Portal Hypertension and Its Complications

Arun J. Sanyal* Jaime Bosch‡ Andres Blei§ Vincente Arroyo

*A Division Of Gastroenterology, Hepatology and Nutrition, Department of Internal Medicine, Virginia Commonwealth University Medical Center, Richmond, Virginia; ‡Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clinic and IDIBAPS, University of Barcelona, Barcelona, Spain; §Division of Hepatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois; and Liver Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain

Portal hypertension is a clinical syndrome defined by a portal venous pressure gradient exceeding 5 mm Hg.1 Cirrhosis is the most common cause of portal hypertension in the Western world.1 The goal of this review is to provide an overview of the current understanding of the pathophysiology and treatment of portal hypertension.

Pathogenesis of Portal Hypertension: Hemodynamic Factors

The hallmark of portal hypertension is a pathologic increase in the pressure gradient between the portal vein and the inferior vena cava, which is measured by the hepatic venous pressure gradient (HVPG).2 Briefly, the wedged hepatic vein pressure (WHVP), a marker of sinusoidal pressure, and the free hepatic vein pressure (FHVP) are measured with radiologic assistance. HVPG is calculated by the following formula2–4:

\[ \text{HVPG} = \text{WHVP} - \text{FHVP} \]  

The FHVP is subtracted from the WHVP to correct for intra-abdominal pressure to provide an accurate measure of the portal vein pressure. As in any other vessel, the pressure within the portal vein is determined by the product of blood flow and resistance to its egress, as defined by Ohm’s law (Figure 1):

\[ P \text{ (pressure)} = Q \text{ (blood flow)} \times R \text{ (resistance)} \]  

Portal hypertension is initiated by increased outflow resistance; this can occur at a presinusoidal (intra- or extrahepatic), sinusoidal, or postsinusoidal level. As the condition progresses, there is a rise in portal blood flow, a combination that maintains and worsens the portal hypertension.5

Increased Hepatic Vascular Resistance: Structural and Dynamic Components

In cirrhosis, the principal site of increased resistance to outflow of portal venous blood is within the liver itself. This results from 2 factors: (1) mechanical obstruction to flow because of fibrotic disruption of architecture and (2) a dynamic component produced by active contraction of vascular smooth muscle cells and activated stellate cells.1–3 Although the former is not acutely modifiable, disease stabilization and improvement, eg, after successful treatment of hepatitis C or abstinence from alcohol, can improve fibrosis and the mechanical component.9 The dynamic component accounts for approximately 30% of the intrahepatic resistance in cirrhosis and is an important target for future therapy.10

Mechanism of Increased Hepatic Vascular Tone: Intrahepatic Endothelial Dysfunction

Cirrhosis is associated with evidence of endothelial dysfunction, both in the systemic circulation and within the liver.11,12 The net effect in the liver is intrahepatic vasoconstriction. This is mediated by decreased endothelial nitric oxide synthetase (eNOS) activity and NO production.12–14 Hepatic eNOS activity is decreased because of impaired Akt-mediated eNOS phosphorylation (which is partially reversible by statins) and increased caveolin expression (particularly if folate deficiency exists).15–17 Other factors that contribute to intrahepatic vasoconstriction include decreased NO

Abbreviations used in this paper: ADH, antidiuretic hormone; EVL, endoscopic variceal ligation; GOV, gastroesophageal varices; HE, hepatic encephalopathy; HRS, hepatorenal syndrome; HVPG, hepatic venous pressure gradient; LVP, large volume paracentesis; SBP, spontaneous bacterial peritonitis; TIPS, transjugular intrahepatic portosystemic shunts; VEGF, vascular endothelial growth factor.

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0016-5085/08/$34.00
doi:10.1053/j.gastro.2008.03.007
availability because of its utilization for nitrosylation reactions secondary to oxidative stress \(^{18}\) and vasoconstriction mediated by endothelin, angiotensinogen, and eicosanoids.\(^ {18,19}\) The role of several other vasoactive mediators such as carbon monoxide, adrenergic tone, endotoxemia, and inflammatory cytokines are currently under investigation.

### Increased Portal Venous Inflow

Mesenteric arterial vasodilation is a hallmark of cirrhosis and contributes to both increased portal venous inflow and a systemic hyperdynamic circulatory state (low systemic vascular resistance and mean arterial pressure with high cardiac output).\(^ {5,20}\) Increased NO production because of increased eNOS activity in the systemic circulation is a major driver of arterial vasodilation.\(^ {21}\) Shear stress, increased vascular endothelial growth factor (VEGF), and tumor necrosis factor-\(\alpha\) are causes of increased splanchic NO production in cirrhosis.\(^ {22-24}\) Increased heme oxygenase activity and CO production may also contribute to the hemodynamic disturbances.\(^ {25}\) Bacteremia can increase vasodilation by stimulating tumor necrosis factor-\(\alpha\) production and activation of endocannabinoids, which are potent vasodilators.\(^ {26}\) Blockade of VEGF signaling attenuates the increase in portal venous inflow seen in cirrhosis.\(^ {27}\)

### Formation of Varices and Mechanism of Variceal Hemorrhage

Nature decompresses the hypertensive portal vein by diverting up to 90% of the portal flow through porto-systemic collaterals back to the heart, resulting in flow-mediated remodeling and enlargement of these vessels. VEGF, NO-driven VEGF type II receptor expression, and platelet-derived growth factor drive this process.\(^ {21,28}\) A common location for such vessels is at the gastroesophageal junction at which they lie immediately subjacent to the mucosa and present as gastric and esophageal varices. Varices do not form until the HVPG exceeds 10 mm Hg and usually do not bleed unless the HVPG exceeds 12 mm Hg.\(^ {29,30}\)

Variceal rupture occurs when the wall tension exceeds the elastic limits of the variceal wall (Figure 1). The wall tension is defined by Frank’s modification of Laplace’s law\(^ {31}\):

\[
T = \frac{(P_{\text{varices}} - P_{\text{esophageal lumen}})}{(\text{radius of varix})/\text{wall thickness}} \times \text{(radius of varix)/wall thickness} \quad (3)
\]

The variceal pressure is dependent on variceal flow and resistance to outflow (see equation 2 above). Variceal flow is driven by the severity of portal hypertension. Thus, a high portal pressure and the variceal diameter are major determinants of variceal hemorrhage; an HVPG > 20 mm Hg has been associated with continued bleeding and failure of medical therapy in acute variceal hemorrhage.\(^ {32}\) In addition, varices are most superficial at the gastroesophageal junction and thus have the thinnest wall in that region: consequently, esophageal variceal hemorrhage invariably occurs in this region.\(^ {33}\)

### Development of Ascites

Ascites is a common complication of cirrhosis.\(^ {34}\) Increased hepatic sinusoidal pressure is an essential prerequisite for the development of ascites. Three interrelated pathophysiologic processes contribute to the development of ascites. These include systemic arteriolar vasodilation, activation of Na\(^ +\) and H\(_2\)O retention, and sinusoidal portal hypertension.

### Systemic Arteriolar Dilation: Its Consequences and Role in Development of Ascites

Cirrhosis is associated with systemic arteriolar dilatation\(^ {35}\) (Figure 2). Systemic arteriolar dilatation increases the fraction of the total capillary bed in the body open for perfusion resulting in decreased filling of the
terms, is disproportionately low for the degree of vaso-paired, and the cardiac output, although high in absolute fact, the inotropic and chronotropic functions are im-

failure, hepatorenal syndrome (HRS) is considered to be filtration rate is decreased enough to cause overt renal pressure with progression of cirrhosis; when the glomerular low glomerular filtration rate and renal perfusion pres-

verse the mesenteric arteriolar vasodilation, they produce severe vasoconstriction in other vascular beds, eg, the kidneys, brain, muscle, and skin.38,39 The renal arteries are very sensitive to the vasoconstrictive effects of angio-
tensin II, norepinephrine, and ADH. This explains the low glomerular filtration rate and renal perfusion pres-
sure with progression of cirrhosis; when the glomerular filtration rate is decreased enough to cause overt renal failure, hepatorenal syndrome (HRS) is considered to be present.40

Activation of Na and Water Retentive Mechanisms
Effective hypovolemia activates the renin-angiotensin-aldosterone pathway and sympathetic nerve activ-
ity. Both cause renal Na and water retention (Figure 2). These pathways are activated late in the course of as-
cites,41,42 suggesting that there are yet other undiscovered mechanisms that are operative early in the course of cirrhosis. ADH secretion increases with more profound vasodilatation, resulting in water retention and hypona-
tremia.43 Hyponatremia is a marker for advanced disease and is an independent predictor of outcome.44

Increased Sinusoidal Pressures: Local Mechanisms for Ascites Formation
Increased sinusoidal hydrostatic pressure leads to increased fluid movement from the sinusoids to the space of Disse, thereby increasing hepatic and thoracic duct lymph flow, which can be as much as 24-fold elevated vs normal.45 Both increased outflow resistance and portal venous inflow contribute to sinusoidal hypertension and the formation of splanchnic lymph. When lymph production exceeds the capacity of the lymphatics to return it to circulation, the excess lymph spills into the peritoneal cavity. This is initially reabsorbed via micro-
scopic stoma on the peritoneal surface of the diaphragm that communicates with supradiaphragmatic lymphat-
ics.46 When ascites formation exceeds its reabsorption, clinically evident ascites occurs.

Cirrhosis is also associated with a closing of the normal fenestrae and the deposition of a basement mem-
brane below the sinusoidal endothelium.47 This decreases sinusoidal endothelial permeability. Thus, for a given elevation of sinusoidal hydrostatic pressure, the ascites that is formed has a low protein and albumin concentra-
tion. A serum to ascites albumin gradient of 1.1 or more is an independent predictor of outcome.44

| NOTE. Based on International Ascites Club Criteria51,52 |

Table 1. Definition of Refractory Ascites and Hepatorenal Syndrome

**Refractory ascites**
- Ascites that is difficult to mobilize, as defined by a failure to lose at least 1.5 kg/week of fluid weight, despite maximal diuretic therapy with spironolactone (400 mg/day) and furosemide (160 mg/day) or an equivalent dose of a distal-acting and loop-acting diuretic, respectively
- Diuretic intractable ascites: Ascites that is difficult to mobilize, as defined above, because of the inability to provide effective doses of diuretics because of diuretic-induced adverse effects, eg, azotemia, hyponatremia, and others

**Hepatorenal syndrome**
- Presence of cirrhosis with ascites
- Presence of renal failure (creatinine level >1.5 mg/dL or 133 mol/L)
- Lack of improvement in serum creatinine after 48 hours of diuretic withdrawal and volume expansion with intravenous albumin administration (1 g/kg/day up to 100 g/day)
- Absence of shock
- Use of nephrotoxic drugs, eg, aminoglycosides
- Parenchymal renal disease (urine protein >500 mg/day, granular or red cell casts, hematuria, urinary obstruction by sonography)
Refactory Ascites and HRS

Initially, ascites is manageable with Na restriction and diuretic therapy. However, over time, some patients cease to respond even to maximal diuretic therapy and are considered to have refractory ascites. This is associated with further exaggeration of the pathophysiologic mechanisms outlined above and decreased glomerular filtration rate, which may manifest as overt renal failure (Table 1).

HRS is functional renal failure that occurs because of marked mesenteric arterial vasodilation, impaired cardiac response to the vasodilatation, and increased renal vasoconstriction. Increased angiotensin, sympathetic nerve activity, and ADH all contribute to renal vasoconstriction. Initially, these are compensated for by intrarenal vasodilatory mechanisms (prostaglandins, NO, and others). As the renal balance between vasodilatation and vasoconstriction tilts toward vasoconstriction, renal perfusion and glomerular filtration rate decrease. This process occurs in the transition from diuretic-responsive ascites to refractory ascites to HRS, and these states often form a clinical continuum rather than distinct clinical-pathophysiologic entities. The progression to and rate of development of renal failure is often accelerated by intermittent bouts of infection, particularly SBP, which are associated with increasing vasodilatation and impaired cardiac response to the vasodilatation. These, in turn, further activate vasoconstrictive pathways, causing renal vasoconstriction. Depending on the rate of development of renal failure, HRS is classified as type 1 (rapidly progressive) or type 2 (slowly progressive). Type 2 HRS is usually seen in the context of refractory ascites. Type 1 HRS is associated with worsening hepatic failure. The latter is believed to be due to decreased hepatic blood flow from increased sinusoidal resistance secondary to angiotensin-II, norepinephrine, and ADH-mediated stellate cell contraction.

Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a broad entity that encompasses mental status changes in subjects with acute and chronic liver failure. Variable degrees of hepatocellular failure and portal-systemic shunting are the anatomic substrate of HE, although either one can produce HE. Several mechanisms have been implicated in the genesis of HE and are reviewed below.

Interorgan Ammonia Metabolism

Ammonia is a key factor in the pathogenesis of HE. In cirrhosis, decreased hepatic uptake of ammonia occurs as a result of intrahepatic portal-systemic shunts and/or reduced urea and glutamine synthesis. A substantial portion of gut-derived ammonia originates in the small bowel from the deamination of glutamine by glutaminase, which is activated in cirrhosis. The potential importance of this enzyme is exemplified by its sensitivity to neomycin, which is used to treat HE.

An often ignored regulator of circulating ammonia levels is the muscle mass. Striated muscle form glutamine from ammonia, which is later circulated to other organs. Decreased muscle mass is often present in cirrhosis; it is associated with decreased muscle capacity to clear ammonia and further contributes to hyperammonemia. Physical activity releases ammonia from muscle and may also contribute to hyperammonemia. Ornithine-asparaginase, used for the treatment of HE, increases muscle glutamine synthetase activity via transcriptional activation and improves the elimination of NH₃ in anhepatic animal models.

Recent studies have focused on the potential role of the kidney in NH₃ homeostasis. Gastrointestinal bleeding and hypovolemia increase release of renal ammonia to the circulation, whereas volume loading and sinusoidal decompression decrease such release. The normal regulation of urinary ammonia excretion is complex and includes roles for ammoniagenic enzymes as well as different transporters. A novel role for Rh glycoproteins, RhBG and RhCG, includes ammonia transport in the kidney as well as in other mammalian cells, including the liver. Several aquaporins may also participate and/or facilitate ammonia transport into cells.

Role of Infections and Systemic Inflammation

Infection, which promotes inflammation, can precipitate HE. Inflammation-induced neurologic dysfunction may result from endothelial activation by infection-induced circulating cytokines, cerebral sequestration of macrophages, altered microglial function, and interactions between cytokines and ammonia. The therapeutic benefits of nonabsorbable antibiotics given orally may include decreased bacterial translocation and activation of inflammatory mechanisms.

Cerebral Blood Flow

Normally, the cerebral cortex receives the bulk of the cerebral blood flow. Positron emission tomography scans, using ¹⁸⁵O (flow) and ¹⁵N (ammonia metabolism), show diversion of blood flow to basal areas along with increased ammonia metabolism and decreased glucose utilization. An inverse relationship between systemic arterial vasodilation and cerebral blood flow has been identified as well. The pathogenesis of cerebral vasoconstriction may be similar to that for renal vasoconstriction in cirrhosis with portal hypertension.

Brain Edema and the Spectrum of HE

Intracranial hypertension can occur in cirrhosis but is rare. However, an increase in brain water content and low-grade brain edema occurs commonly in cirrhosis. These changes are reversed with lactulose and liver transplant. It is believed that increased osmotically
active solutes in the brain, eg, Na, glutamine, and myo-inositol, may play a pathogenic role. The activation of compensatory mechanisms that tightly regulate cerebral osmolyte levels may explain the lack of clinically obvious cerebral edema in cirrhosis.

**Oxidative Stress and HE**

In the brain, ammonia is detoxified in the cytoplasm of astrocytes to form glutamine. Glutamine is transported to mitochondria where glutaminase activity releases ammonia. This generates reactive oxygen species, which can induce the mitochondrial permeability transition, thereby resulting in mitochondrial and glial dysfunction (Figure 3). This pathway has also been described as the “Trojan horse” hypothesis for cerebral dysfunction in HE. Increased heme oxygenase-1 activity may be important as a source of CO production and modulation of cerebral blood flow.

**Hepatic Parkinsonism**

Over 20% of subjects awaiting liver transplantation exhibit features of Parkinsonism. This is associated with increased manganese deposition in the globus pallidus, which is known to induce oxidative stress by altering mitochondrial function.

**Management of Portal Hypertension**

**Variceal Hemorrhage**

Management of the subject who has never bled from varices. Assessment of bleeding risk and identification of those who need intervention. The risk of bleeding from esophageal varices depends on the HVPG (>12 mm Hg), variceal diameter, endoscopic “red signs,” and liver failure. Subjects with medium to large varices as well as those with Child–Pugh class B or C cirrhosis and varices of any size are considered to be at high risk of bleeding. Although liver function, platelet count, and splenomegaly are related to the risk of having such varices, they cannot be used to guide the need for endoscopy at this time. The risk of de novo development of “high risk” varices is 1% at 1 year and 9% by 3 years. All subjects with cirrhosis should undergo a screening endoscopy to determine their risk of bleeding (Figure 4). Subjects with “high risk” varices should be targeted for primary prophylaxis. Those without varices should have follow-up endoscopy in 2 years or at the time of clinical decompensation. Those with small varices and preserved hepatic function (low-risk varices) should have repeat endoscopy at 1-year intervals.

Primary prophylaxis of variceal hemorrhage. Nonsselective β-blockers produce mesenteric arteriolar vasoconstriction and thus decrease portal pressure. They reduce the risk of bleeding from 25% to 15% (relative risk reduction, 40%; number needed to treat (NNT), 10). The best predictor of success is a sustained decrease in HVPG to values less than 12 mm Hg; those with a sustained 20% decrease in HVPG but to values above 12 mm Hg have a risk of bleeding under 10%. The use of β-blockers is limited by the small number of subjects who have a hemodynamic response (~20%–30%), intolerance to therapy (~10%–20%), and rebound portal hypertension if discontinued suddenly. Combination therapy with β-blockers and nitrates cannot be recommended because of the discrepant results of clinical trials. Endoscopic variceal ligation (EVL) reduces the risk of bleeding and
improves survival compared with no treatment.93 Meta-
analysis of trials of EVL vs β-blockers show that EVL
reduces the risk of bleeding from 23% to 14% with an
NNT of 11.94 However, the survival was similar to that
with β-blockers. These 2 treatments are therefore
comparable.

For patients with high-risk varices and no contraindi-
cations to the use of β-blockers, β-blockers are the usual
first-line treatment of choice, although EVL represents an
effective alternative (Figure 4). EVL is often used as the
first-line treatment in those who have a contraindication
for the use of β-blockers or risk factors for intolerance to
β-blockers. There is increasing interest in an a la carte
approach to primary prophylaxis, which is guided by the
HVPG response to initial β-blocker treatment.95 For
those with a hemodynamic nonresponse (HVPG drop less
than 20% and to values over 12 mm Hg), nitrates or EVL
are added in this approach. The clinical utility and cost-
effectiveness of this approach remains to be fully defined.

Management of active hemorrhage. The mortal-
ity from active hemorrhage has declined over the last
decade to approximately 15%–20%.34 Only 40%–50% of all
active bleeds cease to bleed spontaneously. Any bleeding
that occurs more than 48 hours after the initial admis-
sion for variceal hemorrhage and is separated by at least
a 24-hour bleed-free period is considered to represent
rebleeding.96 Rebleeding that occurs within 6 weeks of
onset of an acute bleed represents early rebleeding, and
bleeding episodes that occur at later times are defined as
late rebleeding episodes.

General measures. Packed red cells are transfused to
keep the target hemoglobin after transfusion around 9
gm/dL (hematocrit: 25%–30%); overttransfusion increases
the risk of rebleeding.97 Fresh frozen plasma and plate-
lets, although frequently used, do not reliably correct
coaagulopathy and can induce volume overload.98,99 Re-
combinant factor VII has not been found to improve
survival.100 Airway protection should be provided as re-
quired. Empiric use of a third-generation cephalosporin,
given intravenously, improves the outcomes of active
variceal hemorrhage101 (Table 2).

Control of bleeding. Although terlipressin, a syn-
thetic analogue of vasopressin, and somatostatin are ef-
effective in controlling bleeding, they are not available in
the United States.102,103 A combination of endoscopic
treatment (usually EVL) and pharmacologic treatment
(octreotide in the United States) is the preferred first-line
treatment to achieve hemostasis89,104-106 (Figure 5).

Continued severe hemetemesis with or without hypo-
tension and the need for continued transfusion to main-
tain the hematocrit are all markers of failure to control
active bleeding.96 The severity of portal hypertension
(HVPG > 20 mm Hg), sepsis, and overttransfusion have
all been linked to the risk of failure to control bleeding
and early rebleeding.32,107 The mortality associated with
active variceal hemorrhage rises exponentially with con-
tinued bleeding.

EVL may be attempted once more for early rebleeding,
but the decision to use this must be weighed against the
risks of complications and the need to provide definitive

![Figure 4. An algorithm for the primary prophylaxis of variceal hemorrhage.](image-url)

Table 2. General Measures for the Management of Active Variceal Hemorrhage

<table>
<thead>
<tr>
<th>Measure</th>
<th>Details</th>
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<tbody>
<tr>
<td>Airway protection</td>
<td>Endotracheal intubation if altered mental status or unconscious</td>
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<td></td>
<td>Gastric aspiration</td>
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<td>Hemodynamic resuscitation</td>
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<td>Crystalloids and blood transfusion</td>
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<td></td>
<td>Correction of coagulopathy and thrombocytopenia</td>
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<tr>
<td>Antibiotic prophylaxis for spontaneous bacterial peritonitis</td>
<td>Blood cultures and diagnostic paracentesis if ascites present</td>
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<tr>
<td></td>
<td>Third-generation cephalosporin intravenously and switch to oral</td>
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<tr>
<td></td>
<td>quinolone when patients stable and GI tract is functional</td>
</tr>
<tr>
<td>Renal support</td>
<td>Urine output above 50 mL per hour</td>
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<tr>
<td></td>
<td>Avoid nephrotoxic drugs</td>
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<tr>
<td>Metabolic support</td>
<td>Injectable thiamine when indicated</td>
</tr>
<tr>
<td></td>
<td>Monitoring and treating delerium tremens</td>
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<tr>
<td></td>
<td>Monitoring and treating acid base and electrolyte disturbances</td>
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<tr>
<td></td>
<td>Monitoring blood glucose level</td>
</tr>
<tr>
<td>Neurologic support</td>
<td>Monitor mental state</td>
</tr>
<tr>
<td></td>
<td>Avoid sedation</td>
</tr>
</tbody>
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Table 2: General Measures for the Management of Active Variceal Hemorrhage
therapy. Balloon tamponade can effectively produce temporary hemostasis in 80%–90% of cases. Transjugular intrahepatic portosystemic shunts (TIPS), a radiologic procedure by which a tract is created between the hepatic and portal vein and kept open by deployment of a coated stent, is the salvage procedure of choice in most subjects. TIPS produces hemostasis in over 90% of cases and is effective both for gastric and esophageal variceal bleeding.

**Prevention of recurrent bleeding.** EVL reduces the relative risk (vs sclerotherapy) of rebleeding by 37% and the absolute risk by 13% (NNT, 8). Nonselective \( \beta \)-blockers reduce the relative risk of bleeding by 33% with an NNT of 4.76. Combination therapy of EVL and \( \beta \)-blockers is superior to EVL alone. Although the use of nonselective \( \beta \)-blockers (with or without nitrates) vs sclerotherapy or in combination with sclerotherapy has been studied, their use has been supplanted by EVL + \( \beta \)-blockers. TIPS provide an effective salvage therapy for those who experience recurrent bleeding despite EVL + \( \beta \)-blockers. Liver transplantation should be considered if bleeding recurs despite a patent TIPS. TIPS patency is substantially superior with coated stents, which should be used whenever possible.

**Gastric varices.** Gastric varices are classified as gastroesophageal varices (GOV) or isolated gastric varices. Esophageal varices that extend along the lesser and greater curves are called GOV1 and GOV2, respectively. GOV1 can be treated like esophageal varices. GOV2 bleed more often than GOV1 and have a higher mortality as well. Isolated gastric varices commonly exist in the fundus and are often associated with spontaneous splenorenal collaterals. They bleed at lower HVPG than esophageal varices and bleed more severely. There is no consensus on primary prophylaxis of bleeding for isolated gastric varices. Once bleeding occurs, both cyanoacrylate injection sclerotherapy and TIPS have been used effectively to establish hemostasis and prevent rebleeding.

**Management of Ascites.** Ascites is a common complication of cirrhosis and is a marker of poor outcomes. Although many cases are medically manageable, a fraction of subjects become refractory to medical therapy. HRS often superimposes over refractory ascites. Although 50% of those with refractory ascites die within 6 months, the median survival after onset of type 1 HRS—the rapidly developing form of HRS—is 1.7 weeks.

**Management of uncomplicated ascites.** The initial diagnostic evaluation of ascites should always include a paracentesis. A serum to ascites albumin gradient >1.1 establishes the presence of portal hypertension-related ascites. A neutrophil count >250/mm\(^3\) is diagnostic of SBP. The severity of ascites may vary from that only detectable by imaging studies (grade 1) to that which is clinically obvious but not tense (grade 2) and tense ascites (grade 3). The goals of management of uncomplicated ascites are to provide symptoms relief, create a negative Na balance, and prevent complications of ascites. Na restriction is an important component of the treatment strategy. A low Na diet (60–90 mEq/day), equivalent to 1.5–2 g of salt/day, should be prescribed along with adequate calorie and protein intake to maintain the nutritional status of the patient.

Spironolactone inhibits distal tubular Na reabsorption by antagonizing aldosterone. The biologic effect half-life of spironolactone extends over days. It can therefore be dosed once a day, and dose changes should not be performed at less than 7-day intervals. The adverse effects of spironolactone include hyperpotremia, hyperkalemia, and painful gynecomastia. These may require a switch to amiloride, a less effective diuretic, which has a distinct mechanism of action and does not cause gynecomastia. The utility of canrenoate and eplerenone, which also act on the distal tubule, have not been extensively validated for cirrhotic ascites. Spironolactone has a synergistic effect with furosemide, a loop-acting diuretic that is less effective than spironolactone as a single agent for cirrhotic ascites. These drugs should be used in combination whenever possible. Therapy is usually started with 100 mg/day spironolactone and 40 mg furosemide and doses modified based on either adverse effects or lack of effect.
of response (<1.5 kg weight loss/week). Subjects with edema can tolerate more aggressive diuresis.\textsuperscript{135}

Large volume paracentesis (>5 L removed at a single sitting) (LVP) is used mainly for symptom relief and rapid mobilization of tense ascites.\textsuperscript{136} LVP is sometimes associated with postparacentesis circulatory dysfunction, characterized by worsened vasodilation, hyponatremia, increased renin, and norepinephrine activity.\textsuperscript{137} Intravenous administration of albumin (6–8 g/L ascites removed) reduces the risk of postparacentesis circulatory dysfunction, which has been associated with an increased mortality risk.\textsuperscript{138,139} Total paracentesis can be performed safely as long as albumin is given to prevent postparacentesis circulatory dysfunction.

Management of refractory ascites. Refractory ascites (Table 1) is associated with increasing systemic vasodilation, decreased effective circulating volume, and renal perfusion.\textsuperscript{140} Repeated LVP or total paracentesis are the most commonly used modalities for the treatment of refractory ascites. Although they immediately relieve ascites, they are associated with ascites recurrence in most subjects and do not improve survival.\textsuperscript{141,142} TIPS decompress the hepatic sinusoids and promote an increase in central volume, thereby decreasing proximal tubular Na reabsorption and causing a natriuresis over a period of several weeks.\textsuperscript{143} TIPS are superior to LVP for long-term control of ascites.\textsuperscript{144,145} However, this does not translate into improved survival, and the decrease in ascites-related health care resource utilization is offset by increased encephalopathy-related morbidity.\textsuperscript{145,146} In addition, for the same survival outcomes, TIPS is less cost-effective than LVP.\textsuperscript{147} Hyperbilirubinemia, severe hyperprothrombinemia, and renal failure are risk factors associated with a poor outcome after TIPS.\textsuperscript{148} The outcomes of TIPS for refractory ascites are best in those who have failed repeated LVP and have relatively preserved liver and renal function, ie, a creatinine level <1.5 mg/dL, international normalized ratio <1.5, and bilirubin level <2 mg/dL. Ideally, it should be used as a bridge to liver transplantation.

Management of hepatorenal syndrome. Type 2 HRS usually occurs in the setting of refractory ascites and is managed as refractory ascites. The use of intravenous albumin with initial antibiotic therapy for SBP decreases the risk of developing HRS and must always be given in this situation.\textsuperscript{149} In addition, in a single trial, pentoxyfylline treatment of alcoholic hepatitis decreased the incidence of HRS.\textsuperscript{150} It is important to recognize that HRS only accounts for 15%–20% of cases of renal insufficiency in those with cirrhosis and that hypovolemia, acute tubular necrosis, and iatrogenic renal toxicity remain important causes of renal failure in this population (Table 3).\textsuperscript{151,152}

The initial approach to the evaluation of sudden worsening of renal function in a subject with cirrhosis includes (1) exclusion of iatrogenic or other causes of renal failure, (2) aggressive evaluation for and treatment of sepsis, and (3) excluding volume depletion by clinical assessment and a therapeutic challenge with albumin (1 g/kg or up to 100 g) given intravenously.\textsuperscript{52} Type 1 HRS adds to the value of the Model for End-Stage Liver Disease score to predict mortality with medical treatment.\textsuperscript{153} Liver transplantation is the only definitive treatment of HRS, and the outcomes depend on successful treatment of HRS prior to transplantation.\textsuperscript{154,155} However, renal function may take months to recover and in some subjects may not recover at all. A variety of systemic vasoconstrictors (midodrine, ornipressin, terlipressin, and norepinephrine) have been used to reverse the systemic arterial vasodilation that drives effective hypovolemia and renal vasoconstriction in subjects with HRS.\textsuperscript{156–158} A recent randomized placebo-controlled trial found terlipressin to be effective in reversing type 1 HRS without affecting overall survival.\textsuperscript{159} Moreover, in those with HRS reversal, a marked improvement in survival was noted. In addition, recurrence of HRS after reversal was rare in this study. These exciting preliminary data provide hope for subjects with an otherwise fatal disease. It also provides a means to keep the patient alive while an organ is sought for transplantation.

In subjects with cirrhosis, renal failure, and severe sepsis, hydrocortisone may improve the hemodynamic abnormalities in HRS and may be used especially if a response to vasopressors is not seen.\textsuperscript{160} Dialysis support alone does not improve long-term survival.\textsuperscript{161} Other ascites-related complications. Dilutional hyponatremia results from the release of antiduretic hormone triggered by severe effective hypovolemia. It is a marker of poor outcome and predicts the development of HRS.\textsuperscript{152,162} The initial management includes volume restric-

\begin{table}[h]
\centering
\caption{Typical Urinary Findings in Renal Failure in Patients With Ascites}
\begin{tabular}{|c|c|c|c|}
\hline
Parameter & Osmolality mosm/kg & Urine (Na) mmol/L & Sediment & Protein mg/day \\
\hline
\textbf{Prerenal} & & & & \\
Hypovolemia & >500 & <20 & Normal & <500 \\
Hepatorenal syndrome & >500 & <10 & Normal & <500 \\
\hline
\textbf{Renal} & & & & \\
Acute tubular necrosis & <350 & >40 & Granular casts & 500–1500 \\
Interstitial nephritis & <350 & >40 & WBC eosinophils\textsuperscript{a} & 500–1500 \\
\textbf{Glomerular disease} & Variable & Variable & Red cell casts & Often >1500 \\
\hline
\end{tabular}
\end{table}

WBC, white blood cells.
\textsuperscript{a}Often because of drugs.
tion to 1500 cc/day. For serum Na levels <125 mEq/L, more severe volume restriction is recommended. However, it is difficult to comply with this limit. Preliminary data with aquaretic drugs that promote free water excretion by activating aquaporin channels in the nephron suggest that these could be an exciting class of drugs that can correct both ascites and dilutional hyponatremia.163

Hepatic hydrothorax results from movement of ascites across diaphragmatic fenestrae into the pleural cavity. It is initially managed by Na restriction, diuretics, and intermittent thoracentesis. TIPS have been used effectively in some patients with refractory hydrothorax.164 Placement of an indwelling catheter in the pleural cavity in such cases is associated with infection and a very high mortality and should be avoided.

Primary prophylaxis for SBP with an oral quinolone should be considered in those with low protein ascites.165 SBP should always be considered in the differential diagnosis when a patient with cirrhosis and ascites develops fever, abdominal pain, altered mental status, variceal hemorrhage, or azotemia. It is diagnosed by a diagnostic paracentesis and treated with a third-generation cephalosporin.166 A 5-day course has been found to be as effective as a 10-day course for uncomplicated SBP.167 SBP recurs frequently, and secondary prophylaxis with oral quinolones has been shown to be effective in preventing recurrence and is therefore recommended.168

**Management of HE**

There is a dearth of large scale, rigorously performed clinical trials evaluating the efficacy of various treatment for HE. The approach to management outlined below reflects the best evidence available and expert opinion.

**Approaches for HE.** Removal of the precipitating factor. Volume depletion and azotemia are important precipitants of HE. Diuretic-induced HE may also arise from the effects of hypokalemia and from urea-fueled ammonia genesis. Hydration is the key therapeutic approach. In one study, albumin was more efficacious than saline in reversing diuretic-induced HE.169 The mechanism for this effect is unclear, but the authors postulated a beneficial role for the antioxidant properties of albumin. Systemic infections can also precipitate HE and should be looked for and treated.

Reducing nitrogen and ammonia load. Diet: Prescription of low-protein diets for patients with HE should be abandoned. Even in patients admitted with an episode of HE, a randomized controlled trial showed no difference in the rate of awakening after prompt resumption of protein in the diet vs progressive increments over a 14-day period.170 The ingestion of vegetable protein, the preferred protein source, may be limited by the acceptance of such diets in the Western world, and a consultation with a dietitian may be useful. Randomized-controlled trials have shown benefits of branched-chain amino acid supplementation on a composite outcome of time to decompensation and death.171,172 The beneficial effects may be related to the anabolic effects of leucine.

**Nonabsorbable disaccharides.** Although there is a paucity of placebo controlled randomized clinical trials, there is extensive clinical experience with nonabsorbable disaccharide drugs. The mechanisms of action include acidification of the colon and a reduction in cerebral water content.173,174 In a recent study, lactulose improved neuropsychologic function in a large cohort of Indian patients.175

**Antibiotics.** Neomycin, metronidazole, and rifaximin, which have widely different antimicrobial spectra, have been used to treat HE. A meta-analysis suggested slightly better outcomes with antibiotics compared with nonabsorbable disaccharides.176 A recently completed study showed no differences between rifaximin and placebo in patients with minimal/mild encephalopathy; a subgroup of patients with asterixis was reported to benefit from the drug. Additional studies are currently underway.

**Probiotics.** Probiotics, a term that includes a wide range of nonpathogenic microorganisms, have been used in a wide range of digestive disorders.178,179 Colonization with nonurease containing lactobacilli would result in a reduction in colonic ammoniagenesis. Indeed, in a human study in which a probiotic preparation was combined with fiber in patients with cirrhosis, a reduction in circulating ammonia levels was seen. In this study, positive effects on intestinal permeability were likely because circulating endotoxin levels were decreased.

**Agents that increase ureagenesis.** Ammonia utilization for hepatic urea synthesis can be increased by Na phenylbutyrate (which eliminates 2 nitrogen atoms by forming phenylacetylglutamine) or Na benzoate, which binds to glycine (1 nitrogen atom) and is excreted by the kidneys as hippuric acid.180-182 Experience with these drugs in HE is limited,181,182 but a commercial preparation that combines both agents in an intravenous formulation may undergo testing in the United States. Zinc supplementation has also been used to increase ureagenesis. Although its use is generally considered to be safe, a pathogenic role for Zn in neuronal damage in some neurologic diseases has been reported.183 It should certainly be used if Zn deficiency is present.184 Ornithine-aspartate provides substrate for both urea and glutamine synthesis. It accelerates the recovery from grade 2 encephalopathy and is available in an intravenous formulation outside the United States.185

**Agents that work directly on the brain.** A meta-analysis of flumazenil, a benzodiazepine receptor antagonist, indicated a beneficial effect on short-term awakening from deeper stages of encephalopathy; the drug is, however, not available for chronic administration. Although the brain remains a key direct target for treatment of HE, there are no available agents that have been shown to improve HE by this mechanism.
Clinical scenarios. The different types of HE require different therapeutic approaches.

Precipitant-induced encephalopathy. Removal of the precipitant is a key factor in precipitant-induced encephalopathy. The benefit of other therapies in this situation is difficult to judge because removal of the precipitant per se has a major impact in the resolution of the episode.

Persistent encephalopathy. Two types of patients present with the persistent encephalopathy form of HE. With relatively well-preserved liver function, the possibility of a large spontaneous portal-systemic shunt should be considered because improvement of HE can occur after radiologic closure. For patients with more advanced liver disease, persistent encephalopathy and recurrent episodes of encephalopathy are treated with nonabsorbable disaccharides and/or antibiotics. Other therapies may be considered as second-line approaches. Transplantation is indicated for otherwise appropriate candidates.

Minimal encephalopathy. The need to treat minimal encephalopathy is as yet unclear. In patients in whom functional impairment is present, there may be a potential for improvement. Lactulose and rifaximin are often used, although data from randomized clinical trials are lacking.

References


58. Jover R, Rodrigo R, Felipo V, et al. Brain edema and inflammatory activation in bile duct ligated rats with diet-induced hyper-


