Management of Portal Hypertension

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Abstract: Complications of portal hypertension are the leading cause of death in patients with liver cirrhosis. Rational medical and endoscopic therapy is guided by a thorough understanding of the underlying pathophysiology of ascites, variceal formation and bleeding, hepatorenal syndrome, and hepatic encephalopathy. The pathophysiology of each clinical entity is reviewed followed by an evidence-based diagnostic and management algorithm.

Key Words: portal hypertension, varices, ascites, hepatorenal syndrome, management

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Portal hypertension with its complications is the leading cause of death in patients with liver cirrhosis. The severity of portal hypertension correlates strongly with overall patient survival.[1] This review will focus on the pathophysiology of portal hypertension and the management of esophageal varices, ascites, hepatorenal syndrome, and hepatic encephalopathy.

Pathophysiology

Normal pressures in the human portal venous system range from 3 to 6 mmHg. Portal hypertension is defined by an increase above 10 mmHg. Pressure changes in the portal system follow Ohm's law ($\Delta P = Q \times R$), where pressure (P) is defined as the product of flow (Q) and resistance (R).[2] This simple equation provides the rationale to the two main strategies of therapeutically lowering portal pressures by either decreasing portal inflow or reducing the sinusoidal resistance or a combination of both. The increased resistance is caused by prehepatic or posthepatic obstruction of blood flow; in most of cases of portal hypertension, resistance is secondary to intrahepatic causes due to liver cirrhosis mediated by an increase in sinusoidal pressures.[3] Increased vascular resistance in such cases consists of a fixed and dynamic component caused by liver fibrosis and vasospasm, respectively. The vasospastic component is mediated by endothelin,[4] angiotensin, and other factors. Simultaneously vasodilating factors such as nitric oxide (NO) are decreased in the hepatic circulation leading to an imbalance between vasoconstrictor and vasodilator stimuli.[5] This results in endothelial dysfunction of the hepatic microcirculation and increases splanchnic blood flow into the portal system mediated by arteriolar vasodilation and hence aggravates portal hypertension.[6]

Variceal Bleeding and Management

The most life-threatening complication of portal hypertension is acute variceal bleeding with a mortality as high as 30% depending on the stage of liver disease.[7] Varices are either isolated at the gastroesophageal junction or communicate with fundal veins leading to gastric varices. The risk of bleeding correlates strongly with portal pressures and varices generally do not bleed unless portal pressures are >12 mmHg, which serves as a target pressure to reduce portal hypertension.[8] The risk of venous wall rupture correlates with wall tension described by Laplace's law, wherein tension is defined by the product of the intraluminal to extraluminal pressure gradient ($Pi - Pe$) and the vessel radius (r) divided by the wall thickness (w) ($T = (Pi - Pe) \times r/w$). Endoscopic assessment of risk of variceal bleeding depends on variceal size and signs of wall thinning (hematocystic spots, red wale sign).[9,10] De novo variceal formation is estimated at about 6%/year in compensated cirrhosis.[7] Annual endoscopies for variceal screening are therefore still recommended but might not be cost-effective.[11]

Treatment strategies for portal hypertension can be divided in three categories: primary prevention of bleeding, secondary prevention after a previous bleeding episode, and management of acute hemorrhage.

Acute Variceal Bleeding

The management of acute bleeding requires a multidisciplinary approach. The patient should be admitted to an intensive care unit, where appropriate resuscitation can be performed. It is of paramount importance to prevent pulmonary aspiration and elective early airway management is recommended. The immediate strategy after volume resuscitation is pharmacologic attempt to acutely lower portal pressures, which can be achieved by intravenous administration of a vasopressin analogue (somatostatin, octreotide, terlipressin), which may temporarily lower portal pressures and might lead to better endoscopic visualization of the bleeding source. Vasopressin is no longer used because it can lead to cardiac ischemia.[12] Terlipressin, an N-triglycyl-8-lysine-vasopressin, causes splanchnic vasoconstriction without leading to systemic ischemia and has similar effectiveness compared with somatostatin,[13] octreotide,[14] and sclerotherapy.[15] Terlipressin is the only vasopressin analogue with a significant reduction in mortality as shown by a recent meta-analysis.[16] Prophylactic antibiotics improve short-term survival by reducing infectious complications in the setting of variceal bleeding.[17]

Emergent endoscopy is performed after initial hemodynamic stabilization. Sclerotherapy of esophageal varices was introduced in the late 1970s using a multitude of different

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sclerosants. It is more effective than balloon tamponade[18] but leads to deep esophageal ulcerations with the risk of delayed bleeding, predisposes to infections and pleural effusions.[19] Esophageal ligation therapy was therefore developed in 1986,[20] where rubber bands are applied on the varices leading to mechanical compression and secondary thrombosis and vascular obliteration. Multiple studies have shown the superiority of variceal band ligation in the acute setting and also in secondary prevention trials.[21,22] In the rare case where pharmacologic treatment and endoscopic means fail to achieve hemostasis, temporary esophageal balloon compression or implantation of transjugular intrahepatic portovenous shunt (TIPS) is an alternative, depending on local availability. Esophageal balloon tamponade is usually poorly tolerated and can be complicated by pulmonary aspiration and pressure necrosis of the esophageal wall.[23] Emergency TIPS as a "salvage method" after failed endoscopic hemostasis is very effective, leading to cessation of bleeding in 91% to 100% of patients[24,25] and can be combined with selective embolization of varices and collaterals. It is however technically challenging, and the expertise is not widely available. Emergency surgical portal shunts and esophageal transection carry a very high mortality and are nowadays rarely performed.[26]

Primary Prevention

Current practice guidelines recommend screening for varices in patients with cirrhosis at regular intervals.[27,28] Once varices are identified endoscopically, primary pharmacologic bleeding prophylaxis should be initiated. This is best achieved by the administration of nonselective beta blockers (propanolol, nadolol), which lower portal pressures by reducing cardiac output and lowering splanchnic blood flow by vasoconstriction.[29] A recently published meta-analysis of 12 studies using nonselective beta blocker for primary bleeding prophylaxis showed a reduction of bleeding risk from 25% to 15% over a 2-year period[30] with only minimally decreasing mortality from 27% to 23%. There is however currently no evidence to support the prophylactic treatment of small varices under 5 mm.[27] The therapeutic efficacy is most accurately monitored by hepatic venous pressure gradient (HVPG) measurement, which is however invasive and not routinely performed in most institutions.[32] As a surrogate marker for effective beta blockade, noninvasive hemodynamic monitoring is used with a target reduction in resting pulse rate by 25% or below 55 beats/min, as long as it is tolerated, without leading to symptomatic hypotension.[33] The Barcelona group was recently able to show better survival in patients with pharmacologic treatment of prevention of variceal rebleeding under invasive hemodynamic monitoring to achieve a documented decrease in HVPG $>20\%$ or to <12 mmHg. Responders also had a significantly lower risk of developing worsening ascites, spontaneous bacterial peritonitis, and hepatic encephalopathy. They therefore recommend HVPG monitoring since it provides relevant and unique prognostic information.[34] A combination of nonselective beta blocker and systemic nitrates is theoretically appealing by additionally lowering intrahepatic sinusoidal resistance but is not significantly more effective in preventing a first variceal bleed and is usually poorly tolerated because of significant hypotension and can therefore not be recommended. Endoscopic band ligation should be considered for patients intolerant to medical therapy.

Ascites

Development of significant ascites is a hallmark of decompensated liver cirrhosis and has a complex pathophysiology. Lymphatic drainage of the liver parenchyma is impaired by the disruption of normal liver architecture resulting in increased sinusoidal and lymphatic pressures. Lymphatic drainage from the liver capsule can even sometimes be observed laparoscopically (personal experience). The other main pathophysiologic factor causing ascites and peripheral edema is altered salt and water homeostasis. The serum-to-ascites albumin gradient is used to confirm ascites formation secondary to portal hypertension.[35] A serum-to-ascites albumin gradient of <1 is suggestive of a nonhepatic cause. Patients with decompensated liver cirrhosis show a significant reduction of their peripheral vascular resistance caused by intrinsic vasodilators (NO). This leads to renal activation of the renin-angiotensin-aldosterone system resulting in avid salt and water retention. The urine sodium excretion is markedly reduced.[5] The low oncotic vascular pressure in the setting of hypoalbuminemia is not sufficient to prevent interstitial leakage of water causing edema and ascites. Therapy for ascites is therefore guided by an understanding of the pathophysiology. The architectural disruption of sinusoidal blood flow is permanent in most patients but can sometimes be reduced in the setting of alcoholic hepatitis, where some of the sinusoidal constriction is reversible after alcohol abstinence. The main therapeutic intervention is to influence salt and water homeostasis by reducing the dietary salt intake to 60 to 90 mEq/day and to administer diuretics.[36,37] A frequent cause for diuretic-resistant ascites is inadequate sodium restriction. Aldosterone antagonists like spironolactone have now been used for over 20 years and are especially effective in combination with a loop diuretic. Both diuretics are usually given in a fixed ratio under close monitoring of electrolytes and renal function.[38] Urinary sodium excretion should be measured in patients without significant diuretic response. If the sodium excretion is high despite adequate diuretic therapy, the patient is most likely not compliant with the low salt diet. Low urinary sodium excretion and elevated serum creatinine are warning signs for the development of hepatorenal syndrome or overdiuresis. Patients who fail to have significant reduction of ascites despite high dose diuretic therapy (spironolactone 400 mg qd, furosemide 160 mg qd, or their equivalent) are termed refractory. In contrast, if they develop side effects of diuretic therapy (azotemia, hyponatremia, encephalopathy), they are considered to have diuretic-intractable ascites.[39] Therapeutic alternatives are either repeated large volume paracentesis in combination with plasma expanders or implantation of a TIPS. Repeated paracentesis (used for centuries) can safely be performed, as an outpatient procedure on an as-needed basis. The main complication of large volume paracentesis (>5 L) is hemodynamic dysregulation with transient worsening of renal function, which can be prevented by simultaneous albumin infusion (8 g of albumin per liter of ascites). TIPS implantation is an invasive alternative, where an intrahepatic portosystemic

shunt is created by implantation of a stent between the right hepatic and portal vein. This is very effective for the relief of ascites but has significant potential side effects, mainly worsening hepatic encephalopathy and liver function. The MELD score (Model of End Stage Liver disease) seems to be superior to the CHILD classification in predicting short-term survival after TIPS implantation.[40] Large studies have failed to show a mortality difference between TIPS and repeated paracentesis.[41] An added benefit of TIPS implantation is direct reduction of portal hypertension with associated lower risk of variceal bleeding. After TIPS implantation, surveillance with repeated duplex ultrasonography should be performed, given the high rate of shunt occlusion of 40% to 60% at 1 year and 70% to 85% at 2 years.[42–44] This risk seems to be significantly lower with the new PTFE-covered TIPS stents.[45] Surgical splenorenal shunting can only be recommended in Child-Pugh Class A cirrhosis given the high operative mortality for patients with more advanced liver disease.

Hepatorenal Syndrome (HRS)

Hepatorenal syndrome is defined as deterioration of renal function as a consequence of liver disease after another cause has been ruled out. The exact incidence in patients with cirrhosis and ascites is not known but may be as high as 40% over 5 years.[46] The main pathophysiologic factor is a decrease of renal blood flow caused by vasoconstriction of the renal macrocirculation and microcirculation caused by multiple neurohumeral factors: activation of the renin-angiotensin-aldosterone system, activation of the sympathetic nervous system, endothelins, natriuretic peptide, and several other mechanisms have been implicated.[47] Dilutional hyponatremia and ascites are universal in patients with HRS. The clinical hallmark is an increase of serum creatinine to greater than 1.5 mg/dL or creatinine clearance of less than 40 mL/min in the setting of low urine sodium excretion that is unresponsive to intravenous volume substitution to exclude prerenal azotemia. Arroyo et al developed major and minor diagnostic criteria.[48] The syndrome is clinically divided into two distinct types: a rapid decline in renal function (within 2 weeks) with a dismal transplant-free survival (HRS type 1) and a more protracted renal failure (HRS type 2) which remains stable for months. Common precipitating factors for the onset of HRS include bacterial infections,[49] especially spontaneous bacterial peritonitis, large volume paracentesis without plasma expansion,[50] and gastrointestinal bleeding.[51] Liver transplantation is the therapy of choice in patients with HRS type 1 and will reverse renal failure[52] but is not an option for the majority of patients due to the scarcity of available organs. Given its poor prognosis without transplantation, hemodialysis should only be instituted as a bridge to transplantation. Multiple medical regimens were investigated in the past in an attempt to overcome renal vasoconstriction by increasing splanchnic vascular resistance. Two types of vasopressors were used in most studies: vasopressin analogues (ornipressin, terlipressin) and alpha-adrenergic agonists (norepinephrine, midodrine) usually in combination with albumin as a plasma expander to improve vascular underfilling.[53] Terlipressin has shown the best results with a significantly lower ischemia rate compared with ornipressin. Intravenous administration of terlipressin in a dose of 0.5 to 2 mg every 4 to 6 hours leads to complete resolution of renal failure defined by serum creatinine <133 μmol/L in over 50% of patients and improves overall mortality.[54] TIPS implantation is associated with a reported improvement of HRS type 1 in small series by reducing vasoconstrictor activity and improving circulatory function.[55,56] However, TIPS implantation may lead to serious side effects and can therefore not be recommended routinely given the superior risk-benefit ratio of medical therapy with terlipressin.

Hepatic Encephalopathy

Hepatic encephalopathy (HE) is defined as a change in neurologic function as a consequence of acute or chronic liver disease. Change in mental status and deterioration to coma is an ominous sign in acute liver failure and can lead to brain edema and subsequent herniation and rapid death. Important precipitating factors include hypovolemia, gastrointestinal bleeding, hypokalemia, hypoxia, use of sedatives or tranquilizers, hypoglycemia, infection (especially spontaneous bacterial peritonitis), and TIPS implantation or surgical shunting. The degree of encephalopathy is part of the prognostic assessment in the Child-Pugh score. The pathogenesis of HE is not entirely understood. Extrahepatic and intrahepatic portovenous shunting seems to be a major contributor whereby multiple small molecular substances are directly delivered to the systemic circulation without hepatic modification and subsequently cross the blood-brain barrier to result in the neuropsychologic syndrome of HE. It can be divided into acute and chronic and clinically graded as follows: 0, normal; 1, change in awareness and personality; 2, lethargy, flapping tremor; 3, asleep but arousable; 4, coma. The 11th World Congress of Gastroenterology further defined three clinical categories of HE: type A related to acute liver failure; type B occurs in the setting of normal liver histology and the presence of a hepatic vascular bypass (portocaval shunting, TIPS), and type C due to cirrhosis (acute or chronic).[57] The pathophysiology is still a debate of multiple hypothesis: the prevailing assumption is that false neurotransmitters like GABAergic stimulators,[58] which arise from the splanchnic shunting, function as neuroinhibitors causing the clinical picture of HE (decreased awareness, sleepiness, etc.). Other important small molecules, which contribute to this syndrome, are ammonia,[59,60] glutamine,[61] and dopaminergic substances.[62] Some of the false neurotransmitters are produced by colonic bacterial fermentation. One of the most effective treatments of HE decreases the gut production and absorption of these substances by cleansing the large intestine using lactulose, which also acidifies feces and thereby limits diffusion of ammonia back into the splanchnic vasculature.[63] Lactulose is usually titrated to result in 4 to 6 bowel movements/day (15–30 mL qid). The effectiveness of this treatment strategy was however recently questioned in a Cochrane analysis, which included 22 randomized studies and found that nonabsorbable disaccharides were not significantly better than placebo. They also appeared to be inferior to antibiotics in reducing the risk of worsening HE.[64] The nonabsorbable antibiotic neomycin is used most frequently in this setting as second line treatment, but nephrotoxicity and ototoxicity are described when used long-term.[65] Lactulose enemas are reserved for patients with Grade 3 and 4 HE, who are unable to swallow without aspirating.[66]

Airway management is of utmost importance in those patients and early endotracheal intubation should be considered. The benzodiazepam antagonist flumazenil was used in several small studies with sometimes dramatic transient improvement of HE. Two meta-analyses were recently published showing a significant short-lived reduction of HE in about one fourth of treated patients,[67,68] supporting the hypothesis that GABAergic false neurotransmitters play a significant role in the pathophysiology of HE. However, the routine use of flumazenil cannot be recommended. The new MARS system (molecular absorbent recirculating system) is a nonbiologic liver support method based on the principles of dialysis, filtration, and adsorption. It allows for the safe and efficient removal of both albumin-bound and water-soluble toxic metabolites, including ammonia, aromatic amino acids, tryptophan, and related phenolic and indolic products, as well as benzodiazepines.[69] It has been studied in case series of approximately 60 patients so far, and neurologic improvement has been observed in the majority of patients. The system has also served as an effective bridge to liver transplantation.[70] No randomized comparative studies are yet available, and this treatment modality still needs to be considered experimental. The most effective treatment of HE is liver transplantation usually leading to full recovery.

In summary, complications of portal hypertension will occur in the majority of patients with liver cirrhosis and some of the symptoms can be ameliorated by the treatments outlined above. However, it should be kept in mind that a complete reversal of the underlying pathophysiology can only be achieved by liver transplantation and all suitable patients should be evaluated and referred for this lifesaving operation.

REFERENCES

1. Armonis A, Patch D, Burroughs A. Hepatic venous pressure measurement: an old test as a new prognostic marker in cirrhosis? *Hepatology.* 1997;25:245–248.
2. Bosch J, Pizcueta P, Feu F, et al. Pathophysiology of portal hypertension. *Gastroenterol Clin North Am*. 1992;21:1–14.
3. Shibayama Y, Nakata K. Localisation of increased hepatic vascular resistance in liver cirrhosis. *Hepatology.* 1985;5:643–647.
4. Rockey DC, Weisiger RA. Endothelin induced contractility of stellate cells from normal and cirrhotic rat liver: implications for regulation of portal pressure and resistance. *Hepatology.* 1996;24:233–240.
5. Wiest R, Groszmann RJ. The paradox of nitric oxide in cirrhosis and portal hypertension: too much, not enough. *Hepatology.* 2002;35:478–491.
6. García-Pagán JC, Bosch J, Rodés J. The role of vasoactive mediators in portal hypertension. *Semin Liver Dis*. 1995;6:1–9.
7. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. *Hepatology.* 1995;22:332–354.
8. Feu F, Garcia-Pagan JC, Bosch J, et al. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. *Lancet*. 1995;346:1056–1059.
9. North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices: a prospective multicenter study. *N Engl J Med*. 1988;319:983–989.
10. Beppu K, Inokuchi K, Koyanagi N, et al. Prediction of variceal hemorrhage by esophageal endoscopy. *Gastrointest Endosc*. 1981;27:213–218.
11. Spiegel B, Targownik L, Dulai GS, et al. Endoscopic screening for esophageal varices in cirrhosis: is it ever cost effective? *Hepatology.* 2003;37:366–377.
12. Gimson AE, Westaby D, Hegarty J, et al. A randomized trial of vasopressin and vasopressin plus nitroglycerin in the control of acute variceal hemorrhage. *Hepatology.* 1986;6:410–413.
13. Feu F, Ruiz del Arbol L, Banares R, et al. J. Double-blind randomized controlled trial comparing terlipressin and somatostatin for acute variceal hemorrhage: Variceal Bleeding Study Group. *Gastroenterology.* 1996;111:1291–1299.
14. Pedretti G, Elia G, Calzetti C, et al. Octreotide versus terlipressin in acute variceal hemorrhage in liver cirrhosis: emergency control and prevention of early rebleeding. *Clin Invest*. 1994;72:653–659.
15. Escorsell A, Ruiz del Arbol L, Planas R, et al. Multicenter randomized controlled trial of terlipressin versus sclerotherapy in the treatment of acute variceal bleeding: the TEST study. *Hepatology.* 2000;32:471–476.
16. Ioannou G, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. *Cochrane Database Syst Rev.* 2001;1:CD002147.
17. Bernard B, Grange JD, Khac EN, et al. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. *Hepatology.* 1999;29:1655–1661.
18. Paquet KJ, Feussner H. Endoscopic sclerosis and esophageal balloon tamponade in acute hemorrhage from esophagogastric varices: a prospective controlled randomized trial. *Hepatology.* 1985;5:580–583.
19. Helmy A, Hayes PC. Review article: current endoscopic therapeutic options in the management of variceal bleeding. *Aliment Pharmacol Ther.* 2001;15:575–594.
20. Van Stiegmann G, Cambre T, Sun JH. A new endoscopic elastic band ligating device. *Gastrointest Endosc*. 1986;32:230–233.
21. Gross M, Schiemann U, Muhlhofer A, et al. Meta-analysis: efficacy of therapeutic regimens in ongoing variceal bleeding. *Endoscopy.* 2001;33:737–746.
22. Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding: a meta-analysis. *Ann Intern Med*. 1995;123:280–287.
23. Vlavianos P, Gimson AES, Westaby D, et al. Ballon tamponade in variceal bleeding: use and misuse. *Br Med J.* 1989;298:1158–1165.
24. Chau TN, Patch D, Chan YW, et al. 'Salvage' transjugular intrahepatic portosystemic shunts: gastric fundal compared with esophageal variceal bleeding. *Gastroenterology.* 1998;114:981–987.
25. McCormick PA, Dick R, Panagou EB, et al. Emergency transjugular intrahepatic portosystemic stent shunting as salvage treatment for uncontrolled variceal bleeding. *Br J Surg*. 1994;81:1324–1327.
26. Rikkers LF, Sorrell WT, Jin G. Which portosystemic shunt is best? *Gastroenterol Clin North Am*. 1992;21:179–196.
27. de Franchis R. Updating consensus in portal hypertension: report of the Baveno III Consensus Workshop on definitions, methodology and therapeutic strategies in portal hypertension. *J Hepatol*. 2000;33:846–852.
28. Grace ND. Practice guidelines: diagnosis and treatment of gastrointestinal bleeding secondary to portal hypertension. *Am J Gastroenterol*. 1997;92:1081–1091.
29. Lebrec D, Hillon P, Munoz C, et al. The effect of propanolol on portal hypertension in patients with cirrhosis: a hemodynamic study. *Hepatology.* 1982;2:523–527.
30. D'Amico G, Pagliaro L, Bosch J. Pharmacological treatment of portal hypertension: an evidence-based approach. *Semin Liver Dis*. 1999;19:475–505.
31. Deleted in proof.
32. Thalheimer U, Mela M, Patch D, et al. Targeting portal pressure measurements: a critical reappraisal. *Hepatology.* 2004;39:286–290.
33. Garcia-Pagan JC, Escorsell A, Moitinho E, et al. Influence of pharmacological agents on portal hemodynamics: basis for its use in the treatment of portal hypertension. *Semin Liver Dis*. 1999;19:427–438.
34. Abraldes JG, Tarantino I, Turnes J, et al. Hemodynamic response to pharmacologic treatment of portal hypertension and long-term prognosis of cirrhosis. *Hepatology.* 2003;37:902–908.
35. Pare P, Talbot J, Hoefs JC. Serum-ascites albumin concentration gradient: a physiologic approach to the differential diagnosis of ascites. *Gastroenterology.* 1983;85:240–244.
36. Ginès P, Arroyo V, Rodés J. Pharmacotherapy of ascites associated with cirrhosis. *Drugs*. 1992;43:316–332.
37. Runyon BA. Management of adult patients with ascites caused by cirrhosis. *Hepatology.* 1998;27:264–272.
38. Gerbes AL. Medical treatment of ascites in cirrhosis. *J Hepatol*. 1993;17 (suppl 2):4–9.
39. Gines P, Arroyo V, Rodes J. Pathophysiology, complications, and treatment of ascites. *Clin Liver Dis*. 1997;1:129–155.
40. Salerno F, Merli M, Cazzaniga M, et al. MELD score is better than Child-Pugh score in predicting 3-months survival of patients undergoing

transjugular intrahepatic portosystemic shunt. *J Hepatol*. 2002;36:494–500.
41. Boyer TD. Transjugular intrahepatic portosystemic shunt: current status. *Gastroenterology.* 2003;124:1700–1710.
42. Rossle M, Siegerstetter V, Huber M, et al. The first decade of the transjugular intrahepatic portosystemic shunt (TIPS): state of the art. *Liver*. 1998;18:73–89.
43. Rosch J, Keller FS. Transjugular intrahepatic portosystemic shunt: present status, comparison with endoscopic therapy and shunt surgery, and future perspectives. *World J Surg*. 2001;25:337–345.
44. Saxon RS, Ross PL, Mendel-Hartvig J, et al. Transjugular intrahepatic portosystemic shunt patency and the importance of stenosis location in the development of recurrent symptoms. *Radiology.* 1998;207:683–693.
45. Rossi P, Salvatori FM, Fanelli F, et al. Polytetrafluoroethylene-covered Nitinol stent-graft for transjugular intrahepatic portosystemic shunt creation: 3-year experience. *Radiology.* 2004;231:820–830.
46. Ginès A, Escorsell A, Ginès P, et al. Incidence, predictive factors, and prognosis of hepatorenal syndrome in cirrhosis. *Gastroenterology.* 1993; 105:229–236.
47. Ginès P, Guevera M, Arroyo V, et al. Hepatorenal syndrome. *Lancet*. 2003;362:1819–1827.
48. Arroyo V, Gines P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis: International Ascites Club. *Hepatology.* 1996;23:164–176.
49. Follo A, Llovet JM, Navasa M, et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. *Hepatology.* 1994;20:1495–1501.
50. Gines P, Tito L, Arroyo V, et al. Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. *Gastroenterology.* 1988;94:1493–1502.
51. Cardenas A, Gines P, Uriz J, et al. Renal failure after upper gastrointestinal bleeding in cirrhosis: incidence, clinical course, predictive factors, and short-term prognosis. *Hepatology.* 2001;34:671–676.
52. Pham PT, Pham PC, Wilkinson AH. The kidney in liver transplantation. *Clin Liver Dis*. 2000;4:567–590.
53. Ortega R, Gines P, Uriz J, et al. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective, nonrandomized study. *Hepatology.* 2002;36:941–948.
54. Moreau R, Durand F, Poynard T, et al. Terlipressin in patients with cirrhosis and type 1 hepatorenal syndrome: a retrospective multicenter study. *Gastroenterology.* 2002;122:923–930.
55. Guevara M, Gines P, Bandi JC, et al. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. *Hepatology.* 1998;28:416–422.
56. Brensing KA, Textor J, Perz J, et al. Long term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant cirrhotics with hepatorenal syndrome: a phase II study. *Gut*. 2000;47:288–295.
57. Ferenci P, Lockwood A, Mullen K, et al. Hepatic encephalopathy: definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology.* 2002;35:716–721.
58. Schafer DF, Jones EA. Hepatic encephalopathy and the gamma-aminobutyric-acid neurotransmitter system. *Lancet*. 1982;1:18.
59. Butterworth RF. Pathophysiology of hepatic encephalopathy: a new look at ammonia. *Metab Brain Dis*. 2002;17:221–227.
60. James JH, Zipparo V, Jeppson B, et al. Hyperammonemia, plasma amino acid imbalance and blood-brain amino acid transport: a unified theory of portal-systemic encephalopathy. *Lancet*. 1979;2:772.
61. Michalak A, Rose C, Butterworth J, et al. Neuroactive amino acids and glutamate (NMDA) receptors in frontal cortex of rats with experimental acute liver failure. *Hepatology.* 1996;24:908.
62. Ferenci P, Püspök A, Steindl P. Current concepts in the pathophysiology of hepatic encephalopathy. *Eur J Clin Invest*. 1992;22:573.
63. Ferenci P, Herneth A, Steindl P. Newer approaches to treatment of hepatic encephalopathy. *Semin Liver Dis*. 1996;16:329.
64. Als-Nielsen B, Gluud L, Gluud C. Nonabsorbable disaccharides for hepatic encephalopathy. *Cochrane Database Syst Rev.* 2004;2:CD003044.
65. Conn HO, Leevy CM, Vlahcevic ZR, et al. Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. *Gastroenterology.* 1977;72:573.
66. Uribe M, Campollo O, Vargas F. Acidifying enemas (lactitol and lactulose) vs. nonacidifying enemas (tap water) to treat acute portal-systemic encephalopathy: a double-blind randomized clinical trial. *Hepatology.* 1987;7:639.
67. Als-Nielsen B, Kjaergard LL, Gluud C. Benzodiazepine receptor antagonists for acute and chronic hepatic encephalopathy (Cochrane Review). *Cochrane Database Syst Rev.* 2001;4:CD002798.
68. Goulenok C, Bernard B, Cadranel JF, et al. Flumazenil vs. placebo in hepatic encephalopathy in patients with cirrhosis: a meta-analysis. *Aliment Pharmacol Ther.* 2002;16:361.
69. Mitzner S, Loock J, Peszynski P, et al. Improvement in central nervous system functions during treatment of liver failure with albumin dialysis MARS: a review of clinical, biochemical, and electrophysiological data. *Metab Brain Dis*. 2002;17:463–475.
70. Stange J, Mitzner SR, Klammt S, et al. Liver support by extracorporeal blood purification: a clinical observation. *Liver Transpl*. 2000;6:603–613.