World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v20.i18.5442

World J Gastroenterol 2014 May 14; 20(18): 5442-5460
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (11): Cirrhosis

Cirrhosis and its complications: Evidence based treatment

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Author contributions: Nusrat S and Khan MS contributed to the review of the literature and initial draft of manuscript; Fazili J and Madhoun MF contributed to revising and final approval of the manuscript.

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Received: November 2, 2013 Revised: January 7, 2014
Accepted: February 17, 2014
Published online: May 14, 2014

Abstract

Cirrhosis results from progressive fibrosis and is the final outcome of all chronic liver disease. It is among the ten leading causes of death in United States. Cirrhosis can result in portal hypertension and/or hepatic dysfunction. Both of these either alone or in combination can lead to many complications, including ascites, varices, hepatic encephalopathy, hepatocellular carcinoma, hepatopulmonary syndrome, and coagulation disorders. Cirrhosis and its complications not only impair quality of life but also decrease survival. Managing patients with cirrhosis can be a challenge and requires an organized and systematic approach. Increasing physicians' knowledge about prevention and treatment of these potential complications is important to improve patient outcomes. A literature search of the published data was performed to provide a comprehensive review regarding the management of cirrhosis and its complications.

Key words: Ascites; Hepatic encephalopathy; Portal hypertension; Varices; Portopulmonary hypertension; Hepatopulmonary syndrome

Core tip: Cirrhosis is a leading cause of morbidity and mortality around the world. Recent data suggest treatment of underlying etiology can result in regression of fibrosis and result in improved outcomes. This review provides a comprehensive overview of different clinical manifestations of cirrhosis including compensated cirrhosis, ascites, varices, hepatic encephalopathy, bacterial infections and hepatocellular carcinoma. The review aims to discuss the different modalities used for diagnosis, screening and surveillance, current medical therapies, endoscopic interventions, surgical options and interventional radiology procedures.

Nusrat S, Khan MS, Fazili J, Madhoun MF. Cirrhosis and its complications: Evidence based treatment. *World J Gastroenterol* 2014; 20(18): 5442-5460 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i18/5442.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i18.5442

INTRODUCTION

Cirrhosis results from chronic liver disease, and is characterized by advanced fibrosis, scarring, and formation of regenerative nodules leading to architectural distortion. In the past cirrhosis was generally thought to be irreversible but recent studies have shown that treatments aimed at the underlying cause especially in earlier stages of the disease can improve or even reverse fibrosis[1,2]. Patients with cirrhosis are at increased risk of numerous complications and have a decreased life expectancy[3]. In 2010, cirrhosis was the eight leading cause of death in the United States and, combined with its complications accounted for approximately 49500 deaths[4].

This review will focus on the management of cirrhosis and its complications. The major complications of cirrhosis include varices, ascites, hepatic encephalopathy (HE), hepatopulmonary hypertension, hepatocellular carcinoma, hepatorenal syndrome, spontaneous bacterial peritonitis, and coagulation disorders. These can occur secondary to portal hypertension, abnormal synthetic function, or combination of both.

Portal hypertension can lead to the formation of venous collaterals, biochemical (increased production of vasoconstrictors, vascular endothelial growth factor, nitric oxide, and other splanchnic vasodilators) and functional abnormalities (plasma volume expansion and increased cardiac output), and thus contribute to the pathogenesis of many of the complications of cirrhosis. Measurement of hepatic venous pressure gradient (HVPG) can help quantify portal hypertension. Portal hypertension is present when HVPG is > 5, but is clinically significant when > 10[5,6].

COMPENSATED CIRRHOSIS AND ITS MANAGEMENT

Cirrhosis can remain compensated for years before development of decompensating events like jaundice, ascites, encephalopathy and/or variceal hemorrhage. The median survival of patients with compensated cirrhosis is much longer than in patients with evidence of decompensation and is about 9 years[7].

The main goals of management of compensated cirrhosis are (1) treatment of underlying etiology; (2) early recognition and treatment of complications; and (3) preventing superimposed insults. Specific therapy directed against underlying etiology has shown to improve survival, long-term outcomes and regression of fibrosis[8-12]. Evidence favoring regression of cirrhosis has now been documented in entire spectrum of chronic liver diseases including viral hepatitis, autoimmune hepatitis, primary biliary cirrhosis, biliary obstruction, NASH and hemochromatosis[13-18]. The last few years have seen significant improvement in cure rates for chronic liver disease especially viral hepatitis though the use of more effective anti-viral therapy for hepatitis B virus (HBV), HBC and HBD[19,20]. More importantly regression of fibrosis associated with ant-viral therapy is associated with improved liver function[21].

Patient with established cirrhosis should be monitored for complications and when possible steps should be taken to prevent their occurrence. The two complications in particular warranting screening are esophageal varices and hepatocellular carcinoma (HCC). The screening methods will be discussed in detail later in the review.

If not already immune all patient with cirrhosis should be immunized against Hepatitis A and Hepatitis B[22-24]. Other vaccines like influenza, pneumonia, tetanus, diphtheria, zoster, meningococcal and human papillomavirus (HPV) vaccination are also recommended[22]. All effort should be made to avoid agents that are associated with liver injury like alcohol, non-steroidal anti-inflammatory drugs (NSAIDs) and prescribed drugs with hepatotoxic potential *e.g.*, phenytoin[25-28].

ASCITES AND ITS MANAGEMENT

Ascites is the most common complication of cirrhosis[7]. It is also the most common complication that leads to hospital admission[29]. Approximately 15% of the patients with ascites will die in one year and 44% will die in five years[6].

Our review will focus only on patients with clinically evident ascites due to the paucity of data on patients with ascites evident only by imaging modalities. The American Association of Liver Disease (AASLD) recommends that patients for whom ascites are present on imaging modalities, but not clinically detectable, should be imaged again after an interval of 3 mo or when the ascites become clinically apparent[30]. A diagnostic paracentesis should be performed on all patients with new onset ascites.

Patients often require a combination of pharmacological and non-pharmacological therapies to adequately manage ascites and fluid retention. Controlled salt intake and oral diuretics are the backbone of first-line therapy[30].

Treatment of underlying etiology

Alcoholic liver disease is a leading cause of cirrhosis in western countries and, when present, cessation of alcohol use can lead to drastic improvement in ascites and other reversible components of alcoholic liver disease[31]. Similarly, treatment of hepatitis B, hepatitis C and autoimmune hepatitis can lead to resolution of ascites or a heightened response to medical therapy[32].

Bed rest

In theory, upright posture may further aggravate the plasma renin elevation found in patients with cirrhosis and exacerbate salt retention and impairs response to diuretics[33,34]. However, this theory is not supported by controlled clinical trials and is impractical[7]. Thus, bed rest is not advocated as a treatment[30].

Salt restriction

Treatment often begins with education regarding dietary sodium restriction[30]. Limiting salt intake to 2000 mg/d or 88 mmol/d is often recommended[30]. Fluid and weight loss are related to sodium balance and more stringent dietary restrictions can speed mobilization of fluid. However, restrictions < 2000 mg/d are not recommended because they are less palatable and create the potential to reduce food intake and worsen the coexisting malnutrition[35]. In addition marked reduction in sodium intake does not add efficacy to diuretic treatment, and can lead to increased incidence of diuretic-induced renal failure and hyponatremia[36]. Fluid restriction is not required in majority of patient with cirrhosis.

As previously mentioned, it is the sodium restriction, not the fluid restriction, that is responsible for fluid loss, as loss of sodium leads to passive loss of fluid[32].

Pharmacological therapy

If patients adhere to dietary sodium restriction, one of the goals of treatment is to increase the urinary secretion of sodium to greater than 78 mmol/d[30]. About 10%-15% of the patient have spontaneous urinary sodium excretion greater than 78 mmol/d, and can be managed with sodium restriction alone[32]. However, when given a choice, most patients would prefer a combination of diuretics and mild sodium restriction to strict sodium restriction alone[30].

First-line diuretics

The two most commonly used diuretics in patients with cirrhosis are spironolactone and furosemide[30]. Single-agent spironolactone has been shown to be more efficacious than furosemide[37]. A randomized trial in patients with new onset ascites and well preserved renal function noted slower diuresis and less need for dose adjustment with spironolactone alone, so the authors recommended this approach could be considered appropriate for outpatients[38]. However, a subsequent study which enrolled patient with long standing ascites, many of whom with significantly impaired renal perfusion favored use of combination therapy[39]. In addition hyperkalemia associated with spironolactone and drug's long half-life have limited its role as a single agent for patients with minimal fluid retention[40].

The typical initial diuretic regimen consists of daily oral 100 mg of spironolactone and 40 mg of furosemide[30]. Beginning with combination therapy has been supported by the results of randomized trials, which showed that this approach shortens the time to mobilization of moderate ascites[38]. In addition, most patients with cirrhosis will eventually require combination treatment[38].

If weight loss and natriuresis remain inadequate, the dose can be increased every 3-5 d, maintaining the 100:40 ratio[30]. In general, this ratio helps maintain normokalemia. Post-transplant patients and patients with parenchymal renal disease may tolerate less spironolactone secondary to hyperkalemia[41-43]. Hypokalemia is common in patients with alcoholic hepatitis and, in this scenario, furosemide can be temporarily held[9]. The usual daily maximum doses for spironolactone and furosemide are 400 mg and 160 mg, respectively[30]. Dosing at night or more than once daily reduces compliance and results in nocturia[44].

Second-line diuretics

Triamterene, metolazone and hydrochlorothiazide have been successfully used to treat ascites. However, hydrochlorothiazide can result in extreme hyponatremia when added to a combination of spironolactone and furosemide[45]. Amiloride (10-40 mg/d) is less efficacious and more expensive when compared to spironolactone, but its use can be justified in patients with tender gynecomastia[46]. Other diuretics, such as eplenerone, torasemide, and bumetanide are expensive and have not been extensively studied in the setting of cirrhosis and ascites.

Albumin infusion

An unblinded randomized controlled study showed mortality benefit in patients with new onset ascites who received weekly 25 g infusions of albumin for one year followed by infusions every other week[47]. Another trial noted that combination of diuretics and albumin result in higher response rates, shorted hospital stay, lower readmission rates and lower probability of recurrence[48]. However, further studies are required before this expensive treatment regimen can be advocated by societies like AASLD.

Speed of fluid loss

In patients with significant edema, there is no limit to daily weight loss[42]. After resolution of edema, daily loss of 0.5 kg is a reasonable maximum. In addition to fluid mobilization, other factors such as serum sodium levels, serum potassium levels, serum creatinine levels, and the presence of clinical complications like HE should guide therapy[49].

Utility of paracentesis

Large volume paracentesis is a safe and effective therapy for patients presenting with tense ascites[50]. However, this procedure should be followed by sodium restriction and diuretics for patients who are diuretic sensitive.

Refractory ascites

Refractory ascites occurs in about 5% of patients with cirrhosis. This condition is defined as ascites that cannot be mobilized despite of sodium restricted diet and high dose diuretics and that accumulates after therapeutic paracentesis[51].

Medical treatment options remain limited in patients with refractory ascites. Midodrine 7.5 mg three times a day compared to standard therapy has been shown in a pilot randomized control trial of 40 patients followed for a period of three months to increase urine volume, urine sodium, mean arterial pressures, and survival[52]. The same group in another pilot study compared the combination of midodrine and clonidine to standard therapy and noted an improvement in above parameters except survival[53]. However, at this time evidence supporting the use of midorine in this challenging patient population is weak and bigger studies are needed before routine use of this can be suggested. Other treatment options for this challenging condition include serial therapeutic paracentesis, liver transplantation, and transjugular intrahepatic portasystemic shunt (TIPS). Experimental treatment options include weekly albumin infusions of 50 g[47,54] and clonidine, either alone or in combination with spironolacton[55,56].

TIPS procedure involves placing a side-to-side portocaval shunt[57]. One of the earlier randomized trials comparing TIPS to serial paracentesis showed increased mortality in the TIPS group but this study was not only small but also took place very early in the development of the this new technique and involved patients with advanced liver disease[58]. Recently published clinical trials are more favorable and all show a better control of ascites in the TIPS arm[57,59,60]. In addition one of these showed a significant survival benefit. The results of these more recently published clinical trials is supported by multiple meta-analysis which report better control of ascites at the cost of more encephalopathy[61-63].

Screening of patients using validated scoring system like Model for End Stage Liver Disease (MELD), ejection fraction > 60% and use of poly-tetrafluoroethylene stents may result in further improved outcomes[64-68]. However, at this time TIPS remains a second-line therapy.

Medications that should be used with caution or avoided

NSAIDS can reduce sodium excretion. The AASLD recommends that the use of NSAIDS should generally be avoided in this setting[50].

Arterial pressure is an independent predictor of survival in patient with cirrhosis and is dependent on elevated levels of vasopressin, angiotensin, and aldosterone. Therefore, both the European Association for the study of liver and the AASLD recommend against the use of angiotensin converting inhibitors and angiotensin receptor blockers.

Propranolol, likely due to its negative impact on blood pressure, has been shown to shorten survival in patients with refractory ascites. The risks *vs* benefits of beta-blocker treatment should be weighed carefully and consideration should be given to discontinuing or not initiating this agent in the setting of refractory ascites[69].

HYPONATREMIA AND VAPTANS

Hyponatremia is commonly seen in patients with cirrhosis but symptoms are uncommon unless the levels are < 110 mmol/L or there is a rapid decline in sodium levels[70]. Severe hyponatremia warrants fluid restriction. Although there is no data supporting specific threshold and level of restriction; a serum sodium level < 120 mmol/L is reasonable. The efficacy of vaptans (vasopressin receptor antagonist) in treating hyponatremia and fluid overload has been studied mainly in heart failure but also in cirrhosis[71,72]. These drugs have shown to correct mild hyponatremia and the intravenous agent conuvaptan is approved for the treatment of Euvolemic and hypervolemic hyponatremia in inpatient setting[71]. Tolvaptan orally has shown to correct serum sodium in patients who have pretreatment levels < 130 mmol/L but discontinuation of drug leads to recurrence[72,73]. Rapid correction of hyponatremia can lead to central pontine myelinolysis and requires caution with their use. More studies are needed to prove the safety, efficacy and cost effectiveness of these drugs in patients with less urgent need to correct hyponatremia (levels > 120 mmol/L, chronic, asymptomatic).

BACTERIAL INFECTIONS AND CIRRHOSIS

The world-wide prevalence of bacterial infection in hospitalized patients with cirrhosis ranges between 33% and 47%[74,75]. Infections are a leading cause of death in patients with cirrhosis and mortality has been reported as high as 19% in one study[76]. Prevalence of infection is related to severity of liver disease and is more common in patients with Child C cirrhosis compared to Child A/B cirrhosis. Other risk factors include previous infection, gastrointestinal bleeding and history of alcohol abuse[77]. Medical procedures that can trigger bacterial infection include placement of intravenous catheters and urinary catheters, endoscopic sclerotherapy, variceal ligation, TIPS and paracentesis. Spontaneous bacterial infection (SBP) is the most common infection in cirrhosis and is described in detail below[78]. Urinary tract infections, pneumonia and bacteremia are responsible for 20%, 15% and 12% respectively of the remaining infections in this patient population[74].

The factors that predisposes cirrhotics to infections are not well defined but following mechanism have been suggested (1) portal hypertension results in creation of porto-systemic anastomosis, diverting blood that would normally go to the liver and thus impairing detoxification; (2) dysfunction of reticuloendothelial system; (3) impaired neutrophil phagocytosis; and (4) bacterial translocation resulting from bacterial overgrowth and intestinal barrier dysfunction[79,80].

As expected bacteria of intestinal origin especially *E. coli* are the most commonly recognized pathogens[81]. In hospitalized patients especially those receiving quinolones prophylaxis multiple drug resistant (MDR) gram positive cocci are being increasingly identified[76].

Commonly used diagnostic parameters like C-reactive protein and Systemic Inflammatory Response (SIRS) criteria have limited value secondary to decreased number of baseline polymorphnuclear leucocytes, elevated heart rate at baseline, baseline hyperventilation and blunted elevation of body temperature[82-84]. This can delay diagnosis and worsen outcomes thus a high level of suspicion is warranted.

Prompt and appropriate empirical antibiotic treatment should be instituted. When possible cultures should be obtained prior to starting antibiotics and therapy should be adjusted according to results. A careful strategy of limiting prophylactic antibiotics to high-risk population and selection of antibiotics based on culture results can help reduce the incidence of MDR infections.

SBP

Though the incidence of SBP has decreased from what was reported in earlier series (12%), it still remains com-

mon[85]. This diagnosis requires the presence of an absolute polymorphonuclear leukocyte (PMN) count ≥ 250 cells/mm^3 in the ascitic fluid without an evident intra-abdominal, surgically treatable source of infection[86].

Empirical antibiotics

In a compatible clinical setting, patient meetings the above criteria should be started on antibiotics[86]. Waiting for positive cultures may result in serious and fatal outcomes[19].

Patients with culture-negative neutrocytic ascites present similar signs and symptoms to SBP[86]. A prospective study noted that when serial samples were obtained in culture negative neutrocytic patients before initiation of antibiotics, 34.5% became culture positive[87]. A contrasting scenario is one in which patient presents with sign and symptoms of SBP (fever, abdominal pain and encephalopathy) but a PMN count < 250 cells/mm^3. These patients should also be started on empirical antibiotics until culture results are available[42,87].

Empirical treatment with cefotaxime has shown to be superior to ampicillin and tobramycin[88]. It covers 95% of the flora. Thus, cefotaxime and similar third generation cephalosporins are the treatment of choice when SBP is suspected[88]. No difference in efficacy was noted between 5 d *vs* 10 d of therapy[89].

Treatment of established spontaneous bacterial peritonitis

In a select group of patients with SBP (those without vomiting, shock, grade ≥ 2 HE, or serum creatinine greater than 3 mg/dL) oral ofloxacin was as efficacious as intravenous cefotaxime[90]. However, because of possible resistance, its use is not recommended for patients who had received quinolone for prophylaxis[91].

Adding albumin to cefotaxime has been shown to decrease mortality from 29% to 10%[92]. One of the studies favored addition of albumin in patients with serum creatinine > 1 mg/dL, blood urea nitrogen > 30 mg/dL, or total bilirubin ≥ 3 mg/dL[92].

Prevention of recurrence

Recurrence of SBP is reported to be up to 69% within one year[93]. Risk factors for SBP include a prior episode of SBP, ascitic total protein less than 1 g/dL, or a variceal bleed[94]. Norfloxacin 400 mg daily was successful in preventing SBP in patients with low protein-ascites and history of SBP[42,95].

Based on currently available literature, AASLD favors continuous use of norfloxacin (or trimethoprim/sulfamethoxazole) in patients with history of SBP and those with ascitic fluid total protein < 1.5 g/dL, along with impaired renal function (creatinine ≥ 1.2, BUN ≥ 25 or serum Na ≤ 130) or liver failure (Child score ≥ 9 and bilirubin ≥ 3)[42]. Weekly oral administration of ciprofloxacin 750 mg has shown to be effective; however, intermittent dosing is associated with the concern of rapid selection of resistant strains[96].

Secondary bacterial peritonitis

Secondary bacterial peritonitis is caused by surgically treatable intra-abdominal source *i.e.*, either perforation of viscus or loculated abscesses and is responsible for less than 5% of infected ascites[97,98]. Clinical symptoms don't differentiate SBP from secondary bacterial peritonitis. Finding suggestive of secondary bacterial peritonitis include multiple organism on Gram's stain or culture, total protein > 1 g/dL, LDH > upper limit of normal for serum and glucose < 50 mg/dL[90,96]. Patients with secondary bacterial peritonitis should receive anaerobic antibiotics along with 3rd generation cephalosporin and may require laparotomy[96].

HEPATORENAL SYNDROME

The criteria used to define hepatorenal renal syndrome were updated in 2007 (Table 1). hepatorenal syndrome (HRS) is further classified into two types. Type I is characterized by a doubling of creatinine to a level greater than 2.5 mg/dL in less than 2 wk, while type Ⅱ results in a more progressive loss of renal function. The incidence of HRS after development of cirrhosis with ascites is 18% and 39% at one and five years[99].

Prevention

In the setting of spontaneous bacterial peritonitis, albumin infusion has been shown to prevent HRS and improve survival[92]. In patients with cirrhosis and creatinine clearance between 41-80 mL/min, pentoxifyllin was found to be superior to placebo in preventing HRS[100].

Treatment

As part of general management for HPS, excessive fluid administration should be avoided, to prevent volume overload and hyponatremia. If potassium sparing diuretics are used, patients should be monitored closely for hyperkalemia.

A number of pharmacological agents, primarily vasoconstrictors, have been studied and have shown promise, especially for patients with type I HRS. The most common drug combination used alongside albumin treatment is a combination of midodrine and octreotide[101,102]. This regimen can be used outside of an ICU, even in the patient's home, and has been shown to be superior to dopamine combined with albumin and albumin treatment alone. AASLD recommends use of octreotide and midodrine in treatment of patients with type I HPS.

A multicenter randomized trial of terlipressin and albumin *vs* albumin alone showed an improvement in creatinine, but no survival benefit at 3 mo[103]. A recent meta-analysis of vasoconstrictor treatment (terlipressin, octreotide, midodrine and norepinephrine) of type I and type Ⅱ HPS showed reduced mortality in patients on vasoconstrictors in combination with and without albumin as compared with albumin alone or no intervention[104]. The same study showed a survival advantage with terlipressin and albumin in patients with

Table 1 Diagnostic criteria for hepatorenal syndrome

Chronic or acute hepatic disease with advanced hepatic failure and portal hypertension
Serum creatinine > 1.5 mg/dL
No sustained improvement of serum creatinine after at least 2 d of diuretic withdrawal and volume expansion with albumin or isotine saline
Absence of shock
No current or recent treatment with nephrotoxic drugs
Absence of parenchymal disease as indicated by proteinuria > 500 mg/d microhematuria (> 50 red blood cells per high-power field) and/or abnormal renal ultrasonography

Table 2 Drug therapy for portopulmonary hypertension

Drug	Route of administration	Mechanism of action
Epoprostenol	Intravenous	Vasodilator, anti-platelet and anti-proliferative
Ambrisentan	Orally	Selective endothelin-A receptor antagonist
Bosentan	Orally	Endothelin-A and Endothelin B receptor antagonist
Sildenafil	Orally	Phosphodiesterase inhibitor
Iloprost	Inhaled	Prostacyclin analogue

type I HRS but not in type II HPS.

Use of albumin and norepinephrine or vasopressin can be considered in ICU settings[42].

Liver transplantation is an effective treatment: however, the number of transplanted patients is still very low[105]. Hemodialysis is frequently used to correct electrolyte imbalance and azotemia before liver transplantation[106]. If a patient is dialyzed for more than 8 wk prior liver transplant, simultaneous kidney transplant should be considered[107].

PORTOPULMONARY HYPERTENSION

Portopulmonary hypertension (PPHTN) is a well-recognized complication of cirrhosis. It is defined as pulmonary hypertension (PAH) (mean pulmonary artery pressure > 25 mmHg and pulmonary capillary wedge pressure < 15 mmHg) in a patient with coexisting portal hypertension and no other alternative cause of PAH[108]. Different treatment options are currently being researched as most of the current therapeutic options are carryover from studies conducted in patient with idiopathic pulmonary hypertension.

A baseline assessment of disease severity is important as this aid in accessing response to therapy. The assessment should include right heart catheterization and tests of exercise capacity using New York Heart Association or World Health Organization functional tests[109].

Patients with PPHTN are at increased risk of pulmonary vascular thrombosis. Based on the studies done in IPAH showing increased survival, it is reasonable to start these patients on anti-coagulation drugs, if there are no contraindications[110]. Use of diuretics has been discussed in detail previously.

Other agents that have been used to treat PPHTN include epoprostenol, bosentan, sildenafil, and iloprost (Table 2)[111,112]. These agents have a complex mechanism of action including vasodilators, vascular growth, and remodeling. The availability of only limited data precludes recommendations in favor of a specific agent.

In patients with PPHTN, liver transplantation has been shown to improve and at times completely resolve PAH[113-115]. There are no hemodynamic criteria to determine candidacy, and it is unclear whether the severity of PAH affects outcomes. Limited data suggests that mild to moderate disease does not affect mortality whereas severe PAH (systolic PAP > 60 mmHg) is associated with poor outcomes[108]. There are no studies that have compared advance therapy to liver transplantation.

HEPATOPULMONARY SYNDROME

The triad of liver dysfunction, intrapulmonary vasodilation and arterial oxygenation defect is used to define hepatopulmonary syndrome (HPS)[108]. The prevalence varies from 10% to 17% in the cirrhotic population and is associated with increased mortality[116,117].

Liver transplantation improves 5 years survival from 23% to 63%[118]. Even with transplant, prognosis remains grim for most patients. The factors predictive of poor prognosis include a pre-transplant PaO_2 < 50 mmHg and a macroaggregated albumin (MAA) shunt fraction > 20%, which have a mortality rate as high as 67% post-transplant[118,119]. These findings led to the concept of a "transplant window" in which HPS patients with PaO_2 less than 60 mmHg are prioritized for a transplant, while patients with more severe hypoxemia are excluded.

The role of medical therapy in treatment of HPS is limited and remains an area of active research. Fukushima *et al*[120] (2007) reported two cases demonstrating improvement in liver function following oxygen therapy, but the role of oxygen in the absence of prospective studies is limited to symptomatic therapy, in order to prevent end organ damage. Other medications including methylene blue, allium sativum (garlic), curcumin, somatostatin analogue (*e.g.*, octreotide), nitric oxide synthatase inhibitors, glucocorticoids, beta blockers, and chemotherapy have been tried with little or no evidence for im-

provement of symptoms or mortality benefits[108,121-126].

The transjugular intrahepatic shunt (TIPS) has been used to improve gas exchange and shunt fraction in HPS: however, the data is not very encouraging[127,128]. Intra-arterial coil embolization of discrete pulmonary arteriovenous communications improves right to left shunt and has been used successfully in patients with large fistula amenable to radiographic interventions[129]. Coiled embolization has also been used successfully in a patient with persistent hypoxia 6 mo after liver transplantation[130].

GASTROESOPHAGEAL VARICES

Gastroesophageal varices are present in about half of the patients with cirrhosis. The occurrence of varices correlates with the severity of liver disease[131,132]. Variceal hemorrhage is the most lethal complication of cirrhosis[133]. Despite advancements in therapy, the mortality rate at 6 wk is at least 20%[133]. Size of the varix is the most important predictor of hemorrhage: other predictors include decompensated cirrhosis (Child B/C) and red wale sign[134,135].

Factors predictive of variceal rupture

Variceal wall tension determined by vessel diameter (large > small) is likely the most important factor that determines variceal rupture[136]. In addition, wall tension is affected by pressure in the varix, which is related to HVPG. Studies have shown that variceal rupture rarely occurs when HPVG < 12 mmHg[137,138].

Screening

As previously mentioned prevalence of varices correlates with severity of liver disease and ranges from 40% in Child A patients to 85% in Child C patients[139]. Transient elastography provides a non-invasive means of predicting the presence of esophageal varices and when combined with platelet count > 120000 per micro liter has a negative predictive value approaching 100%[140,141]. In addition, factors like age > 50, platelet count < 150000 per micro liter, albumin < 3.6 g/dL and ascites can help predict the presence of varices but accuracy of these is limited without performing an endoscopic evaluation[142-144]. AASLD now recommends screening EGD once diagnosis of cirrhosis is established[145]. However, due to cost and sedation associated with EGD, AASLD suggests that this can be avoided in patients who are already taking non-selective beta-blockers for other reasons[145]. Recently, capsule endoscopy has been shown to be safe, but sensitivity of this procedure remains to be established[146].

No varices on endoscopic evaluation

A recent study comparing timolol to placebo showed that in patients without varices but with portal hypertension even a mild reduction in HPVG (10% from baseline) after 1 year of therapy significantly lowered development of varices[147]. A larger percentage of patients on timolol achieved this reduction but its use was associated with significantly higher number of moderate to severe adverse events[147]. AASLD does not recommend routine use of beta-blockers in patient without varices. Surveillance endoscopy should be repeated every 2-3 years or annually in cases of decompensation[148].

Primary prophylaxis

In the absence of a prior variceal bleed, treatment with a non-selective beta-blocker is recommended in patients with small varices (< 5 mm) who also present with criteria for increased risk of bleeding (Child B/C and red wale sign)[145]. In patients with small varices and no criteria for increased hemorrhage, non-selective beta-blockers can be used, but their effectiveness is yet to be established[149].

In patients with medium to large varices, both beta-blockers and endoscopic variceal ligation (EVL) can be used. The effectiveness of non-selective beta-blockers is well established in this group of patients, and the use of these drugs has been shown to significantly decrease the rate of first variceal hemorrhage and to improve mortality[52]. Propranolol and nadolol are usually started at 20 mg BID and 40 mg daily, respectively, and titrated to the maximum tolerated dose. Prophylactic therapy should be continued indefinitely[150].

Esophageal varices ligation (EVL) is a local endoscopic therapy during which rubber bands are placed to eradicate the varices. It is more effective and is associated with fewer side effects than sclerotherapy: thus, it is widely accepted as the endoscopic method of choice for the primary prevention of variceal bleeding[151].

Recently, a meta-analysis comparing β-blocker administration to endoscopic variceal ligation (EVL) for primary prophylaxis showed that EVL was associated with a slightly lesser incidence of first variceal bleed, but no difference in mortality[152,153]. Though EVL was associated with lower incidence of adverse events, these events were more severe and included bleeding from ligation ulcers. In addition, adverse events requiring discontinuation of β-blocker resolved after stopping therapy[152,153].

Based on a careful review of available data, a consensus panel concluded that either non-selective β-blocker or EVL can be used for primary prophylaxis in patients with medium to large varices who are at risk of bleeding, based on patient characteristics and local expertise and resources. However, in patients with medium to large varices who are not at higher risk of bleeding, non-selective β-blocker treatment is preferred[145]. AASLD recommends against a repeat EGD in patients who are placed on β-blockers unless there is evidence of decompensation or active GI bleeding[145]. In patients treated with EVL, EGD should be repeated every 1-2 wk until obliteration followed for recurrence[145,154].

Nitrates, TIPS and sclerotherapy are not recommended for primary prophylaxis of variceal bleeding[155,156].

Acute variceal hemorrhage

Patients presenting with acute variceal bleed should be

Table 3 Classification of gastric varices

Gastroesphageal varices		Isolated gastric varices	
Type I	Extend along the lesser curvature	Type I	Involves the fundus
Type II	Extend along the fundus	Type II	Involves the body and/or antrum

admitted to the ICU[157]. Hemoglobin should be maintained around 7 g/dL. Transfusions to achieve replacement of all lost blood should be avoided as it can lead to increased portal pressures and subsequently an increased risk of rebleeding and higher mortality[158]. Transfusion of platelets and fresh frozen plasma can be considered in the presence of severe coagulopathy and thrombocytopenia. Antibiotics are recommended in all patients with or without ascites, as these drugs have been shown to reduce the risk of infections and improve survival[159]. Use of erythromycin has been shown to improve visibility and decreases procedure time[160].

Pharmacological therapy should be initiated as soon as diagnosis of variceal hemorrhage is made[161]. Different treatment options include vasopressin, terlipressin, and somatostatin analogues. Vasopressin is the most potent splanchnic vasoconstrictor, but its use is limited by number of associated side effects[162,163]. Terlipressin is a synthetic analogue of vasopressin with fewer adverse effects and a longer half-life[149]. Somatostatin and its analogue also result in splanchnic vasoconstriction. Results of a meta-analysis of trials of octreotide have been controversial[164].

Though pharmacological therapies have been shown to be safe and effective, an EGD should be performed as soon as possible. A meta-analysis of 10 clinical trials revealed that in the initial control of variceal hemorrhage, EVL is clearly superior to sclerotherapy[153]. The addition of pharmacological therapy to endoscopic therapy (EVL and sclerotherapy) has been demonstrated to improve control of initial bleeding without affecting mortality or adverse events[165].

In about 10%-20% patients variceal bleeding can't be controlled or reoccurs despite of endoscopic and pharmacological therapy. A HVPG > 20 mmHg is predictive of treatment failure[166]. In the event that bleeding cannot be controlled with pharmacological and endoscopic therapy, depending on the local expertise shunt therapy can be considered[167,168]. A recently published small study showed early TIPS placement (within 24 h of hemorrhage) in high-risk patients (HVPG > 20) is associated with significantly improved survival[169]. However, larger studies with longer duration of follow-up are needed before early TIPS can be recommended. Balloon tamponade (Sengstaken-Blakemore tube) can temporarily control bleeding in more than 80% of the patients[170]. It can result in potentially lethal complications such as aspiration, migration and necrosis therefore it should be used only as a temporizing measure in patient with uncontrolled hemorrhage for whom a more definitive therapy (*e.g.*, TIPS) is planned within 24 h of placement[145].

Secondary prophylaxis

Patients who survive an acute variceal bleed should receive therapy to prevent recurrence[154]. A combination of non-selective beta-blocker and EVL is the best possible option. As above, β-blockers should be adjusted to the maximum tolerated dose. EGD should be repeated every 1-2 wk until obliteration, followed by surveillance EGD at 1-3 mo following obliteration, and then every 6-12 mo to check for recurrence[145,154].

Shunt surgery is effective in preventing rebleeding. However, it has no survival benefit and significantly increases the risk of HE[171]. A meta-analysis compared TIPS to endoscopic therapy as first-line treatment and, not surprisingly, showed that TIPS was superior in preventing recurrent hemorrhage but was associated with increased risk of HE and no change in mortality[172,173]. Therefore, the role of TIPS as a first line therapy is limited. It should be used as a rescue therapy in patients who fail to respond to pharmacological plus endoscopic treatment[174].

Gastric varices

Gastric varices are further classified as gastroesophageal (GOV) and isolated gastric varices (IGV) according to their location (Table 3). Data on the management of gastric varices is not as strong as for esophageal varices. Type 1 Gastroesophageal varices (GOV1) are considered an extension of esophageal varices and managed in the same way. The presence of type 1 isolated gastric varices (IGV1) requires the exclusion of splenic vein thrombosis and, if present, the therapy is splenectomy[175]. In contrast to esophageal varices, tissue adhesives such as N-butyl-cyanoacrylate, isobutyl-2-cyanoacylate, or thrombin are more effective in controlling the initial bleed as well as limiting the rate of recurrent hemorrhage in patients with type 2 gastroesophageal varices, type 2 isolated gastric varices, and also in patients with IGV1, if splenic vein thrombosis is excluded[176,177].

The threshold to place a TIPS for bleeding gastric varices is much lower than for esophageal varices and in the absence of above adhesive agents, operator unfamiliarity or failure of single endoscopic treatment, TIPS can be recommended[145].

HE

HE is a complex neuropsychiatric condition ranging from mild confusion to coma and death (Table 4). HE is further classified as overt hepatic encephalopathy (OHE), and minimal hepatic encephalopathy (MHE)[178]. It is estimated that 30%-45% of patients with cirrhosis develop

Table 4 Grades of hepatic encephalopathy

	Symptoms	Asterixis	EEG abnormal
Grade 1	Mild confusion, disordered sleep, slurred speech, shortened attention span, euphoria or depression	Yes/No	No
Grade 2	Lethargy, inappropriate behavior, moderate confusion	Yes	Yes
Grade 3	Sever confusion, incoherent, somnolent but arousable	Yes	Yes
Grade 4	Coma, unresponsive to pain	No	Yes

OHE while 60%-80% of these patients have evidence of mild cognitive dysfunction or MHE. HE results in impaired judgment, poor quality of life, and high risk of accidents[179,180].

Treatment of MHE

Treatment of HE is dependent on the stage and acuity of the disease. Several studies have demonstrated improvement in the psychometric parameters and neurophysiological symptoms in patients with MHE with the use of lactulose and probiotics[181,182]. However, these studies were small and short in duration. In the absence of bigger and well-designed clinical trials, there is currently no standard of care for patients with MHE[183].

Treatment of OHE

Unlike MHE, the management of OHE is better defined, and includes both prevention measures and therapeutic options. Generally, grade I and Ⅱ HE can be managed in the outpatient setting. Patients with more severe HE (grade Ⅲ-Ⅳ) require hospital admission, ideally to an intensive care unit. Such patients should be evaluated for airway protection and intubated if required[184]. All patients should be evaluated for possible precipitating factors like infection, bleeding or electrolyte derangements and treated according.

Nutrition

All patients with HE require nutritional support. The aim should be to provide a total energy intake of about 35-40 Kcal/kg daily[42]. Contrary to previous beliefs, patients with HE should not be protein restricted, and a protein intake of 1.2 to 1.5 g/kg per day should be maintained[185,186].

First-line pharmacological therapy

Lactulose is the mainstay of treatment and results in improvement in approximately 70%-80% of patients with OHE[187]. The usual dose is 30-45 mL two to four times per day. The dose is titrated to achieve three to four soft bowel movements per day. Lactulose can be administered as an enema for patients who are unable to tolerate oral intake. Lactulose has been shown to decrease recurrent episodes of HE, but failed to show any survival benefit[188].

Antibiotics for OHE

As a general rule, antibiotics are added to lactulose rather than used as a substitute. Rifaximin, a non-absorbable antibiotic, is commonly used at a dose of 550 mg twice daily or 400 mg thrice daily. It was found to be equally safe and efficacious for both acute and chronic HE when compared to lactulose[189]. Rifaximin has shown to improve quality of life and performance. For this reason, some authors favor its use as a first-line agent in patients with HE. However, cost remains a hurdle[190].

Neomycin is Food and Drug Administration (FDA) approved for the treatment of acute HE, but not chronic HE[191]. It has been shown to be as effective as lactulose, but due to poor absorption it may result in renal toxicity, ototoxicity, and neurotoxicity[192].

Other oral antibiotics, including vancomycin and nitazoxanide, have been shown to be effective in limited clinical trials. However, these are not as commonly used.

Role of probiotics

The use of probiotics as a treatment for HE is a primary focus of contemporary research. Probiotics work on the principle of decreasing urease-producing bacteria and promoting growth of non-urease producing bacteria. In cirrhotic patients with mild HE (grade I and Ⅱ), treatment with enterococcus faecium was found to be as effective as lactulose in reducing ammonia levels and improving mental status[193]. Of the various probiotics available, the two that appear to be efficacious are lactobacillus and bifidobacteria[194]. However, it must be noted that probiotics are still in early stages of research, and should be used with caution, especially in immune-compromised patients.

Experimental therapies

Oral L-ornithine-L-aspartate (LOLA) is a stable salt of two amino acids[194]. It lowers blood ammonia levels by increasing metabolism of ammonia to glutamine. LOLA has been shown to be effective in treating mild HE, and is frequently used in countries outside the US[195,196].

Other ammonia eliminating medications including L-ornithine phenylacetate, sodium benzoate, and L-carnitine have been shown to be effective, but still require clinical trials to prove their efficacy and safety.

Aromatic amino acids (AAA) are the precursors for monoamine neurotransmitters. In patients with cirrhosis, the AAA to branched-chain amino acid (BCAA) ratio is increased. This increased ratio can result in increased excitability and can potentially precipitate HE. Small studies have shown that BCAA improves symptoms and lowers mortality rate. However, a meta-analysis of 11 randomized trials failed to show any benefit[197,198].

Acarbose, a drug commonly used for the treatment of diabetes mellitus, has been shown to decrease blood

ammonia levels along with clinical improvement[199].

Flumazenil, a benzodiazepine receptor antagonist, has been used to reverse acute symptoms in several randomized trials and observational studies[200,201]. However, it has no survival benefit and two-thirds of the patients who respond deteriorate within two to four hours. These findings suggest that Flumazanil may have some benefit in patients with acute HE, but cannot be used as standard of treatment.

Zinc deficiency is common among cirrhotic patients. Its supplementation has been shown to decrease serum ammonia levels[202]. Given limited available data, Zinc supplementation is not the recommended in treatment of HE.

Manganese deposition has been detected in many cirrhotic patients on magnetic resonance imaging (MRI), which disappears after liver transplantation[203]. Therefore, manganese-chelating agents have been proposed to alleviate symptoms of HE, even though this is still a new area of research.

HCC

Every year more than half a million cases of HCC are diagnosed worldwide[204]. In patients with cirrhosis, the annual incidence of HCC is about 3%-5%[205]. The pathogenesis and management of HCC is complex, and to some extent beyond the scope of our review. Therefore, we will only highlight the important points pertaining to different available therapeutic measures. Because of high incidence and associated morbidity and mortality surveillance using ultrasound (US) every 6-12 mo is recommended[205,206]. Addition of serum alpha-fetoprotein (AFP) to US increases sensitivity but results in higher false-positives and cost. Surveillance with AFP alone is not recommended because of low sensitivity (60%)[207-210]. Lesions less than 1 cm should be followed every 3-6 mo with an US. Lesions > 1 cm should be investigated using either CT or MRI[206]. If characteristic changes (hypervascular with wash-out on portal venous phase) are seen on imaging or AFP > 200 ng/mL these lesions should be treated as HCC[206]. Liver stiffness as marker of fibrosis can be measured non-invasively using TE and can used as a predictor of HCC development[211,212]. Treatment options depend on the disease stage, resources available and the severity of underlying liver disease.

Local resection

Diagnosis of HCC is difficult in the early stages. Surgical resection in the early stages is associated with 90% survival at the end of first year[213]. The presence of cirrhosis puts the patient at risk for recurrence after surgical resection: the five year recurrence rate is about 70%[46]. In patients with cirrhosis who have single lesion, AASLD recommends surgical resection if the liver functions are well-preserved, bilirubin is normal, and the hepatic vein pressure gradient is less than 10 mmHg[214]. In the United States, only 5% of patients meet these criteria at the time of diagnosis and are candidates for hepatic resection[206]. This approach is more common in Asian countries where there are more young patients with Hepatitis B-related HCC with or without minimal cirrhosis[214].

Liver transplant

Transplantation decreases the risk of recurrence in patients with underlying cirrhosis. Secondary to scarcity of organs, strict principles such as the Milan criteria are used to limit transplantation to patients who are likely to have better outcomes (Milan criteria: Single tumor $\leqslant$ 5 cm OR; 3 or less lesions with none > 3 cm). Patients who meet these criteria have an estimated four year survival rate of 85% and four year recurrence-free rate of 92%[215].

Ablation therapy for HCC

Radiofrequency ablation (RFA) has become the most frequently used form of local ablation therapy. It is considered appropriate for patients who cannot undergo resection, or as a bridge to transplantation. Although there is no absolute tumor size beyond which RFA cannot be used, some clinicians restrict RFA to Child-Pugh class A or B cirrhosis[216]. RFA is more effective than conventional percutaneous ethanol injection in treating patients with small HCC tumors with lower rates of recurrence and improved survival[217]. RFA has excellent short term outcomes with overall survival rates of 100% and 98% at one and two years, respectively, but five year recurrence rates are as high as 70%, indicating the non-curative nature of RFA[214].

Transarterial chemoembolization (TACE) involves the injection of a chemotherapeutic agent with or without lipidol or a procoagulant agent directly into hepatic artery in an attempt to obstruct tumor blood supply. TACE is used for large unresectable tumors that are not amenable to other treatments such as RFA. It is also used a bridging therapy prior to transplant. A meta-analysis of randomized, controlled trials showed that arterial embolization, chemoembolization, or both were associated with improved survival when used as primary palliative treatment for HCC as compared to conservative treatment[218]. Portal vein thrombosis, encephalopathy, and biliary obstruction are absolute contraindications for this procedure. Patients should be evaluated before undergoing this procedure.

Other commonly used ablation methods include cryoablation, external beam radiation (RT), stereotactic body radiotherapy (SBRT), and radioembolization. SBRT is utilized in patients with metastatic disease.

Chemotherapy

Chemotherapy has not been used routinely for HCC. Sorafenib is a small-molecule multikinase inhibitor that is administered orally and has antiproliferative and antiangiogenic properties. In recent randomized controlled trials, it has been associated with a 37% increase in overall

survival as compared to placebo in patients with advanced HCC and compensated cirrhosis[219]. The relative success of sorafenib has prompted interest in its use in combination with other modalities, including TACE, for other stages of liver disease. Other chemotherapeutic agents including brivanib, erlotinib, bevacizumab, and cetuximab are currently under investigation for use in patients with HCC[220-223].

COAGULOPATHY AND BLEEDING DIATHESIS

Various factors contribute to coagulation abnormalities in patients with advanced liver disease. Cirrhotic patients are at risk of bleeding as well as venous thromboembolism. Disease management must be tailored based on the individual patient's presentation. Commonly used indicators of coagulopathy, like INR, cannot precisely predict risk of bleeding in patients with cirrhosis[224]. As a result, there have been attempts to develop a liver specific INR, the "INR liver" in patients with cirrhosis[224,225].

A limited number of nonrandomized studies have evaluated the risks and benefits of anticoagulation therapy in cirrhotic patients with portal venous thrombosis. In one series, treatment with anticoagulation therapy resulted in an overall response rate of 60%[226]. Another study found that 75% of the patients treated with low molecular weight heparin (LMWH) for a median time of 11 mo achieved complete recanalization[227]. Preliminary results from a prospective randomized trial suggest that daily low dose LMWH can prevent PVT inpatients with cirrhosis without significant increase in risk of bleeding. In addition prophylactic use of LMWH decreased the incidence of hepatic decompensation[228].

Vitamin K deficiency is commonly seen in cases of decompensated liver cirrhosis. Vitamin K 10 mg injections administered for three days are considered adequate to correct the vitamin K deficiency and should be given to patients with decompensated liver cirrhosis[229]. In cases with acute bleeding, transfusion of platelets and fresh frozen plasma can be considered for patients with thrombocytopenia and coagulopathy[145].

Eltrombopag was previously being used in countries outside US and was recently approved by FDA for the treatment of thrombocytopenia in patients with chronic liver disease. Cirrhotic patients undergoing surgeries should have platelet levels maintained at a minimum of 50000/cc^3 for moderate-risk procedures like liver biopsies, and close to 100000/cc^3 before high risk procedures[230,231].

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ISSN 1007-9327