 µg) significantly enhanced the portal hypotensive effect of propranolol and blunted the postprandial increase in portal pressure. As octreotide blunts the postprandial increase in portal pressure not prevented by long-term propranolol, it could be a useful adjuvant to propranolol in the treatment of portal hypertension.

Carvedilol is a nonselective β-blocker with additional anti-α$_1$ adrenergic activity that could potentially act by reducing both portal blood inflow (β-blocker effect) and intrahepatic resistance (antiadrenergic effect). In a randomized study, the effect of long-term (mean 11 weeks) administration of carvedilol versus propranolol on HVPG was examined in 51 patients who were cirrhotic [12]. Confirming the findings of their previous acute study, these investigators found that long-term carvedilol caused a significantly greater decrease in HVPG than...
propranolol (−19% vs −12%); however, it was associated with a significant decrease in mean arterial pressure and a significant increase in plasma volume and body weight. Therefore, although carvedilol appears more effective than propranolol, its clinical utility may be limited by systemic hypotensive effects. In another similar study, patients were randomized to carvedilol (n = 18) or propranolol (n = 17) and HVPG measured after the first dose and after 7 days on treatment [13]. Although carvedilol was associated with a significant decrease in HVPG, both acutely and chronically, this was not different than that produced by propranolol. However, the 23% decrease in HVPG and the 63% rate of favorable response (reduction in HVPG >20%) in the propranolol group is greater than for the control arm of 28 randomized, controlled prophylactic trials for the primary prevention of variceal hemorrhage shows that, following withdrawal of propranolol, the rate of variceal hemorrhage was the same as in patients withdrawn from placebo, suggesting that the protective effect of propranolol was no longer present [19]. More importantly, survival was significantly decreased in patients withdrawn from propranolol, supporting the current practice of indefinite prophylactic therapy.

**Varices and variceal bleeding**

Variceal wall tension is the key factor that determines variceal rupture. Wall tension is directly proportional to the radius of the varix and to intravariceal pressure and inversely proportional to variceal wall thickness. Elevating intraabdominal pressure, by the use of an inflatable girdle, was shown to increase variceal pressure (assessed by an endoscopic pressure gauge) and variceal radius (assessed by endosonography), thereby dramatically increasing calculated variceal wall tension and volume [14]. It is thereby assumed that daily activities associated with an increase in intraabdominal pressure could contribute to variceal rupture and probably should be avoided in patients with large varices.

Large varices have a higher wall tension and are the ones at highest risk of rupture. The prevalence of large varices in unselected “stable” patients who are cirrhotic is approximately 55% [15]. Therefore, screening endoscopy could be avoided in most patients if reliable nonendoscopic predictors of the presence (or absence) of large varices could be identified. A cross-sectional study of 143 patients who were cirrhotic, mostly compensated, identified three independent predictors of varices: a prothrombin activity less than 70%, a portal vein diameter more than 13 mm (determined by ultrasound), and a platelet count less than 100,000/mm³ [16]. Endoscopy could have been avoided in only 30 patients (20%) who had none of these characteristics, 3 of whom had small varices. However, the presence of an operator-dependent ultrasonographic parameter raises issues of reproducibility and cost.

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 considered the gold standard in the prevention of first variceal hemorrhage. In a prospective trial of primary prophylaxis of variceal hemorrhage, patients who were cirrhotic with medium and large varices were randomized to propranolol (n = 66), isosorbide-5-mononitrate (ISMN) (n = 62), and esophageal variceal ligation (EVL) (n = 44) [17]. Variceal bleeding occurred in 14% of patients in the propranolol group, 23% in the ISMN group, and 7% of patients randomized to EVL. Although a trend was seen for a reduction in the rate of first variceal bleed in patients treated with EVL compared with patients treated with ISMN, no statistically significant differences were observed in bleeding or in mortality among the three groups. This may have been the result of an insufficient sample size and, therefore, no clear conclusions can be drawn from this study. The study suggests that ISMN alone should not be used in primary prophylaxis and this is further supported by another randomized trial that compared nadolol (n = 25) and ISMN (n = 27) in a population of patients with cirrhosis and ascites, who are frequently intolerant to β-blockers [18]. Bleeding occurred in two patients in the nadolol group and ten on ISMN. The probability of bleeding was significantly lower in the nadolol group (P < 0.05), whereas overall survival was similar. Of note, 28 (47%) of 60 patients screened were excluded from participating in the trial because of contraindications to the use of β-blockers. After 21 months of follow-up, treatment had to be withdrawn because of side effects in six patients on nadolol and four on ISMN.

Until more conclusive evidence is available, β-blockers continue to be the first choice in the primary prophylaxis of variceal hemorrhage and EVL should be considered for patients with high-risk varices who cannot tolerate β-blockers.

A question frequently posed is whether β-blocker therapy should be continued indefinitely. A long-term follow-up study of a completed randomized, double-blind, placebo-controlled trial of propranolol for the primary prevention of variceal hemorrhage shows that, following withdrawal of propranolol, the rate of variceal hemorrhage was the same as in patients withdrawn from placebo, suggesting that the protective effect of propranolol was no longer present [19]. More importantly, survival was significantly decreased in patients withdrawn from propranolol, supporting the current practice of indefinite prophylactic therapy.

**Treatment of acute variceal hemorrhage**

Variceal bleeding is a frequent cause of death in patients with cirrhosis and portal hypertension. Over the past 40 years a number of new techniques have been introduced to control active variceal hemorrhage. With the aim of investigating whether the prognosis following the first variceal hemorrhage has improved over the past four decades, the outcome of 1475 patients included in the control arm of 28 randomized, controlled prophylactic trials for the primary prevention of variceal hemorrhage...
between 1960 and 2000 were analyzed. Although the number of patients who had a first variceal hemorrhage in these trials is not specified, bleeding-related mortality reduced significantly over the 40-year period from approximately 55% to approximately 40% ($P = 0.024$).

Emergency sclerotherapy is widely used as a first-line therapy for variceal bleeding in cirrhosis, although pharmacologic treatment may also stop bleeding in most patients. A meta-analysis of twelve trials (including 1146 patients) comparing sclerotherapy with the following vasoactive treatments—vasopressin (one trial), terlipressin (one trial), somatostatin (four trials), and octreotide (six trials)—was reported [20]. No significant differences were found comparing sclerotherapy with each vasoactive drug for any outcomes. Combining all the trials, irrespective of the vasoactive drug, no significant risk differences were seen in failure to control bleeding, rebleeding, mortality, or transfused blood units. Adverse events and serious adverse events were significantly more frequent with sclerotherapy. In conclusion, no convincing evidence supports the use of emergency sclerotherapy for variceal bleeding in cirrhosis as the first, single treatment when compared with vasoactive drugs.

Combination of pharmacologic therapy plus endoscopic therapy appears to be the most promising approach in the treatment of acute variceal hemorrhage. This was explored in a meta-analysis performed to assess whether vasoactive drugs improve the efficacy of endoscopic therapy in the control of acute variceal bleeding and, thus, increase survival rates [21•]. The meta-analysis of eight trials involving 939 patients showed that combined treatment (vasoactive drugs plus sclerotherapy or EVL) improved initial control of bleeding (88% vs 76%) and 5-day hemostasis (77% vs 58%) without differences in mortality or severe adverse events [21], concluding that the ideal therapy for acute variceal hemorrhage is probably a combination of endoscopic and safe pharmacologic therapy.

One of these safe drugs is somatostatin. The dose of somatostatin routinely used for variceal bleeding (250 μg/h) is lower than that proved to effectively decrease portal pressure and azygos blood flow (500 μg/h). With the aim of investigating whether higher doses of somatostatin and repeated boluses can increase its efficacy in controlling variceal bleeding, 174 patients with acute variceal bleeding were randomized to receive a 250 μg bolus plus 250 μg/h infusion; three 250 μg boluses plus 250 μg/h infusion; or three 250 μg boluses plus 500 μg/h infusion [22]. The three schedules of somatostatin were equally effective in controlling variceal bleeding (73%, 75%, and 81%, respectively); however, in patients with active bleeding, the 500 μg/h infusion dose achieved a higher rate of control of bleeding (82 vs 60%), less transfusions (3.7 vs 2.5 units), and better survival (93 vs 70%) than the other two schedules. Therefore, higher doses of somatostatin may be warranted in this subpopulation of patients with actively bleeding varices.

Treatment of bleeding gastric varices is still particularly challenging. A prospective, randomized study was undertaken to compare the efficacy and safety of sclerotherapy using alcohol versus variceal obturation using cyanoacrylate glue in 37 patients with isolated gastric varices, only 17 of whom were actively bleeding [23]. This issue is particularly relevant because cyanoacrylate glue is not approved for use in the United States. The glue was significantly more effective in achieving variceal obliteration than alcohol (100% vs 44%, $P < 0.05$) and did it in a shorter time (2.0 vs 4.7 weeks) and with a smaller volume of the agent. Cyanoacrylate glue injection could achieve arrest of acute gastric varices bleeding more often than alcohol (89% vs 62%); however, this difference was not significant because of the small sample size. Therefore, although cyanoacrylate glue would appear to be more effective than alcohol in the treatment of gastric varices, larger studies in patients with active variceal hemorrhage are warranted.

**Prevention of recurrent variceal hemorrhage**

Currently, the endoscopic therapy of choice is EVL as it has been shown to be superior to sclerotherapy in adults and, more recently, in children with extrahepatic portal vein obstruction [24]. The pharmacologic therapy of choice in the prevention of variceal rebleeding is probably the combination of a nonselective β-blocker and a nitrate. This is based on hemodynamic studies that show a synergistic portal pressure-reducing effect of combination therapy. Also, data collected from different randomized clinical trials show lower median rebleeding rates (~33%) in patients treated with combined pharmacologic therapy compared with rebleeding rates in patients treated with β-blockers alone (~50%) [25].

Three studies published in the last year compared EVL versus combination pharmacologic therapy with β-blockers plus nitrates. The three studies show different results: one showed a benefit of combination pharmacologic therapy with a 49% rebleeding rate for EVL versus 33% for nadolol plus ISMN [26]; another showed a benefit of EVL with a 38% rebleeding rate for EVL versus 57% for nadolol plus ISMN [27]; and the third showed no statistically significant difference between EVL (rebleeding rate 53%) versus propranolol plus ISMN (rebleeding rate 37%) [28]. These differences probably result from the dosage of medications used, patient population, and, ultimately, center expertise [29]. Of great interest, two of the studies performed measurements of HVPG during the course of the study. In the study by Villanueva et al. [26], patients in whom the HVPG, measured 1 to 3 months after starting therapy,
was reduced to a level below 12 mm Hg or in whom HVPG was reduced by more than 20% from baseline (51% of the medication group, 15% of the EVL group) had a significantly greater probability of remaining free of rebleeding and of surviving than patients in whom these goals had not been met. The study by Patch et al. [28] was planned so that the addition of ISMN would be contingent on a lack of a significant reduction in HVPG while on propranolol. Measurement of HVPG, however, was performed 3 months after starting propranolol and at this point more than 50% of patients had already experienced rebleeding, indicating that if this rational approach in the management of patients with variceal bleeding is followed, repeat HVPG measurements should be performed earlier [29].

At this point, the choice between pharmacologic therapy and endoscopic therapy will depend on factors such as local expertise, compliance, tolerance, and patient preference.

It has been suggested that EVL is followed by a higher rate of variceal recurrence (after obliteration) in comparison with sclerotherapy. Although meta-analysis shows no significant difference in variceal recurrence between treatments [30], the efficacy of combination EVL plus sclerotherapy compared with EVL alone has been explored in several trials. A recent meta-analysis of seven such trials showed that the combination of EVL and sclerotherapy offers no advantage over EVL alone in preventing rebleeding or reducing mortality and is associated with a higher complication rate [31]. Therefore, conclusive evidence accumulated so far should discourage the use of combination EVL and sclerotherapy.

Both combination pharmacologic therapy and EVL were compared with the transjugular intrahepatic portosystemic shunt (TIPS) in two recent randomized, controlled trials. In the first trial, combination pharmacologic therapy with propranolol plus ISMN (n = 44) was compared with TIPS (n = 47) in the prevention of variceal rebleeding. The study showed that, although pharmacologic therapy was less effective than TIPS (33% vs 11% rebleeding rate), it caused less de novo encephalopathy, identical survival, and more frequent improvement in Child-Pugh class with lower costs than TIPS [32]. The other smaller randomized study compared EVL (n = 26) versus TIPS (n = 28) in the prevention of variceal rebleeding [33]. After a mean follow-up of 2 years, neither the probability of being free of rebleeding nor mortality were significantly different between study groups.

These studies support the current recommendation that TIPS should not be used as a first-line treatment, but as a rescue for medical or endoscopic treatment failure.

Ascites
Peripheral vasodilatation resulting in sodium retention is a major pathogenic mechanism in the formation of ascites. Evidence in favor of NO as a mediator of vasodilatation and sodium retention in cirrhosis is supported by a study that investigated the effect of the NO inhibitor, L-NMMA, in patients with compensated cirrhosis [34]. The short-term intravenous administration of L-NMMA, but not placebo, was accompanied by an increase in systemic vascular resistance and mean arterial pressure as well as an increase in glomerular filtration rate and sodium excretion. However, another, non–placebo-controlled trial, performed in 10 patients with decompensated cirrhosis, failed to show an increase in glomerular filtration rate or in natriuresis, despite a significant increase in systemic vascular resistance [8].

Refractory ascites occurs in 5% to 10% of patients with cirrhosis and with ascites and is diagnosed when patients fail to respond to diuretics or develop complications that preclude the administration of adequate doses of diuretics. Approved therapy for patients with refractory ascites consists of large volume paracentesis (LVP) plus albumin. Because LVP is a local therapy that does not act on the abnormalities responsible for the formation of ascites (sinusoidal hypertension and sodium retention), recurrence of ascites is almost invariable. On the other hand, TIPS acts on both mechanisms that lead to ascites but, by diverting blood flow away from the liver, it can lead to encephalopathy and liver insufficiency. Although results from two previous prospective, randomized trials of LVP versus TIPS showed, expectedly, that TIPS is more effective than LVP plus albumin in controlling ascites [35, 36], results were divergent regarding mortality. In a recent larger multicenter, randomized study, 70 patients with cirrhosis and refractory ascites were randomized to TIPS (n = 35) or repeated LVP plus intravenous albumin (n = 35) [37••]. Twenty patients treated with TIPS and 18 treated with LVP died during the study period, whereas 7 patients in each group had liver transplantation. The primary end-point, survival without liver transplantation, was 41% at 1 year and 26% at 2 years in the TIPS group, as compared with 35% and 30%, respectively, in the LVP group (P = 0.51). Although recurrence of ascites and development of hepatorenal syndrome were lower in the TIPS group compared with the paracentesis group, the frequency and severity of hepatic encephalopathy and cost were greater in the TIPS group. Based on these results, TIPS cannot be considered first-line therapy for patients with refractory ascites.

Large volume paracentesis is a safe and effective way to treat ascites as long as it is associated with the concomitant infusion of albumin. LVP without albumin infusion is accompanied by a high rate of “postparacentesis circulatory dysfunction” (PCD), an entity characterized by marked activation of plasma renin activity that is not
spontaneously reversible and that is associated with rapid reaccumulation of ascites and a decreased survival [38]. PCD appears to be secondary to further vasodilatation and arterial underfilling [39] that can be prevented by repletion of the intravascular volume. Albumin has been shown to prevent the development of PCD more effectively than synthetic plasma expanders [38], perhaps because of its greater oncotic potency and longer half life. In addition to a lower efficacy, the repeated administration of synthetic plasma volume expanders (eg, hydroxyethyl starch) has been shown to worsen liver function in patients with cirrhosis [40] and, therefore, their use cannot be widely recommended.

Vasoconstrictors, by acting on the primary event—vasodilatation—can achieve a similar increase in effective arterial blood volume as that achieved by albumin, but through a different mechanism. Although albumin increases effective arterial blood volume directly, vasoconstrictors do so by decreasing the size of the intravascular compartment. Terlipressin, a potent vasoconstrictor, was recently compared with albumin in a small randomized pilot study performed in patients with refractory ascites subjected to LVP [41•]. In this study, 20 patients with tense ascites were randomized to LVP plus terlipressin (3 mg intravenously in three separate bolus doses of 1 mg each) versus LVP plus albumin. Plasma renin activity was measured before and 4 to 6 days after LVP. Development of PCD was similar in both groups (three patients in each), suggesting that vasoconstrictors may, in fact, be a reasonable alternative to albumin in this setting. However, the rate of PCD in the albumin group (30%) is higher than shown in previous studies and these results require confirmation in larger, ideally blinded, studies.

Water retention and dilutional hyponatremia, mainly attributable to an impairment of free water excretion and increased vasopressin activity, are well-documented complications in patients with cirrhosis and ascites. In a randomized, double-blind, placebo-controlled trial, the safety and pharmacokinetics of ascending single doses of VPA-985, a selective, nonpeptide, orally active, vasopressin-2-receptor antagonist were investigated in patients with cirrhosis and ascites [42]. Each dose level (25, 50, 100, 200, and 300 mg) was studied in five patients (four active and one placebo). VPA-985 produced a significant dose-related increase in daily urine output and a dose-related decrease in urine osmolality. The free water clearance reached more than 3 mL/min for doses 100 mg or greater. Simultaneously, significant increases in serum osmolality and serum and urinary sodium levels were found. These preliminary findings suggest a therapeutic potential of this compound in the hyponatremia of patients with cirrhosis and ascites.

**Hepatorenal syndrome**

Hepatorenal syndrome (HRS) is a major complication of cirrhosis with a high mortality. As reviewed [43••], HRS represents the result of extreme vasodilatation with an extreme decrease in effective blood volume that leads to maximal activation of vasoconstrictive systems, renal vasoconstriction, and renal failure. The combination of peripheral vasoconstrictors and plasma volume expanders has been shown to (1) increase arterial pressure and total systemic vascular resistance, (2) markedly suppress vasoconstrictor systems, and to (3) lead to an improvement in renal function. Vasoconstrictors plus albumin have been used successfully in patients with HRS in uncontrolled studies.

A retrospective study analyzed the clinical course, predictive factors of improved renal function, and survival in 99 patients, mostly with alcoholic cirrhosis and with type 1 HRS, who had been treated with terlipressin (mean dose 3.2 mg/d) for at least 24 hours (mean duration 11.4 days) [44]. Of 91 patients with available data, 58 (64%) had an improvement in renal function (decrease in creatinine to <1.5 mg/dL or a decrease of at least 20% at treatment end). Factors independently predictive of an improvement in renal function were a younger age and Child-Pugh score no greater than 13 at baseline. Median survival was only 21 days, which is somewhat longer than a 1.7-week median survival in previous studies. Factors predictive of survival were an improvement in renal function during terlipressin therapy and a Child-Pugh score less than or equal to 11 at baseline. Of note, 74% received concomitant intravenous albumin and no differences were seen in percentage of patients receiving albumin or in the dose of albumin between patients with or without improvement in renal function. These findings differ from a prospective non-concurrent study that compared 13 patients treated with terlipressin plus albumin versus 8 patients receiving terlipressin alone [45]. In this small study, albumin administration was the only predictive factor of complete response (decrease of serum creatinine to <1.5 mg/dL) with a 77% complete response in patients receiving terlipressin plus albumin versus 25% in those receiving terlipressin alone.

Terlipressin is not available in the United States. However, the combination of intravenous noradrenaline (at a dose of 0.5 to 3 mg/h) in combination with intravenous albumin given for 10 days was shown to reverse HRS in 10 of 12 patients [46•].

It is notable that, in a significant proportion of patients with complete response, therapy has been discontinued without recurrence of HRS, suggesting that these patients experience either an improvement in liver status (as would occur in alcoholic liver disease with alcohol abstinence) or the resolution of a transient decompensating factor (eg, infection). In fact, the study by Moreau
et al. [44] found a significantly higher rate of alcoholic patients in the group that experienced renal improvement.

Spontaneous bacterial peritonitis and other infections
Bacterial infections are a well-known complication of cirrhosis, with prevalence rates ranging between 15% and 45% in retrospective studies. In a prospective evaluation of consecutive patients with cirrhosis hospitalized between April 1998 and April 2000, bacterial infection was present or developed during hospitalization in 507 of 1567 admissions, a rate of 32% [47••]. Spontaneous bacterial peritonitis (SBP), the most frequent infection (138 cases), was mainly caused by gram-negative bacilli (GNB). Gram-positive cocci were the most frequently isolated bacteria in nosocomial infections and in spontaneous bacteremia. Importantly, 65% of GNB isolated from patients on long-term norfloxacin were resistant to quinolone compared with only 29% of GNB from patients not on long-term norfloxacin. Trimethoprim-sulfamethoxazole (TMP/SMX) is not an alternative in these patients as TMP/SMX-resistance was also significantly more frequent in GNB isolated from patients on long-term norfloxacin (68% vs 44%). Therefore, the development of infections by quinolone- and TMP/SMX-resistant organisms is an emerging problem in patients on long-term norfloxacin prophylaxis, and this practice should be restricted to those patients at the highest risk of developing SBP. In a study of quinolones in the prevention of recurrent SBP, all 12 patients tested had *Escherichia coli* resistant to quinolones in their feces by the end of the study [48]. Importantly, the study showed that daily norfloxacin was more effective than weekly rufloxacin (a quinolone with a longer half-life) in preventing recurrent SBP caused by *Enterobacteriaceae*.

Searching for alternative strategies to antibiotic prophylaxis is important. Bacteriotherapy with *Lactobacilli* has been reported to correct bacterial overgrowth, stabilize mucosal barrier function, and decrease bacterial translocation in rat models of acute liver injury and failure. However, in a study performed in cirrhotic rats with ascites and liver disease, the oral administration of *Lactobacillus* strain GG for 8 to 10 days failed to prevent bacterial translocation to mesenteric lymph nodes and ascitic fluid infection, despite successful intestinal colonization [49].

Bacterial translocation, the passage of bacteria from gut to extraintestinal sites, is the main mechanism involved in the pathogenesis of SBP. However, this phenomenon cannot be assessed in humans. In a study of 28 patients with cirrhosis and ascites, bacterial DNA (by polymerase-chain reaction) was detected simultaneously in blood and ascites in 9 patients, despite negative ascites and blood bacteriologic cultures [50]. In all cases, the similarity between sequences from ascites and blood indicated that the DNA present in both locations originated from a single clone. Oddly, no differences were found in the severity of liver disease between patients with and without bacterial DNA. More remarkably, a tendency was seen for a higher mean arterial pressure in patients in whom bacterial DNA was present (88 mm Hg) compared with those in whom it was absent (81 mm Hg). This is contrary to what would be expected given prior results in experimental animals demonstrating an association between bacterial translocation, a lower mean arterial pressure, and a lower perfusion pressure of the superior mesenteric arterial bed (ie, greater systemic and splanchnic vasodilatation) [51]. In fact, a study performed in rats with biliary cirrhosis showed that elimination of GNB translocation through the chronic administration of norfloxacin (by gavage) led to an amelioration of peripheral and pulmonary vasodilatation [52•].

Hepatic encephalopathy
The final report of a working party commissioned to develop consensus in the controversial area of hepatic encephalopathy was published [53••]. It includes modifications of current nomenclature for the clinical diagnosis of hepatic encephalopathy and proposes guidelines for the performance of future clinical trials in the area. This important paper also proposes considering hepatic encephalopathy a continuous dimension with “minimal” encephalopathy representing a portion of this dimension. In favor of this, an investigation looking at the usefulness of oral glutamine challenge in evaluating risk of overt hepatic encephalopathy in cirrhotic patients found that abnormal ammonia concentrations after 10 g oral glutamine were predictive of overt encephalopathy, particularly in patients with minimal hepatic encephalopathy [54].

Five neuropsychological tests: number connection tests A and B, the line-tracing test, the serial dotting test, and the digit-symbol test (the so-called “PSE-Syndrome Test”) [55] were recommended by consensus in the diagnosis of minimal hepatic encephalopathy. This battery of pencil-paper tests has a high specificity for hepatic encephalopathy as compared with other metabolic encephalopathies and has been extensively validated. More sophisticated neurophysiologic tests (eg, P300 auditory evoked potentials) are limited because of the requirement for special equipment.

A study evaluated a simple and reliable parameter, the critical flicker frequency (CFF) (threshold frequency at which light pulses are perceived as a flickering light) for the diagnosis of minimal hepatic encephalopathy in 92 patients with cirrhosis [56]. Using a cutoff CFF of 39 Hz totally separated patients with overt hepatic encephalopathy from noncirrhotic controls and patients with cirrhosis without hepatic encephalopathy. Using this cutoff, 30% of patients without overt hepatic encephalopathy...
were classified as having minimal hepatic encephalopathy (consistent with studies using well-standardized psychometric measures). However, as mentioned in an accompanying editorial [57], the main concern of the study involves the definition of minimal hepatic encephalopathy. The investigators did not use all of the validated psychometrical tests, and about 40% of the patients who were classified as minimal hepatic encephalopathy by the psychometric tests used had normal CFF and would have remained undetected by using CFF analysis. Therefore, whether CFF adequately represents all cognitive domains affected by hepatic encephalopathy remains uncertain.

Regarding therapy of overt hepatic encephalopathy, a meta-analysis of six double-blind, placebo-controlled trials (including 641 patients) of short-term (5 minutes to 3 days) intravenous flumazenil showed a significantly greater clinical (27% vs 3%) and electroencephalographic (19% vs 2%) improvement in the flumazenil group compared with the placebo group [58]. Of note, most (93%) patients included in these trials had hepatic encephalopathy grade III or IV and no precipitant causes of hepatic encephalopathy or these had been treated before inclusion in the study. No data are available concerning survival and 82% of patients included in the meta-analysis came from a single large study. Future trials should assess whether flumazenil leads to a sustained improvement in hepatic encephalopathy or increased survival. Until then, this therapy can be considered in special cases, but should not be used routinely.

The molecular adsorbent recycling system (MARS) system is designed to remove both low and middle molecular-weight, water-soluble substances (e.g., ammonia and albumin-bound molecules. A prospective, randomized, controlled study of MARS (n = 12) vs conventional therapy (n = 11) in patients with acute-on-chronic liver injury in whom bilirubin levels had risen to >20 mg/dL showed that MARS was associated with an improvement in 30-day survival and in hepatic encephalopathy [59•]. Median hepatic encephalopathy score at entry was 1 (range 0–3) and at weeks 1, 2, 3, and 4 score was significantly lower in patients randomized to MARS (median score 0) compared with patients with conventional therapy (median score 3). Interestingly, and as shown in previous uncontrolled studies, mean arterial pressure increased significantly in the MARS group but decreased in the control group, suggesting removal of vasodilator substances. These exciting results require confirmation in larger controlled trials.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• Of special interest
** Of outstanding interest

12. As octreotide blunts the postprandial increase in portal pressure not prevented by long-term propranolol, it could be a useful adjuvant to propranolol in the treatment of portal hypertension.
23. This meta-analysis shows that the ideal therapy for acute variceal hemorrhage is probably a combination of endoscopic and pharmacologic therapy.
Interesting preliminary study showing that terlipressin may be as effective as albumin in preventing PCD.