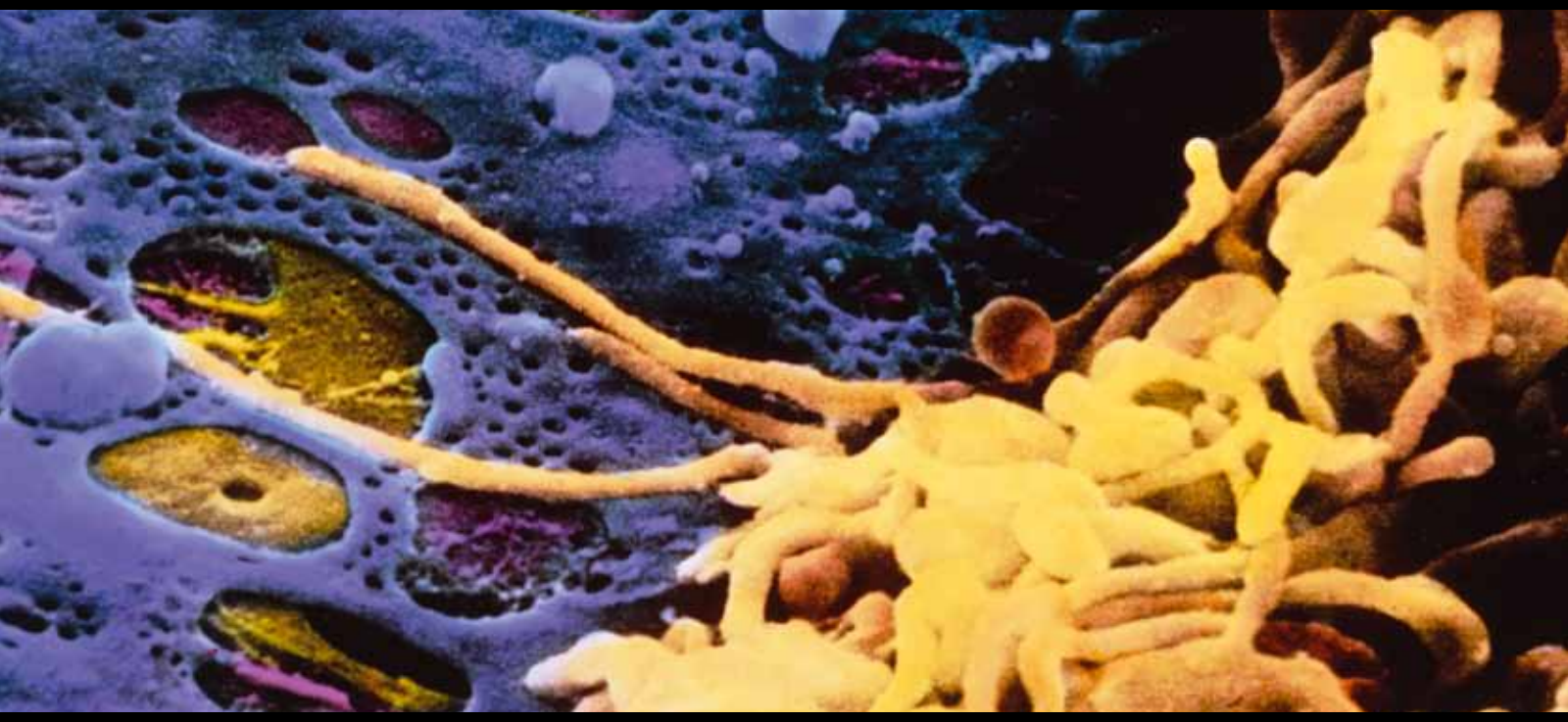
International Journal of Hepatology

Improving Survival in Patients with Decompensated Cirrhosis

Guest Editors: Deepak Amarapurkar, Rajiv Jalan, Richard Guan, and Paul Kwo



Improving Survival in Patients with Decompensated Cirrhosis

International Journal of Hepatology

Improving Survival in Patients with Decompensated Cirrhosis

Guest Editors: Deepak Amarapurkar, Rajiv Jalan, Richard Guan, and Paul Kwo

Editorial Board

Contents

Improving Survival in Patients with Decompensated Cirrhosis, Deepak Amarapurkar, Rajiv Jalan, Richard Guan, and Paul Kwo
Volume 2011, Article ID 565108, 2 pages

Clinicopathological Features and Treatment of Ectopic Varices with Portal Hypertension, Takahiro Sato, Jun Akaike, Jouji Toyota, Yoshiyasu Karino, and Takumi Ohmura
Volume 2011, Article ID 960720, 9 pages

Application of Endoscopy in Improving Survival of Cirrhotic Patients with Acute Variceal Hemorrhage, Yao-Chun Hsu, Chen-Shuan Chung, and Hsiu-Po Wang
Volume 2011, Article ID 893973, 8 pages

Improved Survival with the Patients with Variceal Bleed, Praveen Sharma and Shiv K. Sarin
Volume 2011, Article ID 356919, 7 pages

Management of Renal Failure and Ascites in Patients with Cirrhosis, Kaushal Madan and Ashish Mehta
Volume 2011, Article ID 790232, 7 pages

Role of TIPS in Improving Survival of Patients with Decompensated Liver Disease, Sundeep J. Punamiya and Deepak N. Amarapurkar
Volume 2011, Article ID 398291, 5 pages

Prevention and Management of Bacterial Infections in Cirrhosis, Sunil K. Taneja and Radha K. Dhiman
Volume 2011, Article ID 784540, 7 pages

Management of Hepatic Encephalopathy, G. Wright, A. Chattree, and R. Jalan
Volume 2011, Article ID 841407, 10 pages

Management of Cardiopulmonary Complications of Cirrhosis, Prabha Sawant, C. Vashishtha, and M. Nasa
Volume 2011, Article ID 280569, 11 pages

Management of Coagulopathy in Patients with Decompensated Liver Cirrhosis, Pooja D. Amarapurkar and Deepak N. Amarapurkar
Volume 2011, Article ID 695470, 5 pages

Determination of ADAMTS13 and Its Clinical Significance for ADAMTS13 Supplementation Therapy to Improve the Survival of Patients with Decompensated Liver Cirrhosis, Masahito Uemura, Yoshihiro Fujimura, Saiho Ko, Masanori Matsumoto, Yoshiyuki Nakajima, and Hiroshi Fukui
Volume 2011, Article ID 759047, 12 pages

Treatment of Hepatitis B in Decompensated Liver Cirrhosis, Richard Guan and Hock Foong Lui
Volume 2011, Article ID 918017, 11 pages

Treatment of Decompensated Alcoholic Liver Disease, John Menachery and Ajay Duseja
Volume 2011, Article ID 219238, 7 pages

Prescribing Medications in Patients with Decompensated Liver Cirrhosis, Deepak N. Amarapurkar
Volume 2011, Article ID 519526, 5 pages

Screening for Hepatocellular Carcinoma, Hock-Foong Lui
Volume 2011, Article ID 363151, 4 pages

Indications and Contraindications for Liver Transplantation, Vibha Varma, Naimish Mehta, Vinay Kumaran, and Samiran Nundy
Volume 2011, Article ID 121862, 9 pages

SAGE-Hindawi Access to Research
International Journal of Hepatology
Volume 2011, Article ID 565108, 2 pages
doi:10.4061/2011/565108

Editorial

Improving Survival in Patients with Decompensated Cirrhosis

Deepak Amarapurkar,[1] Rajiv Jalan,[2] Richard Guan,[3] and Paul Kwo[4]

[1] *Department of Gastroenterology, Bombay Hospital and Medical Research Centre, Mumbai 400025, India*
[2] *The London Clinic Liver Centre, 116 Harley Street, London W1G 7JL, UK*
[3] *Mount Elizabeth Medical Centre, Mount Elizabeth No. 17-02, Singapore 228510*
[4] *Liver Transplantation, Division of Gastroenterology and Hepatology, Indiana University, School of Medicine, Indianapolis, IN 46202-5121, USA*

Correspondence should be addressed to Richard Guan, rgyc5@singnet.com.sg

Received 25 October 2011; Accepted 25 October 2011

About 60% of patients with decompensated disease have oesophageal varices. One third of these patients will experience variceal bleed. Each bleeding episode compromises the decompensated state and is associated with a 20% to 30% mortality. Bleeding from ectopic varices is rare but is generally massive and life threatening. The first two articles, "*Clinicopathological features and treatment of ectopic varices with portal hypertension*" and "*Application of endoscopy in improving survival of cirrhotic patients with acute variceal hemorrhage*" discuss the management of variceal bleeding in cirrhotic patients. "*Improved survival with the patients with variceal bleed*" is a review article on how new treatment modalities have improved the outlook of patients with bleeding oesophageal varices.

The hepatorenal syndrome (HRS) signifies advanced liver failure and is a bad prognostic factor in patients with decompensated cirrhosis. Management of this condition is discussed in "*Management of renal failure and ascites in patients with cirrhosis*". One of the features of decompensated liver disease is the occurrence of recurrent or resistant ascites. Transjugular intrahepatic portosystemic shunt (TIPS) is an effective therapy for refractory ascites and HRS at the expense of hepatic encephalopathy and may offer an effective bridge to liver transplantation, by improving short and medium term survivals, as discussed in "*Role of TIPS in improving survival of patients with decompensated liver disease*".

Bacterial infection is responsible for up to a quarter of the deaths of patients with decompensated liver disease. "*Prevention and management of bacterial infections in cirrhosis*" discuss the high index of suspicion that is needed to prevent bacterial infections in patients with decompensated cirrhosis. These patients are immunologically compromised, and prophylactic antibiotics can prevent fatal septicemia and HRS in those with gastrointestinal bleeding. Current thoughts on how to deal with the neuropsychiatric complication of cirrhosis are discussed in "*Management of hepatic encephalopathy*". Cardiomyopathy, hepatopulmonary syndrome, portopulmonary hypertension and right-sided hydrothorax complications that are often overlooked in patients with decompensated liver disease are discussed in "*Management of cardiopulmonary complications of cirrhosis*". Decompensated liver cirrhosis has been traditionally considered as a prototype of hemorrhagic coagulopathy, and routinely performed coagulation profile is abnormal in the majority of these patients. In "*Management of coagulopathy in patients with decompensated liver disease*", the authors discussed recent thoughts on coagulation in end-stage liver disease. The related article entitled "*Determination of ADAMTS13 and its clinical significance for ADAMTS13 supplementation therapy to improve the survival of patients with decompensated liver cirrhosis*" reviews the role of the deficiency of the metalloproteinase ADAMTS13 in end-stage liver cirrhosis in inducing platelet clumping or thrombi and how the resulting sinusoidal microcirculatory disturbances causes further liver damage and is closely related to further deterioration of liver function, hepatic encephalopathy, hepatorenal syndrome, and intractable ascites in advanced liver cirrhosis. Fresh frozen plasma (FFP) is a source of ADAMTS13.

Liver cirrhosis is the common end stage of persistent liver injury. In the Asia Pacific region, these injuries commonly result from chronic hepatitis B and C infections as well as

alcohol. The following two articles, "*Treatment of hepatitis B in decompensated liver cirrhosis* and *treatment of decompensated alcoholic liver disease*" address the management of hepatitis B and alcoholic liver disease in end stage liver disease. Pharmacotherapy in patients with decompensated liver disease is not without complications and side effects and might compromise the decompensated state. The article entitled "*Prescribing medications in patients with decompensated liver cirrhosis*" addresses the above conundrum. A common complication of liver cirrhosis is liver cancer, and treatment of this condition is challenging in patients with liver decompensation to say the least. The paper entitled "*Screening for hepatocellular carcinoma*" discusses early detection of liver cancer in these patients so that appropriate management can be arranged. Finally, liver transplantation for end-stage liver failure is discussed in "*Indications and contraindications for liver transplantation*".

Deepak Amarapurkar
Rajiv Jalan
Richard Guan
Paul Kwo

SAGE-Hindawi Access to Research
International Journal of Hepatology
Volume 2011, Article ID 960720, 9 pages
doi:10.4061/2011/960720

Review Article

Clinicopathological Features and Treatment of Ectopic Varices with Portal Hypertension

Takahiro Sato, Jun Akaike, Jouji Toyota, Yoshiyasu Karino, and Takumi Ohmura

Department of Gastroenterology, Sapporo Kosei General Hospital, Kita 3 Higashi 8, Chuo-ku, Sapporo 060-0033, Japan

Correspondence should be addressed to Takahiro Sato, taka.sato@ja-hokkaidoukouseiren.or.jp

Received 15 January 2011; Accepted 12 May 2011

Academic Editor: Deepak Amarapurkar

Bleeding from ectopic varices, which is rare in patients with portal hypertension, is generally massive and life-threatening. Forty-three patients were hospitalized in our ward for gastrointestinal bleeding from ectopic varices. The frequency of ectopic varices was 43/1218 (3.5%) among portal hypertensive patients in our ward. The locations of the ectopic varices were rectal in thirty-two, duodenal in three, intestinal in two, vesical in three, stomal in one, and colonic in two patients. Endoscopic or interventional radiologic treatment was performed successfully for ectopic varices. Hemorrhage from ectopic varices should be kept in mind in patients with portal hypertension presenting with lower gastrointestinal bleeding.

1. Introduction

Portal hypertension can result in either the reopening of collapsed embryonic channels or reversal of the flow within existing adult veins [1]. Whilst esophagogastric varices are the most common complication in patients with portal hypertension, ectopic varices defined by large portosystemic venous collaterals occurring anywhere in the gastrointestinal tract, other than the esophagogastric region, are less common and account for between 1% and 5% of all variceal bleeding [2, 3]. Ectopic varices that are not esophagogastric are located predominantly in the duodenum, jejunum, ileum, colon, rectum, and enterostomy stoma. Bleeding from ectopic varices, which is rare in patients with portal hypertension, is generally massive and life-threatening. However, there are few reports on the clinicopathological features of ectopic varices. Endoscopic injection sclerotherapy (EIS) is now a standard procedure for the treatment of esophageal varices [4] and, recently, endoscopic band ligation (EBL) has been used widely to treat esophageal varices [5]. Balloon-occluded retrograde transvenous obliteration (B-RTO) is a new interventional modality for gastric fundic varices [6]. However, a definitive treatment has not been established for bleeding ectopic varices.

In this paper, we evaluate the clinicopathological features and treatment of ectopic varices in our ward.

2. Clinicopathological Features of Ectopic Varices

Esophagogastric varices are considered to be the most common complication in patients with portal hypertension, while ectopic varices (i.e., those outside the esophago-gastric region) are less common. Ectopic varices have been reported to occur at numerous sites, including 18% in the jejunum or ileum, 17% in the duodenum, 14% in the colon, 8% in the rectum, and 9% in the peritoneum [7].

From January 1994 to March 2009, we performed endoscopic or interventional radiologic treatment for 1218 portal hypertensive patients with esophagogastric varices. During this period, 43 patients were hospitalized in our ward for gastrointestinal bleeding from ectopic varices. There were 21 males and 22 females, ranging in age from 38 to 84 years (mean, 67.0 years). The underlying pathology of portal hypertension included liver cirrhosis (LC) in 22 patients, cirrhosis associated with hepatocellular carcinoma (HCC) in 9, primary biliary cirrhosis (PBC) in 3, idiopathic portal hypertension (IPH) in 6, extrahepatic portal vein obstruction (EHO) in 2, and another disease in 1 (Table 1). In terms of the clinical staging of cirrhosis, 22 patients were graded Child-Pugh class A, 18 class B, and 3 class C. The etiologies of LC were hepatitis B surface antigen (HBsAg) positivity in 4 patients, antibody to hepatitis C virus (anti-HCV) in

Table 1: Underlying pathologies in patients with ectopic varices.

	Cases (N)
Liver cirrhosis	22
Cirrhosis associated hepatocellular carcinoma	9
Idiopathic portal hypertension	6
Primary biliary cirrhosis	3
Extrahepatic portal vein obstruction	2
Other	1
Total	43

Table 2: Sites of ectopic varices ($n = 43$).

Site	Cases (N)
Rectal varices	32
Duodenal varices	3
Small intestinal varices	2
Vesical varices	3
Colonic varices	2
Stoma varices	1
Total	43

16 patients, alcoholic liver disease in 8 patients, sarcoidosis in 1 patient, and unknown in 2 patients.

The frequency of ectopic varices was 43/1218 (3.5%) among portal hypertensive patients in our ward. The locations of the ectopic varices were rectal in 32, duodenal in 3, small intestinal in 2, vesical in 3, stomal in 1, and colonic in 2 patients (Table 2). Thirty-nine of 43 patients with ectopic varices had previously received emergency or prophylactic EIS for esophageal varices. Nine patients had a history of esophageal variceal bleeding, and emergency EIS had been performed in these cases. Prophylactic EIS had been performed on 30 patients with esophageal varices because of a high risk of bleeding.

3. Rectal Varices

Thirty two rectal variceal patients in our ward had had undergone EIS or EBL. There were 14 males and 18 females, ranging in age from 38 to 84 years (mean, 67.0 years). The underlying pathology causing portal hypertension included LC in 16 patients, cirrhosis associated with HCC in 7 patients, IPH in 4 patients, PBC in 3 patients, and EHO in 2 patients. In terms of the clinical staging of cirrhosis, 15 patients were graded Child-Pugh class A, 15 class B, and 2 class C. The etiologies of LC were HBs Ag-positivity in 3 patients, anti-HCV in 11 patients, alcoholic liver disease in 6 patients, sarcoidosis in 1 patient, and unknown in 2 patients. Thirty of 32 patients with rectal varices had previously received emergency or prophylactic EIS for esophageal varices, and esophageal varices were coexistent in two other patients.

Rectal varices represent portal systemic collaterals that are manifested as discrete dilated submucosal veins and constitute a pathway for portal venous flow between the superior rectal veins of the inferior mesenteric system and the middle inferior rectal veins of the iliac system. Rectal varices have been reported to occur at a high frequency in patients with hepatic abnormalities [8–10]. Massive bleeding from rectal varices occurs rarely, at a frequency ranging from 0.5% to 3.6% [11–13]. Rectal varices are an infrequent but potentially serious cause of hematochezia.

Several diagnostic procedures have been performed to evaluate rectal varices, including endoscopy, magnetic resonance (MR) angiography, and endoscopic ultrasonography (EUS). Endoscopy is the principal method for diagnosis of rectal varices, and MR angiography is useful for evaluating the overall portosystemic collateral circulation [14]. EUS has become a useful modality for hemodynamic diagnosis of esophagogastric varices [15, 16]. The value of EUS [17–19] has been reported for the hemodynamic diagnosis of rectal varices, and Dhiman et al. found rectal varices via endoscopy in 43% and via EUS in 75%, of patients with portal hypertension [19]. Conventional EUS (7.5 or 12 MHz) reveals rectal varices as rounded, oval, or longitudinal echo-free structures in the submucosa and also shows perirectal veins outside the rectal wall [17–19]. EUS was considered superior to endoscopy or MR angiography in making a detailed diagnosis of rectal varices. Sato et al. demonstrated that intramural rectal varices, perirectal collateral veins, and the communicating veins between intramural rectal varices and perirectal collateral veins could be observed clearly via an ultrasonic microprobe [14].

Recently, percutaneous color Doppler ultrasonography (CDUS) has allowed us to detect the flow of blood in fine detail, and it has become widely accepted for the assessment of the hemodynamics of abdominal vascular systems, but few color Doppler findings of gastrointestinal varices have been reported. Komatsuda et al. reported the value of CDUS for the diagnosis of gastric and duodenal varices [20], and Sato et al. have reported the usefulness of CDUS for the hemodynamic evaluation of rectal varices [21].

CDUS cannot be performed successfully without a suitable acoustic window. Impediments such as bowel gas, body habitus, and cirrhosis limit the value of sonography for assessing the portal venous system. In addition, it is difficult to observe the collateral veins far from the probe with color Doppler sonography because of the limitations of Doppler sensitivity. The rectal wall was detected at the posterior area of the vagina in females and the prostate in males by sonography and rectal varices could be observed through the urine-filled bladder via CDUS. Sato et al. suggest that the measurement by CDUS of velocity in rectal varices is useful in diagnosing the grade of rectal varices. CDUS was very useful in screening for rectal varices in portal hypertensive patients [21].

Although EIS and EBL for esophageal varices are well-established therapies for esophageal varices, there is no standard treatment for rectal varices. Various medical treatments have been used to control bleeding from rectal varices, but none of these is currently considered to be a standard method. Surgical approaches include portosystemic

shunting, ligation, and under-running suturing [8]. Some investigators have reported that interventional radiologic techniques such as transjugular intrahepatic portosystemic shunts (TIPSs) were successfully employed for rectal variceal bleeding [22–24]. Wang et al. first reported the usefulness of EIS in treating rectal varices and found it to be effective for controlling bleeding [25]. EBL was introduced as a new method for treating esophageal varices, and it is reportedly easier to perform and safer than EIS. Several cases of successful treatment of rectal varices using EBL have been reported [26–28]. Levine et al. treated rectal varices initially with EIS, and 1 week later, EBL was performed on the remaining rectal varices. These investigators described EBL as a safe and effective therapy for rectal varices. On the other hand, Sato et al. retrospectively evaluated the therapeutic effects and rates of recurrence of rectal varices after EIS or EBL [29], and EIS was successfully performed without complications. The recurrence rate did not differ significantly between the EIS and EBL groups, although recurrence tended to be more frequent with EBL. It is necessary to evaluate the hemodynamics of the rectal varices before EIS to avoid severe complications such as pulmonary embolism, and the sclerosant should be injected slowly under fluoroscopy, taking care to ensure that the agent does not flow into the systemic circulation.

A standard therapy for rectal varices has not been established. More investigations are needed in larger numbers of patients before evidence-based treatment recommendations can be made.

4. Duodenal Varices

Three duodenal variceal patients (2 males and 1 female) underwent interventional radiology in our ward. The underlying pathology causing portal hypertension included LC in two patients, and IPH in one. In terms of the clinical staging of cirrhosis, all three were graded Child-Pugh class A. The etiologies of LC were anti-HCV-positivity in one patient and alcoholic liver disease in the other. All three patients with duodenal varices had previously received emergency or prophylactic EIS for esophageal varices. The sites of the duodenal varices were the second portion of the duodenum in one case and the distal third portion in two.

The duodenum is a rare site of variceal hemorrhage in patients with portal hypertension but bleeding from duodenal varices is generally massive and life-threatening. It is seen not only in patients with extrahepatic portal hypertension but also in patients with cirrhosis of the liver [30–32]. Duodenal varices are considered to be ectopic varices and account for 1–3% of all varices in patients with liver cirrhosis [33]. Diagnosis of ruptured duodenal varices and control of bleeding are difficult.

The duodenum can be a site of severe variceal hemorrhage, with mortality as high as 40% from the initial bleeding [34, 35]. Although more commonly associated with extrahepatic portal hypertension, duodenal varices may occur in intrahepatic portal hypertension. Cirrhosis of liver is the most common intrahepatic cause of duodenal varices, accounting for 30% of cases [31, 36]. Extrahepatic causes vary and include portal vein thrombosis and obstruction of the splenic vein and inferior vena cava [31, 37, 38].

The most common site of duodenal varices is the duodenal bulb [35], followed by the second portion of the duodenum [39]. Varices in the duodenal bulb, which occur most frequently in the United States and Europe, are caused by extrahepatic portal obstruction. In Japan, duodenal varices are observed more commonly in the second portion of the duodenum [40, 41]. On the other hand, duodenal varices in the distal third portion are very rare [42, 43]. Duodenal varices are formed by the developed collateral veins originating from the portal vein trunk or superior mesenteric vein, which empty into the inferior vena cava [31, 34].

The bulb and second portion of duodenum can be observed endoscopically. However, location of the bleeding site often is difficult in the duodenum. In our two cases of duodenal varices in the distal third portion, we could not observe the varices by fibergastroscopic examination and we suspected rupture of duodenal varices via computed tomography (CT).

Duodenoscopy and double-balloon enteroscopy were very useful in evaluating the duodenal varices in the distal third portion.

Recently, medical treatments with interventional radiology and endoscopic procedures have been reported for duodenal varices. EBL for bleeding duodenal varices is challenging because of the difficulty in maintaining the field of vision. EBL may be useful for temporary hemostasis [40, 41] but rebleeding of duodenal varices is a problem with EBL. Additional treatment is recommended following EBL for duodenal varices. EIS has been reported to be successful in controlling duodenal variceal bleeding [44, 45] but there have been reports of cases of rebleeding of duodenal varices after EIS [35, 46]. N-butyl-2-cyanoacrylate (Histoacryl, B.Braun Dexon GmbH Spangenberg, Germany) is a tissue glue monomer that instantly polymerizes and solidifies upon contact with blood. Endoscopic obliterative therapy with Histoacryl seems to be a useful method for bleeding gastric varices [47, 48], and it is also suitable for emergency duodenal variceal bleeding [41, 42].

Interventional radiologic treatment options for duodenal varices include TIPS, B-RTO, and percutaneous transhepatic obliteration (PTO). B-RTO was successfully performed for two cases of duodenal varices, and PTO for one case, in our ward. Successful treatment of duodenal varices by TIPS [35] and B-RTO [49–51] has been reported. Although TIPS is a relatively safe and effective means of decompressing the portal pressure, it has a certain limitation in patients with severe liver atrophy and complications such as encephalopathy and cerebral embolization. B-RTO can obliterate not only varices but also the afferent and efferent veins and should be considered for treating duodenal varices. Successful treatment of duodenal varices by PTO has been reported [52, 53].

5. Small Intestinal Varices

Two small intestinal variceal patients (both male, one jejunal varices, and one ileal varices) had undergone interventional

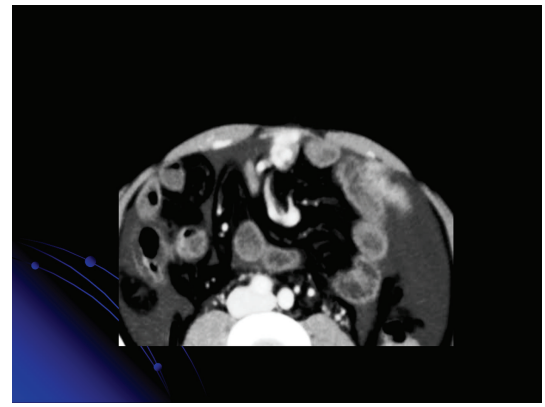
radiology in our ward. The underlying pathology causing portal hypertension was LC in both. In terms of the clinical staging of cirrhosis, one patient was graded Child-Pugh class A and the other class B. The etiologies of LC were HBs Ag-positivity in one patient and anti-HCV-positivity in the other. The jejunal variceal case had previously undergone gastropylorectomy, and esophageal varices coexisted. The ileal variceal patient had previously received prophylactic EIS for esophageal varices and surgery on the ileocecum to remove a benign colonic tumor.

When repeat upper and lower endoscopies are negative in gastrointestinal bleeding, the small intestine should be investigated. Most bleeding jejunal and ileal varices, generally detected previous to intra-abdominal surgery, are serious because of the difficulty of early diagnosis.

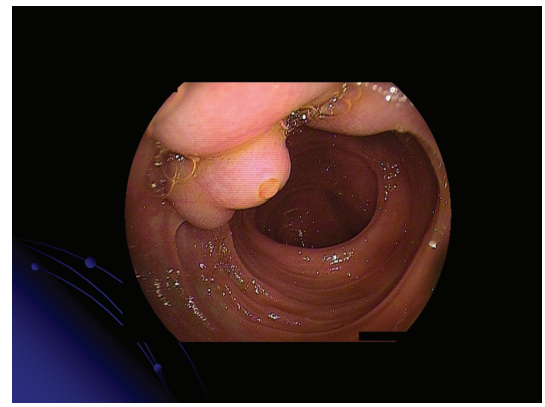
In our two cases, the patients' risk factors included portal hypertension due to liver cirrhosis, and previous surgery. Collaterals formation within adhesions from previous surgery is the usual mechanism for the development of ectopic varices [7]. Adhesions tend to bring the parietal surface of the viscera in contact with the abdominal wall, and portal hypertension results in the formation of varices below the intestinal mucosa.

Location of the bleeding site often is difficult in the intestinal varices. In our two cases, we suspected rupture of intestinal varices via CT. We show jejunal variceal varices, and CT and double-balloon enteroscopy were useful in evaluating the jejunal varices (Figures 1(a) and 1(b)). Lim et al. have reported the usefulness of capsule endoscopy for the diagnosis of bleeding jejunal varices [54].

Several cases of bleeding jejunal [54–59] and ileal varices have been reported [60–68]. A triad of portal hypertension, hematochezia without hematemesis, and previous abdominal surgery characterizes small intestinal varices [69]. Several approaches for the treatment of jejunal varices include surgery [55], portal venous stenting [56, 58, 59], and percutaneous embolization [54, 57]. Surgical approaches such as segmental resection and ligation generally control bleeding from ileal varices successfully [64, 65, 70, 71]. In patients with a poor condition, interventional radiologic treatments, such as insertion of a TIPS for ileal varices, have been performed as a nonsurgical treatment option [3, 66, 68]. Because B-RTO can obliterate not only varices but also the afferent and efferent veins, it is practical for treating ileal varices [72], as described here. In the future, interventional radiologic treatments such as B-RTO may also be applied as therapy for patients in a poor condition. In our cases, B-RTO was successfully performed for jejunal (Figure 2) and ileal varices.



(a)



(b)

Figure 1: (a) Computed tomography showing the vessel image in the jejunum. (b) Double-balloon enteroscopy revealed jejunal varices with a white plug.

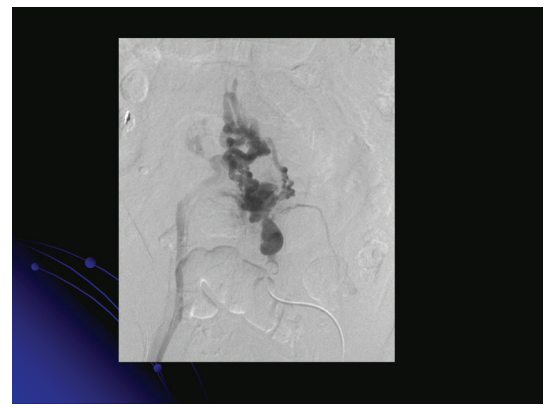
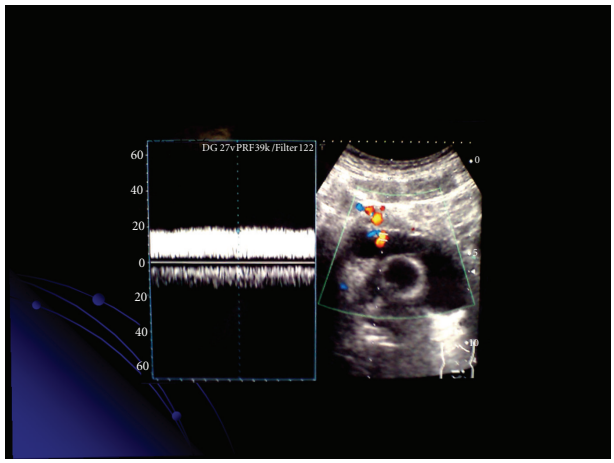


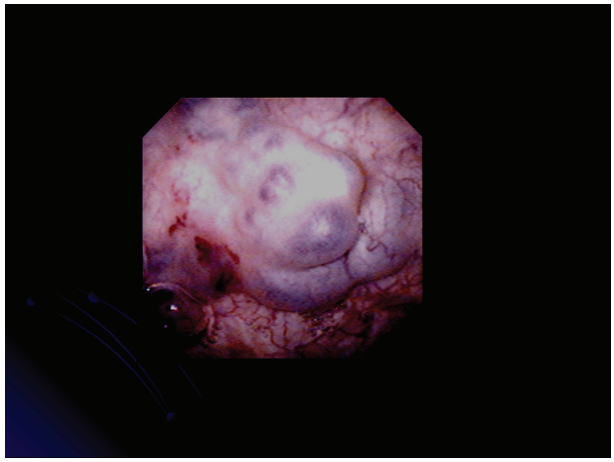
Figure 2: Balloon-occluded retrograde transvenous obliteration was performed successfully for jejunal varices.

6. Vesical Varices

Because our three vesical variceal patients (2 males and 1 female) had a history of EIS for esophageal varices and two had received abdominal surgery, the usual collateral veins from portal hypertension may have been disrupted. Collateral formation within adhesions from previous surgery is the usual mechanism for the development of ectopic varices [7]. The underlying pathology causing portal hypertension was LC in one patient, LC-associated HCC in another, and IPH in the third. In terms of the clinical staging of cirrhosis, one patient was graded Child-Pugh class A, one class B, and one class C. The etiologies of LC were alcoholic in one patient and anti-HCV-positivity in the other.



(a)



(b)

Figure 3: (a) Color flow images of vesical varices can be delineated clearly in the urine-filled bladder. (b) Cystoscopic examination revealed vesical varices on the anterior wall of the bladder.

Bleeding from vesical varices is rare in patients with portal hypertension [7, 73–76] because the bladder wall is an unusual collateral route for the venous splanchnic blood. Previously reported cases of vesical varices had a history of abdominal surgery [73, 74, 76, 77], so that the vesical varices might have appeared after surgery that provided an unusual collateral route resulting from portal hypertension.

CDUS also is very useful for screening for collateral vessels in portal hypertensive patients, in that it can be performed repeatedly. Color flow images of vesical varices can be delineated clearly in the urine-filled bladder. CDUS is very useful for the diagnosis of vesical varices (Figure 3(a)), as is CT. Cystoscopic examination revealed vesical varices on the anterior wall of the bladder in our cases (Figure 3(b)).

No definitive treatment has been established for bleeding vesical varices. We used PTP to reveal the detailed hemodynamics of the collateral circulation in vesical variceal patients, including the afferent and efferent veins, and these patients were successfully treated with PTO [77].

7. Colonic Varices

Two colonic variceal patients (both female, one descending colonic varices and one transverse colonic varices) underwent interventional radiology (PTO) and EIS in our ward. The underlying pathology causing portal hypertension was LC in both. In terms of the clinical staging of cirrhosis, both were graded Child-Pugh class A. Both were anti-HCV-positive and had a history of EIS for esophageal varices, and one had received abdominal surgery.

The most common sites of colorectal varices are the rectum and cecum [78]. Colonic varices can be associated with several conditions, such as portal hypertension, portal venous obstruction, postsurgical changes, and idiopathic factors [3, 79–84].

Colonoscopy is the principal method for the diagnosis of colonic varices, and MR angiography is useful for evaluating the overall portosystemic collateral circulation. CT has been reported rarely but has shown a colonic wall which is thickened with a scalloped appearance [85]. In our cases, we suspected colonic varices via CT [86].

Several therapies, including PTO, colonic resection, portacaval shunt construction, endoscopic procedures, TIPS, variceal embolization, and B-RTO, have been reported [3, 79–84, 86–90]. The treatment of colonic varices is not well defined.

8. Stomal Varices

The (male) stomal variceal patient in our ward had undergone interventional radiology (TIPS). The underlying pathology causing portal hypertension was LC (Child-Pugh class B), and he was anti-HCV-positive. This case had previously received Miles' operation for rectal cancer, and EIS had been performed for esophageal varices.

Stomal varices can occur in patients with stoma in the presence of portal hypertension and remain difficult to diagnose and manage. The overall morbidity of the stomal varices is much higher given the propensity for recurrence and massive bleeding, requiring multiple blood transfusions [91, 92].

The mechanism of stomal variceal hemorrhage is related to variceal erosion or local trauma. Several management strategies have been described for stomal variceal hemorrhage, including local therapy, EIS, TIPS, B-RTO, and surgery. Although local therapies are effective for the initial control of bleeding, these may be not effective in preventing recurrent bleeding [93]. EIS is effective for controlling stomal variceal bleeding [94], and portosystemic surgery is effective for prevention of recurrent bleeding but also is associated with significant morbidity and mortality [95]. PTO has been used safely for acute stomal variceal bleeding [92, 96, 97]; however, recurrent bleeding is frequent. TIPS is an effective therapy for bleeding stomal varices [98–100] but may result in a higher mortality of patients with severe decompensated liver function because of encephalopathy, rather than the stomal variceal bleeding itself [96]. Recently, Minami et al. have reported that B-RTO was useful for recurrent hemorrhage from stomal varices [101].

9. Conclusions

It is difficult to determine the best treatment strategy for ectopic varices because of inaccessibility, initial difficulty in diagnosis, and subsequent difficulty in treatment. Hemorrhage from ectopic varices should be kept in mind in patients with portal hypertension presenting with lower gastrointestinal bleeding.

Acknowledgment

The authors thank Dr. Katsu Yamazaki who contributed clinical data to this paper.

References

[1] G. Walsh and M. P. Williams, "Case report: giant pararectal varices-computed tomographic appearances," *The British Journal of Radiology*, vol. 68, no. 806, pp. 203–204, 1995.

[2] M. Kinkhabwala, A. Mousavi, S. Iyer, and R. Adamsons, "Bleeding ileal varicosity demonstrated by transhepatic portography," *The American Journal of Roentgenology*, vol. 129, no. 3, pp. 514–516, 1977.

[3] I. D. Norton, J. C. Andrews, and P. S. Kamath, "Management of ectopic varices," *Hepatology*, vol. 28, no. 4 I, pp. 1154–1158, 1998.

[4] The Veterans Affairs Cooperative Variceal Sclerotherapy Group, "Prophylactic sclerotherapy for esophageal varices in men with alcoholic liver disease," *The New England Journal of Medicine*, vol. 324, pp. 1779–1784, 1991.

[5] J. S. Goff, R. M. Reveille, and G. V. Stiegmann, "Endoscopic sclerotherapy versus endoscopic variceal ligation: esophageal symptoms, complications and motility," *The American Journal of Gastroenterology*, vol. 83, no. 11, pp. 1240–1244, 1988.

[6] H. Kanagawa, S. Mima, H. Kouyama, K. Gotoh, T. Uchida, and K. Okuda, "Treatment of gastric fundal varices by balloon-occluded retrograde transvenous obliteration," *Journal of Gastroenterology and Hepatology*, vol. 11, no. 1, pp. 51–58, 1996.

[7] D. Lebrec and J. P. Benhamou, "Ectopic varices in portal hypertension," *Clinics in Gastroenterology*, vol. 14, no. 1, pp. 105–121, 1985.

[8] S. W. Hosking, A. G. Johnson, H. L. Smart, and D. R. Triger, "Anorectal varices, haemorrhoids and portal hypertension," *The Lancet*, vol. 1, no. 8634, pp. 349–352, 1989.

[9] T. F. Wang, F. Y. Lee, Y. T. Tsai et al., "Relationship of portal pressure, anorectal varices and hemorrhoids in cirrhotic patients," *Journal of Hepatology*, vol. 15, no. 1-2, pp. 170–173, 1992.

[10] Y. K. Chawla and J. B. Dilawari, "Anorectal varices—their frequency in cirrhotic and non-cirrhotic portal hypertension," *Gut*, vol. 32, no. 3, pp. 309–311, 1991.

[11] T. T. McCormack, H. R. Bailey, J. M. Simms, and A. G. Johnson, "Rectal varices are not piles," *The British Journal of Surgery*, vol. 71, no. 2, p. 163, 1984.

[12] K. Johansen, J. Bardin, and M. J. Orloff, "Massive bleeding from hemorrhoidal varices in portal hypertension," *Journal of the American Medical Association*, vol. 244, no. 18, pp. 2084–2085, 1980.

[13] S. E. Wilson, R. T. Stone, J. P. Christie, and E. Passaro, "Massive lower gastrointestinal bleeding from intestinal varices," *Archives of Surgery*, vol. 114, no. 10, pp. 1158–1161, 1979.

[14] T. Sato, K. Yamazaki, J. Toyota, Y. Karino, T. Ohmura, and T. Suga, "The value of the ultrasonic microprobe in the detection and treatment of rectal varices: a case report," *Hepatology Research*, vol. 27, no. 2, pp. 158–162, 2003.

[15] G. C. Caletti, L. Bolondi, E. Zani et al., "Detection of portal hypertension and esophageal varices by means of endoscopic ultrasonography," *Scandinavian Journal of Gastroenterology*, vol. 123, pp. 74–77, 1986.

[16] G. C. Caletti, E. Brocchi, A. Ferrari, S. Fiorino, and L. Barbara, "Value of endoscopic ultrasonography in the management of portal hypertension," *Endoscopy*, vol. 24, no. 1, pp. 342–346, 1992.

[17] R. K. Dhiman, G. Choudhuri, V. A. Saraswat et al., "Endoscopic ultrasonographic evaluation of the rectum in cirrhotic portal hypertension," *Gastrointestinal Endoscopy*, vol. 39, no. 5, pp. 635–640, 1993.

[18] S. K. Yachha, R. K. Dhiman, R. Gupta, and U. C. Ghoshal, "Endosonographic evaluation of the rectum in children with extrahepatic portal venous obstruction," *Journal of Pediatric Gastroenterology and Nutrition*, vol. 23, no. 4, pp. 438–441, 1996.

[19] R. K. Dhiman, V. A. Saraswat, G. Choudhuri, B. C. Sharma, R. Pandey, and S. R. Naik, "Endosonographic, endoscopic and histologic evaluation of alterations in the rectal venous system in patients with portal hypertension," *Gastrointestinal Endoscopy*, vol. 49, no. 2, pp. 218–227, 1999.

[20] T. Komatsuda, H. Ishida, K. Konno et al., "Color Doppler findings of gastrointestinal varices," *Abdominal Imaging*, vol. 23, no. 1, pp. 45–50, 1998.

[21] T. Sato, K. Yamazaki, J. Toyota, Y. Karino, T. Ohmura, and J. Akaike, "Diagnosis of rectal varices via color Doppler ultrasonography," *The American Journal of Gastroenterology*, vol. 102, no. 10, pp. 2253–2258, 2007.

[22] J. A. Katz, R. A. Rubin, C. Cope, G. Holland, and C. A. Brass, "Recurrent bleeding from anorectal varices: successful treatment with a transjugular intrahepatic portosystemic shunt," *The American Journal of Gastroenterology*, vol. 88, no. 7, pp. 1104–1107, 1993.

[23] D. Shibata, D. P. Brophy, F. D. Gordon, H. T. Anastopoulos, S. M. Sentovich, and R. Bleday, "Transjugular intrahepatic portosystemic shunt for treatment of bleeding ectopic varices with portal hypertension," *Diseases of the Colon and Rectum*, vol. 42, no. 12, pp. 1581–1585, 1999.

[24] A. C. Fantin, G. Zala, B. Risti, J. F. Debatin, W. Schöpke, and C. Meyenberger, "Bleeding anorectal varices: successful treatment with transjugular intrahepatic portosystemic shunting (TIPS)," *Gut*, vol. 38, no. 6, pp. 932–935, 1996.

[25] M. Wang, G. Desigan, and D. Dunn, "Endoscopic sclerotherapy for bleeding rectal varices: a case report," *The American Journal of Gastroenterology*, vol. 80, no. 10, pp. 779–780, 1985.

[26] J. Levine, A. Tahiri, and B. Banerjee, "Endoscopic ligation of bleeding rectal varices," *Gastrointestinal Endoscopy*, vol. 39, no. 2, pp. 188–190, 1993.

[27] B. Firoozi, Z. Gamagaris, E. H. Weinshel, and E. J. Bini, "Endoscopic band ligation of bleeding rectal varices," *Digestive Diseases and Sciences*, vol. 47, no. 7, pp. 1502–1505, 2002.

[28] T. Sato, K. Yamazaki, J. Toyota, Y. Karino, T. Ohmura, and T. Suga, "Two cases of rectal varices treated by endoscopic variceal ligation," *Digestive Endoscopy*, vol. 11, no. 1, pp. 66–69, 1999.

[29] T. Sato, K. Yamazaki, J. Toyota, Y. Karino, T. Ohmura, and T. Suga, "The value of the endoscopic therapies in the treatment

of rectal varices: a retrospective comparison between injection sclerotherapy and band ligation," *Hepatology Research*, vol. 34, no. 4, pp. 250–255, 2006.

[30] Y. Itzchak and M. G. Glickman, "Duodenal varices in extrahepatic portal obstruction," *Radiology*, vol. 124, no. 3, pp. 619–624, 1977.

[31] R. Amin, R. Alexis, and J. Korzis, "Fatal ruptured duodenal varix: a case report and review of literature," *The American Journal of Gastroenterology*, vol. 80, no. 1, pp. 13–18, 1985.

[32] T. Tanaka, K. Kato, T. Taniguchi, D. Takagi, N. Takeyama, and Y. Kitazawa, "A case of ruptured duodenal varices and review of the literature," *Japanese Journal of Surgery*, vol. 18, no. 5, pp. 595–600, 1988.

[33] N. D'Imperio, A. Piemontese, D. Baroncini et al., "Evaluation of undiluted N-butyl-2-cyanoacrylate in the endoscopic treatment of upper gastrointestinal tract varices," *Endoscopy*, vol. 28, no. 2, pp. 239–243, 1996.

[34] F. Khouqeer, C. Morrow, and P. Jordan, "Duodenal varices as a cause of massive upper gastrointestinal bleeding," *Surgery*, vol. 102, no. 3, pp. 548–552, 1987.

[35] S. S. Jonnalagadda, S. Quiason, and O. J. Smith, "Successful therapy of bleeding duodenal varices by TIPS after failure of sclerotherapy," *The American Journal of Gastroenterology*, vol. 93, no. 2, pp. 272–274, 1998.

[36] M. Hashizume, K. Tanoue, M. Ohta et al., "Vascular anatomy of duodenal varices: angiographic and histopathological assessments," *The American Journal of Gastroenterology*, vol. 88, no. 11, pp. 1942–1945, 1993.

[37] K. M. Brown, M. M. Kaplan, and M. Donowitz, "Extrahepatic portal venous thrombosis: frequent recognition of associated diseases," *Journal of Clinical Gastroenterology*, vol. 7, no. 2, pp. 153–159, 1985.

[38] J. H. Grendell and R. K. Ockner, "Mesenteric venous thrombosis," *Gastroenterology*, vol. 82, no. 2, pp. 358–372, 1982.

[39] C. S. Wang, L. B. Jeng, and M. F. Chen, "Duodenal variceal bleeding—successfully treated by mesocaval shunt after failure of sclerotherapy," *Hepato-Gastroenterology*, vol. 42, no. 1, pp. 59–61, 1995.

[40] M. Shiraishi, S. Hiroyasu, T. Higa, S. Oshiro, and Y. Muto, "Successful management of ruptured duodenal varices by means of endoscopic variceal ligation: report of a case," *Gastrointestinal Endoscopy*, vol. 49, no. 2, pp. 255–257, 1999.

[41] Y. Yoshida, Y. Imai, M. Nishikawa et al., "Successful endoscopic injection sclerotherapy with N-butyl-2-cyanoacrylate following the recurrence of bleeding soon after endoscopic ligation for ruptured duodenal varices," *The American Journal of Gastroenterology*, vol. 92, no. 7, pp. 1227–1229, 1997.

[42] K. Ota, Z. Shirai, T. Masuzaki et al., "Endoscopic injection sclerotherapy with n-butyl-2-cyanoacrylate for ruptured duodenal varices," *Journal of Gastroenterology*, vol. 33, no. 4, pp. 550–555, 1998.

[43] H. Selçuk, F. Boyvat, S. Eren et al., "Duodenal varices as an unusual cause of gastrointestinal bleeding due to portal hypertension: a case report," *Turkish Journal of Gastroenterology*, vol. 15, no. 2, pp. 104–107, 2004.

[44] P. Gertsch and L. H. Blumgart, "Cure of a bleeding duodenal varix by sclerotherapy," *The British Journal of Surgery*, vol. 75, no. 7, p. 717, 1988.

[45] A. W. Barbish and M. N. Ehrinpreis, "Successful endoscopic injection sclerotherapy of a bleeding duodenal varix," *The American Journal of Gastroenterology*, vol. 88, no. 1, pp. 90–92, 1993.

[46] M. Hashiguchi, H. Tsuji, J. Shimono, K. Azuma, and M. Fujishima, "Ruptured duodenal varices: an autopsy case report," *Hepato-Gastroenterology*, vol. 46, no. 27, pp. 1751–1754, 1999.

[47] K. Ogawa, S. Ishikawa, Y. Naritaka et al., "Clinical evaluation of endoscopic injection sclerotherapy using n-butyl-2-cyanoacrylate for gastric variceal bleeding," *Journal of Gastroenterology and Hepatology*, vol. 14, no. 3, pp. 245–250, 1999.

[48] Y. H. Huang, H. Z. Yeh, G. H. Chen et al., "Endoscopic treatment of bleeding gastric varices by N-butyl-2-cyanoacrylate (Histoacryl) injection: long-term efficacy and safety," *Gastrointestinal Endoscopy*, vol. 52, no. 2, pp. 160–167, 2000.

[49] M. Ohta, K. Yasumori, M. Saku, H. Saitsu, T. Muranaka, and K. Yoshida, "Successful treatment of bleeding duodenal varices by balloon-occluded retrograde transvenous obliteration: a transjugular venous approach," *Surgery*, vol. 126, no. 3, pp. 581–583, 1999.

[50] Y. Akazawa, I. Murata, T. Yamao et al., "Successful management of bleeding duodenal varices by endoscopic variceal ligation and balloon-occluded retrograde transvenous obliteration," *Gastrointestinal Endoscopy*, vol. 58, no. 5, pp. 794–797, 2003.

[51] T. Sonomura, K. Horihata, K. Yamahara et al., "Ruptured duodenal varices successfully treated with balloon-occluded retrograde transvenous obliteration: usefulness of microcatheters," *The American Journal of Roentgenology*, vol. 181, no. 3, pp. 725–727, 2003.

[52] Y. Menu, B. Gayet, and H. Nahum, "Bleeding duodenal varices: diagnosis and treatment by percutaneous portography and transcatheter embolization," *Gastrointestinal Radiology*, vol. 12, no. 1, pp. 111–113, 1987.

[53] T. Sato, K. Yamazaki, J. Toyota et al., "Efficacy of color Doppler ultrasonography for the diagnosis of duodenal varices successfully treated with percutaneous transhepatic obliteration," *Journal of Medical Ultrasonics*, vol. 34, no. 1, pp. 59–63, 2007.

[54] L. G. Lim, Y. M. Lee, L. Tan, S. Chang, and S. G. Lim, "Percutaneous paraumbilical embolization as an unconventional and successful treatment for bleeding jejunal varices," *World Journal of Gastroenterology*, vol. 15, no. 30, pp. 3823–3826, 2009.

[55] N. Yuki, M. Kubo, Y. Noro et al., "Jejunal varices as a cause of massive gastrointestinal bleeding," *The American Journal of Gastroenterology*, vol. 87, no. 4, pp. 514–517, 1992.

[56] M. Sakai, A. Nakao, T. Kaneko et al., "Transhepatic portal venous angioplasty with stenting for bleeding jejunal varices," *Hepato-Gastroenterology*, vol. 52, no. 63, pp. 749–752, 2005.

[57] A. Sasamoto, J. Kamiya, Y. Nimura, and M. Nagino, "Successful embolization therapy for bleeding from jejunal varices after choledochojejunostomy: report of a case," *Surgery Today*, vol. 40, no. 8, pp. 788–791, 2010.

[58] K. Hiraoka, S. Kondo, Y. Ambo et al., "Portal venous dilatation and stenting for bleeding jejunal varices: report of two cases," *Surgery Today*, vol. 31, no. 11, pp. 1008–1011, 2001.

[59] S. Ota, S. Suzuki, H. Mitsuoka et al., "Effect of a portal venous stent for gastrointestinal hemorrhage from jejunal varices caused by portal hypertension after pancreatoduodenectomy," *Journal of Hepato-Biliary-Pancreatic Surgery*, vol. 12, no. 1, pp. 88–92, 2005.

[60] K. R. Falchuk, M. R. Aiello, C. Trey, and P. Costello, "Recurrent gastrointestinal bleeding from ileal varices associated with intraabdominal adhesions: case report and review of

the literature," *The American Journal of Gastroenterology*, vol. 77, no. 11, pp. 859–860, 1982.

[61] H. F. Arst and J. D. Reynolds, "Acute ileal variceal hemorrhage secondary to esophageal sclerotherapy," *Journal of Clinical Gastroenterology*, vol. 8, no. 5, pp. 603–604, 1986.

[62] J. H. Hojhus and S. A. Pedersen, "Cirrhosis and bleeding ileal varices without previous intraabdominal surgery. A case report," *Acta Chirurgica Scandinavica*, vol. 152, pp. 479–480, 1986.

[63] P. Lewis, B. F. Warren, and D. C. Bartolo, "Massive gastrointestinal haemorrhage due to ileal varices," *The British Journal of Surgery*, vol. 77, no. 11, pp. 1277–1278, 1990.

[64] T. Ohtani, E. Kajiwara, N. Suzuki et al., "Ileal varices associated with recurrent bleeding in a patient with liver cirrhosis," *Journal of Gastroenterology*, vol. 34, no. 2, pp. 264–268, 1999.

[65] K. Kobayashi, J. Yamaguchi, A. Mizoe et al., "Successful treatment of bleeding due to ileal varices in a patient with hepatocellular carcinoma," *European Journal of Gastroenterology and Hepatology*, vol. 13, no. 1, pp. 63–66, 2001.

[66] E. Guth, M. D. Katz, S. E. Hanks, G. P. Teitelbaum, P. Ralls, and J. Korula, "Recurrent bleeding from ileal varices treated by transjugular intrahepatic portosystemic shunt: value of Doppler ultrasonography in diagnosis and follow-up," *Journal of Ultrasound in Medicine*, vol. 15, no. 1, pp. 67–69, 1996.

[67] R. V. Varanasi, A. S. Fleischer, P. E. Darwin, C. E. King, and O. Haluszka, "Colonoscopic sclerotherapy of ileal varices," *Gastrointestinal Endoscopy*, vol. 52, pp. 109–111, 2000.

[68] R. Lopez-Benitez, P. Seidensticker, G. M. Richter, U. Stampfl, and P. Hallscheidt, "Case report: massive lower intestinal bleeding from ileal varices: treatment with transjugular intrahepatic portosystemic shunt (TIPSS)," *Der Radiologe*, vol. 47, pp. 407–410, 2007 (German).

[69] M. S. Cappell and J. B. Price, "Characterization of the syndrome of small and large intestinal variceal bleeding," *Digestive Diseases and Sciences*, vol. 32, no. 4, pp. 422–427, 1987.

[70] J. Ueda, H. Yoshida, Y. Mamada et al., "Successful emergency enterectomy for bleeding ileal varices in a patient with liver cirrhosis," *Journal of Nippon Medical School*, vol. 73, pp. 221–225, 2006 (Japanese).

[71] M. Mashimo, J. Hara, A. Nitta et al., "A case of ruptured ileal varices associated with alcoholic liver cirrhosis," *Nippon Shokakibyo Gakkai Zasshi*, vol. 104, pp. 561–567, 2007 (Japanese).

[72] I. Haruta, Y. Isobe, E. Ueno et al., "Balloon-occluded retrograde transvenous obliteration (BRTO), a promising nonsurgical therapy for ectopic varices," *The American Journal of Gastroenterology*, vol. 91, no. 12, pp. 2594–2597, 1996.

[73] K. Sano, T. Shuin, S. Takebayashi et al., "A case of vesical varices as a complication of portal hypertension and manifested gross hematuria," *Journal of Urology*, vol. 141, no. 2, pp. 369–371, 1989.

[74] P. M. Lugagne, D. Castaing, P. Conort, M. Guerrieri, O. Bousquet, and C. Chatelain, "Portal hypertension: a rare cause of hematuria," *Progres en Urologie*, vol. 2, no. 2, pp. 294–298, 1992.

[75] G. Loganathan, N. K. Shyamkumar, G. Kurian et al., "Vesical varix in cirrhosis of liver," *The Indian Journal of Gastroenterology*, vol. 19, no. 4, pp. 193–194, 2000.

[76] Y. Gaspar, O. Detry, and J. De Leval, "Vesical varices in a patient with portal hypertension," *The New England Journal of Medicine*, vol. 345, no. 20, pp. 1503–1504, 2001.

[77] T. Sato, "Transabdominal color Doppler ultrasonography for the diagnosis of small intestinal and vesical varices in a patient successfully treated with percutaneous transhepatic obliteration," *Clinical Journal of Gastroenterology*, vol. 3, pp. 214–218, 2010.

[78] A. N. Hamlyn, J. S. Morris, M. R. Lunzer, H. Puritz, and R. Dick, "Portal hypertension with varices in unusual sites," *The Lancet*, vol. 2, no. 7896, pp. 1531–1534, 1974.

[79] E. M. Izsak and J. M. Finlay, "Colonic varices. Three case reports and review of the literature," *The American Journal of Gastroenterology*, vol. 73, no. 2, pp. 131–136, 1980.

[80] Y. M. Miao, S. M. Catnach, I. G. Barrison, A. O'Reilly, and A. R. Divers, "Colonic variceal bleeding in a patient with mesenteric venous obstruction due to an ileal carcinoid tumor," *European Journal of Gastroenterology and Hepatology*, vol. 8, pp. 1133–1135, 1996.

[81] S. D. Klein, J. C. Hellinger, M. L. Silverstein, and Q. Cai, "Isolated cecal varices as the source of massive lower GI bleeding in a patient with cirrhosis," *The American Journal of Gastroenterology*, vol. 98, no. 1, pp. 220–221, 2003.

[82] R. J. Detry, A. Kartheuser, R. Moisse et al., "Idiopathic non-familial rectal and colonic varices requiring sigmoidorectal resection and coloanal anastomosis," *European Journal of Gastroenterology and Hepatology*, vol. 8, no. 10, pp. 1023–1026, 1996.

[83] R. Shrestha, J. C. Dunkelberg, and J. W. Schaefer, "Idiopathic colonic varices: an unusual cause of massive lower gastrointestinal hemorrhage," *The American Journal of Gastroenterology*, vol. 90, no. 3, pp. 496–497, 1995.

[84] J. P. Iredale, P. Ridings, F. P. McGinn, and M. J. Arthur, "Familial and idiopathic colonic varices: an unusual cause of lower gastrointestinal haemorrhage," *Gut*, vol. 33, no. 9, pp. 1285–1288, 1992.

[85] T. R. Smith, "CT demonstration of ascending colon varices," *Clinical Imaging*, vol. 18, no. 1, pp. 4–6, 1994.

[86] T. Sato, K. Yamazaki, J. Akaike et al., "Transverse colonic varices successfully treated with endoscopic procedure," *Clinical Journal of Gastroenterology*, vol. 1, pp. 52–55, 2008.

[87] H. P. Allgaier, A. Ochs, K. Haag et al., "Recurrent bleeding from colonic varices in portal hypertension. The successful prevention of recurrence by the implantation of a transjugular intrahepatic stent-shunt (TIPS)," *Deutsche Medizinische Wochenschrift*, vol. 120, no. 51-52, pp. 1773–1776, 1995.

[88] P. Chevallier, J. P. Motamedi, N. Demuth, F. X. Caroli-Bosc, F. Oddo, and B. Padovani, "Ascending colonic variceal bleeding: utility of phase-contrast MR portography in diagnosis and follow-up after treatment with TIPS and variceal embolization," *European Radiology*, vol. 10, no. 8, pp. 1280–1283, 2000.

[89] S. P. Misra and M. Dwivedi, "Ligation of a bleeding colonic varix using an upper gastrointestinal endoscope," *Endoscopy*, vol. 38, no. 6, p. 657, 2006.

[90] A. Anan, M. Irie, H. Watanabe et al., "Colonic varices treated by balloon-occluded retrograde transvenous obliteration in a cirrhotic patient with encephalopathy: a case report," *Gastrointestinal Endoscopy*, vol. 63, no. 6, pp. 880–884, 2006.

[91] N. B. Ackerman, G. M. Graeber, and J. Fey, "Enterostomal varices secondary to portal hypertension: progression of disease in conservatively managed cases," *Archives of Surgery*, vol. 115, no. 12, pp. 1454–1455, 1980.

[92] R. N. Samaraweera, L. Feldman, W. C. Widrich et al., "Stomal varices: percutaneous transhepatic embolization," *Radiology*, vol. 170, no. 3, pp. 779–782, 1989.

[93] P. L. Roberts, F. M. Martin, D. J. Schoetz Jr., J. J. Murray, J. A. Coller, and M. C. Veidenheimer, "Bleeding stomal varices. The role of local treatment," *Diseases of the Colon and Rectum*, vol. 33, no. 7, pp. 547–549, 1990.

[94] H. C. Wolfsen, R. A. Kozarek, J. E. Bredfeldt, L. F. Fenster, and L. L. Brubacher, "The role of endoscopic injection sclerotherapy in the management of bleeding peristomal varices," *Gastrointestinal Endoscopy*, vol. 36, no. 5, pp. 472–474, 1990.

[95] W. D. Warren, W. J. Millikan Jr., J. M. Henderson et al., "Ten years portal hypertensive surgery at Emory: results and new perspectives," *Annals of Surgery*, vol. 195, pp. 530–542, 1982.

[96] K. Kishimoto, A. Hara, T. Arita et al., "Stomal varices: treatment by percutaneous transhepatic coil embolization," *CardioVascular and Interventional Radiology*, vol. 22, pp. 523–525, 1999.

[97] S. G. Naidu, E. P. Castle, J. S. Kriegshauser, and E. A. Huettl, "Direct percutaneous embolization of bleeding stomal varices," *CardioVascular and Interventional Radiology*, vol. 33, pp. 201–204, 2010.

[98] G. D. Weinberg, T. A. Matalon, M. C. Brunner, S. K. Patel, and R. Sandler, "Bleeding stomal varices: treatment with a transjugular intrahepatic portosystemic shunt in two pediatric patients," *Journal of Vascular and Interventional Radiology*, vol. 6, no. 2, pp. 233–236, 1995.

[99] C. S. Morris and K. E. Najarian, "Transjugular intrahepatic portosystemic shunt for bleeding stomal varices associated with chronic portal vein occlusion: long-term angiographic, hemodynamic, and clinical follow-up," *The American Journal of Gastroenterology*, vol. 95, no. 10, pp. 2966–2968, 2000.

[100] R. K. Ryu, A. A. Nemcek, H. B. Chrisman et al., "Treatment of stomal variceal hemorrhage with TIPS: case report and review of the literature," *CardioVascular and Interventional Radiology*, vol. 23, pp. 301–303, 2000.

[101] S. Minami, K. Okada, M. Matsuo, Y. Kamohara, I. Sakamoto, and T. Kanematsu, "Treatment of bleeding stomal varices by balloon-occluded retrograde transvenous obliteration," *Journal of Gastroenterology*, vol. 42, pp. 91–95, 2007.

SAGE-Hindawi Access to Research
International Journal of Hepatology
Volume 2011, Article ID 893973, 8 pages
doi:10.4061/2011/893973

Review Article

Application of Endoscopy in Improving Survival of Cirrhotic Patients with Acute Variceal Hemorrhage

Yao-Chun Hsu,[1] Chen-Shuan Chung,[2] and Hsiu-Po Wang[3, 4]

[1] *Division of Gastroenterology and Hepatology, Department of Internal Medicine, E-Da Hospital/I-Shou University, Kaohsiung 824, Taiwan*
[2] *Division of Gastroenterology and Hepatology, Department of Internal Medicine, Far Eastern Memorial Hospital, New Taipei 220, Taiwan*
[3] *Department of Internal Medicine, National Taiwan University College of Medicine, National Taiwan University Hospital, Taipei 100, Taiwan*
[4] *Department of Internal Medicine, National Taiwan University Hospital, 7, Chung-Shan South Road, Taipei 100, Taiwan*

Correspondence should be addressed to Hsiu-Po Wang, wanghp@ntu.edu.tw

Received 15 March 2011; Accepted 12 May 2011

Academic Editor: Deepak Amarapurkar

Playing a central role in the modern multidisciplinary management of acute gastroesophageal variceal hemorrhage, endoscopy is essential to stratify patient at risk, control active hemorrhage, and prevent first as well as recurrent bleeding. Before endoscopic procedure, antibiotic prophylaxis along with vasoactive medication is now routine practice. Intravenous erythromycin effectively cleanses stomach and may improve the quality of endoscopy. The timing of endoscopy should be on an urgent basis as delay for more than 15 hours after presentation is associated with mortality. Active variceal bleeding on endoscopy in a patient with hepatic decompensation heralds poor prognosis and mandates consideration of aggressive strategy with early portosystemic shunting. Band ligation has become the preferred modality to control and prevent bleeding from esophageal varices, although occasionally sclerotherapy may still be used to achieve hemostasis. Addition of pharmacotherapy with nonselective beta blockade to endoscopic ligation has become the current standard of care in the setting of secondary prophylaxis but remains controversial with inconsistent data for the purpose of primary prophylaxis. Gastric varices extending from esophagus may be treated like esophageal varices, whereas variceal obliteration by tissue glue is the endoscopic therapy of choice to control and prevent bleeding from fundic and isolated gastric varices.

1. Introduction

Acute variceal hemorrhage (AVH) from esophageal varices (EV) or gastric varices (GV) is a devastating complication of portal hypertension. It is a leading cause of death in cirrhotic patients, particularly in those with hepatic decompensation. Early cohort studies observing the natural course of patients with AVH revealed that the short-term mortality rate was as high as 50%, with uncontrolled active hemorrhage and recurrent bleeding as the major causes of death [1–3]. As a witness of progress in modern medicine, the prognosis of AVH has remarkably improved for the last 3 decades, although the short-term mortality (conventionally defined as within 6 weeks of each episode) in recent series remained approximately 15–20% [4]. The improved outcome of cirrhotic patients with AVH probably results from advancement in the multidisciplinary approaches that include pharmacological therapy (vasoactive agents, antibiotic prophylaxis), endoscopic intervention (band ligation for EV, variceal obliteration for GV), transjugular intrahepatic portosystemic shunt (TIPS), and surgery. Being an essential part in the management of acute upper gastrointestinal (UGI) bleeding, endoscopy plays important roles in the confirmation of bleeders, stratification of risks, control of active hemorrhage, and prevention of the first and recurrent bleeding in cirrhotic patients with AVH [5]. The purpose of

this paper is to provide a concise and updated review on the use of endoscopy in managing patients with AVH.

2. Preparation for Endoscopy in Cirrhotic Patients with Acute UGIB

Patients with AVH frequently present with unstable hemodynamics because bleeding characteristically occurs not only massively but also rapidly. Therefore, restoration of circulatory volume by intravenous fluid resuscitation should be carried out immediately at patients' arrival. Blood component therapy usually is needed to correct anemia and bleeding tendency (coagulopathy as well as thrombocytopenia). Vasopressor may occasionally be required to maintain hemodynamic stability. A quick assessment for the indications of airway protection by endotracheal intubation is mandatory, in that the concern of suffocating aspiration is substantial in patients with massive hematemesis, impaired consciousness, and delirious status. Ideally, risks of circulatory collapse and airway compromise should be minimized before patients are transported to endoscopy rooms.

Intravenous administration of erythromycin prior to endoscopy may be considered in cirrhotic patients presenting with hematemesis, because brisk bleeding and large quantity of residual blood in the UGI tract often obscure endoscopic views, add difficulty of therapeutic intervention, and increase chance of aspiration. As a motilin receptor agonist, erythromycin induces peristalsis, stimulates gastrointestinal motility, and shortens gastric emptying time. The efficacy of erythromycin in cleansing stomach and thereby improving quality of endoscopy has been demonstrated in randomized controlled trials [6–8]. Recently, Altraif and colleagues reported in a double-blind randomized trial that erythromycin of 125 mg intravenously administered 30 minutes before endoscopy as compared with placebo significantly increased the proportion of a clear stomach (48.9% versus 23.3%, $P < .01$), decreased the mean procedural duration (19.0 minutes versus 26.0 minutes, $P < .05$), and shorten the hospitalized days (3.4 days versus 5.1 days, $P < .02$) in cirrhotic patients with AVH [7]. Besides, this medication appeared safe in these vulnerable patients without specific adverse reactions. Nevertheless, it remains unclear whether erythromycin also helps in controlling active hemorrhage, preventing recurrent bleeding, or adding survival benefit. So far, erythromycin infusion before endoscopy has not become a routine practice in most hospitals including ours. Finally, vasoactive agents (terlipressin, octreotide, and somatostatin) and prophylactic antibiotics before endoscopy unambiguously improve clinical outcomes and are now considered as an integral part of the evidence-based standard of care in cirrhotic patients presenting with acute UGI bleeding [9–11].

3. Timing of Endoscopy

The optimal timing of endoscopy for patients with AVH has long been controversial. Earlier randomized controlled trials for patients with esophageal variceal bleeding found that endoscopic sclerotherapy as compared with vasoactive pharmacotherapy (terlipressin, somatostatin) was not more effective in terms of hemostasis rate, prevention of recurrent bleeding, or prolonging survival, but was associated with more adverse effects [12, 13]. D'Amico and colleagues thus concluded in a meta-analysis study that endoscopic therapy could be reserved for use after pharmacological treatment failed in EV bleeding [14]. However, this conclusion has become less clinically relevant after band ligation replaced sclerotherapy as the endoscopic therapy of choice for EV bleeding. Solid evidence supports the former was not only more efficacious but also safer than the latter [15]. Furthermore, since endoscopic plus pharmacological therapy is superior to either treatment alone and pharmacotherapy can be readily given before endoscopy [16, 17], it is no longer valid to suggest reserving endoscopic intervention (particularly band ligation for EV bleeding) after failure of vasoactive drugs. What remains unsettled is how urgently endoscopy should be performed in patients already receiving optimal medical therapy. Practice guidelines from the international conference (the Baveno workshop) for the management of AVH recommended UGI endoscopy be performed as soon as possible (<12 hours) after admission [18, 19]. However, this recommendation was supported not so much by objective data as by experts' rational consensus. To address this unresolved issue, we conducted a retrospective analysis of 311 consecutive cases with AVH to examine whether timing of endoscopy was associated with mortality [20]. We found that timing of endoscopy was correlated with in-hospital mortality (Figure 1). In multivariate analysis, delayed endoscopy (>15 hours after presentation to the hospital) was an independent risk factor associated with mortality (odds ratio 3.67; 95% confidence interval, 1.27~10.39). Our study, nonetheless, failed to demonstrate "the sooner the better" concept, in that the association between risk of death and endoscopy timing was nonlinear and mortality did not decrease with every hour earlier of endoscopy. Somewhat inconsistent with our observation, Cheung et al. from Canada reported that endoscopy timing was unrelated with clinical outcomes in hemodynamically stable AVH patients [21]. They found whether endoscopy was performed within 4, 8, or 12 hours within initial assessment at hospital did not influence recurrent bleeding, blood transfusion, need for rescue therapy, length of hospitalization, or mortality. Of note, only half of all patients with AVH were enrolled into analysis in their study, because the results of those with initial unstable hemodynamics were not reported [22]. In view of the understandable difficulty to perform a randomized trial to compare different endoscopy timings in this setting, the controversy will probably continue to exist. Based on currently available data, we believe the rule is to perform endoscopy within 15 hours of presentation, but meanwhile we also acknowledge there is no evidence to support rushing endoscopy in AVH patients, particularly in those with stable hemodynamics. Therefore, while delaying endoscopy for more than 15 hours should be avoided, endoscopists may wait in the first few hours to allow emergency resuscitation, optimal medication, and perhaps preparation for a cleaner stomach to be carried out.

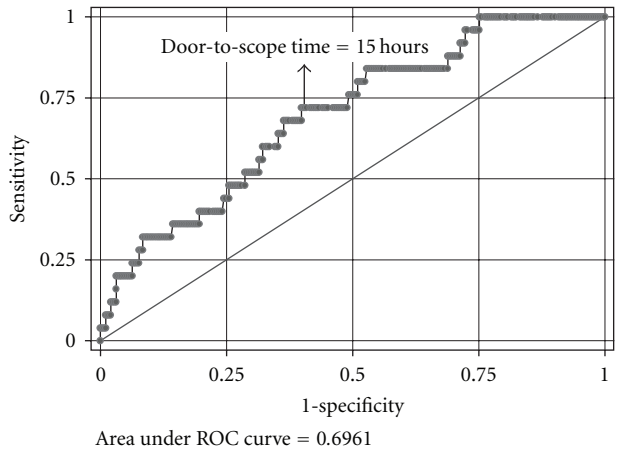


Figure 1: Receiver operating characteristic curve of "door-to-scope" time for in-hospital mortality. The area under curve is 0.696 (95% C.I. 0.595 ~ 0.797). The most optimal cut-off value (in integer) to predict in-hospital mortality was 15 hours, with sensitivity of 72.0% and specificity of 59.4% (adapted from [20]).

4. Risk Stratification with and without Endoscopy

Determination of bleeding source by upper GI endoscopy has important prognostic value in cirrhotic patients with acute UGI bleeding, since patients with variceal bleeding (definite or probable) fared significantly worse than those who bleed from other sources [23, 24]. In addition, active bleeding on endoscopy was shown to predict 5-day treatment failure and 6-week mortality [24, 25]. With regard to the risk prediction for patients with endoscopically confirmed AVH, measurement of hepatic venous pressure gradient (HVPG) is arguably the best method to stratify risk of untoward outcomes. It has been demonstrated that an initial HVPG > 20 mmHg most reliably identified those patients whose clinical course would evolve poorly [26]. Furthermore, a large body of evidence supports reduction of greater than 20% of the initial HVPG value convincingly indicates risk reduction in recurrent bleeding and mortality [27]. However, application of HVPG measurement is regrettably not widespread around the world, and in reality is not incorporated into daily practice in the vast majority of institutions. Fortunately, there is evidence suggesting that easily obtainable clinical variables, as compared with HVPG, may have similar accuracy in predicting failure of treatment during the acute phase of a bleeding episode (5 days) [28]. Among the various clinical parameters that have been investigated, indicators of hepatic reserve (Child-Turcotte-Pugh classification, model for end-stage liver disease (MELD) score), markers of bleeding severity (active bleeding on endoscopy, presentation with hematemesis, amount of blood transfusion, hemoglobin level), underlying liver disease or comorbidity (etiology, hepatocellular carcinoma, portal vein thrombosis), complications during bleeding episodes (encephalopathy, bacterial infection, renal dysfunction), and failure of initial treatment (uncontrolled active hemorrhage, recurrent bleeding) have been shown to predict clinical outcomes [20, 24, 29–32]. Endoscopic identification of AVH patients at risk of unfavorable outcomes may be crucial in guiding subsequent management. Garcia-Pagan and colleagues reported in a randomized trial that EV patients with hepatic decompensation (Child-Turcotte-Pugh scores between 7 and 13) and persistent bleeding at endoscopy would benefit from early TIPS performed within 72 hours [33]. The one-year survival rate was 86% versus 61% ($P < .001$) in patients randomized to early TIPS as compared with those who were assigned to receive optimal pharmacotherapy plus endoscopic band ligation. Therefore, it stands to reason that patients with actively bleeding and compromised liver function may require aggressive therapy to be implemented as early as a continuation to endoscopic therapy rather than as a rescue measure for treatment failure.

Although the prognostic factors for AVH have been extensively studied, those for cirrhotic patients with all sources of acute UGI bleeding remain sparsely explored. Undoubtedly, endoscopy is urgently indicated in cirrhotic patients presenting with UGI bleeding, but it takes time to resuscitate the patients, transfuse blood components, and administer intravenous medications. Therefore, risk stratification explicitly for variceal bleeding may not be applicable for clinicians managing patients in the emergency department, since not all cirrhotic patients bleed from varices. Previous studies that investigated prognostic indices independent of the source of bleeding not only incorporated endoscopic data but also allowed subjective criteria [23, 24]. In our opinion, criteria based on subjective judgment may not be reliable, particularly in the busy emergency setting. For example, uncovering and staging ascites and encephalopathy relies on expertise and is not free of inter-observer variation [34]. We believe a useful stratification system in the setting of emergency room should ideally be built on simple, objective, and readily available parameters. To this end, we have retrospectively studied 542 consecutive episodes of acute UGI bleeding from 389 cirrhotic patients in order to develop a prognostic model consisting of pre-endoscopic clinical factors that were routinely available in the first hour at hospital [35]. We revealed that 6-week mortality was independently associated with male gender, hypoxemia on arrival, hepatocellular carcinoma and another malignancy, serum bilirubin, and prothrombin time (Table 1). The performance of a model built on these 6 variables was superior to the MELD score in predicting 6-week mortality, with c statistic of 0.84 and 0.71 respectively ($P = .002$). Presumably, earlier risk stratification may guide earlier modification of therapeutic approaches to improve the outcomes of those at risk. Further research is now warranted to elucidate how pre-endoscopic risk stratification will influence the early management for cirrhotic patients presenting with acute UGI bleeding.

5. Endoscopic Therapy for Primary Prophylaxis

Screening endoscopy is mandatory to confirm the presence, to determine the size, and to uncover the stigmata of varices in cirrhotic patients, particularly in those with

Table 1: Independent risk factors of 6-week mortality in cirrhotic patients with acute upper gastrointestinal hemorrhage, determined by multivariate logistic regression model.

	Adjusted odds ratio	95% confidence interval
Male sex	4.35	1.14 ~ 16.62
Hypoxemia[#]	9.42	3.65 ~ 24.30
HCC	2.31	1.12 ~ 4.78
Non-HCC malignancy	4.70	1.55 ~ 14.26
Bilirubin (per mg/dL)	1.07	1.02 ~ 1.13
INR (per unit)	2.88	1.28 ~ 6.51

[#] Hypoxemia is defined as peripheral oxygen saturation less than 95%; HCC: hepatocellular carcinoma; INR: international normalized ration (adapted from [35]).

decompensated status [36–38]. Historically endoscopic sclerotherapy had been used in preventing the first bleeding from esophageal varices prior to the era of band ligation [39], but it is no longer recommended in this indication because the risk of complications may outweigh the potential benefits [40, 41]. EVL is technically infeasible for small esophageal varices defined as size <5 mm or F1 according to the classification proposed by Beppu et al. [38], whereas nonselective beta-blocker (NSBB) may slow the growth of small EV and thereby prevent the first variceal hemorrhage [42]. In patients with medium to large (or F2-F3) EV, risk of future bleeding is substantial and primary prophylaxis is indicated. Band ligation is as at least effective as NSBB for primary prophylaxis of EV bleeding [43–46]. The decision to use EVL or NSBB should be individualized according to the local resources and expertise, patients' preference and characteristics, tolerability of side effects, and contraindications to either therapy. In fact, more than half of patients preferred EVL over NSBB use for fear of side effects from beta-blockade, such as light-headedness, shortness of breath, fatigue, and poor memory [47]. Because poor tolerability to NSBB is not uncommon and the response of HVPG to pharmacological therapy cannot be reliably assessed by clinical parameters, we usually perform EVL for primary prophylaxis in our institutes.

There is no doubt that band ligation and NSBB are effective, respectively, to prevent first bleeding in the EV with medium to large size, but it remains unknown whether combination therapy with both treatment modalities is more effective than either therapy alone. Sarin et al. reported in a randomized controlled trial that propranolol plus EVL and EVL alone were not different in bleeding related death, although there was less recurrence of varices in the combination group (5.6% *versus* 15.3%, $P = .03$) [48]. In a randomized trial conducted by Gheorghe et al., propranolol plus EVL as compared with propranolol alone resulted in lower rate of first bleeding from the high risk EV (6% *versus* 31%, $P = .03$), and higher bleeding-free survival rate (96% *versus* 69%, $P = .04$) during the 18-month followup in cirrhotic patients awaiting liver transplantation [49]. Nevertheless, Lo and colleagues demonstrated that EVL plus nadolol was not only not more effective that nadolol alone for primary prophylaxis of EV bleeding but also associated with more adverse events (68% *versus* 40%, $P = .06$) [50]. As the controversy goes on, currently combination therapy with EVL plus NSBB cannot be recommended in patients whose EV has not bled.

6. Endoscopic Therapy to Control Active Bleeding

Endoscopic therapy plays a pivotal role in the hemostasis of AVH. EVL is the recommended endoscopic therapy whenever feasible to control active EV bleeding, because it is unambiguously safer and more effective than sclerotherapy [51–53]. Occasionally, sclerotherapy may be substituted if EVL is technically difficult, for example, in a repeatedly ligated esophagus with scarred mucosa that is difficult to be sucked into the cap. It is important to carefully scrutinize the bleeding stigmata (e.g., hematocystic spot, white nipple) in those without ongoing bleeding at endoscopy. Localization of the origin of bleeding is essential for successful endoscopic therapy, inasmuch as EVL should be initiated at or just below the bleeding point. If the bleeder cannot be clearly localized, ligation may start at the gastroesophageal junction and then advance upward spirally. While active bleeding at endoscopy mandates immediate hemostasis, absence of ongoing hemorrhage during endoscopy should not be erroneously regarded as reassuring to reserve endoscopic therapy. In a randomized trial, Lo and colleagues compared EVL plus terlipressin versus terlipressin alone in cirrhotic patients presenting with acute inactive EV bleeding and demonstrated that EVL was effective in reducing 5-day rebleeding rate (0% versus 15%, $P = .006$), treatment failure rate (2% versus 24%, $P = .002$), and amount blood transfusion [54]. Therefore, EVL cannot be spared in cirrhotic patients with inactive bleeding EV at endoscopy if another bleeding source is unlikely.

Injection therapy with tissue glue (e.g., N-butyl-2-cyanoacrylate and 2-octyl-cyanoacrylate) to obliterate varices has become the endoscopic treatment of choice for isolated gastric varices (IGV) and gastroesophageal varices extending beyond cardia (GOV2) [55]. Regrettably, there is considerably less data regarding the endoscopic therapy in controlling active GV hemorrhage, in contrast to the overwhelming evidence supporting the role of EVL in EV bleeding. Glue injection using cyanoacrylate for acute GV bleeding achieves high rates of immediate hemostatsis, eventual eradication, and low treatment failure-related mortality rate [56]. Consistent results from randomized trials provide convincing evidence to support the superiority of obliteration therapy over either sclerotherapy [57–59], or band ligation [60, 61]. While the techniques to achieve variceal obliteration vary in different institutes, it has been adopted in our daily practice to inject a mixture of N-butyl-2-cyanoacrylate and lipiodol (1:1) without contrast agent. Despite the efficacy and generally acceptable safety profile of injection therapy with tissue adhesives, thromboembolism infrequently occurs and represents the most fearful complication of cyanoacrylate injection that may potentially lead to infarction of multiple organs [62, 63]. Use of thrombin or fibrin has been explored

in the management of acute GV bleeding with promising preliminary results [64–66]. Theoretical advantages of thrombin injection include biocompatibility and minimal mucosal damage, whereas possibility of transmissible infectious disease and excessive cost are major concerns. Before data from controlled trials comparing it with cyanoacrylate is available, thrombin injection should better be viewed as experimental and ideally be confined in the setting of clinical studies.

7. Endoscopic Therapy for Secondary Prophylaxis

As long as the portal hypertension persists, it is simply the natural course of varices to rebleed, with 1-year rebleeding rate approximating 60% [67]. Since gastroesophageal varices result from portal hypertension and occurrence of variceal hemorrhage depends directly on hydrostatic pressure of portal system (as reflected by HVPG), presumably the best treatment to prevent recurrent bleeding is to reduce the severity of portal hypertension, and that is the pathophysiological basis for the efficacy of NSBB. In view of the high recurrence rate, preventive measures for recurrent bleeding should be instituted right after acute bleeding episode is controlled. It is recommended that patients receive secondary prophylaxis before they are discharged from hospital for an bleeding episode, especially for those with large varices, red color signs, and decompensated cirrhosis [55].

Consistent with its superior role in primary prophylaxis and controlling active hemorrhage, EVL remains the preferred endoscopic treatment for secondary prevention of EV bleeding. EVL, again, outperforms sclerotherapy in this indication in terms of lower complication rate and higher efficacy [68–70]. Moreover, there is no evidence to embrace the addition of sclerotherapy to EVL. Singh et al. reported in a meta-analysis that combination of EVL and sclerotherapy as compared with EVL alone was not more effective in preventing recurrent EV bleeding, but was associated with higher complication events such as esophageal stricture [71]. In our opinion, endoscopic sclerotherapy has no role in the secondary prophylaxis of EV bleeding. With regard to variceal obliteration by tissue adhesives, there was a randomized trial demonstrating similar rebleeding rates between histoacryl injection and NSBB administration, but the former treatment was associated with a higher complication rate (47.6% *versus* 10%, $P < .03$) [72]. Moreover, we are unaware of any trial comparing efficacy and safety of glue injection with that of EVL in the secondary prophylaxis of EV bleeding. In contrast to the scenario of primary prophylaxis, in which combination therapy with EVL and NSBB does not fare better than either therapy alone, combining endoscopic therapy plus pharmacological therapy is recommended in the setting of secondary prophylaxis. A meta-analysis including 23 studies showed that rates of rebleeding (both from all sources and specifically from varices) are lower with combination of endoscopic therapy (either sclerotherapy or EVL) plus drug therapy than with either therapy alone [73]. Therefore, cirrhotic patients recovering from acute EV bleeding should receive NSBB and have their varices eradicated by band ligation. In those who are unable or unwilling to undergo EVL, the addition of isosorbide mononitrites to NSBB appears a reasonable option.

Usually several sessions of banding ligation is needed in order to eradicate EV. However, the time interval of band ligation remains an unsettled issue. Although some studies proposed an interval of 1 to 2 weeks [69, 70, 74], others advocated an interval of 1-2 months of band ligation for obliteration of EV [75, 76]. Yoshida et al. found a short interval between sessions of EVL might even be detrimental by showing that the overall rates of variceal recurrence and additional treatment were both higher in patients with EVL at a biweekly interval than those with a bimonthly protocol [76]. Generally, we do not repeat sessions of EVL within 2 weeks because prior ligation-related mucosal ulceration may not have healed by that time and thereby may influence the following deployment of ligating bands. As far as efficacy is concerned, TIPS may be a more effective modality than endoscopic therapy to prevent recurrent bleeding. According to a meta-analysis, patients undergoing TIPS had a lower rebleeding rate than those receiving endoscopic treatment (19% *versus* 47%, $P < .001$). The overall mortality, nevertheless, was not different [77]. The risk of hepatic encephalopathy, development of shunt stenosis, and the cost of a covered stent make TIPS traditionally considered as rescue therapy in patients with repeated AVH. However, as aforementioned in the section of risk prediction, early TIPS strategy (<72 hours) in high-risk patients improves survival significantly and may lead to paradigm shift in the future [33].

Despite the relative paucity of data in the efficacy and safety of using endoscopy to prevent recurrent hemorrhage from GV, tissue adhesives injection using N-butyl-cyanoacrylate is a reasonable choice for patients bleeding from IGV1 or GOV2, similar to control of acute bleeding, [55, 78]. For those who have bled from GOV1, either tissue adhesives injection or band ligation may be used, depending on the location of varices, technical feasibility, and expertise of the endoscopist. Unless it is technically infeasible, we recommend band ligation for EV and GOV1 at the same time.

8. Conclusion

Endoscopy is essential in the modern multidisciplinary management of cirrhotic patients with AVH. Endoscopy should not be delayed for more than 15 hours as it is associated with increased risk of in-hospital mortality, although otherwise the data is insufficient for embracing "the sooner the better" belief, particularly in hemodynamically stable patients. Active bleeding at endoscopy in decompensated cirrhotic patients predicts poor outcomes and may warrant more aggressive treatment, such as early TIPS right after endoscopic therapy. Band ligation is the endoscopic modality of choice in primary prophylaxis, hemostasis of active bleeding, and secondary prophylaxis of EV bleeding. Although occasionally sclerotherapy may still be performed for hemostatic control of acute EV bleeding,

it should no longer be used in the prophylactic setting. Tissue glue injection to attain variceal obliteration is now the preferred endoscopic therapy to control and prevent bleeding from fundic and isolated GV. The paucity of data in the management of GV warrants more research, particularly large controlled trials, to define the evidence-based standard of care. Even though substantial improvement has been achieved for the last several decades in the management of cirrhotic patients with AVH, there is undoubtedly plenty room for continuing improvement in this still highly lethal medical emergency.

References

[1] D. Y. Graham and J. L. Smith, "The course of patients after variceal hemorrhage," *Gastroenterology*, vol. 80, no. 4, pp. 800–809, 1981.

[2] J. L. Smith and D. Y. Graham, "Variceal hemorrhage: a critical evaluation of survival analysis," *Gastroenterology*, vol. 82, no. 5, pp. 968–973, 1982.

[3] E. Christensen, L. Fauerholdt, P. Schlichting, E. Juhl, H. Poulsen, and N. Tygstrup, "Aspects of the natural history of gastrointestinal bleeding in cirrhosis and the effect of prednisone," *Gastroenterology*, vol. 81, no. 5, pp. 944–952, 1981.

[4] N. Carbonell, A. Pauwels, L. Serfaty, O. Fourdan, V. G. Levy, and R. Poupon, "Improved survival after variceal bleeding in patients with cirrhosis over the past two decades," *Hepatology*, vol. 40, no. 3, pp. 652–659, 2004.

[5] W. Qureshi, D. G. Adler, R. Davila et al., "ASGE Guideline: the role of endoscopy in the management of variceal hemorrhage, updated July 2005," *Gastrointestinal Endoscopy*, vol. 62, no. 5, pp. 651–655, 2005.

[6] J. L. Frossard, L. Spahr, P. E. Queneau et al., "Erythromycin intravenous bolus infusion in acute upper gastrointestinal bleeding: a randomized, controlled, double-blind trial," *Gastroenterology*, vol. 123, no. 1, pp. 17–23, 2002.

[7] I. Altraif, F. A. Handoo, A. Aljumah et al., "Effect of erythromycin before endoscopy in patients presenting with variceal bleeding: a prospective, randomized, double-blind, placebo-controlled trial," *Gastrointestinal Endoscopy*, vol. 73, no. 2, pp. 245–250, 2011.

[8] B. Coffin, M. Pocard, Y. Panis et al., "Erythromycin improves the quality of EGD in patients with acute upper GI bleeding: a randomized controlled study," *Gastrointestinal Endoscopy*, vol. 56, no. 2, pp. 174–179, 2002.

[9] B. Bernard, J. D. Grange, E. N. Khac, X. Amiot, P. Opolon, and T. Poynard, "Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis," *Hepatology*, vol. 29, no. 6, pp. 1655–1661, 1999.

[10] K. Soares-Weiser, M. Brezis, R. Tur-Kaspa, M. Paul, J. Yahav, and L. Leibovici, "Antibiotic prophylaxis of bacterial infections in cirrhotic inpatients: a meta-analysis of randomized controlled trials," *Scandinavian Journal of Gastroenterology*, vol. 38, no. 2, pp. 193–200, 2003.

[11] M. C. Hou, H. C. Lin, T. T. Liu et al., "Antibiotic prophylaxis after endoscopic therapy prevents rebleeding in acute variceal hemorrhage: a randomized trial," *Hepatology*, vol. 39, no. 3, pp. 746–753, 2004.

[12] A. Escorsell, J. M. Bordas, L. R. del Arbol et al., "Randomized controlled trial of sclerotherapy versus somatostatin infusion in the prevention of early rebleeding following acute variceal hemorrhage in patients with cirrhosis," *Journal of Hepatology*, vol. 29, no. 5, pp. 779–788, 1998.

[13] A. Escorsell, L. Ruiz del Arbol, R. Planas et al., "Multicenter randomized controlled trial of terlipressin versus sclerotherapy in the treatment of acute variceal bleeding: the TEST study," *Hepatology*, vol. 32, no. 3, pp. 471–476, 2000.

[14] G. D'Amico, G. Pietrosi, I. Tarantino, and L. Pagliaro, "Emergency sclerotherapy versus vasoactive drugs for variceal bleeding in cirrhosis: a cochrane meta-analysis," *Gastroenterology*, vol. 124, no. 5, pp. 1277–1291, 2003.

[15] C. Villanueva, A. Colomo, C. Aracil, and C. Guarner, "Current endoscopic therapy of variceal bleeding," *Best Practice and Research: Clinical Gastroenterology*, vol. 22, no. 2, pp. 261–278, 2008.

[16] R. Banares, A. Albillos, D. Rincon et al., "Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: a meta-analysis," *Hepatology*, vol. 35, no. 3, pp. 609–615, 2002.

[17] M. Ravipati, S. Katragadda, P. D. Swaminathan, J. Molnar, and E. Zarling, "Pharmacotherapy plus endoscopic intervention is more effective than pharmacotherapy or endoscopy alone in the secondary prevention of esophageal variceal bleeding: a meta-analysis of randomized, controlled trials," *Gastrointestinal Endoscopy*, vol. 70, no. 4, pp. 658–664, 2009.

[18] R. de Franchis, "Evolving consensus in portal hypertension report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension," *Journal of Hepatology*, vol. 43, no. 1, pp. 167–176, 2005.

[19] R. de Franchis, "Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension," *Journal of Hepatology*, vol. 53, no. 4, pp. 762–768, 2010.

[20] Y. C. Hsu, C. S. Chung, C. H. Tseng et al., "Delayed endoscopy as a risk factor for in-hospital mortality in cirrhotic patients with acute variceal hemorrhage," *Journal of Gastroenterology and Hepatology*, vol. 24, no. 7, pp. 1294–1299, 2009.

[21] J. Cheung, I. Soo, R. Bastiampillai, Q. Zhu, and M. Ma, "Urgent vs. non-urgent endoscopy in stable acute variceal bleeding," *American Journal of Gastroenterology*, vol. 104, no. 5, pp. 1125–1129, 2009.

[22] Y. C. Hsu, C. C. Chen, and H. P. Wang, "Endoscopy timing in acute variceal hemorrhage: perhaps not the sooner the better, but delay not justified," *American Journal of Gastroenterology*, vol. 104, no. 10, pp. 2629–2631, 2009.

[23] A. Gatta, C. Merkel, P. Amodio et al., "Development and validation of a prognostic index predicting death after upper gastrointestinal bleeding in patients with liver cirrhosis: a multicenter study," *American Journal of Gastroenterology*, vol. 89, no. 9, pp. 1528–1536, 1994.

[24] G. D'Amico and R. De Franchis, "Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators," *Hepatology*, vol. 38, no. 3, pp. 599–612, 2003.

[25] K. Bambha, W. R. Kim, R. A. Pedersen, J. P. Bida, W. K. Kremers, and P. S. Kamath, "Predictors of re-bleeding and mortality following acute variceal haemorrhage in patients with cirrhosis," *Gut*.

[26] E. Moitinho, A. Escorsell, J. C. Bandi et al., "Prognostic value of early measurements of portal pressure in acute variceal bleeding," *Gastroenterology*, vol. 117, no. 3, pp. 626–631, 1999.

[27] G. D'Amico, J. C. Garcia-Pagan, A. Luca, and J. Bosch, "Hepatic vein pressure gradient reduction and prevention of variceal bleeding in cirrhosis: a systematic review," *Gastroenterology*, vol. 131, no. 5, pp. 1611–1624, 2006.

[28] J. G. Abraldes, C. Villanueva, R. Banares et al., "Hepatic venous pressure gradient and prognosis in patients with acute variceal bleeding treated with pharmacologic and endoscopic therapy," *Journal of Hepatology*, vol. 48, no. 2, pp. 229–236, 2008.

[29] Z. Ben-Ari, F. Cardin, A. P. McCormick, G. Wannamethee, and A. K. Burroughs, "A predictive model for failure to control bleeding during acute variceal haemorrhage," *Journal of Hepatology*, vol. 31, no. 3, pp. 443–450, 1999.

[30] K. Bambha, W. R. Kim, R. Pedersen, J. P. Bida, W. K. Kremers, and P. S. Kamath, "Predictors of early re-bleeding and mortality after acute variceal haemorrhage in patients with cirrhosis," *Gut*, vol. 57, no. 6, pp. 814–820, 2008.

[31] N. Chalasani, C. Kahi, F. Francois et al., "Model for end-stage liver disease (MELD) for predicting mortality in patients with acute variceal bleeding," *Hepatology*, vol. 35, no. 5, pp. 1282–1284, 2002.

[32] L. Amitrano, M. A. Guardascione, R. Bennato, F. Manguso, and A. Balzano, "MELD score and hepatocellular carcinoma identify patients at different risk of short-term mortality among cirrhotics bleeding from esophageal varices," *Journal of Hepatology*, vol. 42, no. 6, pp. 820–825, 2005.

[33] J. C. Garcia-Pagan, K. Caca, C. Bureau et al., "Early use of TIPS in patients with cirrhosis and variceal bleeding," *New England Journal of Medicine*, vol. 362, no. 25, pp. 2370–2379, 2010.

[34] M. Malinchoc, P. S. Kamath, F. D. Gordon, C. J. Peine, J. Rank, and P. C. Ter Borg, "A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts," *Hepatology*, vol. 31, no. 4, pp. 864–871, 2000.

[35] Y. C. Hsu, J. M. Liou, C. S. Chung et al., "Early risk stratification with simple clinical parameters for cirrhotic patients with acute upper gastrointestinal bleeding," *American Journal of Emergency Medicine*, vol. 28, no. 8, pp. 884–890, 2010.

[36] O. Riggio, S. Angeloni, G. Nicolini, and M. Merli, "Endoscopic screening for esophageal varices in cirrhotic patients," *Hepatology*, vol. 35, no. 2, pp. 501–502, 2002.

[37] M. Kovalak, J. Lake, N. Mattek, G. Eisen, D. Lieberman, and A. Zaman, "Endoscopic screening for varices in cirrhotic patients: data from a national endoscopic database," *Gastrointestinal Endoscopy*, vol. 65, no. 1, pp. 82–88, 2007.

[38] K. Beppu, K. Inokuchi, N. Koyanagi et al., "Prediction of variceal hemorrhage by esophageal endoscopy," *Gastrointestinal Endoscopy*, vol. 27, no. 4, pp. 213–218, 1981.

[39] J. M. Fardy and A. Laupacis, "A meta-analysis of prophylactic endoscopic sclerotherapy for esophageal varices," *American Journal of Gastroenterology*, vol. 89, no. 11, pp. 1938–1948, 1994.

[40] B. M. Schuman, J. W. Beckman, F. J. Tedesco, J. W. Griffin Jr., and R. T. Assad, "Complications of endoscopic injection sclerotherapy: a review," *American Journal of Gastroenterology*, vol. 82, no. 9, pp. 823–830, 1987.

[41] P. B. Gregory, "Prophylactic sclerotherapy for esophageal varices in men with alcoholic liver disease: a randomized, single-blind, multicenter clinical trial," *New England Journal of Medicine*, vol. 324, no. 25, pp. 1779–1784, 1991.

[42] C. Merkel, R. Marin, P. Zanella et al., "A placebo-controlled clinical trial of nadolol in the prophylaxis of growth of small esophageal varices in cirrhosis," *Gastroenterology*, vol. 127, no. 2, pp. 476–484, 2004.

[43] G. H. Lo, W. C. Chen, M. H. Chen et al., "Endoscopic ligation vs. nadolol in the prevention of first variceal bleeding in patients with cirrhosis," *Gastrointestinal Endoscopy*, vol. 59, no. 3, pp. 333–338, 2004.

[44] S. K. Sarin, G. S. Lamba, M. Kumar, A. Misra, and N. S. Murthy, "Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding," *New England Journal of Medicine*, vol. 340, no. 13, pp. 988–993, 1999.

[45] L. L. Gluud, S. Klingenberg, D. Nikolova, and C. Gluud, "Banding ligation versus beta-blockers as primary prophylaxis in esophageal varices: systematic review of randomized trials," *American Journal of Gastroenterology*, vol. 102, no. 12, pp. 2842–2848, 2007.

[46] T. F. Imperiale and N. Chalasani, "A meta-analysis of endoscopic variceal ligation for primary prophylaxis of esophageal variceal bleeding," *Hepatology*, vol. 33, no. 4, pp. 802–807, 2001.

[47] A. V. Longacre, A. Imaeda, G. Garcia-Tsao, and L. Fraenkel, "A pilot project examining the predicted preferences of patients and physicians in the primary prophylaxis of variceal hemorrhage," *Hepatology*, vol. 47, no. 1, pp. 169–176, 2008.

[48] S. K. Sarin, M. Wadhawan, S. R. Agarwal, P. Tyagi, and B. C. Sharma, "Endoscopic variceal ligation plus propranolol versus endoscopic variceal ligation alone in primary prophylaxis of variceal bleeding," *American Journal of Gastroenterology*, vol. 100, no. 4, pp. 797–804, 2005.

[49] C. Gheorghe, L. Gheorghe, S. Iacob, R. Iacob, and I. Popescu, "Primary prophylaxis of variceal bleeding in cirrhotics awaiting liver transplantation," *Hepato-Gastroenterology*, vol. 53, no. 70, pp. 552–557, 2006.

[50] G. H. Lo, W. C. Chen, H. M. Wang, and C. C. Lee, "Controlled trial of ligation plus nadolol versus nadolol alone for the prevention of first variceal bleeding," *Hepatology*, vol. 52, no. 1, pp. 230–237, 2010.

[51] L. Laine, H. M. El-Newihi, B. Migikovsky, R. Sloane, and F. Garcia, "Endoscopic ligation compared with sclerotherapy for the treatment of bleeding esophageal varices," *Annals of Internal Medicine*, vol. 119, no. 1, pp. 1–7, 1993.

[52] M. C. Hou, H. C. Lin, B. I. Kuo, C. H. Chen, F. Y. Lee, and S. D. Lee, "Comparison of endoscopic variceal injection sclerotherapy and ligation for the treatment of esophageal variceal hemorrhage: a prospective randomized trial," *Hepatology*, vol. 21, no. 6, pp. 1517–1522, 1995.

[53] G. H. Lo, K. H. Lai, J. S. Cheng et al., "A prospective, randomized trial of sclerotherapy versus ligation in the management of bleeding esophageal varices," *Hepatology*, vol. 22, no. 2, pp. 466–471, 1995.

[54] G. H. Lo, W. C. Chen, H. M. Wang et al., "Low-dose terlipressin plus banding ligation versus low-dose terlipressin alone in the prevention of very early rebleeding of oesophageal varices," *Gut*, vol. 58, no. 9, pp. 1275–1280, 2009.

[55] S. K. Sarin, D. C. Valla, and R. D. Franchis, "Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension," *Journal of Hepatology*, vol. 54, no. 5, pp. 1082–1083, 2011.

[56] P. J. Belletrutti, J. Romagnuolo, R. J. Hilsden et al., "Endoscopic management of gastric varices: efficacy and outcomes of gluing with N-butyl-2-cyanoacrylate in a North American patient population," *Canadian Journal of Gastroenterology*, vol. 22, no. 11, pp. 931–936, 2008.

[57] S. K. Sarin, A. K. Jain, M. Jain, and R. Gupta, "A randomized controlled trial of cyanoacrylate versus alcohol injection in patients with isolated fundic varices," *American Journal of Gastroenterology*, vol. 97, no. 4, pp. 1010–1015, 2002.

[58] K. Oho, T. Iwao, M. Sumino, A. Toyonaga, and K. Tanikawa, "Ethanolamine oleate versus butyl cyanoacrylate for bleeding

gastric varices: a nonrandomized study," *Endoscopy*, vol. 27, no. 5, pp. 349–354, 1995.

[59] K. Ogawa, S. Ishikawa, Y. Naritaka et al., "Clinical evaluation of endoscopic injection sclerotherapy using n- butyl-2-cyanoacrylate for gastric variceal bleeding," *Journal of Gastroenterology and Hepatology*, vol. 14, no. 3, pp. 245–250, 1999.

[60] P. C. Tan, M. C. Hou, H. C. Lin et al., "A randomized trial of endoscopic treatment of acute gastric variceal hemorrhage: N-butyl-2-cyanoacrylate injection versus band ligation," *Hepatology*, vol. 43, no. 4, pp. 690–697, 2006.

[61] G. H. Lo, K. H. Lai, J. S. Cheng, M. H. Chen, and H. T. Chiang, "A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices," *Hepatology*, vol. 33, no. 5, pp. 1060–1064, 2001.

[62] A. Turler, M. Wolff, D. Dorlars, and A. Hirner, "Embolic and septic complications after sclerotherapy of fundic varices with cyanoacrylate," *Gastrointestinal Endoscopy*, vol. 53, no. 2, pp. 228–230, 2001.

[63] Y. M. Tan, K. L. Goh, A. Kamarulzaman et al., "Multiple systemic embolisms with septicemia after gastric variceal obliteration with cyanoacrylate," *Gastrointestinal Endoscopy*, vol. 55, no. 2, pp. 276–278, 2002.

[64] M. A. Heneghan, A. Byrne, and P. M. Harrison, "An open pilot study of the effects of a human fibrin glue for endoscopic treatment of patients with acute bleeding from gastric varices," *Gastrointestinal Endoscopy*, vol. 56, no. 3, pp. 422–426, 2002.

[65] W. L. Yang, D. Tripathi, G. Therapondos, A. Todd, and P. C. Hayes, "Endoscopic use of human thrombin in bleeding gastric varices," *American Journal of Gastroenterology*, vol. 97, no. 6, pp. 1381–1385, 2002.

[66] J. Ramesh, J. K. Limdi, V. Sharma, and A. J. Makin, "The use of thrombin injections in the management of bleeding gastric varices: a single-center experience," *Gastrointestinal Endoscopy*, vol. 68, no. 5, pp. 877–882, 2008.

[67] J. Bosch and J. C. García-Pagán, "Prevention of variceal rebleeding," *The Lancet*, vol. 361, no. 9361, pp. 952–954, 2003.

[68] T. Sauerbruch and M. Schepke, "Sclerotherapy is out—nearly," *Endoscopy*, vol. 29, no. 4, pp. 281–282, 1997.

[69] A. E. Gimson, J. K. Ramage, M. Z. Panos et al., "Randomised trial of variceal banding ligation versus injection sclerotherapy for bleeding oesophageal varices," *The Lancet*, vol. 342, no. 8868, pp. 391–394, 1993.

[70] G. V. Stiegmann, J. S. Goff, P. A. Michaletz-Onody et al., "Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices," *New England Journal of Medicine*, vol. 326, no. 23, pp. 1527–1532, 1992.

[71] P. Singh, N. Pooran, A. Indaram, and S. Bank, "Combined ligation and sclerotherapy versus ligation alone for secondary prophylaxis of esophageal variceal bleeding: a meta-analysis," *American Journal of Gastroenterology*, vol. 97, no. 3, pp. 623–629, 2002.

[72] S. Evrard, J. M. Dumonceau, M. Delhaye, P. Golstein, J. Devière, and O. Le Moine, "Endoscopic histoacryl obliteration vs. propranolol in the prevention of esophagogastric variceal rebleeding: a randomized trial," *Endoscopy*, vol. 35, no. 9, pp. 729–735, 2003.

[73] R. Gonzalez, J. Zamora, J. Gomez-Camarero, L. M. Molinero, R. Bañares, and A. Albillos, "Meta-analysis: combination endoscopic and drug therapy to prevent variceal rebleeding in cirrhosis," *Annals of Internal Medicine*, vol. 149, no. 2, pp. 109–122, 2008.

[74] G. Garcia-Tsao, A. J. Sanyal, N. D. Grace et al., "Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis," *Hepatology*, vol. 46, no. 3, pp. 922–938, 2007.

[75] G. H. Lo, "Management of acute esophageal variceal hemorrhage," *Kaohsiung Journal of Medical Sciences*, vol. 26, no. 2, pp. 55–67, 2010.

[76] H. Yoshida, Y. Mamada, N. Taniai et al., "A randomized control trial of bi-monthly versus bi-weekly endoscopic variceal ligation of esophageal varices," *American Journal of Gastroenterology*, vol. 100, no. 9, pp. 2005–2009, 2005.

[77] G. V. Papatheodoridis, J. Goulis, G. Leandro, D. Patch, and A. K. Burroughs, "Transjugular intrahepatic portosystemic shunt compared with endoscopic treatment for prevention of variceal rebleeding: a meta-analysis," *Hepatology*, vol. 30, no. 3, pp. 612–622, 1999.

[78] G. Mehta, J. G. Abraldes, and J. Bosch, "Developments and controversies in the management of oesophageal and gastric varices," *Gut*, vol. 59, no. 6, pp. 701–705, 2010.

SAGE-Hindawi Access to Research
International Journal of Hepatology
Volume 2011, Article ID 356919, 7 pages
doi:10.4061/2011/356919

Review Article

Improved Survival with the Patients with Variceal Bleed

Praveen Sharma and Shiv K. Sarin

Department of Hepatology and Transplant Hepatology, Institute of Liver & Biliary Sciences, New Delhi 110 070, India

Correspondence should be addressed to Shiv K. Sarin, shivsarin@gmail.com

Received 13 February 2011; Accepted 12 May 2011

Academic Editor: Deepak Amarapurkar

Variceal hemorrhage is a major cause of death in patients with cirrhosis. Over the past two decades new treatment modalities have been introduced in the management of acute variceal bleeding (AVB) and several recent studies have suggested that the outcome of patients with cirrhosis and AVB has improved. Improved supportive measures, combination therapy which include early use of portal pressure reducing drugs with low rates of adverse effects (somatostatin, octerotide or terlipressin) and endoscopic variceal ligation has become the first line treatment in the management of AVB. Short-term antibiotic prophylaxis, early use of lactulose for prevention of hepatic encephalopathy, application of early transjugular intrahepatic portasystemic shunts (TIPS), fully covered self-expandable metallic stent in patients for AVB may be useful in those cases where balloon tamponade is considered. Early and wide availability of liver transplantation has changed the armamentarium of the clinician for patients with AVB. High hepatic venous pressure gradient (HVPG) >20 mmHg in AVB has become a useful predictor of outcomes and more aggressive therapies with early TIPS based on HVPG measurement may be the treatment of choice to reduce mortality further.

1. Introduction

Portal hypertension (PHT) worsens with increasing severity of cirrhosis and is responsible for many of its complications, which lead to clinical decompensation. The prevention and treatment of these complications have therefore been a cornerstone of the management of the patient with cirrhosis. Gastroesophageal varices are present in 50% of patients with cirrhosis, and variceal hemorrhage develops in up to one-third of these patients [1–3]. The initial appearance of varices in patients with compensated cirrhosis indicates a progression of the disease from a low-risk state to an intermediate one. Once bleeding occurs, this indicates decompensation and progression to a high risk of death [4, 5]. The risk of variceal hemorrhage is increased in patients who have large varices and advanced stages of liver disease, as assessed on the basis of the Child-Pugh class [6, 7]. Several studies published between 1942 and 1981 showed poor outcomes after variceal hemorrhage, with mortality rates of 40% at 6 weeks and 70% at 1 year [4, 8–11]. Over the past five decades, a number of randomized trials have shown an improvement in the efficacy of endoscopic, pharmacologic, surgical, and radiologic techniques for arresting hemorrhage [12–14]. Subsequently, retrospective single-center and multicenter studies have shown a decrease in hospital mortality associated with variceal hemorrhage over the past two decades [14–19].

In a study by Chalasani et al. [14] a total of 231 subjects were included, and their in-hospital, 6-week, and overall mortality rates were 14.2%, 17.5%, and 33.5%, respectively. The mortality rate after variceal bleeding in this study was substantially lower than previously reported. This suggests that advances made in the management of variceal bleeding have improved outcomes after variceal bleeding. Similarly Carbonell et al. [12] reviewed the clinical records of all patients with cirrhosis due to variceal bleeding during the years 1980, 1985, 1990, 1995, and 2000. Whereas balloon tamponade was still the first-line treatment in 1980, patients treated in 2000 received a vasoactive agent, an endoscopic treatment, and an antibiotic prophylaxis in, respectively, 90%, 100%, and 94% of cases. The in-hospital mortality rate steadily decreased over the study period: 42.6%, 29.9%, 25%, 16.2%, and 14.5% in 1980, 1985, 1990, 1995, and 2000, respectively ($P < .05$). Mortality decreased from 9% in 1980 to 0% in 2000 in Child-Turcotte-Pugh class A patients, from 46% to 0% in class B patients, and from 70% to 32% in class C patients. This improved survival

Table 1: Antibiotics compared to placebo in acute variceal bleed.

Author	Outcome	Drugs	Placebo (n) P	Antibiotics (n) A	Infections P versus A	efficacy
Pauwels et al. [27]	Bacterial infections	ciprofloxacin and a amoxicillin and clavulanic acid	34	30	53% versus 13%	$A > P$
Soriano et al. [30]	Bacterial infection	Norflox	59	60	10% versus 37%	$A > P$
Hsieh et al. [28]	Bacterial infection	ciprofloxacin	60	60	45% versus 10%	$A > P$
Jun et al. [29]	Bacterial infection	Cefotaxime	62	58	16% versus 3%	$A > P$

Table 2: Antibiotics preventing mortality in acute variceal bleed.

Author	Outcome	Drug	Drug	Relative risk	CI
Gulberg et al. [34]	Bacterial infection	Ceftriaxone 1 gm (1/40)	Ceftriaxone 2 gm (1/42)	1.05	0.11–9.80
Lata et al. [35]	Mortality	Ampicillin and sulbactam 3 g (12/21)	Norfloxacin 800 mg (7/25)	2.04	0.98–4.23
Fernández et al. [36]	Mortality	Ceftriaxone 1 g (8/54)	Norfloxacin 800 mg (6/57)	1.41	0.52–3.79

was associated with a decrease of rebleeding (from 47% in 1980 to 13% in 2000) and bacterial infection rates (from 38% to 14%). On multivariable analysis, endoscopic therapy and antibiotic prophylaxis were independent predictors of survival. Thomopoulos et al. [18] studied 141 patients with acute variceal bleed and found 6-week, 1-year, and overall mortality were 12.1%, 18.4%, 32.6% and 48.2%, respectively. The rate of recurrent bleeding was 10.7% during initial hospitalisation. Being Child-Pugh C ($P = .003$) and shock on admission ($P = .037$) were independent predictors of 6-week mortality, while being Child-Pugh C ($P = .028$), presence of hepatocellular carcinoma or other neoplasia ($P = .04$), and partial thromboplastin time ($P = .021$) during the initial admission were independent predictors for 1-year mortality. Mortality was not affected by the presence of active bleeding and/or white nipple at emergency endoscopy. Also presence of infection was not an adverse factor of clinical outcome in our patients. In all these studies the decrease in mortality was largely due to improvement in general measures, more effective endoscopic therapy in combination with vasoactive medications, prevention of sepsis through the use of antibiotic prophylaxis, and the prevention of rebleeding.

2. Improvement in General Measures

There is evidence that current treatment strategies for acute variceal hemorrhage, including general and specific measures, have resulted in an improved survival [12, 18]. Initial resuscitation by multidisciplinary team involves basic measures including assessing the patient's airway and obtaining peripheral venous access. Blood volume resuscitation should be undertaken promptly but with caution, with the goals of maintaining hemodynamic stability and a hemoglobin of approximately 7-8 g/dL [19, 20]. This recommendation is based on experimental studies that show that restitution of all lost blood leads to increases in portal pressure to levels higher than baseline [21] and to more rebleeding and mortality [22]. Similarly, vigorous resuscitation with saline solution should generally be avoided because, in addition to possibly precipitating recurrent variceal hemorrhage, this can worsen or precipitate the accumulation of ascites or fluid at other extravascular sites.

3. Prophylactic Antibiotics in Acute Variceal Bleed

Currently, it is recommended that short-term antibiotic prophylaxis, a measure that reduces bacterial infections [23], variceal rebleeding, and death [24], be used in every patient with cirrhosis admitted with gastrointestinal hemorrhage [20, 25, 26]. Different antibiotics have been used in different trials compared with placebo (Table 1, [27–30]). Bacterial infection is commonly associated with variceal hemorrhage and appears to be an independent risk factor for failure to control bleeding [31] and predicts both early rebleeding and death [32, 33]. The routine use of prophylactic broad-spectrum antibiotics has shown a marked improvement in outcome in acute variceal hemorrhage. Routine intravenous ceftriaxone or postendoscopic norfloxacin reduces rebleeding rates compared to on-demand antibiotics (Table 2) [24, 29, 34–36]. A Cochrane meta-analysis of antibiotic prophylaxis in cirrhotic patients with gastrointestinal bleeding involving 12 trials with 1241 patients evaluated antibiotic prophylaxis compared with placebo or no antibiotic prophylaxis. Antibiotic prophylaxis compared with no intervention or placebo was associated with beneficial effects on mortality (RR 0.79, 95% CI 0.63 to 0.98), mortality from bacterial infections (RR 0.43, 95% CI 0.19 to 0.97), bacterial infections (RR 0.36, 95% CI 0.27 to 0.49). They concluded that prophylactic antibiotic use in patients with cirrhosis

and upper gastrointestinal bleeding significantly reduced bacterial infections, and seems to have reduced all-cause mortality, bacterial infection mortality, rebleeding events, and hospitalisation length. These benefits were observed independently of the type of antibiotic used [37, 38]. The rationale behind the oral administration of norfloxacin, a poorly absorbed quinolone, is the selective eradication (or at least reduction) of Gram-negative bacteria in the gut, the source of bacteria. However, quinolone antibiotics with similar spectrum of activity, such as ciprofloxacin, could also be recommended. When oral administration is not possible, quinolones can be administered intravenously (IV). In a recent study performed in patients with advanced cirrhosis (Child B/C) and GI hemorrhage, IV ceftriaxone (1 g/day) was more effective than oral norfloxacin in preventing bacterial infections mostly those due to Gram-negative organisms [36]. It has now become standard practice to administer prophylactic antibiotics in acute variceal hemorrhage and in cirrhotic patients with gastrointestinal bleeding of any cause. The clear survival benefit associated with prophylactic antibiotics in gastrointestinal hemorrhage associated with cirrhosis is not in doubt. Both American and British guidelines recommend the administration of antibiotics prior to endoscopy in patients with AVB [39, 40].

4. Use of Newer Pharmacologic Treatment in Reducing Mortality

Pharmacological therapy has the advantages of being generally applicable and capable of being initiated as soon as a diagnosis of variceal hemorrhage is suspected, even prior to diagnostic EGD [20, 25, 26]. Newer development of drugs like somatostatin and analogues such as octreotide and vapreotide also causes splanchnic vasoconstriction at pharmacological doses due to an inhibition of the release of vasodilatory peptides mainly glucagon. The advantage of somatostatin and analogues such as octreotide and vapreotide is that they are safe and can be used continuously for 5 days or even longer [20].

However, results of meta-analysis of trials of octreotide are controversial [41, 42]. In a recent metaanalysis twenty studies were identified for all the comparison groups that indicates that terlipressin was associated with a statistically significant reduction in all-cause mortality compared to placebo (relative risk 0.66, 95% confidence interval 0.49 to 0.88). There was no significant difference between the terlipressin group and any of the comparison groups in the number of adverse events that caused death or withdrawal of medication. On the basis of a 34% relative risk reduction in mortality, terlipressin should be considered to be effective in the treatment of acute variceal hemorrhage [43].

Endoscopic therapy with either band ligation or injection sclerotherapy is an integral component of the management of acute variceal bleeding and of the long-term treatment of patients after a variceal bleed. Regarding the best endoscopic therapy, a metaanalysis of 10 randomized controlled trials including 404 patients shows an almost significant benefit of EVL in the initial control of bleeding compared to sclerotherapy (pooled relative risk of 0.53 with a confidence interval of 0.28–1.01) [44]. Variceal eradication with endoscopic ligation requires fewer endoscopic treatment sessions and causes substantially less esophageal complications than does injection sclerotherapy. Although the incidence of early gastrointestinal rebleeding is reduced by endoscopic ligation in most studies, there is no overall survival benefit relative to injection sclerotherapy.

In a recent metaanalysis pharmacotherapy is found to be as effective as emergency sclerotherapy in patients with acute variceal bleed. Seventeen trials including 1817 patients were identified. No significant differences were found comparing sclerotherapy with each vasoactive drug for any outcome. Combining all the trials irrespective of the vasoactive drug, the risk differences (95% confidence intervals) were failure to control bleeding −0.02 (−0.06 to 0.02), five-day failure rate −0.05 (−0.10 to 0.01), rebleeding 0.01 (−0.03 to 0.05), mortality (17 randomised trials, 1817 patients) −0.02 (−0.06 to 0.02), and transfused blood units (8 randomised trials, 849 patients) (weighted mean difference) −0.24 (−0.54 to 0.07). Adverse events 0.08 (0.03 to 0.14) and serious adverse events 0.05 (0.02 to 0.08) were significantly more frequent with sclerotherapy [45].

5. Combination Therapy as Standard of Therapy

Combination of both pharmacologic and endoscopic therapy in the treatment of AVB is strongly supported by numerous trials showing that the efficacy of both emergency EST and EBL is significantly improved when they are associated with pharmacologic treatment [41, 46]. Although both methods are highly effective in controlling AVB, EBL has become the treatment of choice both for controlling variceal hemorrhage and for variceal obliteration in secondary prophylaxis [20, 26]. A meta-analysis has shown that EBL is better than EST for all major outcomes including initial control of bleeding, recurrent bleeding, side effects, time to variceal obliteration, and survival [47]. Thus, combination therapy with a vasoactive drug plus EBL is considered the standard of care for AVB, and it is currently recommended by guidelines [20]. Combination therapy improves the 5-day success rate compared with endoscopic ligation therapy alone [48, 49], but this is not associated with any differences in mortality. Given these reasons, EBL at present is the endoscopic method of choice to treat esophageal varices in most cases. However, EST is an accepted method if EBL cannot be performed.

6. Evaluation of Hepatic Venous Pressure Measurement in Patient with Acute Variceal Bleed

Assessment of portal pressure by the hepatic venous pressure gradient (HVPG) has been a useful predictor of outcomes in both stages. In patients with compensated cirrhosis, an HVPG greater or equal to 10 mmHg is the most important predictor of the development of varices and clinical decompensation [50, 51]. Prospective cohort studies in which

HVPG has been measured within 48 hours of admission for hemorrhage show that levels greater than 20 mmHg are associated with increased rebleeding and mortality [52–54].

A more recent study performed in the era of combined vasoactive drug plus endoscopic therapy confirms this HVPG cutoff and shows that an index including CTP score and blood pressure at admission has similar prognostic value [55]. Furthermore, a drug-induced HVPG reduction of less than 10% predicts 5-day failure. This response may improve by doubling the dose of somatostatin or switching to another agent (such as terlipressin).

In acute complications of cirrhosis, such as variceal bleeding, there have been fewer studies of portal pressure, but, also in this setting, HVPG has been shown to be prognostic for both survival and the course of bleeding. Vinel et al. [56] documented that short-term prognosis in alcoholic cirrhotic patients with variceal bleeding was independently associated with portohepatic gradient measured within 48 h of admission. This was confirmed in a small study of 22 patients, in which the best cutoff for continued bleeding or early rebleeding was HVPG >16 mmHg [53]. Villanueva et al. [57] showed that HVPG > 20 mmHg and a decrease <10 mmHg under vasoactive therapy were independent predictors of further bleeding. An HVPG > 20 mmHg has been shown to correlate with important clinical outcomes such as more difficulty in controlling acute variceal bleeding, more early rebleeding, more blood transfusion need, more days in intensive care and increased hospital mortality [58]. Lastly Avgerinos et al. [59] showed that HVPG > 16 mmHg was independently associated with death and/or early rebleeding evaluating HVPG measurements before and immediately after endoscopic treatment and every 24 h for a 5-day period.

7. Transjugular Intrahepatic Portosystemic Shunt in Acute Variceal Hemorrhage

Transjugular intrahepatic portosystemic shunt (TIPS) is a reasonable alternative in the face of failure of combined pharmacologic plus endoscopic therapy. In the Baveno conference, it was considered that a second attempt at endoscopic therapy was one possibility but that one could perform TIPS after failure of the first endoscopic therapy. An elevated hepatic venous pressure gradient (>20 mm Hg) measured within 24 hours after the start of bleeding is the best predictor of treatment failure [26]. The use of TIPS to control variceal bleeding has largely been reserved for patients who require rescue therapy because hemostasis has not been achieved, either during the index bleeding or during the secondary-prophylaxis period. TIPS is extremely effective in controlling bleeding, with a reported rate of immediate hemostasis of 93% and with rebleeding in only 12% of patients. Nevertheless, mortality at 6 weeks among patients treated with rescue TIPS for uncontrolled index bleeding and rebleeding is very high (35%), reflecting the severity of their underlying liver disease as well as additional organ dysfunction that may have occurred owing to hypotension, infection, and aspiration [60].

Recently García-Pagán and colleagues report the results of a randomized, multicenter study that compared early TIPS with optimal medical therapy (endoscopic therapy plus vasoactive drugs) in patients at high risk for rebleeding who were either in Child-Pugh class B with active bleeding at endoscopy or in Child-Pugh class C. This study shows the benefit of early TIPS in patients with Child-Pugh class B or C disease who-are at high risk for uncontrolled bleeding with standard therapy. Patients who were randomly assigned to receive TIPS had a significantly better chance of remaining free of bleeding than did those who received the standard care (97% versus 50%), possibly owing to a greater reduction in portal pressure with TIPS than could be achieved with pharmacologic therapy. The rate of survival at 6 weeks was 97% in the TIPS group as compared with 67% in the medical therapy group, as a result of reductions in rebleeding, sepsis and liver failure [61]. Use of the newer stents, which are covered with extended polytetrafluoroethylene (e-PTFE), probably has an important bearing on the outcome of this study [15].

8. Newer Methods

The recent introduction of a fully covered self-expandable metallic stent for AVB may be useful in those cases where balloon tamponade is considered. The stent is placed over a guide wire previously passed to the stomach. The stent has a distal balloon that is inflated with a syringe to ensure proper location in the cardias and lower esophagus so no fluoroscopy is needed. The stent can be left in place for up to 14 days, and it can be retrieved by endoscopy with a hook system. There are limited data with its use. A pilot study of 20 patients who failed standard of care treatment reported 100% success without any significant complications [62].

9. Summary

AVB is a dreaded complication of patients with portal hypertension. Initial management includes appropriate volume replacement, transfusion of blood to keep hemoglobin levels at 7-8 g/L, antibiotic prophylaxis, and endotracheal intubation in selected cases. Standard of care mandates for early administration of vasoactive drug therapy and then EBL or injection ES (if EBL cannot be performed) within the first 12 hours of the index bleed. The use of pharmacologic agents may be prolonged for up to 5 days. Patients who fail endoscopic therapy may require temporary placement of balloon tamponade or stents. All patients surviving an episode of AVB should undergo further prophylaxis to prevent rebleeding. However, despite the application of these gold-standard treatments, 10% to 15% of cirrhotic patients still have treatment failure. Despite the high success of rescue TIPS in controlling bleeding in treatment failures, the mortality of patients in whom the initial approach failed is high due to liver failure. It is possible that in the near future, patients may be treated "á la carte." Indeed, in high-risk patients, more aggressive therapies with early PTFE TIPS based on HVPG measurement may be the treatment of choice to reduce mortality further.

References

[1] R. de Franchis and M. Primignani, "Natural history of portal hypertension in patients with cirrhosis," *Clinics in Liver Disease*, vol. 5, no. 3, pp. 645–663, 2001.

[2] A. J. Sanyal, R. J. Fontana, A. M. DiBisceglie et al., "The prevalence and risk factors associated with esophageal varices in subjects with hepatitis C and advanced fibrosis," *Gastrointestinal Endoscopy*, vol. 64, pp. 855–864, 2006.

[3] G. D'Amico, G. Garcia-Tsao, and L. Pagliaro, "Natural history and prognostic indicators of survival in cirrhosis. A systematic review of 118 studies," *Journal of Hepatology*, vol. 44, no. 1, pp. 217–231, 2006.

[4] D. Y. Graham and J. L. Smith, "The course of patients after variceal hemorrhage," *Gastroenterology*, vol. 80, no. 4, pp. 800–809, 1981.

[5] J. L. Smith and D. Y. Graham, "Variceal hemorrhage: a critical evaluation of survival analysis," *Gastroenterology*, vol. 82, no. 5, pp. 968–973, 1982.

[6] The 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," *The New England Journal of Medicine*, vol. 319, pp. 983–989, 1988.

[7] G. D'Amico, A. Morabito, L. Pagliaro, and E. Marubini, "Survival and prognostic indicators in compensated and decompensated cirrhosis," *Digestive Diseases and Sciences*, vol. 31, no. 5, pp. 468–475, 1986.

[8] M. M. Nachlas, J. E. O'Neil, and A. J. Campbell, "The life history of patients with cirrhosis of the liver and bleeding esophageal varices," *Annals of Surgery*, vol. 141, pp. 10–23, 1955.

[9] W. J. Powell Jr. and G. Klatskin, "Duration of survival in patients with Laennec's cirrhosis: influence of alcohol withdrawal, and possible effects of recent changes in general management of the disease," *The American Journal of Medicine*, vol. 44, no. 3, pp. 406–420, 1968.

[10] H. C. Pinto, A. Abrantes, A. V. Esteves, H. Almeida, and J. P. Correia, "Long-term prognosis of patients with cirrhosis of the liver and upper gastrointestinal bleeding," *The American Journal of Gastroenterology*, vol. 84, no. 10, pp. 1239–1243, 1989.

[11] A. J. Garceau and T. C. Chalmers, "The natural history of cirrhosis. I. Survival with esophageal varices," *The New England Journal of Medicine*, vol. 268, pp. 469–473, 1963.

[12] N. Carbonell, A. Pauwels, L. Serfaty, O. Fourdan, V. G. Lévy, and R. Poupon, "Improved survival after variceal bleeding in patients with cirrhosis over the past two decades," *Hepatology*, vol. 40, no. 3, pp. 652–659, 2004.

[13] H. B. El-Serag and J. E. Everhart, "Improved survival after variceal hemorrhage over an 11-year period in the Department of Veterans Affairs," *The American Journal of Gastroenterology*, vol. 95, no. 12, pp. 3566–3573, 2000.

[14] N. Chalasani, C. Kahi, F. Francois et al., "Improved patient survival after acute variceal bleeding: a multicenter, cohort study," *The American Journal of Gastroenterology*, vol. 98, no. 3, pp. 653–659, 2003.

[15] B. Angermayr, M. Cejna, F. Koenig et al., "Survival in patients undergoing transjugular intrahepatic portosystemic shunt: ePTFE-covered stent grafts versus bare stents," *Hepatology*, vol. 38, no. 4, pp. 1043–1050, 2003.

[16] P. A. McCormick and C. O'Keefe, "Improving prognosis following a first variceal haemorrhage over four decades," *Gut*, vol. 49, no. 5, pp. 682–685, 2001.

[17] G. D'Amico, R. de Franchis, and Cooperative Study Group, "Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators," *Hepatology*, vol. 38, pp. 599–612, 2003.

[18] K. Thomopoulos, G. Theocharis, K. Mimidis, C. Lampropoulou-Karatza, E. Alexandridis, and V. Nikolopoulou, "Improved survival of patients presenting with acute variceal bleeding. Prognostic indicators of short- and long-term mortality," *Digestive and Liver Disease*, vol. 38, no. 12, pp. 899–904, 2006.

[19] R. de Franchis, "Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension," *Journal of Hepatology*, vol. 43, no. 1, pp. 167–176, 2005.

[20] R. de Franchis, "Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension," *Journal of Hepatology*, vol. 53, no. 4, pp. 762–768, 2010.

[21] D. Kravetz, E. Sikuler, and R. J. Groszmann, "Splanchnic and systemic hemodynamics in portal hypertensive rats during hemorrhage and blood volume restitution," *Gastroenterology*, vol. 90, no. 5, pp. 1232–1240, 1986.

[22] B. Castañeda, J. Morales, R. Lionetti et al., "Effects of blood volume restitution following a portal hypertensive-related bleeding in anesthetized cirrhotic rats," *Hepatology*, vol. 33, no. 4, pp. 821–825, 2001.

[23] B. Bernard, J. D. Grange, E. N. Khac, X. Amiot, P. Opolon, and T. Poynard, "Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis," *Hepatology*, vol. 29, no. 6, pp. 1655–1661, 1999.

[24] M. C. Hou, H. C. Lin, T. T. Liu et al., "Antibiotic prophylaxis after endoscopic therapy prevents rebleeding in acute variceal hemorrhage: a randomized trial," *Hepatology*, vol. 39, no. 3, pp. 746–753, 2004.

[25] G. Garcia-Tsao, A. J. Sanyal, N. D. Grace et al., "Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis," *The American Journal of Gastroenterology*, vol. 102, no. 9, pp. 2086–2102, 2007.

[26] G. Garcia-Tsao, A. J. Sanyal, N. D. Grace, and W. Carey, "Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis," *Hepatology*, vol. 46, no. 3, pp. 922–938, 2007.

[27] A. Pauwels, N. Mostefa-Kara, B. Debenes, E. Degoutte, and V. G. Lévy, "Systemic antibiotic prophylaxis after gastrointestinal hemorrhage in cirrhotic patients with a high risk of infection," *Hepatology*, vol. 24, no. 4, pp. 802–806, 1996.

[28] W. J. Hsieh, H. C. Lin, S. J. Hwang, M. C. Hou, and F. Y. Lee, "The effect of ciprofloxacin in the prevention of bacterial infection in patients with cirrhosis after upper gastrointestinal bleeding," *The American Journal of Gastroenterology*, vol. 93, no. 6, pp. 962–966, 1998.

[29] C. H. Jun, C. H. Park, W. S. Lee, Y. E. Joo, H. S. Kim, and S. K. Choi, "Antibiotic prophylaxis using third generation cephalosporins can reduce the risk of early rebleeding in the first acute gastroesophageal variceal hemorrhage: a prospective randomized study," *Journal of Korean Medical Science*, vol. 21, no. 5, pp. 883–890, 2006.

[30] G. Soriano, C. Guarner, A. Tomás et al., "Norfloxacin prevents bacterial infection in cirrhotics with gastrointestinal hemorrhage," *Gastroenterology*, vol. 103, no. 4, pp. 1267–1272, 1992.

[31] J. Goulis, A. Armonis, D. Patch, C. Sabin, L. Greenslade, and A. K. Burroughs, "Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage," *Hepatology*, vol. 27, no. 5, pp. 1207–1212, 1998.

[32] B. Bernard, J. F. Cadranel, D. Valla, S. Escolano, V. Jarlier, and P. Opolon, "Prognostic significance of bacterial infec-tion in bleeding cirrhotic patients: a prospective study," *Gastroenterology*, vol. 108, no. 6, pp. 1828–1834, 1995.

[33] O. J. Garden, H. Motyl, W. H. Gilmour, R. J. Utley, and D. C. Carter, "Prediction of outcome following acute variceal haemorrhage," *The British Journal of Surgery*, vol. 72, no. 2, pp. 91–95, 1985.

[34] V. Gulberg, P. Deibert, A. Ochs, M. Rossle, and A. L. Gerbes, "Prevention of infectious complications after transjugular intrahepatic portosystemic shunt in cirrhotic patients with a single dose of ceftriaxone," *Hepato-Gastroenterology*, vol. 46, no. 26, pp. 1126–1130, 1999.

[35] J. Lata, J. Juránková, L. Husová et al., "Variceal bleeding in portal hypertension: bacterial infection and comparison of efficacy of intravenous and per-oral application of antibiotics—a randomized trial," *The European Journal of Gastroenterology and Hepatology*, vol. 17, no. 10, pp. 1105–1110, 2005.

[36] J. Fernández, L. R. del Arbol, C. Gómez et al., "Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage," *Gastroenterology*, vol. 131, no. 4, pp. 1049–1056, 2006.

[37] K. Soares-Weiser, M. Brezis, R. Tur-Kaspa, and L. Leibovici, "Antibiotic prophylaxis for cirrhotic patients with gastrointestinal bleeding," *Cochrane Database of Systematic Reviews*, no. 2, article CD002907, 2002.

[38] N. C. Chavez-Tapia, T. Barrientos-Gutierrez, F. I. Tellez-Avila, K. Soares-Weiser, and M. Uribe, "Antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding," *Cochrane Database of Systematic Reviews*, no. 9, article CD002907, 2010.

[39] M. C. Allison, J. A. Sandoe, R. Tighe, I. A. Simpson, R. J. Hall, and T. S. Elliott, "Antibiotic prophylaxis in gastrointestinal endoscopy," *Gut*, vol. 58, no. 6, pp. 869–880, 2009.

[40] S. Banerjee, B. Shen, T. H. Baron et al., "Antibiotic prophylaxis for GI endoscopy," *Gastrointestinal Endoscopy*, vol. 67, no. 6, pp. 791–798, 2008.

[41] G. D'Amico, L. Pagliaro, and J. Bosch, "Pharmacological treatment of portal hypertension: an evidence-based approach," *Seminars in Liver Disease*, vol. 19, no. 4, pp. 475–505, 1999.

[42] D. A. Corley, J. P. Cello, W. Adkisson, W.-F. Ko, and K. Kerlikowske, "Octreotide for acute esophageal variceal bleeding: a meta-analysis," *Gastroenterology*, vol. 120, no. 4, pp. 946–954, 2001.

[43] G. Ioannou, J. Doust, and D. C. Rockey, "Terlipressin for acute esophageal variceal hemorrhage," *Cochrane Database of Systematic Reviews*, no. 1, article CD002147, 2003.

[44] R. Jutabha, D. M. Jensen, P. Martin, T. Savides, S. H. Han, and J. Gornbein, "Randomized study comparing banding and propranolol to prevent initial variceal hemorrhage in cirrhotics with high-risk esophageal varices," *Gastroenterology*, vol. 128, no. 4, pp. 870–881, 2005.

[45] G. D'Amico, L. Pagliaro, G. Pietrosi, and I. Tarantino, "Emergency sclerotherapy versus vasoactive drugs for bleeding oesophageal varices in cirrhotic patients," *Cochrane Database of Systematic Reviews*, no. 3, article CD002233, 2010.

[46] W. Qureshi, D. G. Adler, R. Davila et al., "ASGE guideline: the role of endoscopy in the management of variceal hemorrhage, updated," *Gastrointestinal Endoscopy*, vol. 62, no. 5, pp. 651–655, 2005.

[47] L. Laine, H. M. El-Newihi, B. Migikovsky, R. Sloane, and F. Garcia, "Endoscopic ligation compared with sclerotherapy for the treatment of bleeding esophageal varices," *Annals of Internal Medicine*, vol. 119, no. 1, pp. 1–7, 1993.

[48] C. Villanueva, J. Ortiz, M. Sàbat et al., "Somatostatin alone or combined with emergency sclerotherapy in the treatment of acute esophageal variceal bleeding: a prospective randomized trial," *Hepatology*, vol. 30, no. 2, pp. 384–389, 1999.

[49] R. Baares, A. Albillos, D. Rincón et al., "Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: a meta-analysis," *Hepatology*, vol. 35, no. 3, pp. 609–615, 2002.

[50] R. J. Groszmann, G. Garcia-Tsao, J. Bosch et al., "Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis," *The New England Journal of Medicine*, vol. 353, no. 21, pp. 2254–2261, 2005.

[51] C. Ripoll, R. Groszmann, G. Garcia-Tsao et al., "Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis," *Gastroenterology*, vol. 133, no. 2, pp. 481–488, 2007.

[52] E. Moitinho, A. Escorsell, J. C. Bandi et al., "Prognostic value of early measurements of portal pressure in acute variceal bleeding," *Gastroenterology*, vol. 117, no. 3, pp. 626–631, 1999.

[53] J. B. Ready, A. D. Robertson, J. S. Goff, and W. G. Rector Jr., "Assessment of the risk of bleeding from esophageal varices by continuous monitoring of portal pressure," *Gastroenterology*, vol. 100, no. 5, pp. 1403–1410, 1991.

[54] C. Villanueva, J. Ortiz, J. Minana et al., "Somatostatin treatment and risk stratification by continuous portal pressure monitoring during active variceal bleeding," *Gastroenterology*, vol. 121, pp. 110–117, 2001.

[55] J. G. Abraldes, C. Villanueva, R. Banares et al., "Hepatic venous pressure gradient and prognosis in patients with acute variceal bleeding treated with pharmacologic and endoscopic therapy," *Journal of Hepatology*, vol. 48, pp. 229–236, 2008.

[56] J. P. Vinel, J. Cassigneul, M. Levade, J. J. Voigt, and J. P. Pascal, "Assessment of short-term prognosis after variceal bleeding in patients with alcoholic cirrhosis by early measurement of portohepatic gradient," *Hepatology*, vol. 6, no. 1, pp. 116–117, 1986.

[57] C. Villanueva, J. Ortiz, J. Miana et al., "Somatostatin treatment and risk stratification by continuous portal pressure monitoring during acute variceal bleeding," *Gastroenterology*, vol. 121, no. 1, pp. 110–117, 2001.

[58] A. Monescillo, F. Martínez-Lagares, L. Ruiz-Del-Arbol et al., "Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding," *Hepatology*, vol. 40, no. 4, pp. 793–801, 2004.

[59] A. Avgerinos, A. Armonis, G. Stefanidis et al., "Sustained rise of portal pressure after sclerotherapy, but not band ligation, in acute variceal bleeding in cirrhosis," *Hepatology*, vol. 39, no. 6, pp. 1623–1630, 2004.

[60] T. D. Boyer and Z. J. Haskal, "The role of transjugular intrahepatic portosystemic shunt in the management of portal hypertension," *Hepatology*, vol. 41, no. 2, pp. 386–400, 2005.

[61] J. C. García-Pagán, K. Caca, C. Bureau et al., "Early use of TIPS in patients with cirrhosis and variceal bleeding," *The New England Journal of Medicine*, vol. 362, no. 25, pp. 2370–2379, 2010.

[62] R. Hubmann, G. Bodlaj, M. Czompo et al., "The use of self-expanding metal stents to treat acute variceal bleeding," *Endoscopy*, vol. 38, pp. 896–901, 2006.

SAGE-Hindawi Access to Research
International Journal of Hepatology
Volume 2011, Article ID 790232, 7 pages
doi:10.4061/2011/790232

Review Article

Management of Renal Failure and Ascites in Patients with Cirrhosis

Kaushal Madan and Ashish Mehta

Medanta Institute of Digestive and Hepatobiliary Sciences, Medanta-The Medicity Hospital, Sector 38, Gurgaon, Haryana 122001, India

Correspondence should be addressed to Kaushal Madan, k_madan_2000@yahoo.com

Received 20 April 2011; Accepted 13 June 2011

Academic Editor: Deepak Amarapurkar

Ascites and renal dysfunction in cirrhosis occur when the liver disease is decompensated and signify the presence of advanced liver failure. However, the precipitating causes should be looked for and treated. Although liver transplantation is the treatment of choice in patients with advanced liver failure, mild to moderate ascites can be treated effectively with medical management. Similarly, renal failure in cirrhotics is reversible if the precipitating causes can be treated effectively and by use of combination of vasoconstrictors and albumin. Transjugular intrahepatic portosystemic shunts also offer an effective therapy for refractory ascites and HRS. Such treatments may offer effective bridge to liver transplantation, by improving short and medium term survivals. Here, we shall discuss all the options available for the management of these complications of cirrhosis.

1. Introduction

Ascites is one of the indicators of decompensation and poor prognosis in patients with cirrhosis of any etiology. Once ascites develops, the predicted mortality is approximately 50% at 2 years [1]. Ascites is also an indicator of advanced portal hypertension. In many natural history series of cirrhosis, ascites is the most frequent first complication of cirrhosis preceded only by hepatocellular carcinoma [2]. In addition to being a poor prognostic factor, it also leads to significant morbidity in cirrhotics. But it is important to remember that patients with cirrhosis are not immune to develop ascites due to other causes, such as tuberculosis, malignancy, intrinsic renal disease, or heart failure. For this reason, it is important to carry out a complete evaluation and treat it appropriately.

2. Diagnosis of Ascites

When a cirrhotic presents for the first time with abdominal distension then, unless proved otherwise, the ascites is secondary to portal hypertension. A reasonable estimate can be made from a detailed history, examination, and biochemical assessment.

2.1. Ascitic Fluid Analysis. A detailed laboratory assessment of the ascitic fluid is a must in all patients who present with ascites for the first time. It confirms the diagnosis of cirrhotic ascites, rules out other causes of ascites, and also detects presence of spontaneous bacterial peritonitis. Measurement of serum to ascitic fluid albumin gradient (SAAG) readily differentiates ascites due to portal hypertension and ascites due to other causes. Almost simultaneous measurement of ascitic fluid and serum albumin is required. SAAG of ≥ 1.1 suggests the presence of portal hypertension with an accuracy of 97% [3]. The importance of measuring total ascitic fluid protein is to assess the risk of developing spontaneous bacterial peritonitis (SBP) later and therefore recommending antibiotics for primary prophylaxis of SBP. Cirrhotics who have total ascitic fluid protein concentration less than 1.5 gm/dL are at an increased risk of developing SBP [4]. Measurement of total and differential cell count is essential at both the initial evaluation and all subsequent times when ascitic fluid is drained, in order to look for

evidence of SBP. SBP is diagnosed when the neutrophil count of the ascitic fluid is more than 250/cumm. The prevalence of SBP in cirrhotic patients attending the outpatient clinics is 1.5–3.5% [5]. At the same time ascitic fluid should be sent for culture by inoculating in the blood culture bottles bed side. This technique can yield a positive culture in about 40% of the cases.

Patients who have high ascitic fluid protein content along with lymphocyte predominant ascites usually have other inflammatory or malignant causes for ascites, such as peritoneal tuberculosis [6] or peritoneal metastatic deposits. Adenosine deaminase enzyme which is released from lymphocytes has been shown to be raised in patients with peritoneal tuberculosis. In a meta-analysis of 4 studies which included 264 patients, peritoneal fluid ADA had a sensitivity of 100% and specificity of 97% for making a diagnosis of tubercular ascites. The optimal cut-off value defined was 39 IU/L [7]. In another article, the ADA among patients with tubercular ascites was found to be significantly higher than the values in patients with other causes of ascites (septic peritonitis, malignant ascites, and transudative ascites) [8].

3. Ascites and Its Management

Ascites in cirrhotics should be treated because it is associated with discomfort, reduced respiratory excursion, reduced appetite because of pressure effect, and predisposition to SBP. Presence of current ascites also negatively impacts the quality-of-life scores in cirrhotics and therefore warrants treatment [9]. For management purposes, ascites has be classified into mild or grade 1 (only detectable by ultrasonography), moderate or grade 2 (moderate symmetrical distension of abdomen), and severe or grade 3 (large or tense ascites), by the international ascites club.

3.1. Salt Restriction. Dietary salt restriction should be recommended for all patients who present with ascites for the first time and have grade 1 or 2 ascites. The recommended salt intake in such patients is between 80–120 mmol of sodium per day, which corresponds to 4.6–6.9 gm of salt. A negative sodium balance can be obtained by reducing dietary salt intake in 10–20% of cirrhotics with ascites [10].

3.2. Diuretics. In the initial management of mild to moderate ascites (which is not tense), aldosterone antagonists should be started first, since the pathophysiology of sodium retention in cirrhotics is due to increased reabsorption of sodium from the proximal and distal tubule and the mediator of this reabsorption is secondary hyperaldosteronism [11]. Spironolactone, which is an aldosterone antagonist, should be started first in a dose of 100 mg/day and the dose increased in 100 mg increment every 7 days till 400 mg. Beyond this, loop diuretic, furosemide should be added in a dose of 40 mg per day and added in increment of 40 mg till a total of 160 mg. The dose of diuretics should be adjusted to achieve a weight reduction of 0.5 kg/day in patients without pedal edema and about 1.0 kg/day in patients with pedal edema. Higher doses of diuretics in patients without pedal edema can result in complications such as hyponatremia or azotemia. It has been suggested that for patients with mild to moderate ascites who present for the first time, the above mentioned regimen should be followed, but for patients with resistant ascites or recurrent ascites, a combination of spironolactone and furosemide (100 mg and 40 mg, resp.) should be started at the outset [12]. The newer loop diuretic torsemide is more potent than furosemide and has been shown to be as effective and safe as furosemide in a small study of 46 cirrhotics with ascites [13].

Diuretics can induce electrolyte imbalances; furosemide can induce hypokalemia, spironolactone can induce hyperkalemia because of its potassium sparing effect, and both these diuretics can induce hyponatremia. Therefore, furosemide should be discontinued if serum potassium is <3 mmol/L, and spironolactone should be stopped if serum potassium is ≥ 6 mmol/L. If the serum sodium is <120 mmol/L, no diuretic should be given. Diuretics should also be discontinued if there are other diuretic induced complications such as renal failure, worsening hepatic encephalopathy, or severe muscle cramps.

3.3. Large Volume Paracentesis (LVP). LVP, as the name suggests, is defined as drainage of large volumes (>5-6 litres) of ascites. It is the treatment of choice for tense ascites (grade 3 ascites). It is more effective and safer than just diuretic therapy for tense ascites. But diuretics should always be given after LVP in order to prevent reaccumulation of ascites, since diuretics would be required to reverse the pathophysiology of sodium retention.

However, LVP may be associated with the development of post-paracentesis circulatory dysfunction (PPCD) which involves a rise in cardiac output, fall in systemic vascular resistance, and a rise in serum rennin and aldosterone. These changes are usually maintained for up to 24 hours, and the hormonal changes may last up to 6 days [14]. PPCD can be prevented by concomitant administration of plasma expanders, and the most effective plasma expander for this purpose has been demonstrated to be albumin which should be given in a dose of 8 gm/litre of ascitic fluid drained. Although cheaper alternatives such as dextran-70 have also been used effectively to prevent PPCD associated with LVP [15], albumin has been shown to be more effective than other plasma expanders if volumes of >5 litres are removed. In this randomized controlled trial, the incidence of PPCD was 18.5%, 34.4%, and 37.85 in patients receiving albumin, dextran-70, and polygeline, respectively, and the type of plasma expander used has been shown to be an independent predictor of development of PPCD [16, 17].

LVP is also an effective treatment for refractory ascites. Refractory ascites can be divided into two categories: diuretic-resistant ascites (defined as the ascites that cannot be mobilized, or early recurrence of which cannot be prevented due to lack of response to adequate sodium restriction and diuretic treatment; patients should be taking at least 400 mg of spironolactone and 160 mg of furosemide for at least one week, along with salt restricted diet of <90 mmol/L) and

diuretic-intractable ascites (defined as the ascites that cannot be mobilized, or early recurrence of which cannot be prevented because of development of complications of diuretic dose such as, diuretic-induced hepatic encephalopathy, renal dysfunction, hyponatremia, hypo- or hyperkalemia) [18].

3.4. Transjugular Intrahepatic Portosystemic Shunts (TIPS). Since ascites in cirrhosis develops due to portal hypertension, it would seem logical to decompress the portal system to reduce the ascites. So TIPS has been tried in several uncontrolled and controlled trials for refractory ascites. TIPS is useful and safe in patients with refractory ascites, where portal hypertension is not associated with presence of advanced liver failure. The randomized trials which assessed the role of TIPS versus LVP had excluded patients who had evidence of advanced liver disease (serum bilirubin > 5 mg%, INR > 2, presence of recurrent or persistent hepatic encephalopathy, renal failure). These trials consistently showed better control of ascites with TIPS, but the effect on survival was inconsistent. The studies that included small number of patients or included a mix of refractory and recurrent ascites did show some survival advantage [19–21], but the studies which included purely refractory ascites and had significant sample sizes did not show any survival advantage of TIPS over LVP [22, 23]. Meta-analysis including these five trials (>300 patients) again demonstrated that there was significantly better control of ascites (OR ranging from 0.07–0.56) with a higher incidence of hepatic encephalopathy (OR ranging from 1.72 to 2.26) in the TIPS group [24–27], and only one meta-analysis demonstrated an increase in transplant-free survival in patients undergoing TIPS ($P = 0.035$) [28]. TIPS appears to be an effective therapy for refractory ascites, but it should be emphasized that the patients should be carefully selected for this procedure.

3.5. Aquaretics. Since the basic pathophysiology of water retention and dilutional hyponatremia in cirrhotics is antidiuretic hormone or arginine vasopressin (AVP) induced water resorption from the distal collecting duct, it would appear logical to block this action of AVP and inhibit the pure water resorption. AVP acts at this level through the V2 receptors on the distal collecting tubule. Recently, a new class of drugs called vaptans, which act by blocking the V2 receptors have been shown to improve free water clearance in patients with a number of conditions associated with water retention, such as congestive heart failure and cirrhosis.

Initial studies with an orally active V2 receptor blocker, satavaptan, did show improvement in hyponatremia and control of ascites in combination with diuretics, but a phase 3 RCT in combination with diuretics failed to demonstrate a significant effect on control of ascites. In addition, there was an increase in morbidity and mortality in the active treatment arm [29]. Recently, another V2 receptor blocker, tolvaptan, has been approved for management of dilutional hyponatremia in cirrhotics [30] and is expected to help in reduction of water retention as well in these patients.

3.6. Liver Transplantation. All patients with refractory ascites have advanced liver failure and therefore should be offered liver transplantation, if all other precipitating causes of acute deterioration have been ruled out. However, many patients who have ascites may not meet the MELD score cutoffs where transplantation is recommended. MELD score, alone, probably underestimates the risk of mortality in patients who have ascites [31].

4. Renal Failure in Cirrhosis and Its Management

Renal dysfunction among cirrhotics is associated with a very poor prognosis, so it forms a part of the prognostic MELD score. Acute renal dysfunction or acute kidney injury (AKI) (abrupt rise in serum creatinine by 0.3 mg%) in cirrhotics can be classified into prerenal azotemia (volume responsive prerenal AKI), acute tubular necrosis (ATN) and hepatorenal syndrome (HRS) (volume unresponsive prerenal, functional type AKI). In an Indian tertiary care hospital, the most common cause of AKI in cirrhotics was found to be acute tubular necrosis (44.4%), followed by prerenal azotemia (36.4%), and hepatorenal syndrome (HRS) (19.2%) [32]. However, studies from the west indicate that the most common form of AKI among cirrhotics is prerenal (volume responsive) azotemia (66%) followed by ATN and HRS being the least common form [33]. Here, we shall discuss the management of HRS in cirrhotics since it is the most severe and prognostically most important form of renal failure in this group of patients.

Other forms of renal failure can be differentiated from HRS, in cirrhotics, by urine routine and microscopic examination (presence of significant proteinuria, casts and/or hematuria suggests intrinsic renal disease), ultrasound examination of kidney, ureters and bladder (presence of shrunken kidneys with loss of corticomedullary differentiation or presence of obstructive uropathy suggests non-HRS AKI), response to fluid replacement (improvement in serum creatinine with volume replacement suggests prerenal AKI), and by history of recent use of nephrotoxic drugs and active sepsis (suggest acute tubular necrosis). The principles of management of non-HRS AKI depend on the cause of AKI. However, when it is difficult to rule out other causes, it is important to replace volume as is described below; stop all nephrotoxic drugs, and treat active sepsis if present. This would take care of most forms of renal failure. Dialysis may be required for specific indications (hyperkalemia, metabolic acidosis, uremic encephalopathy, and pericarditis).

5. Hepatorenal Syndrome

HRS is defined as the development of renal failure in patients with advanced liver disease in the absence of other identifiable causes of renal failure. Recently, modified criteria have been laid down for the diagnosis of hepatorenal syndrome (Table 1). So it is important to exclude hypovolemia, use of nephrotoxic drugs, and presence of intrinsic renal disease before a diagnosis of HRS can be made. One of

Table 1: Diagnostic criteria for hepatorenal syndrome.

Modified criteria for diagnosis of hepatorenal syndrome
Cirrhosis with ascites
Serum creatinine > 1.5 mg%
Absence of shock
Absence of hypovolemia (no improvement in renal function after at least 2 days of diuretic withdrawal and volume expansion with albumin in a dose of 1 gm/kg/day)
No ongoing or recent treatment with nephrotoxic drugs
Absence of intrinsic renal disease (proteinuria < 0.5 gm/day; urine RBCs < 50/HPF; normal renal ultrasound)

the important changes from the previous definition of HRS is the understanding that HRS can also be diagnosed in the presence of active sepsis, which earlier used to be an exclusion criteria. HRS can be of two types. Type 1 HRS develops rapidly with a rise in serum creatinine to >2.5 mg% in less than 2 weeks. It is usually preceded by a precipitating event, and the most common being some bacterial infection such as spontaneous bacterial peritonitis. Type 2 HRS is characterized by a slower development of renal dysfunction and usually develops in the setting of refractory ascites. According to another recent, modified classification of renal failure among cirrhotics, given by a working party, type 1 HRS may be considered as a form of AKI in cirrhotics and type 2 HRS may be considered as CKD in cirrhotics [34]. HRS type I has a very poor prognosis in cirrhotics and predicts a median survival of only 3 months [35], and untreated type 1 HRS has a median survival of about 1 month.

6. Treatment of HRS (Table 2)

As has been mentioned earlier, hypovolemia needs to be corrected by stopping all diuretics for at least 48 hours and by administration of albumin before labelling a patient as having HRS. Sepsis should be actively looked for (since sepsis is the most common precipitant of HRS), by blood cultures, urine cultures, ascitic fluid cytology and cultures, and chest radiographs, and treated with appropriate antibiotics.

6.1. Vasoconstrictors. Vasoconstrictors act by counteracting the strong splanchnic vasodilatation, which is characteristic of advanced cirrhosis. The most common drug used for this purpose is the vasopressin analogue, terlipressin. Terlipressin is used at a dose of 1mg every 4–6 hrly and increased, if there is no response (<25% reduction in serum creatinine at day 3), to a maximum of 2 mg every 4–6 hourly". Treatment is to be continued till the serum creatinine falls to less than 1.5 mg%. Trial of treatment with terlipressin should be continued up to 2 weeks. Beyond this, if there is no response, it should be discontinued. This has to be given along with albumin in a dose of 1 gm/kg on day 1 followed by 20–40 gm per day. Treatment with terlipressin is associated with improvement in urine output, reduction in creatinine levels, reduction in renin levels, and improvement in mean arterial pressure. Effect on survival was demonstrable in some but not all studies. A systemic review of the use of vasoconstrictors in patients with type 1 and type 2 HRS demonstrated that terlipressin plus albumin improved short term survival (15 days survival) (RR 0.81, 0.68–0.97) in patients with type 1 HRS, but not in type 2 HRS. There was no improvement in 30-day, 90-day, or 180-day survival [36]. Another systematic review, which included 4 RCTs of terlipressin in type 1 HRS, demonstrated reversal of HRS and trend towards improved 90 days survival [37]. Use of terlipressin is associated with ischemic side effects (cardiac, digital, and mesenteric) in as many as 12% of patients, and it is usually contraindicated in patients who have coronary artery disease and peripheral vascular disease.

Table 2: Therapeutic modalities used in HRS and their effect on renal function and survival.

Therapeutic modality	Studies	Improved renal function	Improved survival
Terlipressin plus albumin	RCTs and meta-analysis	Yes	Yes
Noradrenaline plus Albumin	RCTs	Yes	? yes
Midodrine plus octreotide plus albumin	Single small RCT	Yes	No
TIPS	Non-RCTs	Yes	No
Albumin dialysis	Small RCT	Yes	No
Liver transplantation		Yes	Yes

Noradrenaline infusion (dose ranging from 0.5 to 3 mg/hour) along with albumin has also been shown to be as effective as terlipressin plus albumin in improving renal function and circulatory function in patients with HRS [38]. Another larger open lablelled RCT (20 patients in each arm; noradrenaline plus albumin versus terlipressin plus albumin), published from India, demonstrated similar improvement in renal functions and similar survival rates in the two groups [39].

Alpha-adrenergic agonist, midodrine, is another vasoconstrictor which has been used in patients with HRS. Midodrine was used in a dose of 2.5 to 12.5 mg orally every 8 hourly in combination with octreotide 100 μg subcutaneously, 8 hourly in 5 patients with HRS type 1. These were compared with 8 patients who were managed with standard therapy. Both groups also received albumin (50–100 mL daily). Patients who received the combination therapy had reversal of HRS with significant increase in GFR and reduction in plasma renin activity. There were no ischemic side effects [40].

6.2. Transjugular Intrahepatic Portosystemic Shunts (TIPS) for HRS. TIPS has been used to control portal hypertension and has been found to be useful in patients with HRS as well. However, many patients with advanced liver disease with renal failure have contraindications for the use of TIPS. A single centre study in 129 patients with long-term followup demonstrated a significant improvement in creatinine values

after placement of TIPS. Amount of iodinated contrast medium administered did not affect creatinine levels [41]. Among 41 patients (21 with HRS type 1 and 20 with HRS type 2), TIPS placement not only improved creatinine clearance (18 ± 15 to 48 ± 42 mL/min) and urinary sodium excretion (9 ± 16 to 77 ± 78 mmol/24 hours), but also gave a one-year survival of 48% [42]. However, there is no RCT comparing TIPS with other forms of therapy in patients with HRS.

6.3. Albumin Dialysis. Albumin dialysis is supposed to act on the principle of removing albumin bound toxins, which in case of HRS would be cytokines and vasodilators. In a small RCT among 13 patients with type 1 HRS, there was a significant improvement in renal function and short-term mortality (100% at day 7 in the standard medical therapy group ($n = 5$) versus 26.5% in the MARS group ($n = 8$)) in patients undergoing molecular adsorbent and recirculating system (MARS) therapy [43]. However, a recent pilot study in 6 patients with HRS who had failed therapy with vasoconstrictors could not demonstrate any benefit of this therapy, either on systemic hemodynamics or on survival [44].

6.4. Liver Transplantation. Patients with HRS have advanced liver failure and therefore qualify to undergo liver transplantation. Over all, long-term survival after liver transplantation has been reported to be around 65%. Presence of HRS, if sepsis is excluded, should be an indication for urgent/semiurgent liver transplantation. In such cases, other forms of therapy such as vasoconstrictors or albumin dialysis may be used as a bridge to transplantation. Although recent studies suggest that there is no difference in survival between patients with or without HRS (95% 1-year survival in presence of HRS versus 86% in its absence) [45], who are transplanted, it is always desirable to have the renal dysfunction corrected before a patient is taken up for transplantation. In a retrospective study, 9 patients with HRS were first treated with vasoconstrictors and then transplanted. These were compared with 27 patients without HRS who were also transplanted. The outcomes following transplantation were similar between the two groups with similar three-year survival probability (100% in treated HRS group versus 83% in the non-HRS group) [46]. So after reversal of HRS by vasoconstrictors, the patients should be listed for a semiurgent liver transplantation even if the serum creatinine has normalized.

7. Summary

Ascites and renal failure in cirrhotics suggest advanced portal hypertension and poor liver function and therefore predict poor prognosis. Ascites may be the first sign of progression of liver dysfunction or may even suggest an underlying complication such as development of a hepatocellular carcinoma. Mild or moderate ascites can usually be managed by salt restriction along with diuretics. For severe or tense ascites, large volume paracentesis with albumin infusion is required along with continued use of diuretics. For refractory ascites, the options are either repeated LVP plus albumin or TIPS. Renal failure in cirrhotics can be because of a number of causes, and HRS is not the most common cause of renal failure among cirrhotics. The most common cause is either volume responsive prerenal failure or acute tubular necrosis. Presence of HRS signifies advanced liver dysfunction, and ideal treatment is liver transplantation for such patients. But it is advisable to reverse HRS prior to transplantation. Treatment is initiated by excluding/treating precipitating causes such as SBP, correction of hypovolemia, and discontinuation of diuretics. Specific treatment involves the use of a combination of vasoconstrictors and albumin. Terlipressin has been shown to be effective in most cases, and noradrenaline has also been shown to be as effective as terlipressin. Another strategy which has been found to be effective is a combination of midodrine, octreotide, and albumin. TIPS has also been shown to be effective in improving renal failure in patients with HRS but should only be used as a bridge to liver transplantation. Finally, for both patients with ascites and HRS, the treatment of choice remains liver transplantation which corrects the basic pathophysiology of these two complications.

References

[1] M. Guevara, A. Cardenas, J. Uriz, and P. Gines, "Prognosis in patients with cirrhosis and ascites," in *Ascites and Renal Dysfunction in Liver Disease: Pathogenesis, Diagnosis, and Treatment*, P. Gines, V. Arroyo, J. Rhodes, and R. W. Schrier, Eds., pp. 260–270, Blackwell, Malden, Mass, USA, 2005.

[2] L. Benvegnu, M. Gios, S. Boccato, and A. Alberti, "Natural history of compensated viral cirrhosis: a prospective study on the incidence and hierarchy of major complications," *Gut*, vol. 53, no. 5, pp. 744–749, 2004.

[3] B. A. Runyon, A. A. Montano, E. A. Akriviadis, M. R. Antillon, M. A. Irving, and J. G. McHutchison, "The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites," *Annals of Internal Medicine*, vol. 117, no. 3, pp. 215–220, 1992.

[4] A. Rimola, G. Garcia-Tsao, M. Navasa et al., "Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International ascites club," *Journal of Hepatology*, vol. 32, no. 1, pp. 142–153, 2000.

[5] L. T. Evans, W. R. Kim, J. J. Poterucha, and P. S. Kamath, "Spontaneous bacterial peritonitis in asymptomatic outpatients with cirrhotic ascites," *Hepatology*, vol. 37, no. 4, pp. 897–901, 2003.

[6] N. J. Kim, E. J. Choo, Y. G. Kwak et al., "Tuberculous peritonitis in cirrhotic patients: comparison of spontaneous bacterial peritonitis caused by Escherichia coli with tuberculous peritonitis," *Scandinavian Journal of Infectious Diseases*, vol. 41, no. 11-12, pp. 852–856, 2009.

[7] A. Riquelme, M. Calvo, F. Salech et al., "Value of adenosine deaminase (ADA) in ascitic fluid for the diagnosis of tuberculous peritonitis: a meta-analysis," *Journal of Clinical Gastroenterology*, vol. 40, no. 8, pp. 705–710, 2006.

[8] J. M. Martinez-Vazquez, I. Ocaña, and E. Ribera, "Adenosine deaminase activity in the diagnosis of tuberculous peritonitis," *Gut*, vol. 27, no. 9, pp. 1049–1053, 1986.

[9] I. Les, E. Doval, M. Flavià et al., "Quality of life in cirrhosis is related to potentially treatable factors," *European Journal of Gastroenterology and Hepatology*, vol. 22, no. 2, pp. 221–227, 2010.

[10] A. Gatta, P. Angeli, L. Caregaro, F. Menon, D. Sacerdoti, and C. Merkel, "A pathophysiological interpretation of unresponsiveness to spironolactone in a stepped-care approach to the diuretic treatment of ascites in nonazotemic cirrhotic patients," *Hepatology*, vol. 14, no. 2, pp. 231–236, 1991.

[11] M. Bernardi, D. Servadei, and F. Trevisani, "Importance of plasma aldosterone concentration on the natriuretic effect of spironolactone in patients with liver cirrhosis and ascites," *Digestion*, vol. 31, no. 4, pp. 189–193, 1985.

[12] M. Bernardi, "Optimum use of diuretics in managing ascites in patients with cirrhosis," *Gut*, vol. 59, no. 1, pp. 10–11, 2010.

[13] R. Abecasis, M. Guevara, C. Miguez, S. Cobas, and R. Terg, "Long-term efficacy of torsemide compared with frusemide in cirrhotic patients with ascites," *Scandinavian Journal of Gastroenterology*, vol. 36, no. 3, pp. 309–313, 2001.

[14] M. Pozzi, G. Osculati, G. Boari et al., "Time course of circulatory and humoral effects of rapid total paracentesis in cirrhotic patients with tense, refractory ascites," *Gastroenterology*, vol. 106, no. 3, pp. 709–719, 1994.

[15] S. K. Acharya, S. Balwinder, A. K. Padhee, S. Nijhawan, and B. N. Tandon, "Large volume paracentesis and intravenous dextran to treat tense ascites," *Journal of Clinical Gastroenterology*, vol. 14, no. 1, pp. 31–35, 1992.

[16] A. Gines, G. Fernandez-Esparrach, A. Monescillo et al., "Randomized trial comparing albumin, dextran 70, and polygeline in cirrhotic patients with ascites treated by paracentesis," *Gastroenterology*, vol. 111, no. 4, pp. 1002–1010, 1996.

[17] G. Nasr, A. Hassan, S. Ahmed, and A. Serwah, "Predictors of large volume paracantesis induced circulatory dysfunction in patients with massive hepatic ascites," *Journal of Cardiovascular Disease Research*, vol. 1, no. 3, pp. 136–144, 2010.

[18] K. P. Moore, F. Wong, P. Gines et al., "The management of ascites in cirrhosis: report on the consensus conference of the international ascites club," *Hepatology*, vol. 38, no. 1, pp. 258–266, 2003.

[19] M. Rossle, A. Ochs, V. Gulperg et al., "A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites," *The New England Journal of Medicine*, vol. 342, no. 23, pp. 1701–1707, 2000.

[20] D. Lebrec, N. Giuily, A. Hadengue et al., "Transjugular intrahepatic portosystemic shunts: comparison with paracentesis in patients with cirrhosis and refractory ascites: a randomized trial," *Journal of Hepatology*, vol. 25, no. 2, pp. 135–144, 1996.

[21] F. Salerno, M. Merli, O. Riggio et al., "Randomized controlled study of TIPS versus paracentesis plus albumin in cirrhosis with severe ascites," *Hepatology*, vol. 40, no. 3, pp. 629–635, 2004.

[22] P. Gines, J. Uriz, B. Calahorra et al., "Transjugular intrahepatic portosystemic shunting versus paracentesis plus albumin for refractory ascites in cirrhosis," *Gastroenterology*, vol. 123, no. 6, pp. 1839–1847, 2002.

[23] A. J. Sanyal, C. Genning, K. R. Reddy et al., "The North American study for the treatment of refractory ascites," *Gastroenterology*, vol. 124, no. 3, pp. 634–641, 2003.

[24] A. Albillos, R. Banares, M. Gonzalez, M.-V. Catalina, and L.-M. Molinero, "A meta-analysis of transjugular intrahepatic portosystemic shunt versus paracentesis for refractory ascites," *Journal of Hepatology*, vol. 43, no. 6, pp. 990–996, 2005.

[25] P. Deltenre, P. Mathurin, S. Dharancy et al., "Transjugular intrahepatic portosystemic shunt in refractory ascites: a meta-analysis," *Liver International*, vol. 25, no. 2, pp. 349–356, 2005.

[26] G. D'Amico, A. Luca, A. Morabito, R. Miraglia, and M. D'Amico, "Uncovered transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis," *Gastroenterology*, vol. 129, no. 4, pp. 1282–1293, 2005.

[27] S. Saab, J. M. Nieto, S. K. Lewis, and B. A. Runyon, "TIPS versus paracentesis for cirrhotic patients with refractory ascites," *Cochrane Database of Systematic Reviews*, no. 4, article CD004889, 2006.

[28] F. Salerno, C. Camma, M. Enea, M. Rossle, and F. Wong, "Transjugular intrahepatic portosystemic shunt for refractory ascites: a meta analysis of individual patient data," *Gastroenterology*, vol. 133, no. 3, pp. 825–834, 2007.

[29] F. Wong, M. Bernardi, Y. horasmans, Z. Cabrijan, H. Watson, and P. Gines, "Effects of satavaptan, an oral vasopressin V2 receptro antagonist, on management of ascites and morbidity in liver cirrhosis in a long term, placebo-controlled study," *Journal of Hepatology*, vol. 50, supplement 1, pp. S42–S43, 2009.

[30] R. W. Schrier, P. Gross, M. Gheorghiade et al., "Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia," *The New England Journal of Medicine*, vol. 355, no. 20, pp. 2099–2112, 2006.

[31] D. M. Heuman, S. G. Abou-assi, A. Habib et al., "Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death," *Hepatology*, vol. 40, no. 4, pp. 802–810, 2004.

[32] J. Prakash, A. K. Mahapatra, B. Ghosh, P. Arora, and A. K. Jain, "Clinical spectrum of renal dysfunction in patients with cirrhosis of liver," *Renal Failure*, vol. 33, no. 1, pp. 40–46, 2011.

[33] G. Garcia-Tsao, C. R. Parikh, and A. Viola, "Acute kidney injury in cirrhosis," *Hepatology*, vol. 48, no. 6, pp. 2064–2077, 2008.

[34] F. Wong, M. K. Nadim, J. A. Kellum et al., "Working party proposal for a revised classification system of renal dysfunction in patients with cirrhosis," *Gut*, vol. 60, no. 5, pp. 702–709, 2011.

[35] A. Gines, A. Escorsell, P. Gines et al., "Incidence, predictive factors, and prognosis of the hepatorenal syndrome in cirrhosis with ascites," *Gastroenterology*, vol. 105, no. 1, pp. 229–236, 1993.

[36] L. L. Gluud, K. Christensen, E. Christensen, and A. Krag, "Systematic review of randomized trials on vasoconstrictor drugs for hepatorenal syndrome," *Hepatology*, vol. 51, no. 2, pp. 576–584, 2010.

[37] S. V. Sagi, S. Mittal, K. S. Kasturi, and G. K. Sood, "Terlipressin therapy for reversal of type 1 hepatorenal syndrome: a meta-analysis of randomized controlled trials," *Journal of Gastroenterology and Hepatology*, vol. 25, no. 5, pp. 880–885, 2010.

[38] C. Alessandria, A. Ottobrelli, W. Debernardi-Venon et al., "Noradrenalin vs terlipressin in patients with hepatorenal syndrome: a prospective, randomized, unblinded, pilot study," *Journal of Hepatology*, vol. 47, no. 4, pp. 499–505, 2007.

[39] P. Sharma, A. Kumar, B. C. Shrama, and S. K. Sarin, "An open label, pilot, randomized controlled trial of noradrenaline versus terlipressin in the treatment of type 1 hepatorenal syndrome and predictors of response," *American Journal of Gastroenterology*, vol. 103, no. 7, pp. 1689–1697, 2008.

[40] P. Angeli, R. Volpin, G. Gerunda et al., "Reversal of type 1 hepatorenal syndrome with the administration of midodrine

and octreotide," *Hepatology*, vol. 29, no. 6, pp. 1690–1697, 1999.

[41] C. L. Anderson, W. E. A. Saad, S. D. Kalagher et al., "Effect of transjugular intrahepatic portosystemic shunt placement on renal function: a 7-year, single-center experience," *Journal of Vascular and Interventional Radiology*, vol. 21, no. 9, pp. 1370–1376, 2010.

[42] K. A. Brensing, J. Textor, J. Perz et al., "Long term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant cirrhotics with hepatorenal syndrome: a phase II study," *Gut*, vol. 47, no. 2, pp. 288–295, 2000.

[43] S. R. Mitzner, J. Stange, S. Klammt et al., "Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: results of a prospective, randomized, controlled clinical trial," *Liver Transplantation*, vol. 6, no. 3, pp. 277–286, 2000.

[44] F. Wong, N. Raina, and R. Richardson, "Molecular adsorbent recirculating system is ineffective in the management of type 1 hepatorenal syndrome in patients with cirrhosis with ascites who have failed vasoconstrictor treatment," *Gut*, vol. 59, no. 3, pp. 381–386, 2010.

[45] I. Park, E. Moon, J. A. Hwang et al., "Does hepatorenal syndrome affect the result of liver transplantation? Clinical observations," *Transplantation Proceedings*, vol. 42, no. 7, pp. 2563–2566, 2010.

[46] T. Restuccia, R. Ortega, M. Guevara et al., "Effects of treatment of hepatorenal syndrome before transplantation on posttransplantation outcome. A case-control study," *Journal of Hepatology*, vol. 40, no. 1, pp. 140–146, 2004.

SAGE-Hindawi Access to Research
International Journal of Hepatology
Volume 2011, Article ID 398291, 5 pages
doi:10.4061/2011/398291

Review Article

Role of TIPS in Improving Survival of Patients with Decompensated Liver Disease

Sundeep J. Punamiya[1] and Deepak N. Amarapurkar[2]

[1] *Department of Radiology, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433*
[2] *Department of Gastroenterology, Bombay Hospital, 12 Marine Lines, Mumbai 400020, India*

Correspondence should be addressed to Sundeep J. Punamiya, sundeep_punamiya@ttsh.com.sg

Received 26 February 2011; Accepted 13 April 2011

Academic Editor: Richard Guan

Liver cirrhosis is associated with higher morbidity and reduced survival with appearance of portal hypertension and resultant decompensation. Portal decompression plays a key role in improving survival in these patients. Transjugular intrahepatic portosystemic shunts are known to be efficacious in reducing portal venous pressure and control of complications such as variceal bleeding and ascites. However, they have been associated with significant problems such as poor shunt durability, increased encephalopathy, and unchanged survival when compared with conservative treatment options. The last decade has seen a significant improvement in these complications, with introduction of covered stents, better selection of patients, and clearer understanding of procedural end-points. Use of TIPS early in the period of decompensation also appears promising in further improvement of survival of cirrhotic patients.

1. Introduction

Portal hypertension is a universal consequence of cirrhosis, responsible for many important complications such as variceal bleeding, ascites, hepatic encephalopathy, hepatorenal syndrome, and hepatic insufficiency. The onset of these complications marks the transition of liver disease from a compensated to a decompensated stage. Each year, approximately 5 to 7% of cirrhotic patients advance to decompensation, and this is associated with a reduction in survival from a median of 12 years to just 2 years [1]. Liver transplantation is the only therapy that improves survival and quality of life of such patients. Unfortunately the shortage of donors has limited its role in most parts of the world. Hence, other therapeutic measures are required to manage complications of cirrhosis and prolong survival of patients with decompensated cirrhosis.

Pharmacological and endoscopic therapies are simple and effective in control of PHT in majority of patients. Meta-analysis of many studies have clearly demonstrated that nonselective beta blockers and endoscopic band ligation are useful in primary and secondary prophylaxis of variceal bleeding, and that such interventions significantly improve survival in patients with cirrhosis [2]. Despite these good results of endoscopy and pharmacotherapy, 10–15% of patients have refractory or recurrent bleeding [3]. Pharmacotherapy has hardly any effects on other complications of cirrhosis, like ascites and hepatorenal syndrome. Endoscopic therapy also does not reduce portal pressure and so obviously has no effect on complications like ascites and hepatorenal syndrome.

For many years, surgical shunts were used in patients that did not respond to medical therapy. However, surgery is associated with significant morbidity and mortality in patients with decompensated liver disease [4]. Transjugular intrahepatic portosystemic shunts (TIPS) were introduced as an alternative to surgery in the 1990s and have since gained acceptance worldwide to replace surgical shunts in most centres where TIPS are available.

2. Effects of Transjugular Intrahepatic Portosystemic Shunts

TIPS is a portosystemic shunt created within the liver parenchyma with the help of a stent placed between the

hepatic vein and portal vein. It behaves like a side-to-side portocaval shunt, causing a direct reduction of portal venous pressure, to achieve an ideal portosystemic gradient of less than 12 mm of Hg required for adequate portal decompression and prevention of variceal bleeding [5]. The reduction in portal venous pressure also reduces the filtration into the peritoneal space, allowing lymphatic absorption of ascitic fluid and thereby control of ascites and hydrothorax [6]. Additionally, TIPS increases glomerular filtration and urine output, promotes natriuresis, and reduces the plasma rennin activity, aldosterone levels, and noradrenaline levels. All these help in improving the renal function that is altered from advanced cirrhosis [7, 8]. TIPS also improves protein metabolism and nutrition, alongwith an overall improvement in quality of life [9, 10].

TIPS has been well studied in various randomized controlled trials and nonrandomized studies, based on which, it has been recommended for various indications (Table 1) [11].

3. Strategies to Improve Survival of Patients Undergoing TIPS

Initial studies showed TIPS to be highly effective in controlling variceal bleeding and ascites compared to conventional methods like endoscopic therapy, pharmacotherapy, and large-volume paracentesis [12–29]. Despite such high success rate, there was no survival advantage due to TIPS. In addition, morbidity due to hepatic encephalopathy and deterioration of liver function made the procedure less attractive. The last decade, however, witnessed a resurgent interest in the procedure, largely due to better outcome of TIPS from improvement in the TIPS device and better selection of patients.

3.1. Use of Stent-Graft Device for TIPS. Restenosis of TIPS has been the bug-bear of TIPS for many years, occurring in 18% to 78% of all TIPS [11]. When it occurs, it almost invariably results in reappearance of symptoms of portal hypertension and would require a secondary procedure such as balloon angioplasty and/or insertion of another stent to improve its patency. Stenosis usually occurs within the stent or along the outflow hepatic vein. Permeation of bile and/or mucin has been implicated by some investigators to be the cause of this stenosis [30]. In an attempt to improve its patency, covered stents or stent-grafts were introduced, with the concept that a PTFE covering would prevent bile/mucin permeation and tissue proliferating into the TIPS [31]. Initial recommendation was to use these covered stents for revision of dysfunctional bare-stent TIPS, but as confidence grew, de novo use was strongly encouraged, and it is now the recommended device for almost all TIPS. The covered stent has been used over a decade now, and the results in large cohort and comparative studies clearly demonstrate its superiority over bare stents [32–36]. The patency of covered stents is approximately >85% patency rate at 1 year, a marked improvement from the 40–60% patency noted with bare stents at that period. The patency is enhanced further if the TIPS device is positioned appropriately, that is, extending all the way to the IVC [32]. The improved patency has resulted in a clear reduction in recurrence of portal hypertension and also the number of reinterventions needed to improve TIPS patency. Additionally, covered stents offer a significant survival benefit. In a large, retrospective study by Angermayr et al., the 3-month, 1-year, and 2-year survival rates were 93%, 88%, and 76% for covered stent TIPS and 83%, 73%, and 62% for bare stent TIPS [37]. Similar outcomes have been described in many other studies too [27, 38, 39]. Yang et al. recently reported a meta-analysis on patency and clinical outcomes of TIPS comparing ePTFE-covered stents and bare stents, based on 1 randomized trial and 5 retrospective studies, involving more than 1200 patients. The findings are of improved shunt patency of covered stents without increasing the incidence of hepatic encephalopathy, and there was a trend towards improved survival at the end of one year [40]. A similar meta-analysis based on 8 studies (1 randomized controlled trial and 7 retrospective studies) and 479 patients was presented as an abstract at the Digestive Diseases Week meeting last year. The authors likewise concluded that covered stents much better overall survival than bare stents, with pooled odds of overall survival at 1 year being 2.37 times more in the PTFE group as compared to bare TIPS group [41].

3.2. Identification of High-Risk Patients and Appropriate Patient Selection. When TIPS were performed in the early years, they were offered to a variety of patients with problematic variceal bleeding or ascites, often regardless of the underlying clinical status. Hence the initial years saw TIPS-related liver failure and mortality reaching up to 44%, making it at times a worse option than conservative therapy. Subsequent efforts were made towards identifying the high-risk patients that were likely to decompensate following TIPS. Clinical and biochemical factors identified include advanced age, pre-existing encephalopathy, presence of ascites, increased prothrombin time, elevated bilirubin level, low sodium and albumin levels, and emergent indication for TIPS [42–45]. Various clinical-biochemical scoring systems (Child-Pugh score, MELD score, Emory score, and APACHE II score) were also described to help prognosticate and counsel patients being considered for TIPS [46–50]. In general, poor outcome is expected in patients undergoing TIPS with a Child-Pugh score >12, MELD score >18, Emory score >3, or an APACHE II score >18. While all these scoring systems are reasonably accurate, the MELD score is considered superior—most in predicting long-term survival following TIPS [50]. Judicious selection of patients using these indices could potentially prevent mortality from a TIPS procedure.

3.3. Prevention and Control of Post-TIPS Hepatic Encephalopathy (HE). Perhaps the most unresolved problem of TIPS has been encephalopathy. 30–35% of patients have HE following TIPS which largely related to diversion of toxins and portal hypoperfusion [51, 52]. It is mild, transient, and episodic on most occasions and can be easily managed conservatively. Also, the frequency and intensity of HE tends

Table 1: Indications for TIPS.

(1) Acute variceal bleeding unresponsive to medical and endoscopic therapy
(2) Recurrent variceal bleeding unresponsive to medical and endoscopic therapy
(3) Ectopic variceal bleeding (e.g., bleeding from duodenal varices, rectal varices, stomal varices, caput medusae, etc.)
(4) Nonvariceal bleeding secondary to hypertensive gastropathy/enteropathy
(5) Ascites resistant or intolerant to optimal medical therapy
(6) Hepatic hydrothorax resistant or intolerant to optimal medical therapy
(7) Budd-Chiari syndrome
(8) Hepatorenal syndrome
(9) Hepatopulmonary syndrome
(10) Veno-occlusive disease

to diminish with time, probably from cerebral adaptation to gut-derived neurotoxins [53]. However, about 3–7% of the TIPS tend to have recurrent or refractory encephalopathy, necessitating shunt occlusion or reduction.

Post-TIPS encephalopathy is anticipated to be higher with a wider shunt lumen. Thus, its frequency and severity would expectantly be higher with covered stents, as its diameter remains unchanged over a long period of time, unlike bare-stents, which show progressive reduction of the shunt diameter from intimal hyperplasia. Interestingly, not only has the incidence of HE been found to be similar with either device, but also some studies have in fact showed a lower frequency of HE with covered stents [54].

Prevention of HE is difficult, predicted vaguely by presence of pre-TIPS encephalopathy, renal impairment, advanced age, female sex, nonalcoholic etiology of liver disease, severity of liver disease, hypoalbuminemia, and higher degree of portal decompression [9, 12, 51, 52, 55–58]. While there is a general consensus that too much decompression is detrimental, it is difficult to estimate how much would be ideal. Most interventionists would prefer to reduce the portosystemic gradient to not more than half the pre-TIPS level, and certainly not below 5 mm Hg [59]. This can be achieved by under-dilating the TIPS device at time of insertion and then expanding it further to attain the desired portosystemic gradient or clinical outcome. Additional embolisation of competing portosystemic shunts would help reduce further diversion and potentially increase hepatic portal inflow. Use of smaller diameter shunts, especially in higher risk patients, has also been considered to reduce the risk of encephalopathy. However, a recent randomized trial by Riggio et al. comparing 8 mm and 10 mm shunts clearly showed no difference in encephalopathy rates. The authors additionally showed the 8 mm shunts to be ineffective in portal decompression and hence do not recommend their use over the 10 mm shunts, even in high-risk cases [60].

3.4. Use of TIPS in Early Decompensation of Cirrhosis. The next game-changer, arguably, involves the use of TIPS at a much earlier stage of decompensation. For many years, TIPS has been used to treat complications of portal hypertension after conventional medical therapy has been exhausted. In a recent landmark publication by Garcia-Pagan, significant improvement in survival was noted in high-risk cirrhosis with variceal bleeding if TIPS was offered early [61]. In this multicentre study, patients with Child B and Child C liver cirrhosis having acute oesophageal variceal bleeding were randomized either to continued vasoactive drug therapy-endoscopic band ligation or to TIPS within 72 hours of presentation, using covered stents. A distinct improvement in survival was noted with patients in the TIPS group than in the pharmacotherapy-endoscopic group (97% versus 67% at 6 weeks and 86% versus 61% at 1 year). It would be interesting to see if the same effect is noted in patients with severe ascites and hydrothorax if TIPS is offered early, rather than wait till it gets refractory to conventional medical therapy.

4. Conclusion

Survival of decompensated cirrhotics is largely dependent on the control of portal hypertension. The TIPS shunt is a highly effective method in portal decompression. While the initial use found extreme promise in controlling complications such as variceal bleeding and ascites, the last decade has witnessed an improved survival among decompensated liver disease patients who have undergone TIPS, largely due to improved devices, better patient selection, better understanding of procedural end-points, and early use of the procedure.

References

[1] G. D'Amico, G. Garcia-Tsao, and L. Pagliaro, "Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies," *Journal of Hepatology*, vol. 44, no. 1, pp. 217–231, 2006.

[2] G. Garcia-Tsao, J. Bosch, and R. J. Groszmann, "Portal hypertension and variceal bleeding—unresolved issues. Summary of an American Association for the study of liver diseases and European Association for the study of the liver single-topic conference," *Hepatology*, vol. 47, no. 5, pp. 1764–1772, 2008.

[3] A. A. Mihas and A. J. Sanyal, "Recurrent variceal bleeding despite endoscopic and medical therapy," *Gastroenterology*, vol. 127, no. 2, pp. 621–629, 2004.

[4] J. C. Collins and I. J. Sarfeh, "Surgical management of portal hypertension," *Western Journal of Medicine*, vol. 162, no. 6, pp. 527–535, 1995.

[5] M. Casado, J. Bosch, J. C. Garcia-Pagan et al., "Clinical events after transjugular intrahepatic portosystemic shunt: correlation with hemodynamic findings," *Gastroenterology*, vol. 114, no. 6, pp. 1296–1303, 1998.

[6] M. Rössle and A. L. Gerbes, "TIPS for the treatment of refractory ascites, hepatorenal syndrome and hepatic hydrothorax: a critical update," *Gut*, vol. 59, no. 7, pp. 988–1000, 2010.

[7] F. Wong, K. Sniderman, P. Liu, Y. Allidina, M. Sherman, and L. Blendis, "Transjugular intrahepatic portosystemic stent shunt: effects on hemodynamics and sodium homeostasis in cirrhosis and refractory ascites," *Annals of Internal Medicine*, vol. 25, pp. 135–144, 1995.

[8] M. Guevara, P. Ginès, J. C. Bandi et al., "Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems," *Hepatology*, vol. 28, no. 2, pp. 416–422, 1998.

[9] M. Plauth, T. Schütz, D. P. Buckendahl et al., "Weight gain after transjugular intrahepatic portosystemic shunt is associated with improvement in body composition in malnourished patients with cirrhosis and hypermetabolism," *Journal of Hepatology*, vol. 40, no. 2, pp. 228–233, 2004.

[10] V. Gülberg, I. Liss, M. Bilzer, T. Waggershauser, M. Reiser, and A. L. Gerbes, "Improved quality of life in patients with refractory or recidivant ascites after insertion of transjugular intrahepatic portosystemic shunts," *Digestion*, vol. 66, no. 2, pp. 127–130, 2002.

[11] T. D. Boyer and Z. J. Haskal, "American association for the study of liver diseases practice guidelines: the role of transjugular intrahepatic portosystemic shunt creation in the management of portal hypertension," *Journal of Vascular and Interventional Radiology*, vol. 16, no. 5, pp. 615–629, 2005.

[12] J. Cabrera, M. Maynar, R. Granados et al., "Transjugular intrahepatic portosystemic shunt versus sclerotherapy in the elective treatment of variceal hemorrhage," *Gastroenterology*, vol. 110, no. 3, pp. 832–839, 1996.

[13] M. Rössle, P. Deibert, K. Haag et al., "Randomised trial of transjugular-intrahepatic-portosystemic shunt versus endoscopy plus propranolol for prevention of variceal rebleeding," *Lancet*, vol. 349, no. 9058, pp. 1043–1049, 1997.

[14] P. Sauer, L. Theilmann, W. Stremmel et al., "Transjugular intrahepatic portosystemic stent versus sclerotherapy plus propranolol for rebleeding," *Gastroenterology*, vol. 113, pp. 1623–1631, 1997.

[15] A. J. Sanyal, A. M. Freedman, V. A. Luketic, P. P. Purdum, M. L. Shiffman, and P. E. Cole, "Transjugular intrahepatic portosystemic shunts compared with endoscopic sclerotherapy for the prevention of recurrent variceal hemorrhage: a randomized, controlled trial," *Annals of Internal Medicine*, vol. 126, no. 11, pp. 849–857, 1997.

[16] J. P. Cello, E. J. Ring, E. W. Olcott et al., "Endoscopic sclerotherapy compared with percutaneous transjugular intrahepatic portosystemic shunt after initial sclerotherapy in patients with acute variceal hemorrhage: a randomized, controlled trial," *Annals of Internal Medicine*, vol. 126, no. 11, pp. 858–865, 1997.

[17] R. Jalan, E. H. Forrest, A. J. Stanley et al., "A randomized trial comparing transjugular intrahepatic portosystemic stent-shunt with variceal band ligation in the prevention of rebleeding from esophageal varices," *Hepatology*, vol. 26, no. 5, pp. 1115–1122, 1997.

[18] M. Merli, F. Salerno, O. Riggio et al., "Transjugular intrahepatic portosystemic shunt versus endoscopic sclerotherapy for the prevention of variceal bleeding in cirrhosis: a randomized multicenter trial," *Hepatology*, vol. 27, no. 1, pp. 48–53, 1998.

[19] Groupe d'Etude des Anastomoses Intra-Hepatiques, "TIPS vs sclerotherapy + propranolol in the prevention of variceal rebleeding: preliminary results of a multicenter randomized trial," *Hepatology*, vol. 22, article A297, 1995.

[20] L. García-Villarreal, F. Martínez-Lagares, A. Sierra et al., "Transjugular intrahepatic portosystemic shunt versus endoscopic sclerotherapy for the prevention of variceal rebleeding after recent variceal hemorrhage," *Hepatology*, vol. 29, no. 1, pp. 27–32, 1999.

[21] P. Sauer, C. Benz, L. Thielmann et al., "Transjugular intrahepatic portosystemic stent shunt (TIPS) vs. endoscopic banding in the prevention of variceal rebleeding: final results of a randomized study," *Gastroenterology*, vol. 114, article A1334, 1998, Abstract.

[22] G. Pomier-Layrargues, J. P. Villeneuve, M. Deschênes et al., "Transjugular intrahepatic portosystemic shunt (TIPS) versus endoscopic variceal ligation in the prevention of variceal rebleeding in patients with cirrhosis: a randomised trial," *Gut*, vol. 48, no. 3, pp. 390–396, 2001.

[23] Y. Narahara, H. Kanazawa, H. Kawamata et al., "A randomized clinical trial comparing transjugular intrahepatic portosystemic shunt with endoscopic sclerotherapy in the long-term management of patients with cirrhosis after recent variceal hemorrhage," *Hepatology Research*, vol. 21, no. 3, pp. 189–198, 2001.

[24] V. Gülberg, M. Schepke, G. Geigenberger et al., "Transjugular intrahepatic portosystemic shunting is not superior to endoscopic variceal band ligation for prevention of variceal rebleeding in cirrhotic patients: a randomized, controlled trial," *Scandinavian Journal of Gastroenterology*, vol. 37, no. 3, pp. 338–343, 2002.

[25] M. Rössle, A. Ochs, V. Gülberg et al., "A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites," *New England Journal of Medicine*, vol. 342, no. 23, pp. 1701–1707, 2000.

[26] P. Ginès, J. Uriz, B. Calahorra et al., "Transjugular intrahepatic portosystemic shunting versus paracentesis plus albumin for refractory ascites in cirrhosis," *Gastroenterology*, vol. 123, no. 6, pp. 1839–1847, 2002.

[27] A. J. Sanyal, C. Genning, K. R. Reddy et al., "The North American study for the treatment of refractory ascites," *Gastroenterology*, vol. 124, no. 3, pp. 634–641, 2003.

[28] F. Salerno, M. Merli, O. Riggio et al., "Randomized controlled study of TIPS versus paracentesis plus albumin in cirrhosis with severe ascites," *Hepatology*, vol. 40, no. 3, pp. 629–635, 2004.

[29] V. Siegerstetter, P. Deibert, A. Ochs, M. Olschewski, H. E. Blum, and M. Rössle, "Treatment of refractory hepatic hydrothorax with transjugular intrahepatic portosystemic shunt: long-term results in 40 patients," *European Journal of Gastroenterology and Hepatology*, vol. 13, no. 5, pp. 529–534, 2001.

[30] M. Cura, A. Cura, R. Suri, F. El-Merhi, J. Lopera, and G. Kroma, "Causes of TIPS dysfunction," *American Journal of Roentgenology*, vol. 191, no. 6, pp. 1751–1757, 2008.

[31] K. Nishimine, R. R. Saxon, K. Kichikawa et al., "Improved transjugular intrahepatic portosystemic shunt patency with PTFE- covered stent-grafts: experimental results in swine," *Radiology*, vol. 196, no. 2, pp. 341–347, 1995.

[32] K. A. Hausegger, F. Karnel, B. Georgieva et al., "Transjugular intrahepatic portosystemic shunt creation with the viatorr expanded polytetrafluoroethylene-covered stent-graft," *Journal of Vascular and Interventional Radiology*, vol. 15, no. 3, pp. 239–248, 2004.

[33] P. Rossi, F. M. Salvatori, F. Fanelli et al., "Poly tetrafluoroethylene-covered nitinol stent-graft for transjugular intrahepatic portosystemic shunt creation: 3-year experience," *Radiology*, vol. 231, no. 3, pp. 820–830, 2004.

[34] G. Maleux, F. Nevens, A. Wilmer et al., "Early and long-term clinical and radiological follow-up results of expanded-polytetrafluoroethylene-covered stent-grafts for transjugular intrahepatic portosystemic shunt procedures," *European Radiology*, vol. 14, no. 10, pp. 1842–1850, 2004.

[35] J. P. M. Charon, F. H. Alaeddin, S. A. Pimpalwar et al., "Results of a retrospective multicenter trial of the Viatorr expanded polytetrafluoroethylene-covered stent-graft for transjugular intrahepatic portosystemic shunt creation," *Journal of Vascular and Interventional Radiology*, vol. 15, no. 11, pp. 1219–1230, 2004.

[36] S. Angeloni, M. Merli, F. M. Salvatori et al., "Polytetrafluoroethylene-covered stent grafts for TIPS procedure: 1-year patency and clinical results," *American Journal of Gastroenterology*, vol. 99, no. 2, pp. 280–285, 2004.

[37] B. Angermayr, M. Cejna, F. Koenig et al., "Survival in patients undergoing transjugular intrahepatic portosystemic shunt: ePTFE-covered stentgrafts versus bare stents," *Hepatology*, vol. 38, no. 4, pp. 1043–1050, 2003.

[38] J. Barrio, C. Ripoll, R. Bañares et al., "Comparison of transjugular intrahepatic portosystemic shunt dysfunction in PTFE-covered stent-grafts versus bare stents," *European Journal of Radiology*, vol. 55, no. 1, pp. 120–124, 2005.

[39] D. Tripathi, J. Ferguson, H. Barkell et al., "Improved clinical outcome with transjugular intrahepatic portosystemic stent-shunt utilizing polytetrafluoroethylene-covered stents," *European Journal of Gastroenterology and Hepatology*, vol. 18, no. 3, pp. 225–232, 2006.

[40] Z. Yang, G. Han, Q. Wu et al., "Patency and clinical outcomes of transjugular intrahepatic portosystemic shunt with polytetrafluoroethylene-covered stents versus bare stents: a meta-analysis," *Journal of Gastroenterology and Hepatology*, vol. 25, no. 11, pp. 1718–1725, 2010.

[41] S. Mittal, K. S. Kasturi, and G. Sood, "Metaanalysis of comparison of shunt patency and clinical outcomes between bare and polytetrafluorethylene (PTFE) stent in transjugular intrahepatic portosystemic shunt (TIPS)," *Gastroenterology*, vol. 138, p. S816, 2010.

[42] D. K. Rajan, Z. J. Haskal, and T. W. I. Clark, "Serum bilirubin and early mortality after transjugular intrahepatic portosystemic shunts: results of a multivariate analysis," *Journal of Vascular and Interventional Radiology*, vol. 13, no. 2, pp. 155–161, 2002.

[43] J. G. Tyburski, M. J. Noorily, and R. F. Wilson, "Prognostic factors with the use of the transjugular intrahepatic portosystemic shunt for bleeding varices," *Archives of Surgery*, vol. 132, no. 6, pp. 626–632, 1997.

[44] D. Patch, V. Nikolopoulou, A. McCormick et al., "Factors related to early mortality after transjugular intrahepatic portosystemic shunt for failed endoscopic therapy in acute variceal bleeding," *Journal of Hepatology*, vol. 28, no. 3, pp. 454–460, 1998.

[45] R. Bañares, M. Casado, J. M. Rodríguez-Láiz et al., "Urgent transjugular intrahepatic portosystemic shunt for control of acute variceal bleeding," *American Journal of Gastroenterology*, vol. 93, no. 1, pp. 75–79, 1998.

[46] P. S. Kamath, R. H. Wiesner, M. Malinchoc et al., "A model to predict survival in patients with end-stage liver disease," *Hepatology*, vol. 33, no. 2, pp. 464–470, 2001.

[47] H. Ferral, P. Gamboa, D. W. Postoak et al., "Survival after elective transjugular intrahepatic portosystemic shunt creation: prediction with model for end-stage liver disease score," *Radiology*, vol. 231, no. 1, pp. 231–236, 2004.

[48] B. Angermayr, M. Cejna, F. Karnel et al., "Child-Pugh versus MELD score in predicting survival in patients undergoing transjugular intrahepatic portosystemic shunt," *Gut*, vol. 52, no. 6, pp. 879–885, 2003.

[49] R. A. Rubin, Z. J. Haskal, C. B. O'Brien, C. Cope, and C. A. Brass, "Transjugular intrahepatic portosystemic shunting: decreased survival for patients with high APACHE II scores," *American Journal of Gastroenterology*, vol. 90, no. 4, pp. 556–563, 1995.

[50] M. Schepke, F. Roth, R. Fimmers et al., "Comparison of MELD, child-pugh, and emory model for the prediction of survival in patients undergoing transjugular intrahepatic portosystemic shunting," *American Journal of Gastroenterology*, vol. 98, no. 5, pp. 1167–1174, 2003.

[51] A. J. Sanyal, A. M. Freedman, M. L. Shiffman, P. P. Purdum, V. A. Luketic, and A. K. Cheatham, "Portosystemic encephalopathy after transjugular intrahepatic portosystemic shunt: results of a prospective controlled study," *Hepatology*, vol. 20, no. 1 I, pp. 46–55, 1994.

[52] K. A. Somberg, J. L. Riegler, J. M. LaBerge et al., "Hepatic encephalopathy after transjugular intrahepatic portosystemic shunts: incidence and risk factors," *American Journal of Gastroenterology*, vol. 90, no. 4, pp. 549–555, 1995.

[53] W. Nolte, J. Wiltfang, C. Schindler et al., "Portosystemic hepatic encephalopathy after transjugular intrahepatic portosystemic shunt in patients with cirrhosis: clinical, laboratory, psychometric, and electroencephalographic investigations," *Hepatology*, vol. 28, no. 5, pp. 1215–1225, 1998.

[54] C. Bureau, J. C. G. Pagan, G. P. Layrargues et al., "Patency of stents covered with polytetrafluoroethylene in patients treated by transjugular intrahepatic portosystemic shunts: long-term results of a randomized multicentre study," *Liver International*, vol. 27, no. 6, pp. 742–747, 2007.

[55] R. Jalan, R. A. Elton, D. N. Redhead, N. D. C. Finlayson, and P. C. Hayes, "Analysis of prognostic variables in the prediction of mortality, shunt failure, variceal rebleeding and encephalopathy following the transjugular intrahepatic portosystemic stent-shunt for variceal haemorrhage," *Journal of Hepatology*, vol. 23, no. 2, pp. 123–128, 1995.

[56] M. Rössle, P. Deibert, K. Haag et al., "Randomised trial of transjugular-intrahepatic-portosystemic shunt versus endoscopy plus propranolol for prevention of variceal rebleeding," *Lancet*, vol. 349, no. 9058, pp. 1043–1049, 1997.

[57] D. A. Zuckerman, M. D. Darcy, T. P. Bocchini, and C. F. Hildebolt, "Encephalopathy after transjugular intrahepatic portosystemic shunting: analysis of incidence and potential risk factors," *American Journal of Roentgenology*, vol. 169, no. 6, pp. 1727–1731, 1997.

[58] M. Casado, J. Bosch, J. C. Garcia-Pagan et al., "Clinical events after transjugular intrahepatic portosystemic shunt: correlation with hemodynamic findings," *Gastroenterology*, vol. 114, no. 6, pp. 1296–1303, 1998.

[59] H. H. Chung, M. K. Razavi, D. Y. Sze et al., "Portosystemic pressure gradient during transjugular intrahepatic portosystemic shunt with Viatorr stent graft: what is the critical low threshold to avoid medically uncontrolled low pressure gradient related complications?" *Journal of Gastroenterology and Hepatology*, vol. 23, no. 1, pp. 95–101, 2008.

[60] O. Riggio, L. Ridola, S. Angeloni et al., "Clinical efficacy of transjugular intrahepatic portosystemic shunt created with covered stents with different diameters: results of a randomized controlled trial," *Journal of Hepatology*, vol. 53, pp. 267–272, 2010.

[61] J. C. García-Pagán, K. Caca, C. Bureau et al., "Early use of TIPS in patients with cirrhosis and variceal bleeding," *New England Journal of Medicine*, vol. 362, no. 25, pp. 2370–2379, 2010.

SAGE-Hindawi Access to Research
International Journal of Hepatology
Volume 2011, Article ID 784540, 7 pages
doi:10.4061/2011/784540

Review Article

Prevention and Management of Bacterial Infections in Cirrhosis

Sunil K. Taneja and Radha K. Dhiman

Department of Hepatology, Postgraduate Institute of Medical Education & Research, Chandigarh 160012, India

Correspondence should be addressed to Radha K. Dhiman, rkpsdhiman@hotmail.com

Received 20 April 2011; Accepted 3 June 2011

Academic Editor: Deepak Amarapurkar

Patients with cirrhosis of liver are at risk of developing serious bacterial infections due to altered immune defenses. Despite the widespread use of broad spectrum antibiotics, bacterial infection is responsible for up to a quarter of the deaths of patients with liver disease. Cirrhotic patients with gastrointestinal bleed have a considerably higher incidence of bacterial infections particularly spontaneous bacterial peritonitis. High index of suspicion is required to identify infections at an early stage in the absence of classical signs and symptoms. Energetic use of antibacterial treatment and supportive care has decreased the morbidity and mortality over the years; however, use of antibiotics has to be judicious, as their indiscriminate use can lead to antibiotic resistance with potentially disastrous consequences. Preventive strategies are still in evolution and involve use of antibiotic prophylaxis in patients with gastrointestinal bleeding and spontaneous bacterial infections and selective decontamination of the gut and oropharynx.

1. Introduction

Bacterial infections are a common, recurrent complication of cirrhosis associated with poor outcome [1]. Decompensated cirrhosis has more frequent episodes of infections than compensated cirrhosis. Once infection develops, renal failure, shock, and encephalopathy may follow, which adversely affect survival. Recent prospective studies have shown that 32–34% of cirrhotic patients develop a bacterial infection either at the time of admission or later during their hospitalization [2]. Among cirrhotic patients being admitted for gastrointestinal hemorrhage, the rate of infection is even higher at an estimated 45% and has been shown to be associated with failure to control bleeding and with early variceal rebleeding [3–7]. These numbers contrast sharply with the 5–7% overall infection rates for the general population and emphasize the concept of cirrhosis as an acquired immunodeficient state. The development of infection in cirrhosis is associated with a significantly higher mortality that has been shown to be independent of the severity of liver disease [2, 8–10]. In fact, the in-hospital mortality of cirrhotic patients with infection is approximately 15%, more than twice that of patients without infection. More importantly, infection is directly responsible for 30–50% of deaths in cirrhosis [11].

The mechanisms of increased susceptibility to infections in cirrhosis are unclear. Numerous mechanisms implicated in altered and diminished immunity include increased shunting of blood away from the liver, qualitative dysfunction of the reticuloendothelial system, decreased opsonisation capacity of the ascitic fluid, and increased intestinal permeability of bacteria and associated endotoxins [12]. It has been suggested that there is a role for deficiencies in C3 and C4, downregulation of monocyte human leukocyte antigen-DR expression (and subsequent impaired antigen presentation ability), and impairment of macrophage Fcγ-receptor-mediated clearance of antibody-coated bacteria. Patients with alcoholic cirrhosis have depressed neutrophil phagocytic and intracellular killing of microorganisms [13, 14].

The most common infections in cirrhotics are spontaneous bacterial peritonitis (SBP) (25%), followed by urinary tract infection (20%), pneumonia (15%), bacteremia following a therapeutic procedure, cellulitis, and spontaneous bacteremia [1]. Infections are culture positive in 50%–70% of cases. The causative organisms of community-acquired infection are Gram-negative bacilli (GNB), especially *Escherichia coli*, in about 60%, Gram-positive cocci (GPC) in

about 30%–35%, and mixed in the last 5%–10%. Nosocomial infections behave differently with 60% GPC and 30%–35% positive for GNB, as a result of the use of therapeutic procedures and previous antibiotic therapies [15]. Beside *Escherichia coli*, the most frequently isolated bacteria are *Staphylococcus aureus*, *Enterococcus faecalis,* and *Streptococcus pneumoniae*. In cirrhotics less virulent organisms cause infections suggesting that, in advanced cirrhosis, bacteria do not need to develop strategies to circumvent host defenses and invade the host [16]. While GNB notably *Escherichia coli* are the causative agents in spontaneous bacterial peritonitis (SBP) and urinary tract infections, Gram-positive bacteria (GPB) predominate in pneumonia (*Streptococcus pneumoniae*) and procedure-associated bacteremia (*Staphylococcus aureus*). Fungal infections especially *Candida* species are involved in up to 15% of severe sepsis in cirrhosis [17].

Most of the available information on bacterial infections in cirrhosis refers to SBP, an entity that is essentially unique to the cirrhotic patient and shares its pathogenesis and management with spontaneous bacteremia and spontaneous bacterial empyema. Gram-positive infections in cirrhosis such as pneumonia or secondary bacteremia are managed according to conventional criteria.

2. Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP), that is, spontaneous infection of ascitic fluid without any apparent intra-abdominal source of infection, is the most characteristic infective complication in cirrhosis [18]. The one-year probability of development of the first SBP in cirrhotic patients with ascites is approximately 10%. This probability is higher in cirrhotic patients with coexisting gastrointestinal bleed, low ascitic fluid protein concentration (<1 g/dl), and/or severe hepatic insufficiency [19–21]. When first described, the mortality of SBP exceeded 90%; however, with early recognition of the disease and prompt and appropriate antibiotic therapy, mortality has been reduced to around 30% [22].

As SBP may pass unrecognized, diagnostic paracentesis should be done in all cirrhotics with ascites on admission to hospital, in-patients with ascites who develop signs of sepsis, hepatic encephalopathy, renal impairment, or altered gastrointestinal motility, and all ascitic patients with a gastrointestinal bleed [23]. SBP is diagnosed with an ascites polymorphonuclear cell count >250/mm^3, independent of ascites bacteriological culture results [24]. The use of reagent strips may provide a rapid bedside diagnosis of SBP. The test is a quick, safe, and relatively inexpensive screening tool that can be employed at the bedside while awaiting formal cell count and culture analysis. The reagent strip checks for leukocyte esterase activity of activated granulocytes. High numbers of activated leukocytes result in increased hydrolysis of the tested compound and generate a color change on the strip. The results of 8 trials using different types of strips are available [25–32]. Most trials include a very small number of ascites samples with a PMN count >250/mm^3, and, therefore, although median sensitivity results are ~85%, there is lack of sufficient data for its use in clinical practice unless larger trials validate these observations.

2.1. Treatment of Spontaneous Bacterial Peritonitis. Cefotaxime is the most widely studied cephalosporin in patients with SBP and is suitable for empirical therapy for this condition. Prior to 1985, treatment of the condition was suboptimal. A landmark study comparing the combination ampicillin/tobramycin with cefotaxime showed that cefotaxime significantly increased the resolution of bacterial infections, including SBP in cirrhotic patients [33]. Following this study, cefotaxime is considered as one of the first-choice antibiotic therapies in the empirical treatment of SBP in patients with cirrhosis. Recent studies have demonstrated that ceftriaxone is highly effective in the treatment of SBP, with a resolution rate of 100% and a hospital mortality rate of 30% [34, 35]. The combination of amoxicillin and clavulanic acid has also shown to be as effective and safe as cefotaxime in the treatment of SBP [36]. The use of fluoroquinolones for treatment of SBP has shown similar efficacy. Oral ofloxacin has been shown to be as effective as intravenous cefotaxime in the treatment of patients with "uncomplicated" SBP, defined by the absence of gastrointestinal hemorrhage, severe encephalopathy, ileus or septic shock, and a creatinine <3 mg/dL [37].

2.2. Spontaneous Bacterial Peritonitis Prophylaxis. The gut appears to be the main source of bacteria that cause SBP and other Gram-negative infections in cirrhosis. Given that SBP is thought to result from the translocation of enteric GNB, the ideal agent should be safe, affordable, and effective at eliminating GNB from the gut while preserving the protective anaerobic flora. Bacterial translocation, the phenomenon by which viable microorganisms from the intestinal lumen migrate to mesenteric lymph nodes and other extraintestinal sites, has been postulated as one of the main mechanisms in the pathogenesis of these infections. Therefore, prophylaxis has been based on the oral administration of nonabsorbable or poorly absorbed antibiotics that will eliminate or reduce the concentration of Gram-negative gut bacteria without affecting Gram-positive organisms or anaerobes, the so-called selective intestinal decontamination. Given the high cost and inevitable risk of developing resistant organisms, the use of prophylactic antibiotics must be strictly restricted to those at highest risk of SBP.

Long-term administration of orally administered norfloxacin, a poorly absorbed quinolone, has been shown to produce a marked reduction of GNB from the fecal flora of cirrhotic patients with no significant effects on GPC or anaerobic bacteria [38]. The development of infections by quinolone-resistant organisms is the main complication of long-term norfloxacin prophylaxis. A recent study showed clear differences in the type of bacteria causing infections in cirrhotic patients on chronic quinolone prophylaxis: while 67% of infections in untreated cirrhotic patients were due to Gram-negative organisms, infections in patients receiving quinolone prophylaxis were mostly due to Gram-positive organisms (79%). This study also showed the emergence of severe nosocomial *Staphylococcal* infections due to

methicillin-resistant strains [39]. Therefore, SBP prophylaxis should be considered only in high-risk populations or the patients awaiting liver transplantation.

Three patient populations considered at high risk and in whom prophylactic antibiotic therapy has been recommended are patients with prior history of SBP, patients admitted with gastrointestinal bleed, and patients with low total protein content in ascitic fluid.

2.2.1. Prophylaxis in Patients with a Previous Episode of Spontaneous Bacterial Peritonitis. The 1-year and 2-year probabilities of survival after an episode of SBP are of 30–50% and 25–30%, respectively, [18]. Therefore, patients recovering from an episode of SBP should be considered as potential candidates for liver transplantation. As such, it is imperative to initiate long-term prophylactic therapy in all patients with prior history of SBP. Norfloxacin, a poorly absorbed quinolone selective to GNB, was shown to decrease the 1-year probability of SBP from 68% to 20% when dosed at 400 mg daily. In this study, the probability of developing SBP specifically from GNB was reduced from 60% to 3% [40]. Subsequently economic analysis studies have shown substantial cost savings in initiating prophylactic therapy in patients with a prior episode of SBP rather than treating at time of diagnosis [41, 42]. Another trial using oral trimethoprim/sulfamethoxazole also showed efficacy in the prevention of SBP. It can be used as an alternative in patients who are unable to take or develop resistance to quinolones [43]. Prophylactic therapy should be instituted after the completion of antibiotics for acute SBP and continued until death, transplant, or resolution of ascites [44].

2.2.2. Prophylaxis in the Setting of Gastrointestinal Bleeding. All cirrhotic patients who develop an upper gastrointestinal bleed are at risk of a variety of bacterial infections, including SBP, within the first few days following the bleed. Bacteria of enteric origin are most commonly implicated, and the development of infection is associated with a poor prognosis [45–47]. Among all hospitalized cirrhotic patients, those admitted specifically with a gastrointestinal hemorrhage have a higher rate of infection than cirrhotic patients hospitalized for other reasons (45% versus 33%). Furthermore those with gastrointestinal hemorrhage complicated by an uncontrolled infection are at substantial risk of rebleeding, difficult to control bleed, and underlying sepsis-associated coagulopathy [48]. A meta-analyses of trials in patients with variceal hemorrhage has shown that antibiotic prophylaxis reduced the incidence of severe infection and decreased mortality [49]. There has been a decrease in mortality from variceal hemorrhage from 43% to 15% over a 20-year period, and antibiotic prophylaxis is independently associated with improved survival [50]. Oral norfoxacin, 400 mg b.d. for at least 7 days, is recommended by the International Ascites Club [44] and oral ciprofoxacin, 500 mg b.d. for 7 days, by the recent British Society of Gastroenterology (BSG) guidelines [51]. The benefit is greatest in those patients with more advanced liver disease. A recent RCT has shown that intravenous ceftriaxone (1 g/day for 7 days) was more effective than oral norfloxacin to prevent severe infections in patients with advanced cirrhosis (characterized by at least two of the following: ascites, severe malnutrition, encephalopathy, or bilirubin >3 mg/dL) and variceal bleeding [52].

2.2.3. Prophylaxis in Patients with Low Ascitic Fluid Total Protein. Ascitic fluid total protein has been shown to be an independent predictor of SBP. The risk of developing SBP in these patients depends largely on ascites protein content. Patients with an ascites protein >1.0 g/dL will not develop SBP in a follow-up period of 2 years, while patients with a low (<1.0 g/dL) ascites protein have a 1-year probability of developing SBP of around 20%. A prospective study in cirrhotic patients during hospitalization found that 15% of patients with ascitic protein <1.0 g/dL developed SBP compared to 2% of those with ascitic protein >1.0 g/dL. The incidence was greatest in those with Child C liver disease and in those who did not receive short-term prophylaxis if admitted with a gastrointestinal bleed. Two non-placebo-controlled studies, which showed a benefit of antibiotic prophylaxis in patients with low ascites protein, included patients with and without prior episodes of SBP and cannot be considered as reliable determinants of primary prophylaxis [43, 53]. Oral norfloxacin administration (400 mg/day) in patients with low protein ascitic levels (<1.5 g/dL) and advanced cirrhosis or impaired renal function without prior SBP episode reduces the probability of SBP and HRS and improved the 3-month survival [54]. Similarly, oral ciprofloxacin (500 mg/day) reduces the 1-year mortality rate in patients with ascitic protein levels <1.5 g/dL and without prior SBP episode [55].

2.3. Role of Albumin in Spontaneous Bacterial Peritonitis. In patients with SBP, there is a risk that their systemic hemodynamic parameters can deteriorate, with further arterial and splanchnic vasodilatation. These patients are, therefore, at high risk of developing renal insufficiency [56]. The development of renal failure is the most important indicator of reduced survival in patients with SBP compared with patients without SBP [57]. Renal impairment develops in approximately one-third of patients with SBP and is postulated to arise as a result of a further reduction in effective arterial blood volume, mediated by vasoactive cytokines, with a resultant increased renin-angiotensin-aldosterone system activity [58, 59]. In a multicentre randomized study, 126 patients with SBP were assigned to receive treatment with cefotaxime alone (2 g intravenously every six hours) or cefotaxime plus intravenous albumin. The albumin was given at a dose of 1.5 g/kg in the first 6 h after diagnosis, followed by a further infusion of 1 g/kg on the third day. With the standard treatment, renal impairment developed in 33% of patients, whereas with the combination therapy it occurred in only 10%. The in-hospital mortality rates were 28% and 10%, respectively, [60]. As the development of renal failure in cirrhotic patient with SBP carries a high risk of morbidity and mortality, the use of albumin infusion as an adjunctive therapy in the treatment of patients with SBP will continue until further studies are available.

2.4. Role of Probiotics in Prevention of Spontaneous Bacterial Peritonitis. Recent research in the use of certain probiotic agents has shown promise in decreasing cytokine release and improving neutrophil function in cirrhotic patients [61, 62]. The use of probiotics in this setting is attractive not only because of its ability to modulate gut flora in favor of protective anaerobic organisms but also because of its effects in promoting gut barrier function. However, there is no data to support decreasing infection rates or improved outcomes with probiotics in this population. Bacteriotherapy with *Lactobacillus* has been reported to correct bacterial overgrowth, stabilize mucosal barrier function, and decrease bacterial translocation in rat models of acute liver injury and failure. However, the administration of *Lactobacillus acidophilus*- and *Lactobacillus* GG-fermented diets to animals with portal hypertension and cirrhosis failed to show any reduction in bacterial translocation or in ascites infection rates [63, 64].

Two prospective randomized studies demonstrated the efficacy of probiotics in reducing postorthotopic liver transplantation (OLT) infections [65, 66]. In the first study, OLT patients receiving *Lactobacillus plantarum* 299 and fiber had less posttransplant infections than groups receiving selective bowel decontamination. The second study used Synbiotic 2000 in post-OLT patients for 14 days and also found a lower 30-day infection rate. Importantly, no serious adverse effects were noted in either study. As it is a cheap and feasible alternative to selective intestinal decontamination, further studies are needed to evaluate the effect of this combination in other cirrhotic populations.

3. Urinary Tract Infections

Urinary tract infections are the most frequent infective complications in cirrhosis. As in the noncirrhotic population, cirrhotics with indwelling catheters are highly predisposed to develop urinary tract infections. The incidence is markedly higher in female than in male cirrhotics [67]. Urinary tract infections in cirrhosis are usually asymptomatic, and bacteriuria alone is found in a high proportion of urinary tract infections episodes in cirrhotics [68]. The majority of infections are caused by Gram-negative bacilli, and, although urine cultures for identification and in vitro sensitivity testing of causative organisms are always recommended, cases requiring immediate therapy should be empirically started on a quinolone or the older but effective cotrimoxazole. These agents are very active against Gram-negative bacteria and reach high concentrations in urine. Other antibiotic regimes might include amoxicillin plus clavulanic acid or an oral cephalosporin [18, 69].

4. Pneumonias

Pneumonias are the third most common infections in patients of cirrhosis after SBP and urinary tract infections. Community-acquired infections are the most frequent, although hospitalized patients admitted to intensive care units have high incidence of nosocomial pneumonias due to predisposing factors such as tracheal intubation, esophageal tamponade, or hepatic encephalopathy. Alcoholics are predisposed to chest infections, *Streptococcus* pneumonia being the causative organism in most lower respiratory tract infections [70]. A significant number of cases of pneumonia are caused by other pathogens normally present in the oropharyngeal area, especially anaerobic bacteria or *Haemophilus influenzae*, or by Gram-negative bacilli, particularly *Klebsiella pneumoniae*, mycoplasma and legionella species [70–72]. Antibiotic regimes combining macrolides and one of the following: cefotaxime, ceftriaxone, amoxicillin-clavulanic acid, are the initial treatment of choice although piperacillin-tazobactam or imipenem may also be used in critically ill patients.

Hospital-acquired pneumonia is predominantly caused by Gram-negative bacilli and staphylococci [71, 72]. Although the identification of the responsible organism in hospital-acquired pneumonia is important for selection of antibiotic treatment, the empiric administration of third-generation cephalosporins (i.e., cefotaxime) should be considered as the first choice of antibiotic. Cirrhotic patients with hydrothorax can develop spontaneous bacterial empyema, which is thought to have the same pathogenesis as SBP, since their isolated bacteria are the same [73]. Therefore, patients with spontaneous bacterial empyema may be treated with the same antibiotic regimens.

5. Skin and Soft Tissue Infections

Soft tissue infections, particularly lymphangitis of the lower extremities and abdominal wall, are relatively frequent in cirrhotic patients with ankle edema or ascites. *Staphylococcus aureus* and *Streptococcus pyogenes* are the most frequent causative organisms [74]. Empirical antibiotic with Cloxacillin has been considered the first-choice antibiotic, but, considering these causative organisms, amoxicillin-clavulanic acid and ceftazidime may be a more adequate empiric antibiotic treatment. Clindamycin, vancomycin, and teicoplanin are the other antibiotics with broad-spectrum Gram-positive coverage.

6. Meningitis

More commonly reported in alcoholic cirrhosis with high overall is one month case fatality rate exceeding 50%. *Streptococcus pneumoniae*, *Escherichia coli*, and *Listeria* are the commonest pathogens implicated. Signs of meningeal irritation including nuchal rigidity may be a delayed or even absent clinical sign. Mortality is significantly high and may reach up to 80% in Child-Pugh stage C [75, 76].

7. Bacteremia and Sepsis

Patients with hepatic dysfunction have an increased risk for bacteremia and sepsis [77]. Bacteria may enter the bloodstream by multiple mechanisms and may quickly progress to sepsis and multiorgan failure due to the immune dysfunctions occurring in cirrhotic patients. Although bacteremia

may occur secondary to a preexisting infection or recent instrumentation, this group of patients often develops spontaneous bacteremia. Many of these cases may be incited by occult or overt gastrointestinal bleeding, which is known to greatly increase the risk of bacterial infections [78]. A recent Cochrane Database review found that the accumulated data in eight trials demonstrated that antibiotic prophylaxis at time of gastrointestinal hemorrhage had a significant benefit by decreasing mortality and the incidence of bacterial infections [79]. Despite general adoption of bacterial prophylaxis, cirrhotic patients still have a high rate of bacterial diseases, which often progress to sepsis and severe sepsis.

Given the degree of immune dysfunction and the morbidity of infections, patients with significant cirrhosis who present with, or with probable, bacteremia or sepsis should undergo rapid diagnostic testing and should receive intravenous antibiotics that treat the likely organisms as soon as possible. In septic patients, early antibiotic initiation with the appropriate agents significantly improves outcomes, and this effect is especially important in immune-compromised patients [80, 81].

8. Catheter-Related Infections

These infections are common in critically ill patients with cirrhosis. These patients may benefit from appropriate hand hygiene, use of chlorhexidine for skin preparation, use of full-barrier precautions during the insertion of central venous catheters, use of the subclavian vein as the preferred site for insertion of the catheter, and the removal of unnecessary central venous catheters [82].

9. Conclusion

Patients with chronic liver diseases sustain impairment to their immune systems, which worsens over time and with disease progression. These defects in their host defense lead to augmented risks of bacterial infections and increased morbidity when they are incurred. Providers caring for patients with hepatic dysfunction should have a heightened surveillance for infectious diseases and suspect that one is present with any acute change in a patient's status. With early diagnosis and proper antibiotic treatment, the mortality of bacterial infections has decreased significantly over the years.

References

[1] J. Fernandez, M. Navasa, J. Gómez et al., "Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis," *Hepatology*, vol. 35, no. 1, pp. 140–148, 2002.

[2] M. Borzio, F. Salerno, L. Piantoni et al., "Bacterial infection in patients with advanced cirrhosis: a multicentre prospective study," *Digestive and Liver Disease*, vol. 33, no. 1, pp. 41–48, 2001.

[3] B. Bernard, J. D. Grange, E. N. Khac, X. Amiot, P. Opolon, and T. Poynard, "Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis," *Hepatology*, vol. 29, no. 6, pp. 1655–1661, 1999.

[4] J. Goulis, A. Armonis, D. Patch, C. Sabin, L. Greenslade, and A. K. Burroughs, "Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage," *Hepatology*, vol. 27, no. 5, pp. 1207–1212, 1998.

[5] S. Vivas, M. Rodriguez, M. A. Palacio, A. Linares, J. L. Alonso, and L. Rodrigo, "Presence of bacterial infection in bleeding cirrhotic patients is independently associated with early mortality and failure to control bleeding," *Digestive Diseases and Sciences*, vol. 46, no. 12, pp. 2752–2757, 2001.

[6] B. Bernard, J. F. Cadranel, D. Valla, S. Escolano, V. Jarlier, and P. Opolon, "Prognostic significance of bacterial infection in bleeding cirrhotic patients: a prospective study," *Gastroenterology*, vol. 108, no. 6, pp. 1828–1834, 1995.

[7] M. C. Hou, H. C. Lin, T. T. Liu et al., "Antibiotic prophylaxis after endoscopic therapy prevents rebleeding in acute variceal hemorrhage: a randomized trial," *Hepatology*, vol. 39, no. 3, pp. 746–753, 2004.

[8] A. Rimola, F. Bory, R. Planas, A. Xaubet, M. Bruguera, and J. Rodes, "Infecciones bacterianas agudas en la cirrosis hepatica," *Gastroenterología y Hepatología*, vol. 4, pp. 453–458, 1981.

[9] G. Bleichner, R. Boulanger, P. Squara, J. P. Sollet, and A. Parent, "Frequency of infections in cirrhotic patients presenting with acute gastrointestinal haemorrhage," *British Journal of Surgery*, vol. 73, no. 9, pp. 724–726, 1986.

[10] W. R. Caly and E. Strauss, "A prospective study of bacterial infections in patients with cirrhosis," *Journal of Hepatology*, vol. 18, no. 3, pp. 353–358, 1993.

[11] F. Wong, M. Bernardi, R. Balk et al., "Sepsis in cirrhosis: report on the 7th meeting of the International Ascites Club," *Gut*, vol. 54, no. 5, pp. 718–725, 2005.

[12] G. Garcia-Tsao and R. Wiest, "Gut microflora in the pathogenesis of the complications of cirrhosis," *Best Practice and Research: Clinical Gastroenterology*, vol. 18, no. 2, pp. 353–372, 2004.

[13] H. E. Wasmuth, D. Kunz, E. Yagmur et al., "Patients with acute on chronic liver failure display "sepsis-like" immune paralysis," *Journal of Hepatology*, vol. 42, no. 2, pp. 195–201, 2005.

[14] I. A. Rajkovic and R. Williams, "Abnormalities of neutrophil phagocytosis, intracellular killing and metabolic activity in alcoholic cirrhosis and hepatitis," *Hepatology*, vol. 6, no. 2, pp. 252–262, 1986.

[15] T. Gustot, F. Durand, D. Lebrec, J. L. Vincent, and R. Moreau, "Severe sepsis in cirrhosis," *Hepatology*, vol. 50, no. 6, pp. 2022–2033, 2009.

[16] F. Bert, X. Panhard, J. Johnson et al., "Genetic background of *Escherichia coli* isolates from patients with spontaneous bacterial peritonitis: relationship with host factors and prognosis," *Clinical Microbiology and Infection*, vol. 14, no. 11, pp. 1034–1040, 2008.

[17] A. Plessier, M. H. Denninger, Y. Consigny et al., "Coagulation disorders in patients with cirrhosis and severe sepsis," *Liver International*, vol. 23, no. 6, pp. 440–448, 2003.

[18] A. Rimola and M. Navasa, "Infections in liver disease," in *Oxford Textbook of Clinical Hepatology*, J. Bircher, J. P. Benhamou, N. McIntyre, M. Rizzetto, and J. Rode's, Eds., pp. 1861–1876, Oxford University Press, Oxford, UK, 2nd edition, 1999.

[19] C. Guarner and B. A. Runyon, "Macrophage function in cirrhosis and the risk of bacterial infection," *Hepatology*, vol. 22, no. 1, pp. 367–369, 1995.

[20] B. A. Runyon, "Patients with deficient ascitic fluid opsonic activity are predisposed to spontaneous bacterial peritonitis," *Hepatology*, vol. 8, no. 3, pp. 632–635, 1988.

[21] J. Llach, A. Rimola, M. Navasa et al., "Incidence and predictive factors of first episode of spontaneous bacterial peritonitis in cirrhosis with ascites: relevance of ascitic fluid protein concentration," *Hepatology*, vol. 16, no. 3, pp. 724–727, 1992.

[22] G. Garcia-Tsao, "Spontaneous bacterial peritonitis: a historical perspective," *Journal of Hepatology*, vol. 41, no. 4, pp. 522–527, 2004.

[23] M. Segarra-Newnham and A. Henneman, "Antibiotic prophylaxis for prevention of spontaneous bacterial peritonitis in patients without gastrointestinal bleeding," *Annals of Pharmacotherapy*, vol. 44, no. 12, pp. 1946–1954, 2010.

[24] A. Rimola, G. García-Tsao, M. Navasa et al., "Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document," *Journal of Hepatology*, vol. 32, no. 1, pp. 142–153, 2000.

[25] G. Vanbiervliet, C. Rakotoarisoa, J. Filippi et al., "Diagnostic accuracy of a rapid urine-screening test (Multistix8SG) in cirrhotic patients with spontaneous bacterial peritonitis," *European Journal of Gastroenterology and Hepatology*, vol. 14, no. 11, pp. 1257–1260, 2002.

[26] J. Castellote, C. Lopez, J. Gornals et al., "Rapid diagnosis of spontaneous bacterial peritonitis by use of reagent strips," *Hepatology*, vol. 37, no. 4, pp. 893–896, 2003.

[27] R. C. Butani, R. T. Shaffer, R. D. Szyjkowski, B. E. Weeks, L. G. Speights, and S. C. Kadakia, "Rapid diagnosis of infected ascitic fluid Using leukocyte esterase dipstick testing," *American Journal of Gastroenterology*, vol. 99, no. 3, pp. 532–537, 2004.

[28] T. Thevenot, J. F. Cadranel, E. Nguyen-Khac et al., "Diagnosis of spontaneous bacterial peritonitis in cirrhotic patients by use of two reagent strips," *European Journal of Gastroenterology and Hepatology*, vol. 16, no. 6, pp. 579–583, 2004.

[29] T. Sapey, D. Kabisa, E. Fort, C. Laurin, and M. H. Mendler, "Instant diagnosis of spontaneous bacterial peritonitis using leukocyte esterase reagent strips: Nephur-Test vs. MultistixSG," *Liver International*, vol. 25, no. 2, pp. 343–348, 2005.

[30] D. Y. Kim, J. H. Kim, C. Y. Chon et al., "Usefulness of urine strip test in the rapid diagnosis of spontaneous bacterial peritonitis," *Liver International*, vol. 25, no. 6, pp. 1197–1201, 2005.

[31] J. Castellote, C. Lopez, J. Gornals, A. Domingo, and X. Xiol, "Use of reagent strips for the rapid diagnosis of spontaneous bacterial empyema," *Journal of Clinical Gastroenterology*, vol. 39, no. 4, pp. 278–281, 2005.

[32] B. Campillo, J. P. Richardet, and C. Dupeyron, "Diagnostic value of two reagent strips (Multistix 8 SG and Combur 2 LN) in cirrhotic patients with spontaneous bacterial peritonitis and symptomatic bacterascites," *Gastroenterologie Clinique et Biologique*, vol. 30, no. 3, pp. 446–452, 2006.

[33] J. Felisart, A. Rimola, V. Arroyo et al., "Cefotaxime is more effective than is ampicillin-tobramycin in cirrhotics with severe infections," *Hepatology*, vol. 5, no. 3, pp. 457–462, 1985.

[34] J. Mercader, J. Gomez, J. Ruiz, M. C. Garre, and M. Valdes, "Use of ceftriaxone in the treatment of bacterial infections in cirrhotic patients," *Chemotherapy*, vol. 35, no. 2, supplement, pp. 23–26, 1989.

[35] J. Gomez-Jimenez, E. Ribera, I. Gasser et al., "Randomized trial comparing ceftriaxone with cefonicid for treatment of spontaneous bacterial peritonitis in cirrhotic patients," *Antimicrobial Agents and Chemotherapy*, vol. 37, no. 8, pp. 1587–1592, 1993.

[36] E. Ricart, G. Soriano, M. T. Novella et al., "Amoxicillin-clavulanic acid versus cefotaxime in the therapy of bacterial infections in cirrhotic patients," *Journal of Hepatology*, vol. 32, no. 4, pp. 596–602, 2000.

[37] M. Navasa, A. Follo, J. M. Llovet et al., "Randomized, comparative study of oral ofloxacin versus intravenous cefotaxime in spontaneous bacterial peritonitis," *Gastroenterology*, vol. 111, no. 4, pp. 1011–1017, 1996.

[38] P. Gines, A. Rimola, R. Planas et al., "Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial," *Hepatology*, vol. 12, no. 4 I, pp. 716–724, 1990.

[39] J. Ortiz, M. C. Vila, G. Soriano et al., "Infections caused by *Escherichia coli* resistant to norfloxacin in hospitalized cirrhotic patients," *Hepatology*, vol. 29, no. 4, pp. 1064–1069, 1999.

[40] P. Gines, A. Rimola, R. Planas et al., "Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial," *Hepatology*, vol. 12, no. 4 I, pp. 716–724, 1990.

[41] J. Inadomi and A. Sonnenberg, "Cost-analysis of prophylactic antibiotics in spontaneous bacterial peritonitis," *Gastroenterology*, vol. 113, no. 4, pp. 1289–1294, 1997.

[42] Z. M. Younossi, J. G. McHutchison, and T. G. Ganiats, "An economic analysis of norfloxacin prophylaxis against spontaneous bacterial peritonitis," *Journal of Hepatology*, vol. 27, no. 2, pp. 295–298, 1997.

[43] N. Singh, T. Gayowski, V. L. Yu, and M. M. Wagener, "Trimethoprim-sulfamethoxazole for the prevention of spontaneous bacterial peritonitis in cirrhosis: a randomized trial," *Annals of Internal Medicine*, vol. 122, no. 8, pp. 595–598, 1995.

[44] A. Rimola, G. García-Tsao, M. Navasa et al., "Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document," *Journal of Hepatology*, vol. 32, no. 1, pp. 142–153, 2000.

[45] P. F. Barnes, C. Arevalo, L. S. Chan, S. F. Wong, and T. B. Reynolds, "A prospective evaluation of bacteremic patients with chronic liver disease," *Hepatology*, vol. 8, no. 5, pp. 1099–1103, 1988.

[46] G. Bleichner, R. Boulanger, P. Squara, J. P. Sollet, and A. Parent, "Frequency of infections in cirrhotic patients presenting with acute gastrointestinal haemorrhage," *British Journal of Surgery*, vol. 73, no. 9, pp. 724–726, 1986.

[47] B. Bernard, J. F. Cadranel, D. Valla, S. Escolano, V. Jarlier, and P. Opolon, "Prognostic significance of bacterial infection in bleeding cirrhotic patients: a prospective study," *Gastroenterology*, vol. 108, no. 6, pp. 1828–1834, 1995.

[48] G. Garcia-Tsao, "Bacterial infections in cirrhosis: treatment and prophylaxis," *Journal of Hepatology*, vol. 42, no. 1, pp. S85–S92, 2005.

[49] B. Bernard, J. D. Grange, E. N. Khac, X. Amiot, P. Opolon, and T. Poynard, "Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis," *Hepatology*, vol. 29, no. 6, pp. 1655–1661, 1999.

[50] N. Carbonell, A. Pauwels, L. Serfaty, O. Fourdan, V. G. Lévy, and R. Poupon, "Improved survival after variceal bleeding in patients with cirrhosis over the past two decades," *Hepatology*, vol. 40, no. 3, pp. 652–659, 2004.

[51] R. Jalan and P. C. Hayes, "BSG guidelines on variceal bleeding," *Gut*, vol. 46, no. 4, supplement 3-4, pp. III1–III15, 2000.

[52] J. Fernández, L. R. del Arbol, C. Gómez et al., "Norfloxacin vs Ceftriaxone in the prophylaxis of infections in patients with

advanced cirrhosis and hemorrhage," *Gastroenterology*, vol. 131, no. 4, pp. 1049–1056, 2006.

[53] A. Rolachon, L. Cordier, Y. Bacq et al., "Ciprofloxacin and long-term prevention of spontaneous bacterial peritonitis: results of a prospective controlled trial," *Hepatology*, vol. 22, no. 4 I, pp. 1171–1174, 1995.

[54] J. Fernández, M. Navasa, R. Planas et al., "Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis," *Gastroenterology*, vol. 133, no. 3, pp. 818–824, 2007.

[55] R. Terg, E. Fassio, M. Guevara et al., "Ciprofloxacin in primary prophylaxis of spontaneous bacterial peritonitis: a randomized, placebo-controlled study," *Journal of Hepatology*, vol. 48, no. 5, pp. 774–779, 2008.

[56] A. Follo, J. M. Llovet, M. Navasa et al., "Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis," *Hepatology*, vol. 20, no. 6, pp. 1495–1501, 1994.

[57] J. C. Hoefs et al., "Spontaneous bacterial peritonitis," *Hepatology*, vol. 2, no. 4, pp. 399–407, 1982.

[58] A. Billiau and F. Vandekerckhove, "Cytokines and their interactions with other inflammatory mediators in the pathogenesis of sepsis and septic shock," *European Journal of Clinical Investigation*, vol. 21, no. 6, pp. 559–573, 1991.

[59] J. A. Giron-Gonzalez, C. Rodriguez-Ramos, J. Elvira et al., "Serial analysis of serum and ascitic fluid levels of soluble adhesion molecules and chemokines in patients with SBP," *Clinical and Experimental Immunology*, vol. 123, no. 1, pp. 56–61, 2001.

[60] P. Sort, M. Navasa, V. Arroyo et al., "Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis," *The New England Journal of Medicine*, vol. 341, no. 6, pp. 403–409, 1999.

[61] C. Loguercio, A. Federico, C. Tuccillo et al., "Beneficial effects of a probiotic VSL#3 on parameters of liver dysfunction in chronic liver diseases," *Journal of Clinical Gastroenterology*, vol. 39, no. 6, pp. 540–543, 2005.

[62] V. Stadlbauer, R. P. Mookerjee, S. Hodges, G. A. K. Wright, N. A. Davies, and R. Jalan, "Effect of probiotic treatment on deranged neutrophil function and cytokine responses in patients with compensated alcoholic cirrhosis," *Journal of Hepatology*, vol. 48, no. 6, pp. 945–951, 2008.

[63] T. M. Bauer, J. Fernandez, M. Navasa, J. Vila, and J. Rodes, "Failure of Lactobacillus spp. to prevent bacterial translocation in a rat model of experimental cirrhosis," *Journal of Hepatology*, vol. 36, no. 4, pp. 501–506, 2002.

[64] R. Wiest, F. Chen, G. Cadelina, R. J. Groszmann, and G. Garcia-Tsao, "Effect of Lactobacillus-fermented diets on bacterial translocation and intestinal flora in experimental prehepatic portal hypertension," *Digestive Diseases and Sciences*, vol. 48, no. 6, pp. 1136–1141, 2003.

[65] N. Rayes, D. Seehofer, A. R. Muller, S. Hansen, S. Bengmark, and P. Neuhaus, "Influence of probiotics and fibre on the incidence of bacterial infections following major abdominal surgery—results of a prospective trial," *Zeitschrift fur Gastroenterologie*, vol. 40, no. 10, pp. 869–876, 2002.

[66] N. Rayes, D. Seehofer, T. Theruvath et al., "Supply of pre and probiotics reduces bacterial infection rates after liver transplantation—arandomized, double-blind trial," *American Journal of Transplantation*, vol. 5, no. 1, pp. 125–130, 2005.

[67] A. K. Burroughs, I. J. Rosenstein, and O. Epstein, "Bacteriuria and primary biliary cirrhosis," *Gut*, vol. 25, no. 2, pp. 133–137, 1984.

[68] B. A. Lipsky, "Urinary tract infections in men. Epidemiology, pathophysiology, diagnosis and treatment," *Annals of Internal Medicine*, vol. 110, no. 2, pp. 138–150, 1989.

[69] J. F. Westphal, F. Jehl, and D. Vetter, "Pharmacological, toxicologic, and microbiological considerations in the choice of initial antibiotic therapy for serious infections in patients with cirrhosis of the liver," *Clinical Infectious Diseases*, vol. 18, no. 3, pp. 324–335, 1994.

[70] H. G. Adams and C. Jordan, "Infections in the alcoholic," *Medical Clinics of North America*, vol. 68, no. 1, pp. 179–200, 1984.

[71] R. W. Bradsher, "Overwhelming pneumonia," *Medical Clinics of North America*, vol. 67, no. 6, pp. 1233–1250, 1983.

[72] M. Levy, F. Dromer, N. Brion, F. Leturdu, and C. Carbon, "Community-acquired pneumonia. Importance of initial noninvasive bacteriologic and radiographic investigations," *Chest*, vol. 93, no. 1, pp. 43–48, 1988.

[73] M. A. Flaum, "Spontaneous bacterial empyema in cirrhosis," *Gastroenterology*, vol. 70, no. 3, pp. 416–417, 1976.

[74] M. N. Swartz, "Cellulitis and superficial infections," in *Principles and Practice of Infectious Diseases*, G. L. Mandell, R. G. Douglas Jr., and J. E. Bennett, Eds., vol. 88, pp. 34–37, Churchill Livingstone, New York, NY, USA, 3rd edition, 1990.

[75] I. Molle, A. M. Thulstrup, N. Svendsen, H. C. Schonheyder, and H. T. Sorensen, "Risk and case fatality rate of meningitis in patients with liver cirrhosis," *Scandinavian Journal of Infectious Diseases*, vol. 32, no. 4, pp. 407–410, 2000.

[76] A. Pauwels, E. Pines, M. Abboura, I. Chiche, and V. G. Lévy, "Bacterial meningitis in cirrhosis: review of 16 cases," *Journal of Hepatology*, vol. 27, no. 5, pp. 830–834, 1997.

[77] P. Tandon and G. Garcia-Tsao, "Bacterial infections, sepsis, and multiorgan failure in cirrhosis," *Seminars in Liver Disease*, vol. 28, no. 1, pp. 26–42, 2008.

[78] M. Deschenes and J. P. Villeneuve, "Risk factors for the development of bacterial infections in hospitalized patients with cirrhosis," *American Journal of Gastroenterology*, vol. 94, no. 8, pp. 2193–2197, 1999.

[79] K. Soares-Weiser, M. Brezis, R. Tur-Kaspa, and L. Leibovici, "Antibiotic prophylaxis for cirrhotic patients with gastrointestinal bleeding," *Cochrane Database of Systematic Reviews*, vol. 2, Article ID CD002907, 2002.

[80] A. M. Kumar, D. M. Roberts, K. E. D. Wood et al., "Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock," *Critical Care Medicine*, vol. 34, no. 6, pp. 1589–1596, 2006.

[81] E. H. Ibrahim, G. Sherman, S. Ward, V. J. Fraser, and M. H. Kollef, "The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting," *Chest*, vol. 118, no. 1, pp. 146–155, 2000.

[82] P. Pronovost, D. Needham, S. Berenholtz et al., "An intervention to decrease catheter-related bloodstream infections in the ICU," *The New England Journal of Medicine*, vol. 355, no. 26, pp. 2725–2732, 2006.

SAGE-Hindawi Access to Research
International Journal of Hepatology
Volume 2011, Article ID 841407, 10 pages
doi:10.4061/2011/841407

Review Article

Management of Hepatic Encephalopathy

G. Wright,[1] A. Chattree,[2] and R. Jalan[1]

[1] *University College London Institute of Hepatology, The Royal Free Hospital, Pond Street, London NW3 2PF, UK*
[2] *Department of Gastroenterology, King Georges Hospital, Barley Lane, Goodmayes, Ilford, Essex IG3 8YB, UK*

Correspondence should be addressed to G. Wright, gavin.wright@ucl.ac.uk

Received 28 April 2011; Accepted 8 June 2011

Academic Editor: Deepak Amarapurkar

Hepatic encephalopathy (HE), the neuropsychiatric presentation of liver disease, is associated with high morbidity and mortality. Reduction of plasma ammonia remains the central therapeutic strategy, but there is a need for newer novel therapies. We discuss current evidence supporting the use of interventions for both the general management of chronic HE and that necessary for more acute and advanced disease.

1. Introduction

There are a plethora of therapeutic approaches to targeting varying severities of hepatic encephalopathy (HE), the neuropsychiatric presentations of liver disease. There is a need for newer therapies for patients with advanced HE and worsening acute liver injury. Reduction of plasma ammonia remains the central strategy although novel strategies may be beneficial. We discuss current evidence supporting the use of therapeutic interventions for both the general management of chronic HE and that necessary for more acute and advanced disease.

2. General Management of Chronic Encephalopathy (Table 1)

2.1. Ammonia-Lowering Strategies

2.1.1. Dietary Protein Supplementation. Patients with cirrhosis often have a poor nutritional reserve due to anorexia, poor diet, malabsorption, and altered metabolic state. Hospitalized patients are often hypermetabolic and hypercatabolic, worsened by complications such as gastrointestinal bleeding, continued anorexia, and fasting for tests. Yet dietary protein has the potential to drive further ammoniagenesis, and so previously dietary protein restriction was common practice. However, protein restriction is no longer advocated as does not improve HE and may be harmful [1]. In fact high-protein diets are well tolerated in cirrhotic patients [2], with consensus supporting the need for normal or high dietary protein (1–1.5 g/kg protein and 25–40 kcal/kg per day) [2, 3]. Rare exceptions arise occasionally with inborn errors of metabolism or acute liver failure (ALF) patients intubated for grade 3-4 HE associated with high circulating ammonia when protein restriction with maintained calorie intake (e.g., dextrose infusion) is necessary.

2.1.2. Branched-Chain Amino Acids (BCAAs). BCAAs are chiefly derived from dairy products and vegetables and account for 25% of total dietary protein. They are a good substrate for protein synthesis, both conserving and restoring muscle mass in advanced liver disease. In cirrhosis, poor dietary intake leads to a deficiency of BCAA and resultant accumulation of aromatic amino acids, both worsening protein-energy deficits and glutaminergic neurotransmission (increased false neurotransmitter precursors). In "high protein diet" intolerant and severely malnourished patients, BCAA supplements may be useful to provide the necessary nitrogen intake without a decline in mental state, with vegetable proteins likely to be better tolerated due to their higher BCAA content. As BCAAs are under the influence of circulating insulin, the insulin resistance state of cirrhosis may limit there nutritional benefit unless systemic insulin replacement is implemented. However, a number of meta-analyses have failed to find consensus on the use of BCAAs in cirrhosis from a wealth of conflicting data [4, 5].

In most cirrhotic patients, a modified eating pattern, based on several meals and a late evening snack, is adequate [4, 6].

Table 1: Treatment stratagems used in HE.

HE grade: I-II
General management
Hyperammonemia
Dietary protein supplementation
Purgatives
(i) Nonabsorbable disaccharides
(ii) Enemas
Non-absorbable antibiotics
Modulation of interorgan ammonia
(i) L-ornithine, L-aspartate (LOLA)
(ii) Sodium benzoate
(iii) Phenylacetate
Others
(i) Flumazenil "Bromocriptine" acarbose
Emerging therapies
(i) Probiotics
HE grade: III-IV
Cerebral edema & elevated ICP
General
(i) Ventilate
(ii) Sedate (e.g., Propofol)
Specific
(i) Antimicrobials
(ii) Hypertonic saline
(iii) Mannitol
(iv) Dexamethasone
(v) Induced hypothermia
(vi) Thiopentone
(vii) Indomethacin
(viii) Antiepileptic drugs (AED'S)
(ix) N-acetylcysteine (NAC)
Transplantation
Orthotopic liver transplant (OLT)
Partial hepatectomy
Liver assist devices

2.1.3. Glycaemic Control. Disturbed glycaemic and lipid control is common in progressive liver disease and only worsened by the stress response in critically unwell patients. Therefore, once feeding has commenced, tight glycaemic control using insulin may be necessary to reduce oxidative stress (which triggers insulin resistance), limit mitochondrial liver damage, and improve endothelial activation (e.g., NO production), which will improve blood flow, limiting tissue injury, and improve outcome [7, 8].

2.1.4. Vitamins and Nutrients. Cirrhosis also leads to deficiencies of lipid-soluble vitamins, minerals, and micronutrients. For example, Zinc is a cofactor in the urea cycle [9] and also found in vesicles of predominately glutamatergic presynaptic terminals thereby having a role in neurotransmission [10]. Zinc supplementation (600 mg/day) has been studied without obvious benefit though replacement should be considered if the patient is deficient [11]. Autopsy specimens from patients with hepatic coma and pallidal MR images of patients with HE suggest that manganese deposition in the basal ganglia may be a factor [12, 13]. However, as with earlier studies evaluating the role of gut bacterial products like mercaptans, phenols and medium- and short-chain fatty acids [14], there has been little cumulative evidence to support targeted treatment strategies.

3. Probiotics

Most of the ammonia produced by the gut is from the deamination of dietary amino acids by bacteria, with a small contribution from the urea produced by urease-positive bacteria. In the critically ill and malnourished patient, levels of the predominant defensive bacteria strains (Bifidobacterium and Lactobacillus) decline. Antibiotics may further lead to ammonia-producing bacteria ameliorating hyperammonaemia. Probiotics are living nonpathogenic microorganisms utilized as food ingredients that may have a role in the treatment of HE. Probiotics are thought to exert an effect in HE by reducing intestinal ammonia production by enterocyte glutaminase and reduce bacterial translocation, modulate proinflammatory responses, and modulate gut permeability [15]. Furthermore, probiotics bypass the small bowel and get fermented by colonic bacteria to form lactic, acetic, and butyric acids, and gas (mainly hydrogen); any resultant intestinal hurry may increase the expulsion of ammoniagenic bacteria. In randomized placebo controlled trials [16], probiotics have been shown to reduce gut ammonia production and inflammation [16, 17]. It is worth noting that fermentable fibres alone were also beneficial in that study. This is not unexpected as the common effect of probiotics, aside from a decline of substrate for other bacteria [18] and reduced translocation, is the fermentation of nonabsorbed sugars (e.g., mono-, di- and oligosaccharides). This fermentation of sugars leads to the production of differential amounts of lactic acid, ethanol, and CO_2 to modulate intestinal acidity and gas production.

4. Purgatives

A purgative is an agent which cleanses the bowel by increasing the evacuation of luminal contents. This is beneficial in HE as it allows for reduced intestinal ammonia production and despite limited evidence from randomized controlled trials remain the most widely used therapy for HE.

4.1. Nonabsorbable Disaccharides. It is unclear how non-absorbable disaccharides exert a beneficial effect. There have been many proposed mechanisms (1) enhanced growth of nonurease-producing bacteria [19], (2) catharsis secondary to bowel acidification reducing ammonia absorption [20, 21], (3) proliferation of healthy bacteria by providing additional carbohydrate and thus nitrogen (even as ammonia) into protein, and/or (4) providing carbon and energy and so spare bacterial ammonia metabolism [22]. More specifically, lactulose (a sugar) passes through the small bowel completely undigested (unlike glucose, sucrose, and lactose, which are

easily fermented in the small bowel). Once in the colon, lactulose is fermented by anaerobic bacteria, especially *Bacteroides spp*. Fermentation of lactulose by colonic bacteria yields important weak acids (lactic, acetic & butyric) and gases (e.g., hydrogen). This leads to the acidification of ammonia into ammonium which is poorly absorbed. However, physiologically a total daily dose of 10–20 g is small compared to 500–1000 g faeces/day, such that the impact on acidity/reduced faecal pH on the faecal flora is likely to be limited. This is supported by the failure of mannitol and sorbitol, which both cause low pH, to improve HE [23]. The production of colonic hydrogen may be more important as only 7 g of lactulose produces 1 Litre of hydrogen that could induce intestinal hurry and shift massive amounts of colonic bacteria [24]. However, it may be the provision of energy in preference to ammonia that accounts for the benefit of non-absorbable disaccharides.

A comprehensive meta-analysis of non-absorbable disaccharides has suggested that current data from randomised clinical trials do not support its routine use in clinical practice [25] though newer clinical studies suggest benefit with lactulose conferring improved neuropsychometric and quality of life scores [26], which lends weight to the overwhelming amount of anecdotal evidence that disaccharides are beneficial. It is likely that the impact of other therapies initiated at the same time often confounds any benefit on HE severity by the established ammonia-lowering effect of non-absorbable disaccharides.

Compliance, adverse effects, clinical safely, and cost effectiveness are necessary concerns. It is often overlooked that aggressive use of lactulose causes significant gaseous distension, discomfort, and diarrhoea which may lead to poor compliance. Furthermore, frank dehydration, prerenal uraemia, hyponatraemia, or aspiration of lactulose can occur. Therefore, although non-absorbable disaccharides are relatively cheap, their cost effectiveness should be balanced against clinical outcomes.

4.2. Other Purgatives. Enemas are beneficial as a means of expelling ammonia-producing gut flora by both cleansing and colonic acidification [27] but are no better than oral purgatives like lactulose. Therefore, if bowel motions can be maintained at $\geq$2/day, then enemas may not offer any additional benefit.

5. Nonabsorbable Antibiotics

The contribution of intestinal urease-positive bacteria to gut ammonia production is mainly in the colon rather than gastric mucosa (e.g., Helicobacter pylori), due to their number and more alkaline colonic pH which favours enhanced ammonia diffusion, such that Helicobacter pylori eradication has no therapeutic benefit [28]. Oral, non-absorbable, synthetic antibacterial agents such as Neomycin and Rifaximin have been used to inhibit the growth or kill susceptible ammoniagenic bacterial species, showing comparable efficacy to lactulose [29]. Rifaximin is a synthetic antibiotic related to rifamycin, with wide antibacterial activity against both aerobic and anaerobic gram-negative and gram-positive bacteria. In random controlled studies Rifaximin is proven efficacious (maintaining remission and reducing hospitalization with HE even in patients already on lactulose), and a superior safety profile and thus preferred to neomycin [30, 31], Although beneficial, non-absorbable antibiotics are often reserved for patients who fail to respond to non-absorbable disaccharides.

6. Modulators of Interorgan Ammonia Metabolism (**Figure 1**)

The concept of manipulating endogenous biosynthetic pathways to eliminate nonurea waste nitrogen as a substitute for defective urea synthesis is well established [32]. Despite abnormal urea-cycle functioning, reducing total body nitrogen by promoting the synthesis of non-urea nitrogen-containing metabolites with high excretion rates appears to be of benefit.

6.1. Arginine Supplementation. L-arginine is an important dietary substrate for the urea cycle which allows for ammonia detoxification to urea (via arginase). L-arginine is a semi-essential amino acid, as although metabolically produced, in some disease states may require dietary supplementation. In cases of the childhood urea cycle disorders (e.g., deficiency of argininosuccinate synthetase (AS) and argininosuccinase (AL)), dietary restriction of L-arginine triggers the rapid development (15–68 hours) of symptomatic hyperammonaemia (e.g., vomiting, lethargy, or irritability) [33]. In these disorders, there is a significant reduction in urea production, with nitrogen instead accumulating as mainly glutamine, ammonium, and to a limited extent alanine and glutamate. In AS and AL deficiency, the provision of additional dietary L-arginine promotes the synthesis of citrulline and argininosuccinate, allowing for the urinary excretion of nitrogen.

In ALF, systemic hypotension and cerebral oedema may be associated with increased plasma nitric oxide (NO) levels. L-arginine is the rate-limiting substrate for NO production but is deficient in ALF due possibly to increased arginase activity in the liver which converts it to urea and ornithine. There have been no clinical studies evaluating a role for L-arginine supplementation in HE, though animal studies suggest that correcting L-arginine deficiency may alter portal hypertension and cerebral oedema via arginase-dependent reduction in hyperammonaemia and/or NO-dependent mechanism(s).

6.2. Phenylbutyrate. Phenylbutyrate (converted to phenylacetate in vivo) is an established therapy for hyperammonaemia associated with urea cycle disorders [34], which are characterized by elevated glutamine levels. This excess can be mopped up by phenylacetate, which covalently combines with circulating glutamine to form renally excreted phenylacetylglutamine, removing glutamine as a substrate for ammoniagenesis. So far phenylbutyrate has proved ineffective in the treatment of HE associated with liver failure, probably because a high glutamate state, a prerequisite for phenylacetate to work, is absent in liver failure.

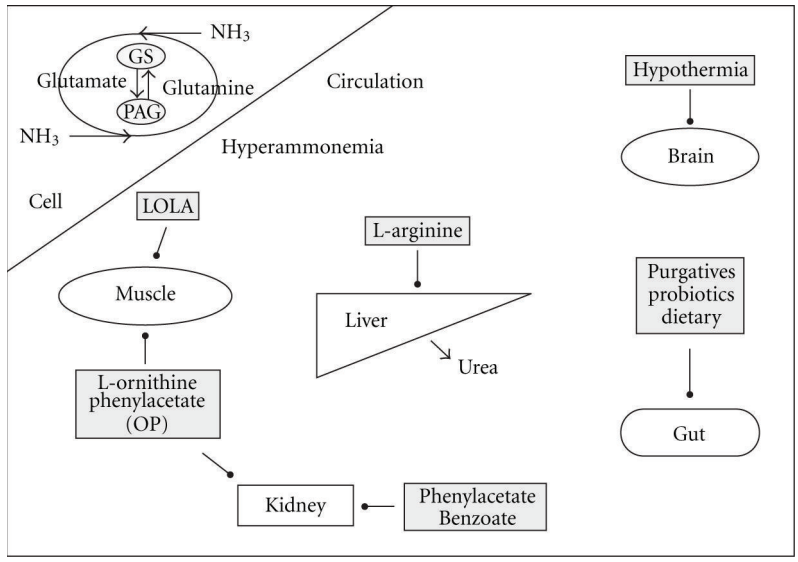


Figure 1: Therapies manipulating interorgan ammonia and amino acid metabolism. In liver failure, the relative activities of cellular glutamine syntheses (GS) and phosphate-activated glutaminase (PAG) in different organs influence interorgan ammonia and amino acid metabolism. With a loss of hepatic urea cycle capacity, hyperammonaemia is predominately due to worsening intestinal and renal ammonia efflux, with skeletal muscle having the potential to increase its ability to detoxify ammonia. Though the brain also detoxifies ammonia, this is counterproductive as resultant astrocyte glutamine accumulation induces brain swelling. This schematic highlights not only current standard therapies for hyperammonaemia which principally act on individual organs (e.g., purgatives targeting intestinal ammonia production), but also newer interventions targeting multiple organs (e.g., LOLA and OP).

6.3. Sodium Benzoate. Similarly sodium benzoate increases the renal excretion of ammonia but as hippuric acid (hippurate), the glycine conjugate of benzoic acid [32]. Sodium benzoate also improves the encephalopathy with inborn errors of metabolism [35] and is as effective as lactulose in the treatment of acute portosystemic HE [36].

6.4. Combined Intravenous Sodium Phenylbutyrate and Benzoate (Ammonul, Ucyclyd Pharma). In urea-cycle disorders, combination therapy results in a 79% reduction in plasma ammonia, and 84–98% improved survival with late onset disease, though poor in neonates and high peak ammonia values [37]. If untreated, only 16% of neonates survive, compared to 72% with late onset disease [38]. However, as the N-acyltransferases that conjugate glutamine to phenylacetate and glycine to benzoate are located in the liver and kidney, the severe hepatotoxicity of ALF may eventually lead to response failure, especially with the saturation of enzyme capacity (e.g., phenylacetate to PAG) [39, 40].

6.5. L-Ornithine L-Aspartate (LOLA). LOLA provides L-ornithine and L-aspartate as substrates for glutamate production in muscle leading to a reduction in circulating ammonia and in models of liver failure further suggest that LOLA reduces brain oedema of advanced HE [41]. In a double-blind randomized control study of cirrhotics with mild HE, one week of LOLA reduced ammonia and improved mental function [42]. A cross-over study showed that 20–40 g/day of infused LOLA ameliorated postprandial increases in ammonia following oral protein loading [43]. However, at higher doses, this study increased plasma glutamate, unchanged glutamine, and increased urea production [43] contradicting the muscle ammonia detoxification hypothesis. Furthermore, 40g dosing induced hyperglycaemia and hyperinsulinaemia [43]. As yet, there are no studies in patients with ALF, and its use in ALF is currently not recommended. Critically, there are concerns that the ammonia-lowering effects of LOLA may only be transient, due to rebound hyperammonaemia on stopping LOLA [44], as a significant rise in glutamine levels eventually becomes a source for ammoniagenesis by the kidney and intestines (through glutaminase) [45]. Additionally, aspartate is unlikely to offer added benefit as in animal models it failed to reduce ammonia [46].

6.6. L-Ornithine Phenylacetate (OP). OP is a novel therapy targeting interorgan ammonia and amino acid metabolism [44]. OP reduces toxic levels of ammonia by ornithine acting as a substrate for glutamine synthesis from ammonia in skeletal muscle. This combination unlike other therapies targeting interorgan ammonia metabolism (e.g., LOLA), by stopping the recycling of ammonia (trapped as ornithine-glutamine) via phenylacetate excreting the ornithine-related glutamine as phenylacetylglutamine in the kidneys. It has been shown to correct the hyperammonemic state in animal models of cirrhosis [47] and ALF [48], limiting brain oedema and rises in ICP. Clinical studies are currently underway.

7. Others

7.1. Acarbose. The hypoglycaemic agent acarbose which stimulates gut motility, through the inhibition of intestinal glucose absorption by promoting intestinal saccharolytic

Table 2: Precipitating factors in hepatic encephalopathy.

Precipitating factors in HE
Constipation
Dehydration
Gastrointestinal bleeding
Infection
Excessive dietary protein
Hypokalaemia
Hypoglycaemia
Hypothyroidism
Hypoxia
Metabolic alkalosis
Anaemia
Azotaemia/uraemia
Medications (narcotics, sedatives, etc.)
Hepatoma
TIPS, surgical shunt
Vascular occlusion

bacterial flora in preference to proteolytic flora, thereby reducing substrate for ammonia production. In a cross-over randomized trial of cirrhotic patients with low-grade HE and type-2 diabetes mellitus, 8 weeks of acarbose (100 mgs TDS) significantly decreased ammonia blood levels, and intellectual function, aside from decreasing fasting and postprandial glucose, and reducing glycosylated haemoglobin levels [49]. However, acarbose is unlikely to be an option except in those with coexistent type-2 diabetes mellitus.

7.2. Bromocriptine. Bromocriptine, a dopamine agonist, has been used with limited success for disturbances in dopaminergic neurotransmission associated with chronic intractable HE [50, 51], but such studies failed to show a clear benefit over standard therapy [49]. Furthermore, in cirrhotic patients with ascites, it can induce hyponatraemia [52]. However, there is anecdotal evidence to suggest a benefit in a small number of cirrhotic patients with low-grade encephalopathy and basal ganglia injury with associated dopamine deficiency.

8. Correction of Precipitating Factors (Table 2)

Worsening encephalopathy is often precipitated by a number of factors which can be anticipated and promptly corrected. Though HE may be triggered by uncommon events, it is important to outline the management of the more common precipitants.

8.1. Constipation. Enemas are beneficial as a mean of expelling ammonia producing gut flora either due by cleansing or colonic acidification [27]. However, there is only limited evidence to show a benefit over the use of oral purgatives like lactulose. Therefore, if bowel motions can be maintained at $\geq$2/day, enemas are only used as an adjunct to the primarily used non-absorbable disaccharides.

8.2. Infections. bacterial infections predispose to variceal bleeding in cirrhotic patients. A meta-analysis of antibiotic use in variceal bleeding reported a 30% decrease in rate of infection and 9% improvement in short-term survival [53, 54]. Septic encephalopathy may also confound or mimic HE.

8.3. Gastrointestinal Bleeding. Due to the high-protein content of blood and thus nitrogenous load, there is increased intestinal ammonia production. This ammoniagenic blood meal and precipitation of HE are potentially related to an absence of the branched-chain amino acid isoleucine which protects the inhibitory effect of ammonia on the TCA cycle in neuronal cells.

8.4. Portosystemic Shunts. Persistent shunts may account for worsening HE poorly responsive to standard oral therapies and may be best treated by shunt closure.

8.5. TIPSS Insertion. The creation of a portosystemic shunt (used to stabilize patients with uncontrolled variceal bleeding or intractable ascites) may induce HE (especially within the first few months). Prophylaxis against encephalopathy with Lactitol (60 g/day) or Rifaximin (1200 mg/day) is not proven to be effective during the first month after TIPSS [55]. Therefore, careful selection of patients for a TIPSS or surgical shunt is necessary.

9. Acute Severe HE: Intracranial Hypertension and Cerebral Oedema (Table 1)

ALF is characterised by rapid onset HE with cerebral oedema and intracranial hypertension and progression to coma stages, independently associated with a 30% mortality [56]. Early ventilation, intensive care unit admission and judicious use of available therapies have led to a significant decline in deaths as a result of cerebral oedema. Aiding liver recovery by prompt and specific treatment of the cause of acute liver injury, treating precipitating factors such as dehydration, electrolyte and acid-base imbalance, [57], infection [58], and ameliorating hyperammonaemia remain at the forefront of therapy. The following therapeutic strategies are utilized in the management of severe HE requiring ventilation.

10. General

Early airway maintenance is necessary to protect the airway and prevent high carbon dioxide tension and hypoxia which can result in cerebral hyperaemia [59]. Sedation and mechanical ventilation is also essential to safely manage agitation. Once intubated, the head should be elevated by 10–20° with minimal intervention and care when moving patients and optimize intracranial pressure (ICP) without compromising the cerebral perfusion pressure [60, 61]. Airway protection will also reduce the likelihood of aspiration, pneumonia, defective gas exchange, and infection. Sedative requirements (e.g., fentanyl, midazolam, or propofol) are low with worsening severity of HE but are likely to increase with recovery. Propofol is a useful sedative because it will

reduce ICP, and because of its nonhepatic metabolism will not accumulate. It may, however, induce hypotension [62].

10.1. Circulatory Support and Fluid Management. ALF is a hyperdynamic state with high cardiac output, low mean arterial pressure, and low systemic vascular resistance [63]. Generalized vasodilatation, which produces profound activation of the neurohormonal system, culminates in vasoconstriction of regional vascular beds [64]. Mean arterial pressure should be maintained at a level to keep the cerebral perfusion pressure between 50 and 65 mmHg [65]. The onset of multiorgan failure often necessitates the use of inotropes. Circulatory failure often becomes refractory to inotropes and up to 70% of patients die [66]. A routine short synacthen test on admission to guide the use of steroids is important as adrenal insufficiency is a common complication of ALF [67].

10.2. Renal Support. Renal dysfunction is common due to either prerenal, hepatorenal, or nephrotoxic (e.g., acetaminophen) injury [68]. This frequently requires renal replacement [66] with continuous (compared to intermittent) haemofiltration [69]. This avoids rapid water shifts seen with intermittent therapy [70], providing greater haemodynamic stability and improved cerebral perfusion pressure [69, 71]. Furthermore, due to impaired hepatic lactate metabolism, lactate-free dialysates are preferred [72].

10.3. Electrolyte Imbalance. Electrolyte imbalance should be corrected aggressively. Hyponatraemia $\leq$125 mmol/L may precipitate cerebral oedema and is a contraindication for orthotopic liver transplant (OLT) [73, 74]. Induced hypernatraemia has been shown to improve ICP and reduce inotropic requirements in traumatic brain injury and ALF [75].

10.4. Antimicrobial Agents. The incidence of sepsis in ALF is a significant factor in mortality and a contraindication to transplantation. Around 75% develop bacterial and 30% fungal infections [76, 77]. The administration of broad-spectrum antibiotics/antifungal therapy should be initiated at the first sign of infection, with focused treatment once the organism is identified. Despite the absence of randomized control trials of prophylactic systemic antimicrobials in ALF, their use is widespread [78, 79].

10.5. Glycaemic Control. Both hyper- and hypoglycaemia need rapid correction as they may worsen brain oedema. The role of tight glycaemic control in ALF has not been ascertained but must be instituted with caution because of the tendency for the development of hypoglycaemia.

11. Specific

11.1. Mannitol. Mannitol (an osmotic diuretic) increases brain capillary osmolality, drawing water from the brain tissue into the capillaries, and has been shown to significantly reduce the extent of cerebral oedema and improve survival [80, 81]. Bolus doses of 20% mannitol at 1 g/kg are preferred. Plasma osmolality should be kept <320 Osm/L, as mannitol is less effective with increasing osmolality. If patient is oliguric, mannitol may accumulate and can only be used with concomitant haemofiltration.

11.2. Dexamethasone. In ALF, reducing inflammation (whether systemic or local) by utilizing the anti-inflammatory effects of steroids may improve cerebral haemodynamics and prevent/treat intracranial hypertension [79, 82, 83]. However, trials using dexamethasone in advanced ALF have shown little effect on the frequency of cerebral oedema or survival [80].

11.3. Mild Hypothermia. In models of ALF, induced hypothermia significantly reduces brain water, duration of encephalopathy, and improved outcome [84–86]. Using cooling blankets to induce moderate hypothermia (target core temp. 32–33°C) can lead to a reduction in ICP, even in patients unresponsive to mannitol and/or ultrafiltration [87, 88]. Hypothermia also significantly improves cardiovascular haemodynamics with reduced noradrenaline requirements [88], likely related to a reduction in arterial ammonia and also brain ammonia extraction and flux [87, 89]. As yet, there is no data from randomized control trials on the use of hypothermia in ALF but is worth considering in patients with uncontrolled intracranial hypertension.

11.4. Thiopental Sodium. By inducing cerebral vasoconstriction through the inhibition of nitric oxide synthetase, intermittent bolus injections of thiopental (1.5–3.5 mg/kg) reduce elevations of ICP [90]. However, its use is limited to intractable increases in ICP unresponsive to other therapies. Because of profound negative effects on systemic haemodynamics, its use is limited.

11.5. Indomethacin. Nonsteroidal anti-inflammatory (NSAIDS) may modulate brain function [91] (with possible effects on cognitive function via modulation of the glutamate-nitric oxide-cyclic GMP pathway [92]). Indomethacin (0.5 mg/kg), a nonselective cyclooxygenase inhibitor [93], can reduce ICP and cerebral oedema independent of a change in cerebral blood flow [94]. However, its use is limited by nephrotoxicity, platelet dysfunction, and risk of gastrointestinal bleeding. Poor brain penetration of NSAIDs at therapeutic levels requires high doses which increases the risk of toxicity [92, 95].

11.6. Antiepileptic Drugs (AED's). In some ALF patients with grade 3-4 HE, subclinical seizures occur, and the use of phenytoin was shown to significantly reduced seizure frequency and the development of increased ICP [96].

11.7. N-Acetylcysteine (NAC). In a case of acetaminophen overdose, NAC must be continued irrespective of the time between the overdose and presentation and acetaminophen level as it can prevent the progression of ALF and reduces mortality especially in those who progress to grade III–IV HE [97]. There is less convincing evidence for NAC in nonacetaminophen overdose [98, 99]. In nonacetaminophen ALF, NAC may improve survival by its effects on cardiac output, oxygen extraction and consumption, and due to its

antioxidant effects that ameliorate the significant oxidative stresses that occur with liver failure.

11.8. Flumazenil. In a large placebo controlled trial focusing on intensive care patients with advanced HE (grade III-IV), the short-acting benzodiazepine-receptor antagonist flumazenil was shown to rapidly improve the neurological score in 15% and electroencephalogram (EEG) findings in 30% of patients within minutes of its administration [100]. However, flumazenil does not lead to any lasting effect or correct HE, unless coadministered with a long-acting therapy [101], and as such is not recommended.

12. Liver Support and Transplantation

12.1. Transplantation. Transplantation offers definitive intervention for liver failure with a swift return to a normal mental state though minimal HE may persist in a few due to some as yet unknown irreversible cerebral changes [102]. Disparity between donor organs and recipients has led to a plethora of extracorporeal liver assist devices [103, 104] and even partial hepatectomy [83, 105] to aid or supplant the failing liver.

12.2. Extracorporeal Liver Assist Devices. Such devices may be either "*biological*" (using either immortalised cultured hepatocytes or whole animal livers), or "*nonbiological*" (using extracorporeal blood purification to dialyse albumin-bound hydrophobic substances), ultimately mimicking endogenous excretory and synthetic liver function. The extracorporeal devices under clinical evaluation include the following.

Molecular Adsorbent Recirculating System (MARS). It provides counter-current haemodialysis against albumin and bicarbonate circuits.

Single-Pass Albumin Dialysis (SPAD). It provides counter-current albumin dialysis against high-flow blood in a fibre haemodiafilter, which unlike MARS is discarded after passing the filter. As it uses a standard renal dialysis device, continuous venovenous haemodiafiltration is possible.

Prometheus system. It provides direct albumin adsorption with high-flux haemodialysis after selective filtration of the albumin fraction through a specific polysulfone filter.

All devices successfully remove protein-bound toxins but have variable effects on systemic (versus portal) haemodynamics, and the potential to worsen coagulopathy. The clinical benefit of such devices is unclear but may at least offer a bridge to either transplantation or liver recovery.

13. Conclusion

Ammonia-lowering therapy remains at the cornerstone of standard medical care for HE, along with measures to treat precipitating factors and specific interventions for the cerebral sequelae of advanced disease. Understanding interorgan ammonia metabolism and the pathophysiological basis of HE are most likely to lead to the development of new therapeutic approaches [45]. However, there is a lack of conclusive evidence from clinical studies even for current best practice [25, 106] and, therefore, a requirement for robust randomized controlled trials to drive a more evidence-based approach.

References

[1] J. Cordoba, J. Lopez-Hellin, M. Planas et al., "Normal protein diet for episodic hepatic encephalopathy: results of a randomized study," *Journal of Hepatology*, vol. 41, pp. 38–43, 2004.

[2] M. Plauth, M. Merli, J. Kondrup, A. Weimann, P. Ferenci, and M. J. Muller, "ESPEN guidelines for nutrition in liver disease and transplantation," *Clinical Nutrition*, vol. 16, no. 2, pp. 43–55, 1997.

[3] H. Lochs and M. Plauth, "Liver cirrhosis: rationale and modalities for nutritional support—the European Society of Parenteral and Enteral Nutrition consensus and beyond," *Current Opinion in Clinical Nutrition and Metabolic Care*, vol. 2, no. 4, pp. 345–349, 1999.

[4] G. Marchesini, R. Marzocchi, M. Noia, and G. Bianchi, "Branched-chain amino acid supplementation in patients with liver diseases," *Journal of Nutrition*, vol. 135, no. 6, pp. 1596S–1601S, 2005.

[5] B. Als-Nielsen, R. L. Koretz, L. L. Kjaergard, and C. Gluud, *Branched-Chain Amino Acids for Hepatic Encephalopathy (Cochrane Review)*, Cochrane Library, John Wiley & Sons, Chichester, UK, 2004.

[6] G. Marchesini, G. Bianchi, B. Rossi, M. Brizi, and N. Melchionda, "Nutritional treatment with branched-chain amino acids in advanced liver cirrhosis," *Journal of Gastroenterology*, vol. 35, 12, pp. 7–12, 2000.

[7] L. Langouche, I. Vanhorebeek, D. Vlasselaers et al., "Intensive insulin therapy protects the endothelium of critically ill patients," *Journal of Clinical Investigation*, vol. 115, no. 8, pp. 2277–2286, 2005.

[8] N. Houstis, E. D. Rosen, and E. S. Lander, "Reactive oxygen species have a causal role in multiple forms of insulin resistance," *Nature*, vol. 440, no. 7086, pp. 944–948, 2006.

[9] G. Marchesini, A. Fabbri, G. Bianchi, M. Brizi, and M. Zoli, "Zinc supplementation and amino acid-nitrogen metabolism in patients with advanced cirrhosis," *Hepatology*, vol. 23, no. 5, pp. 1084–1092, 1996.

[10] Z. S. Agus, I. D. Dukes, and M. Morad, "Divalent cations modulate the transient outward current in rat ventricular myocytes," *American Journal of Physiology*, vol. 261, no. 2, pp. C310–C318, 1991.

[11] P. Reding, J. Duchateau, and C. Bataille, "Oral zinc supplementation improves hepatic encephalopathy. Results of a randomised controlled trial," *The Lancet*, vol. 2, no. 8401, pp. 493–495, 1984.

[12] C. Rose, R. F. Butterworth, J. Zayed et al., "Manganese deposition in basal ganglia structures results from both portal-systemic shunting and liver dysfunction," *Gastroenterology*, vol. 117, no. 3, pp. 640–644, 1999.

[13] G. P. Layrargues, C. Rose, L. Spahr, J. Zayed, L. Normandin, and R. F. Butterworth, "Role of manganese in the pathogenesis of portal-systemic encephalopathy," *Metabolic Brain Disease*, vol. 13, no. 4, pp. 311–317, 1998.

[14] L. Zieve, W. M. Doizaki, and F. J. Zieve, "Synergism between mercaptans and ammonia or fatty acids in the production of coma: a possible role for mercaptans in the pathogenesis of hepatic coma," *Journal of Laboratory and Clinical Medicine*, vol. 83, no. 1, pp. 16–28, 1974.

[15] G. W. Elmer and L. V. McFarland, "Biotherapeutic agents in the treatment of infectious diarrhea," *Gastroenterology Clinics of North America*, vol. 30, no. 3, pp. 837–854, 2001.

[16] Q. Liu, Z. P. Duan, D. K. Ha, S. Bengmark, J. Kurtovic, and S. M. Riordan, "Synbiotic modulation of gut flora: effect on minimal hepatic encephalopathy in patients with cirrhosis," *Hepatology*, vol. 39, no. 5, pp. 1441–1449, 2004.

[17] S. F. Solga, "Probiotics can treat hepatic encephalopathy," *Medical Hypotheses*, vol. 61, no. 2, pp. 307–313, 2003.

[18] G. Bongaerts, R. Severijnen, and H. Timmerman, "Effect of antibiotics, prebiotics and probiotics in treatment for hepatic encephalopathy," *Medical Hypotheses*, vol. 64, no. 1, pp. 64–68, 2005.

[19] J. Bircher, J. Muller, P. Guggenheim, and U. P. Haemmerli, "Treatment of chronic portal-systemic encephalopathy with lactulose," *The Lancet*, vol. 1, no. 7443, pp. 890–892, 1966.

[20] A. Bennett and K. G. Eley, "Intestinal pH and propulsion: an explanation of diarrhoea in lactase deficiency and laxation by lactulose," *Journal of Pharmacy and Pharmacology*, vol. 28, no. 3, pp. 192–195, 1976.

[21] A. Bennett and K. G. Eley, "Proceedings: stimulation of intestinal propulsion by lowered intraluminal pH," *British Journal of Surgery*, vol. 63, no. 2, pp. 160–161, 1976.

[22] A. Vince, M. Killingley, and O. M. Wrong, "Effect of lactulose on ammonia production in a fecal incubation system," *Gastroenterology*, vol. 74, no. 3, pp. 544–549, 1978.

[23] L. Agostini, P. F. Down, J. Murison, and O. M. Wrong, "Faecal ammonia and pH during lactulose administration in man: comparison with other cathartics," *Gut*, vol. 13, no. 11, pp. 859–866, 1972.

[24] C. Cherbut, "Motor effects of short-chain fatty acids and lactate in the gastrointestinal tract," *Proceedings of the Nutrition Society*, vol. 62, no. 1, pp. 95–99, 2003.

[25] B. Als-Nielsen, L. L. Gluud, and C. Gluud, "Non-absorbable disaccharides for hepatic encephalopathy: systematic review of randomised trials.," *British Medical Journal*, vol. 328, no. 7447, pp. 1046–1050, 2004.

[26] S. Prasad, R. K. Dhiman, A. Duseja, Y. K. Chawla, A. Sharma, and R. Agarwal, "Lactulose improves cognitive functions and health-related quality of life in patients with cirrhosis who have minimal hepatic encephalopathy," *Hepatology*, vol. 45, no. 3, pp. 549–559, 2007.

[27] M. Uribe, O. Campollo, F. Vargas et al., "Acidifying enemas (lactitol and lactose) vs. nonacidifying enemas (tap water) to treat acute portal-systemic encephalopathy: a double-blind, randomized clinical trial," *Hepatology*, vol. 7, pp. 639–643, 1987.

[28] J. Miquel, R. Barcena, D. Boixeda et al., "Role of Helicobacter pylori infection and its eradication in patients with subclinical hepatic encephalopathy," *European Journal of Gastroenterology & Hepatology*, vol. 13, pp. 1067–1072, 2001.

[29] H. O. Conn, C. M. Leevy, Z. R. Vlahcevic et al., "Comparison of lactulose and neomycin in the treatment of chronic portal-systemic encephalopathy. A double blind controlled trial," *Gastroenterology*, vol. 72, pp. 573–583, 1977.

[30] F. Miglio, D. Valpiani, S. R. Rossellini, A. Ferrieri, and N. Canova, "Rifaximin, a non-absorbable rifamycin, for the treatment of hepatic encephalopathy. A double-blind, randomised trial," *Current Medical Research and Opinion*, vol. 13, no. 10, pp. 593–601, 1997.

[31] S. Di Piazza, M. G. Filippazzo, L. M. Valenza et al., "Rifaximine versus neomycin in the treatment of portosystemic encephalopathy," *Italian Journal of Gastroenterology*, vol. 23, no. 7, pp. 403–407, 1991.

[32] S. W. Brusilow, D. L. Valle, and M. L. Batshaw, "New pathways of nitrogen excretion in inborn errors of urea synthesis," *The Lancet*, vol. 2, no. 8140, pp. 452–454, 1979.

[33] S. W. Brusilow, "Arginine, an indispensable amino acid for patients with inborn errors of urea synthesis," *Journal of Clinical Investigation*, vol. 74, no. 6, pp. 2144–2148, 1984.

[34] I. Smith, "The treatment of inborn errors of the urea cycle," *Nature*, vol. 291, no. 5814, pp. 378–380, 1981.

[35] M. L. Batshaw, S. Brusilow, and L. Waber, "Treatment of inborn errors of urea synthesis: activation of alternative pathways of waste nitrogen synthesis and excretion," *New England Journal of Medicine*, vol. 306, no. 23, pp. 1387–1392, 1982.

[36] S. Sushma, S. Dasarathy, R. K. Tandon, S. Jain, S. Gupta, and M. S. Bhist, "Sodium benzoate in the treatment of acute hepatic encephalopathy: a double-blind randomized trial," *Hepatology*, vol. 16, no. 1, pp. 138–144, 1992.

[37] G. M. Enns, S. A. Berry, G. T. Berry, W. J. Rhead, S. W. Brusilow, and A. Hamosh, "Survival after treatment with phenylacetate and benzoate for urea-cycle disorders," *The New England Journal of Medicine*, vol. 356, no. 22, pp. 2282–2292, 2007.

[38] M. C. Nassogne, B. Heron, G. Touati, D. Rabier, and J. M. Saudubray, "Urea cycle defects: management and outcome," *Journal of Inherited Metabolic Disease*, vol. 28, no. 3, pp. 407–414, 2005.

[39] A. Thibault, M. R. Cooper, W. D. Figg et al., "A phase I and pharmacokinetic study of intravenous phenylacetate in patients with cancer," *Cancer Research*, vol. 54, no. 7, pp. 1690–1694, 1994.

[40] V. Praphanphoj, S. A. Boyadjiev, L. J. Waber, S. W. Brusilow, and M. T. Geraghty, "Three cases of intravenous sodium benzoate and sodium phenylacetate toxicity occurring in the treatment of acute hyperammonaemia," *Journal of Inherited Metabolic Disease*, vol. 23, no. 2, pp. 129–136, 2000.

[41] C. Rose, A. Michalak, K. V. R. Rao, G. Quack, G. Kircheis, and R. F. Butterworth, "L-ornithine-L-aspartate lowers plasma and cerebrospinal fluid ammonia and prevents brain edema in rats with acute liver failure," *Hepatology*, vol. 30, no. 3, pp. 636–640, 1999.

[42] G. Kircheis, R. Nilius, C. Held et al., "Therapeutic efficacy of L-ornithine-L-aspartate infusions in patients with cirrhosis and hepatic encephalopathy: results of a placebo-controlled, double-blind study," *Hepatology*, vol. 25, no. 6, pp. 1351–1360, 1997.

[43] U. Staedt, H. Leweling, R. Gladisch, C. Kortsik, E. Hagmuller, and E. Holm, "Effects of ornithine aspartate on plasma ammonia and plasma amino acids in patients with cirrhosis. A double-blind, randomized study using a four-fold crossover design," *Journal of Hepatology*, vol. 19, no. 3, pp. 424–430, 1993.

[44] R. Jalan, G. Wright, N. A. Davies, and S. J. Hodges, "L-ornithine phenylacetate (OP): a novel treatment for hyperammonemia and hepatic encephalopathy," *Medical Hypotheses*, vol. 69, no. 5, pp. 1064–1069, 2007.

[45] S. W. Olde Damink, N. E. P. Deutz, C. H. C. Dejong, P. B. Soeters, and R. Jalan, "Interorgan ammonia metabolism in liver failure," *Neurochemistry International*, vol. 41, no. 2-3, pp. 177–188, 2002.

[46] L. Zieve, C. Lyftogt, and D. Raphael, "Ammonia toxicity: comparative protective effect of various arginine and ornithine derivatives, aspartate, benzoate, and carbamyl glutamate," *Metabolic Brain Disease*, vol. 1, no. 1, pp. 25–35, 1986.

[47] N. A. Davies, G. Wright, L. M. Ytrebo et al., "L-ornithine and phenylacetate synergistically produce sustained reduction in ammonia and brain water in cirrhotic rats," *Hepatology*, vol. 50, no. 1, pp. 155–164, 2009.

[48] L. M. Ytrebø, R. G. Kristiansen, H. Maehre et al., "L-ornithine phenylacetate attenuates increased arterial and extracellular brain ammonia and prevents intracranial hypertension in pigs with acute liver failure," *Hepatology*, vol. 50, pp. 165–174, 2009.

[49] S. Gentile, G. Guarino, M. Romano et al., "A randomized controlled trial of acarbose in hepatic encephalopathy," *Clinical Gastroenterology and Hepatology*, vol. 3, no. 2, pp. 184–191, 2005.

[50] M. Y. Morgan, A. Jakobovits, and A. Elithorn, "Successful use of bromocriptine in the treatment of a patient with chronic portasystemic encephalopathy," *The New England Journal of Medicine*, vol. 296, no. 14, pp. 793–794, 1977.

[51] M. Y. Morgan, A. W. Jakobovits, I. M. James, and S. Sherlock, "Successful use of bromocriptine in the treatment of chronic hepatic encephalopathy," *Gastroenterology*, vol. 78, no. 4, pp. 663–670, 1980.

[52] M. Uribe, A. Farca, and M. A. Marquez, "Treatment of chronic portal systemic encephalopathy with bromocriptine: a double-blind controlled trial," *Gastroenterology*, vol. 76, no. 6, pp. 1347–1351, 1979.

[53] B. Bernard, J. D. Grange, E. N. Khac, X. Amiot, P. Opolon, and T. Poynard, "Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis," *Hepatology*, vol. 29, no. 6, pp. 1655–1661, 1999.

[54] M. C. Hou, H. C. Lin, T. T. Liu et al., " Antibiotic prophylaxis after endoscopic therapy prevents rebleeding in acute variceal hemorrhage: a randomized trial," *Hepatology*, vol. 39, no. 3, pp. 746–753, 2004.

[55] O. Riggio, A. Masini, C. Efrati et al., "Pharmacological prophylaxis of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt: a randomized controlled study," *Journal of Hepatology*, vol. 42, no. 5, pp. 674–679, 2005.

[56] A. J. Makin, J. Wendon, and R. Williams, "A 7-year experience of severe acetaminophen-induced hepatotoxicity (1987–1993)," *Gastroenterology*, vol. 109, no. 6, pp. 1907–1916, 1995.

[57] R. Jalan and D. Kapoor, "Reversal of diuretic-induced hepatic encephalopathy with infusion of albumin but not colloid," *Clinical Science*, vol. 106, no. 5, pp. 467–474, 2004.

[58] D. L. Shawcross, N. A. Davies, R. Williams, and R. Jalan, "Systemic inflammatory response exacerbates the neuropsychological effects of induced hyperammonemia in cirrhosis," *Journal of Hepatology*, vol. 40, no. 2, pp. 247–254, 2004.

[59] R. J. Ede, A. E. S. Gimson, D. Bihari, and R. Williams, "Controlled hyperventilation in the prevention of cerebral oedema in fulminant hepatic failure," *Journal of Hepatology*, vol. 2, no. 1, pp. 43–51, 1986.

[60] A. Davenport, E. J. Will, and A. M. Davison, "Effect of posture on intracranial pressure and cerebral perfusion pressure in patients with fulminant hepatic and renal failure after acetaminophen self-poisoning," *Critical Care Medicine*, vol. 18, no. 3, pp. 286–289, 1990.

[61] G. Strauss, B. A. Hansen, G. M. Knudsen, and F. S. Larsen, "Hyperventilation restores cerebral blood flow autoregulation in patients with acute liver failure," *Journal of Hepatology*, vol. 28, no. 2, pp. 199–203, 1998.

[62] E. F. M. Wijdicks and S. L. Nyberg, "Propofol to control intracranial pressure in fulminant hepatic failure," *Transplantation Proceedings*, vol. 34, no. 4, pp. 1220–1222, 2002.

[63] A. Ellis and J. Wendon, "Circulatory, respiratory, cerebral, and renal derangements in acute liver failure: pathophysiology and management," *Seminars in Liver Disease*, vol. 16, no. 4, pp. 379–387, 1996.

[64] R. Jalan, "Acute liver failure: current management and future prospects," *Journal of Hepatology*, vol. 42, no. 1, pp. S115–S123, 2005.

[65] M. H. Davies, D. Mutimer, J. Lowes, E. Elias, and J. Neuberger, "Recovery despite impaired cerebral perfusion in fulminant hepatic failure," *The Lancet*, vol. 343, no. 8909, pp. 1329–1330, 1994.

[66] R. Jalan, "Intracranial hypertension in acute liver failure: pathophysiological basis of rational management," *Seminars in Liver Disease*, vol. 23, no. 3, pp. 271–282, 2003.

[67] R. Harry, G. Auzinger, and J. Wendon, "The clinical importance of adrenal insufficiency in acute hepatic dysfunction," *Hepatology*, vol. 36, no. 2, pp. 395–402, 2002.

[68] K. Moore, "Renal failure in acute liver failure," *European Journal of Gastroenterology & Hepatology*, vol. 11, no. 9, pp. 967–975, 1999.

[69] A. Davenport, E. J. Will, A. M. Davison et al., "Changes in intracranial pressure during haemofiltration in oliguric patients with grade IV hepatic encephalopathy," *Nephron*, vol. 53, no. 2, pp. 142–146, 1989.

[70] R. J. Winney, D. M. Kean, J. J. K. Best, and M. A. Smith, "Changes in brain water with haemodialysis," *The Lancet*, vol. 2, no. 8515, pp. 1107–1108, 1986.

[71] A. Davenport, E. J. Will, and A. M. Davidson, "Improved cardiovascular stability during continuous modes of renal replacement therapy in critically ill patients with acute hepatic and renal failure," *Critical Care Medicine*, vol. 21, no. 3, pp. 328–338, 1993.

[72] N. D. Murphy, S. K. Kodakat, J. A. Wendon et al., "Liver and intestinal lactate metabolism in patients with acute hepatic failure undergoing liver transplantation," *Critical Care Medicine*, vol. 29, no. 11, pp. 2111–2118, 2001.

[73] R. Jalan, K. Dabos, D. N. Redhead, A. Lee, and P. C. Hayes, "Elevation of intracranial pressure following transjugular intrahepatic portosystemic stent-shunt for variceal haemorrhage," *Journal of Hepatology*, vol. 27, no. 5, pp. 928–933, 1997.

[74] J. Cordoba, J. Gottstein, and A. T. Blei, "Chronic hyponatremia exacerbates ammonia-induced brain edema in rats after portacaval anastomosis," *Journal of Hepatology*, vol. 29, no. 4, pp. 589–594, 1998.

[75] N. Murphy, G. Auzinger, W. Bernel, and J. Wendon, "The effect of hypertonic sodium chloride on intracranial pressure in patients with acute liver failure," *Hepatology*, vol. 39, no. 2, pp. 464–470, 2004.

[76] N. Rolando, J. Philpott-Howard, and R. Williams, "Bacterial and fungal infection in acute liver failure," *Seminars in Liver Disease*, vol. 16, no. 4, pp. 389–402, 1996.

[77] N. Rolando, J. J. Wade, A. Stangou et al., "Prospective study comparing the efficacy of prophylactic parenteral antimicrobials, with or without enteral decontamination, in patients with acute liver failure," *Liver Transplantation and Surgery*, vol. 2, no. 1, pp. 8–13, 1996.

[78] N. Rolando, F. Harvey, J. Brahm et al., "Prospective study of bacterial infection in acute liver failure: an analysis of fifty patients," *Hepatology*, vol. 11, no. 1, pp. 49–53, 1990.

[79] N. Rolando, J. Wade, M. Davalos, J. Wendon, J. Philpott-Howard, and R. Williams, "The systemic inflammatory response syndrome in acute liver failure," *Hepatology*, vol. 32, no. 4 I, pp. 734–739, 2000.

[80] J. Canalese, A. E. S. Gimson, and C. Davis, "Controlled trial of dexamethasone and mannitol for the cerebral oedema of fulminant hepatic failure," *Gut*, vol. 23, no. 7, pp. 625–629, 1982.

[81] M. A. Hanid, M. Davies, P. J. Mellon et al., "Clinical monitoring of intracranial pressure in fulminant hepatic failure," *Gut*, vol. 21, pp. 866–869, 1980.

[82] R. Jalan and R. Williams, "The inflammatory basis of intracranial hypertension in acute liver failure," *Journal of Hepatology*, vol. 34, no. 6, pp. 940–942, 2001.

[83] R. Jalan, A. Pollok, S. H. A. Shah, K. K. Madhavan, and K. J. Simpson, "Liver derived pro-inflammatory cytokines may be important in producing intracranial hypertension in acute liver failure," *Journal of Hepatology*, vol. 37, no. 4, pp. 536–538, 2002.

[84] M. Peignoux, J. Bernuau, and J. P. Benhamou, "Total hepatectomy and hepatic vascular exclusion in the rat: a comparison, with special reference to the influence of body temperature," *Clinical Science*, vol. 62, no. 3, pp. 273–277, 1982.

[85] P. Traber, M. DalCanto, D. Ganger, and A. T. Blei, "Effect of body temperature on brain edema and encephalopathy in the rat after hepatic devascularization," *Gastroenterology*, vol. 96, no. 3, pp. 885–891, 1989.

[86] S. Eguchi, A. Kamlot, J. Ljubimova et al., "Fulminant hepatic failure in rats: Survival and effect on blood chemistry and liver regeneration," *Hepatology*, vol. 24, no. 6, pp. 1452–1459, 1996.

[87] R. Jalan, S. W. M. O. Damink, N. E. P. Deutz, A. Lee, and P. C. Hayes, "Moderate hypothermia for uncontrolled intracranial hypertension in acute liver failure," *The Lancet*, vol. 354, no. 9185, pp. 1164–1168, 1999.

[88] R. Jalan, S. W. M. Olde Damink, N. E. P. Deutz, P. C. Hayes, and A. Lee, "Moderate hypothermia in patients with acute liver failure and uncontrolled intracranial hypertension," *Gastroenterology*, vol. 127, no. 5, pp. 1338–1346, 2004.

[89] G. I. Strauss, G. M. Knudsen, J. Kondrup, K. Moller, and F. S. Larsen, "Cerebral metabolism of ammonia and amino acids in patients with fulminant hepatic failure," *Gastroenterology*, vol. 121, no. 5, pp. 1109–1119, 2001.

[90] A. Forbes, G. J. M. Alexander, J. G. O'Grady et al., "Thiopental infusion in the treatment of intracranial hypertension complicating fulminant hepatic failure," *Hepatology*, vol. 10, no. 3, pp. 306–310, 1989.

[91] G. R. Bernard, A. P. Wheeler, J. A. Russell et al., "The effects of ibuprofen on the physiology and survival of patients with sepsis. The Ibuprofen in sepsis study group," *The New England Journal of Medicine*, vol. 336, no. 13, pp. 912–918, 1997.

[92] O. R. Cauli, R. Piedrafita, B. Boix, and J. B. Felipo, "Inflammation and hepatic encephalopathy: ibuprofen restores learning ability in rats with chronic liver failure," *Hepatology*, vol. 46, no. 2, pp. 514–519, 2007.

[93] K. Jensen, J. Ohrstrom, G. E. Cold, and J. Astrup, "Indomethacin (Confortid) in severe head injury and elevated intracranial pressure (ICP)," *Acta Neurochirurgica Supplementum*, vol. 55, pp. 47–48, 1992.

[94] F. Tofteng and F. S. Larsen, "The effect of indomethacin on intracranial pressure, cerebral perfusion and extracellular lactate and glutamate concentrations in patients with fulminant hepatic failure," *Journal of Cerebral Blood Flow and Metabolism*, vol. 24, no. 7, pp. 798–804, 2004.

[95] M. S. Abdel-Halim, B. Sjoquist, and E. Anggard, "Inhibition of prostaglandin synthesis in rat brain," *Acta Pharmacol Toxicol*, vol. 43, pp. 266–272, 1978.

[96] A. J. Ellis, J. A. Wendon, and R. Williams, "Subclinical seizure activity and prophylactic phenytoin infusion in acute liver failure: a controlled clinical trial," *Hepatology*, vol. 32, no. 3, pp. 536–541, 2000.

[97] P. M. Harrison, R. Keays, G. P. Bray, G. J. M. Alexander, and R. Williams, "Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine," *The Lancet*, vol. 335, no. 8705, pp. 1572–1573, 1990.

[98] R. Keays, P. M. Harrison, J. A. Wendon et al., "Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial," *British Medical Journal*, vol. 303, no. 6809, pp. 1026–1029, 1991.

[99] Z. Ben-Ari, H. Vaknin, and R. Tur-Kaspa, "N-acetylcysteine in acute hepatic failure (non-paracetamol-induced)," *Hepato-Gastroenterology*, vol. 47, no. 33, pp. 786–789, 2000.

[100] G. Barbaro, G. Di Lorenzo, M. Soldini et al., "Flumazenil for hepatic encephalopathy grade III and IVa in patients with cirrhosis: an Italian multicenter double-blind, placebo-controlled, cross-over study," *Hepatology*, vol. 28, no. 2, pp. 374–378, 1998.

[101] K. D. Mullen, P. Amodio, and M. Y. Morgan, "Therapeutic studies in hepatic encephalopathy," *Metabolic Brain Disease*, vol. 22, no. 3-4, pp. 407–423, 2007.

[102] S. Mechtcheriakov, I. W. Graziadei, M. Mattedi et al., "Incomplete improvement of visuo-motor deficits in patients with minimal hepatic encephalopathy after liver transplantation," *Liver Transplantation*, vol. 10, no. 1, pp. 77–83, 2004.

[103] S. Sen, R. Jalan, and R. Williams, "Liver failure: basis of benefit of therapy with the molecular adsorbents recirculating system," *International Journal of Biochemistry and Cell Biology*, vol. 35, no. 9, pp. 1306–1311, 2003.

[104] V. Stadlbauer, N. A. Davies, S. Sen, and R. Jalan, "Artificial liver support systems in the management of complications of cirrhosis," *Seminars in Liver Disease*, vol. 28, no. 1, pp. 96–109, 2008.

[105] B. Ringe, N. Lubbe, E. Kuse, U. Frei, and R. Pichlmayr, "Total hepatectomy and liver transplantation as two-stage procedure," *Annals of Surgery*, vol. 218, no. 1, pp. 3–9, 1993.

[106] D. Shawcross and R. Jalan, "Dispelling myths in the treatment of hepatic encephalopathy," *The Lancet*, vol. 365, no. 9457, pp. 431–433, 2005.

SAGE-Hindawi Access to Research
International Journal of Hepatology
Volume 2011, Article ID 280569, 11 pages
doi:10.4061/2011/280569

Review Article

Management of Cardiopulmonary Complications of Cirrhosis

Prabha Sawant, C. Vashishtha, and M. Nasa

Department of Gastroenterology, Lokmanya Tilak Municipal Medical College, Lokmanya Tilak Municipal General Hospital, Sion, Mumbai 400022, India

Correspondence should be addressed to Prabha Sawant, prabhasawant@hotmail.com

Received 18 February 2011; Accepted 12 May 2011

Academic Editor: Deepak Amarapurkar

Advanced portal hypertension accompanying end-stage liver disease results in an altered milieu due to inadequate detoxification of blood from splanchnic circulation by the failing liver. The portosystemic shunts with hepatic dysfunction result in an increased absorption and impaired neutralisation of the gastrointestinal bacteria and endotoxins leads to altered homeostasis with multiorgan dysfunction. The important cardiopulmonary complications are cirrhotic cardiomyopathy, hepatopulmonary syndrome, portopulmonary hypertension, and right-sided hydrothorax.

1. Cirrhotic Cardiomyopathy

Cardiovascular abnormalities have been reported by several investigators. Systemic hemodynamic changes occur in cirrhotic patients. There is hyperdynamic circulatory state, decreased arterial blood pressure, decreased peripheral resistance, and increased cardiac output [1]. Because of reduced systemic vascular resistance and increased arterial compliance, left ventricular failure may be latent in cirrhosis. Impaired ventricular function become manifest under strain or treatment with vasoconstrictors. This type of cardiac dysfunction has been termed as cirrhotic cardiomyopathy.

Three major pathophysiologic abnormalities are observed: cardiac electrophysiological abnormalities, structural and functional ventricular abnormalities, and abnormal ventricular response in presence of pharmacologic, physiologic, or surgical stress.

Cirrhotic patients have hyperdynamic circulation with decreased peripheral vascular resistance, increased cardiac output and stroke volume, increased organ blood flow, low systemic arterial pressure, and decreased arteriovenous oxygen difference. The level of circulating vasoactive substances which are not inactivated by liver is increased such as vasoactive intestinal peptide, glucagon, tumour necrosis factor-α, prostacyclin, nitric oxide, endothelin-1, and endothelin-3 [2].

The impaired ventricular response to stress and exercise is due to impaired beta adrenergic signalling pathways, cardiomyocyte dysfunction because of NO overproduction, increased endocannabinoids and carbon mono-oxide, and/or decreased sensitivity to vasoconstrictors (endothelin-1). Increased cell membrane fluidity with beta-receptor dysfunctioning occurs. Endocannabinoids act through CB1 receptors and result in arterial hypotension. CB1 receptor stimulation also enhances the apoptosis of hepatic stellate cells thus producing portal hypertension. Cardiac dysfunction due to local endocannabinoids also occurs [3]. Increased NO production that occurs in cirrhosis decreases vascular responsiveness to vasoconstrictors. NO antagonism can lead to improved responsiveness to vasoconstrictors. There is impaired function of membrane L-type calcium channels. The intracellular storage and release of calcium is not affected.

There is decreased ventricular systolic response to stress. Cardiac response to exercise is blunted. On stress testing, cirrhotic patients have impaired increase in ejection fraction, chronotropic incompetence, and decreased cardiac index. Impaired cardiac performance occurs in alcoholic and non-alcoholic cirrhotic patients; severity of disturbance depends on degree of hepatic failure [4]. Patients primarily have diastolic dysfunction with left ventricular hypertrophy, left

atrial enlargement, isovolumetric relaxation time prolongation, and decreased early to late diastolic flow ratio (E/A ratio). Systolic function of heart is related to heart rate, stroke volume, and cardiac output. During exercise left ventricular dimensions increase because of impaired cardiac systolic function. The right ventricular and pulmonary artery pressure, as well as pulmonary capillary wedge pressure (PCWP) range around upper limit of normal [5].

Pathologically, in cirrhotic patients heart weight is increased, dilatation of cardiac chambers, myocardial hypertrophy, and structural changes such as myocardial cell edema, nuclear vacuolation, fibrosis, exudates, and pigmentation occur. The ventricular contractility is regulated by beta adrenergic receptor signalling pathway. The activation of receptor acts through stimulatory G protein (Gsa) with increased cyclic AMP. The cyclic AMP promotes phosphorylation and activation of various cellular proteins by stimulation of protein kinase, with increased intracellular calcium and positive inotropic response [6].

The myocardial contractility is regulated by intracellular calcium availability. ATP pumps transfer calcium from cytoplasm into the sarcoplasmic reticulum (SR), the release of calcium from sarcoplasmic reticulum is regulated by calcium channels. Influx of calcium through L-type calcium channels of cell membrane stimulates further release of calcium from the SR. Abnormal functioning of these L-type calcium channels with resultant abnormal release of calcium may explain the abnormality of myocardial contraction in cirrhotic patients [7].

Due to altered lipid metabolism in cirrhosis, the cholesterol content of membrane is increased with increased membrane fluidity resulting in desensitization of beta adrenergic receptors. There is decreased Gsa levels in the membrane and increased catecholamines levels in cirrhotic patients. The myocardial performance improves in cirrhotic patients after administration of NO-synthetase inhibitor [8].

The increased level of nitric oxide attenuates the activation of L-type of calcium channels. Nitric oxide is produced by NO-synthetase from L-arginine. There is transient bacteremia and increased levels of cytokines and endotoxins, which stimulate the enzyme NO synthetase [9]. Nitric oxide has inhibitory effect on myocardial contractility through increased cGMP. Increased cyclic GMP impair beta adrenergic receptor signalling and calcium release from SR. There is transient bacteremia and endotoxin release in cirrhotic patients with overproduction of cytokines. Carbon monoxide levels are increased in cirrhotic patients. CO induces guanylyl cyclase activity with increased cyclic GMP. Inhibition of heme oxygenase activity can result in improved myocardial contractility [10].

There is increased in corrected QT interval. The increased interval correlates with a higher incidence of sudden cardiac death [11]. The pathogenesis of increased QT interval is unclear. The structural changes in cardiomyocyte membrane with increased cholesterol content with resultant membrane fluidity that compromises the calcium and potassium pumps. In cirrhotics increased plasma levels of estrogens has also been implicated for the increased incidence of QT interval prolongation. This interval is increased in 30 to 60% of patients and level of increase relates to degree of hepatic dysfunction. It is also increased in persons with mild portal hypertension thus portosystemic shunting is related to the increase in QTc interval. Increased interval improves with liver transplantation [12].

Cirrhotic cardiomyopathy [CCM] remains clinically undetectable but manifests under stressful stimuli. Cirrhotic patients have peripheral vasodilatation thus reduced afterload that prevents development of congestive heart failure. Cardiac dysfunction may become manifest during stressful conditions. Clinical interventions in cirrhotic patients such as during TIPS placement may result in appearance of signs of frank congestive heart failure.

The patients undergoing liver transplantation may develop pulmonary edema because of cardiac dysfunction together with volume replacement. Thus post transplant patient must have careful fluid replacement because of reduced cardiac reserve. Another complication seen in these post transplant patients is post perfusion syndrome, characterised by decrease of mean arterial pressure of at least 30% for 1 minute within 5 minutes after reperfusion with decrease of heart rate. Likely etiology of which is hyperkalemia, acidosis, and increased tumour necrosis factor-α.

There are no clinical, imaging, or biochemical findings that predict development of CCM so no precise diagnostic criteria has been put forward. As there is no definite diagnostic criteria for CCM treatment guidelines for management have not been clear. Because of the vasodilatation in cirrhotic patients afterload is reduced so cardiac dysfunction remains subtle. In patients with clinically evident heart failure measures include bed rest, supplemental oxygen, and careful use of diuretics.

The cirrhotic patients have reduced afterload so their tolerability to drugs that decrease preload/afterload is reduced. There is beta receptor signalling defect because of reduced density of receptors in cardiomyocyte membrane. Use of beta agonists such as dobutamine and isoproterenol is less likely to be of benefit. There is increased sympathetic catecholamine stimulation in noncirrhotic heart failure. Thus, the use of beta adrenoreceptor antagonists is preferred over beta agonists in treating noncirrhotic patients with heart failure. Use of aldosterone antagonists such as aldosterone results in ventricular remodelling with reduced left ventricular chamber size and thickness. There is also an improvement in diastolic function with aldosterone antagonists. Orthotopic liver transplantation has been associated with the gradual improvement of the cardiac function over a period of 6 to 12 months. Thus cirrhotic cardiomyopathy represents one of the complication of cirrhosis that can be reversed with the liver transplantation [13].

2. Hepatopulmonary Syndrome

This terminology first described in 1977 by Kennedy and Knudson, is defined by classical triad of presence of chronic liver disease or portal hypertension, alteration of arterial oxygenation, defined as widened age corrected alveolar-arterial oxygen gradient with or without arterial hypoxemia

and evidence of intrapulmonary vascular dilatations [IPVD] [14].

IPVD includes a variety of pulmonary vascular alteration with resultant altered gas exchange due to diffuse peripheral dilatation of pulmonary capillaries. The prevalence of HPS is approximately 10 to 20% in cirrhotic patients evaluated for liver transplant. Patients with cirrhosis should be evaluated for HPS irrespective to the stage of the liver injury. The median survival for HPS without liver transplant is 2 years. The survival is worse if PO_2 is less than 50 mm Hg, however death is more so due to the complications of liver disease or portal hypertension-related events rather than hypoxemic respiratory failure [15, 16].

In HPS nearly 20% or more of the cardiac output bypasses the functioning alveoli. With exercise this shunt fraction increases. Patients with HPS mostly present with dyspnoea on exertion and subsequently at rest. Most patients will present with the signs and symptoms of liver disease, including gastrointestinal bleeding, esophageal varices, ascites, palmar erythema, and splenomegaly. Digital clubbing, cyanosis, dyspnea, platypnea, and orthodeoxia are the associated other pulmonary signs. Krowka et al. found dyspnea to be the presenting symptom in 18% of patients [17]. Platypnea, defined as dyspnea induced by the upright position and relieved by recumbency [18] and orthodeoxia, defined as arterial deoxygenation accentuated in the upright position and relieved by recumbency [19]. Five percent of patients of cirrhosis have platypnea and orthodeoxia [20, 21].

The main cause for severe hypoxemia related to HPS is IPVD. Number of mechanisms have been described in literature. The major mediator of pulmonary vascular abnormality is nitric oxide (NO) a vasodilator molecule guanylyl cyclase in vascular smooth muscle [22, 23]. There is failure of the diseased liver to clear the pulmonary vasodilators. Pulmonary vascular dilatation which results in intrapulmonary shunting is the main determining factor of an impaired gas exchange in HPS and can develop in absence of ascites. There is dilatation of pulmonary precapillary and capillary vessels and there is an alveolar capillary disequilibirium or diffusion-perfusion impairment. The increased diameter of the capillary results in inability of oxygen molecules in adjacent alveoli to diffuse in dilated vessels resulting in impairment of oxygen uptake by RBCs in the central stream of blood vessels [24].

There is also hyperdynamic circulation in the patients with liver disease and there is shortened transit time to the lung vasculature. Bacterial translocation in cirrhosis leads to increased TNF-a, which leads to increased macrophage adherence to pulmonary microvasculature with increased inducible NO-synthase-derived NO production [25]. HPS is not associated with any specific etiology of liver disease and degree of hepatic dysfunction. It should be considered independently of stage of liver disease. HPS has also been diagnosed in noncirrhotic portal hypertension and in liver diseases where portal hypertension is not a feature, such as chronic viral hepatitis without cirrhosis. In patients who do not undergo liver transplantation, the 5-year survival rate is diminished in those who have HPS (20% versus 32–63% without HPS) [26].

3. Diagnosis

Several screening algorithms have been proposed. One simple and useful approach is by using pulse oximetry. Oxygen saturation <96% has a sensitivity of 100% and specificity of 88% to detect PaO_2 < 70 mm Hg and may be used to guide further workup for HPS [27].

In the evaluation of the hypoxemic cirrhotic patient the exclusion of other contributing cardiopulmonary causes such as pulmonary atelectasis, ascites, chronic obstructive pulmonary disease, and hepatic hydrothorax is mandatory.

Chest radiography shows prominent pulmonary vascular markings in bilateral lower lobes, but finding is not specific. However, a chest X-ray must still be taken to rule out reversible conditions. Similarly, pulmonary function test should be performed to rule out the common intrinsic pulmonary disorders such as chronic obstructive pulmonary disease.

Contrast echocardiography is the most sensitive test to demonstrate intrapulmonary shunting [28]. It is done using intravenous injections of agitated saline or indocyanine green to produced bubbles of at least 15 microns in diameter. Normally these microbubbles are trapped in the pulmonary vasculature and absorbed. In intracardiac right to left shunts, these microbubbles are seen in the left heart within the first three cardiac cycles [29]. In hepatopulmonary syndrome, because of intrapulmonary shunting, the bubbles are seen in the left heart after the third heart beat, usually between the third and sixth heart beat. Studies have shown that transesophageal echocardiography is more sensitive than transthoracic echocardiography in demonstrating intrapulmonary shunting [30].

There are certain indirect evidences of HPS on echocardiography. A left atrial volume >50 mL is a simple and reliable parameter to detect HPS [31]. Right ventricular diastolic dysfunction is more common in cirrhotic patients with HPS than cirrhotic patients without HPS [32].

There are however a number of limitations of contrast-enhanced echocardiography. It cannot quantify the shunting. It cannot differentiate between intrapulmonary vascular dilatation and direct arteriovenous communication. Although contrast echocardiography is highly sensitive for HPS, it lacks specificity [33]. In patients with concomitant intrinsic lung diseases, contrast echocardiography is a less useful investigation to detect HPS.

To overcome the disadvantages of low specificity of contrast echocardiography, 99mTechnetium macroaggregated albumin (Tc-99m MAA) lung perfusion scan is used. Albumin macroaggregates with more than 20 μm in diameter, normally are entrapped in the pulmonary vasculature. In patients with intrapulmonary shunts, these albumin macroaggregates escape from the pulmonary vasculature and are taken up by other organs. Normally, less than 5% of isotope reaches brain circulation compared to the lung. In HPS patients, the fraction is more than 6% [34].

In cirrhotic patients with concomitant intrinsic pulmonary disorders, Tc-99m MAA scan can diagnose HPS. However, the major disadvantage of Tc-99m MAA scan is its inability to differentiate intracardiac from intrapulmonary

shunting. Pulmonary angiography is another diagnostic modality with potential usefulness [35].

It is however an invasive procedure. Hence, it is reserved for those patients who have a poor response to 100% oxygen, that is, increase in the PaO_2 to less than 300 mm Hg. Two angiographic patterns have been described. type 1 HPS is characterized by precapillary pulmonary artery dilatation without arteriovenous fistulas. In type 2 HPS there is localized pulmonary arteriovenous fistulous communications. type 1 angiographic findings can vary from normal to diffuse, spider-like, or spongy appearance. type 1 HPS patients with diffuse pulmonary changes have more severe hypoxemia and respond poorly to 100% oxygen. Type 2 HPS is less common. Patients with type 2 HPS do not respond to 100% oxygen. These patients should be considered for embolotherapy although there are case reports of coil embolization in patients with type 1 HPS also.

Two newer diagnostic modalities for assessing HPS are high-resolution chest computerized tomography (CT) and evaluation of pulmonary blood transit time. The degree of pulmonary microvascular dilation observed on chest CT shows good correlation with the severity of gas exchange abnormalities in patients with HPS. It also helps in quantification of intrapulmonary vasodilatation [36].

Recently, pulmonary transit time of erythrocytes, by using echocardiographic analysis of human serum albumin air microbubble complexes, also correlated with gas exchange abnormalities in a small group of patients with HPS [37]. These two modalities should be tested further in large-scale studies to explore their potential in diagnosis of HPS.

4. Therapy

The only established effective therapy for HPS is liver transplantation. There is significant improvement in gas exchange postoperatively in more than 85% of reported patients. However, it may take more than one year for the gas exchange abnormalities to normalise [38].

There is increased mortality after transplantation in patients who have HPS compared with subjects who do not have HPS. Specifically patients with marked hypoxemia (PaO_2 < 50 mm Hg) and intrapulmonary shunting (shunt fraction > 20%) have increased mortality. Interestingly, unique complications such as pulmonary hypertension, cerebral embolic hemorrhages, and immediate postoperative deoxygenation requiring prolonged mechanical ventilation may contribute to increased postoperative mortality and morbidity [39–42].

Because of the complex relationship between hypoxia secondary to HPS and liver transplantation, MELD exceptions points have been given to patients with HPS and a resting PaO_2 of <60 mm Hg by the UNOS. Oxygen supplementation, although not studied in the treatment of HPS, is commonly used when PaO_2 < 60 mm Hg or in conditions with exercise-induced oxygen desaturation. There are anecdotal reports supporting its use demonstrating enhancement of arterial oxygenation, improvement in exercise tolerance, and quality of life. Thus oxygen supplementation is a low-risk treatment option [43].

A number of medical agents have been tried without any robust data showing their benefits. Small uncontrolled studies have shown lack of efficacy using sympathomimetic agents, somatostatin, almitrine, indomethacin, and plasma exchange [44]. An open label trial using garlic also suggests a beneficial effect. In this trial, garlic powder was administered for a minimum of 6 months. Six out of 15 (40%) patients with HPS demonstrated improvements greater than 10 mm Hg in the PaO_2, and one had even resolution of hypoxemia (PaO_2: 46–80 mm Hg) over a 1.5-year period [45].

Methylene blue infusion, a dye that inhibits the effect of NO on soluble guanylate cyclase, has also shown a transient improvement in oxygenation. Inhaled L-NAME which inhibits nitric oxide production, also transiently has improved oxygenation in one patient (PaO_2: 52–70 mm Hg), but failed in another group of 10 patients [46]. There is a single case report suggesting that norfloxacin also may be beneficial in improving oxygen saturation in HPS [47].

A few case reports have documented variable improvements in gas exchange using transjugular intrahepatic portosystemic shunts (TIPSs). In a more recent study involving 3 patients with HPS the use of TIPS did not lead to any overall improvement and hence TIPS specifically to treat HPS is not recommended [48].

However, there are reports of success of transcatheter coil embolization of the arteriovenous pulmonary fistulas in type 2 HPS before and after liver transplantation [49]. Embolotherapy may thus be a reasonable first-line option for bridging patients with Type 2 HPS prior to transplantation. Even in patients with type 1 HPS, benefits in reducing morbidity pretransplantation have been described with coil embolization [50].

5. Portopulmonary Hypertension

Portopulmonary hypertension [POPH] is defined as pulmonary arterial hypertension, with or without associated liver disease. It was first described by Mantz and Craige in 1951 [51]. The criteria for diagnosis is the presence of portal hypertension, mean pulmonary arterial pressure more than 25 mm Hg at rest with a pulmonary capillary wedge pressure less than 15 mm Hg, associated with the pulmonary vascular resistance greater than 240 dynes·sec·cm^5.

Most patients of POPH have underlying cirrhosis but it can also develop in noncirrhotic portal hypertension. There is no direct correlation between severity of POPH and etiology or severity of liver disease. POPH is found in 2 to 10% of cirrhotic patients [52–58]. In patients of refractory ascites evaluated for TIPS an unusual high prevalence of POPH of around 16% has been reported.

Male-to-female ratio is 1.1 : 1. POPH can occur at any age but most commonly presents in fifth decade of life. Diagnosis of portal hypertension precedes the diagnosis of POPH by more than 4 years. The natural history of POPH has not been fully elucidated. Spontaneous resolution of POPH has not

been reported. In pretransplant era median survival as low as 6 months was noted. The overall 3-to-5 year survival ranges from 30 to 50% [59, 60].

Death occurs due to complications of liver disease and complications related to POPH in equal proportion of cases. Probability of death due to cardiopulmonary complications is high in those with low cardiac index. An increase in plasma brain natriuretic peptide (BNP) indicates stress on the right ventricle. The differential diagnosis of dyspnea in a patient of liver disease includes intrinsic cardiopulmonary conditions such as chronic obstructive pulmonary disease, pneumonia, pulmonary embolism, congestive heart failure, valvular heart disease, and conditions related to underlying liver disease and portal hypertension such as ascites, hepatic hydrothorax, and muscle wasting [61, 62].

Arterial blood gas analysis shows hypocapnia, an increased alveolar-arterial oxygen gradient and mild hypoxemia. The X-ray chest may show cardiomegaly and prominent main pulmonary artery.

POPH is graded according to the degree of elevation of mean pulmonary arterial pressure. Mild POPH (mPAP = 25–35 mm Hg) is not associated with increased operative risk for liver transplantation and may not require medical therapy. Moderate POPH (mPAP = 35–50 mm Hg) has increased operative risk for liver transplantation and requires medical therapy. Severe POPH (mPAP > 50 mm Hg) has high operative mortality and is managed with medical therapy [52]. Histologically POPH has medial proliferation and hypertrophy, plexiform arteriopathy, and in situ vascular thrombosis of pulmonary vasculature. Cirrhosis is associated with hyperdynamic circulation with increased shearing stress on pulmonary vasculature with resultant progressive pulmonary vascular remodelling and thrombosis. There is an imbalance between vasodilators and vasoconstrictors. The associated bowel wall congestion due to splanchnic vasodilatation leads to the release of endotoxins such as endothelin-1 and thromboxane [58, 63, 64].

The most common symptom is exertional dyspnoea, other symptoms like chest discomfort, fatigue, syncope, and light headedness may also occur. The signs include elevated jugular venous pressure, loud second pulmonic heart sound, murmur of tricuspid regurgitation, and lower extremity edema. Peripheral edema out of proportion to degree of ascites in a cirrhotic patient, right ventricular dysfunction secondary to pulmonary hypertension should be considered [65, 66].

Transthoracic echocardiography is the recommended screening test. It evaluates right heart function and estimates the right ventricular systolic pressure. Echocardiography excludes valvular heart disease and other causes of elevated mPAP. Echocardiography may reveal changes due to raised resistance to pulmonary flow such as pulmonary valvular insufficiency, right atrial dilatation, right ventricular hypertrophy and dilatation, interventricular septal thickening, and paradoxical movement of septum. The correlation of right ventricular pressure measured during echocardiography and that from right heart catheterization is not good. As echocardiography cannot estimate pulmonary vascular resistance, approximately 30–40% of patients with estimated right ventricular systolic pressure threshold can have normal pulmonary vascular resistance during right heart catheterization and will not be diagnosed as POPH [67].

Another parameter measured during echocardiography evaluation is pulmonary acceleration time. The value of pulmonary acceleration time greater than 100 m sec indicates POPH. Echocardiography apart from the screening is also helpful in followup of patients with POPH.

Right heart catheterization helps in estimation of mPAP, pulmonary capillary wedge pressure, and cardiac output; calculation of pulmonary and systemic vascular resistance. Patients of liver disease have hyperdynamic circulation and volume overload. Those with pulmonary capillary wedge pressure greater than 15 mm Hg, the diagnosis of POPH may be missed. The use of transpulmonary pressure gradient helps in identifying patients with obstruction to flow, independent of pulmonary capillary wedge pressure. It is calculated by subtracting pulmonary wedge pressure from mean pulmonary arterial pressure [68]. Right ventricular systolic pressure greater than 40 mm Hg or presence of right ventricular abnormalities support further evaluation for POPH. In all patients with echocardiographic abnormalities suggestive of POPH, pulmonary artery catheterization is performed to establish diagnosis and assess severity of POPH.

Vasodilator testing using either inhaled nitric oxide or intravenous epoprostenol during right heart catheterization may be done. If the diagnosis of POPH is made, a decrease in mPAP and PVR more than 20% from baseline without decrease in cardiac output indicates reversible vasoconstriction. Studies on long-term pharmacologic management of POPH are lacking.

6. Medical Therapy

Supplemental oxygen is commenced if hypoxemia is present. Diuretics are used for volume overload. If patients are on B blockers, drugs are to be withdrawn. Treat the varices with band ligation. Endothelin receptor antagonist, Bosentan is dual ETA and ETB receptor antagonist given orally. It is started at the dose of 62.5 mg twice daily and then the dose can be increased to 125 to 250 mg twice daily [69]. Dose-dependant increase of liver enzymes is seen because of inhibition of bile salt export protein. Treatment with low-to-medium dose bosentan improves exercise capacity and pulmonary hemodynamics. Phosphodiesterase inhibitor, sildenafil, inhibits the enzyme phosphodiesterase-5. inhibition of degradation of NO promotes vasodilatation, but may exacerbate portal hypertension and hyperdynamic circulation [70].

Prostacyclin analogue, esoprostenol, is a potent systemic and pulmonary vasodilator with antiplatelet aggregating properties. It has a half-life of 3 to 5 minutes so requires long-term continuous intravenous infusion [71]. It improves pulmonary hemodynamic status. In some transplant centres this may improve patient's status for listing for liver transplantation. Common side effects include headache, flushing,

diarrhoea, and hypotension [72]. More stable analogues such as iloprost and treprostinil are being investigated [73, 74].

Denovo POPH, transition from HPS to POPH and recurrences of POPH in cases of graft failure have been noted after LT. All candidates for liver transplantation should undergo screening for portopulmonary hypertension by echocardiography. If the echocardiography shows elevated pulmonary arterial pressures, right heart catheterization is performed to confirm the diagnosis. The ideal medical regimen remains to be determined. Although drug treatment may lower pulmonary artery pressures in selected patients so that liver transplantation can be safely done, morbidity and mortality rates are higher in patients with moderate-to-severe portopulmonary hypertension [75]. Moderate-to-severe POPH with mPAP > 50 mm Hg is contraindication to LT. Liver transplantation is not the treatment of choice for portopulmonary hypertension.

7. Hepatic Hydrothorax

Hepatic hydrothorax is defined as the presence of pleural fluid (usually greater than 500 cc) in a patient with cirrhosis after ruling out primary cardiac or pulmonary disease. This occurs in approximately 6–10% of patients with advanced cirrhosis [76]. It is more commonly associated with alcohol-induced liver disease and with the concomitant presence of ascites. Regarding the side of involvement in hepatic hydrothorax, 85% have been right sided, 13% left sided, and 2% bilateral [77].

8. Pathogenesis

Several mechanisms have been postulated for the development of hepatic hydrothorax. The direct passage of peritoneal fluid via diaphragmatic defects appears to be the most acceptable explanation. Lieberman et al. demonstrated the defects by introducing CO_2 into the peritoneal cavity of patients with hepatic hydrothorax [78].

A pneumothorax indicative of a diaphragmatic defect was seen in these patients on chest radiographs, taken within 48 hours. Intraperitoneal injection of methylene blue can be used intraoperatively to localize the defect(s).

Several scintigraphic studies using intraperitoneal instillation of 99mTc-human serum albumin or 99mTc-sulphor-colloid have demonstrated radioactivity in the pleural cavity minutes to hours after administration [79, 80].

The movement of radioisotope is unidirectional towards the pleural cavity due to negative intrathoracic pressure compared to increased intra-abdominal pressure. Microscopic examinations of these defects have showed gaps in the collagen bundles in the tendinous portion of the diaphragm. In patients of ascites, there is increase in the intra-abdominal pressure. This tends to stretch the diaphragm; thereby, creating or enlarging these microscopic defects. The increase in abdominal pressure results in herniation of peritoneum through these gaps in the pleural cavity. This leads to the formation of pleuroperitoneal blebs. These blebs tend to rupture, creating free communication between the peritoneal and pleural cavities. For certain unknown reasons the left hemidiaphragm is more muscular and relatively resistant to blebs formation.

9. Clinical Features

It may simply be an incidental finding on a chest radiograph performed for unrelated reasons in a patient of cirrhosis. However, a small subset of cirrhotic patients may present primarily with pulmonary complaints related to hydrothorax such as dyspnea, nonproductive cough, pleuritic chest pain, or fatigue related to hypoxemia [81]. With large pleural effusions severe dyspnea and potential respiratory compromise can occur.

There are several causes of pleural effusion in general and patients of cirrhosis can have any of those. In a study on patients with end-stage liver disease patients with pleural effusions 30% of patients upon thoracentesis yielded a diagnosis other than hepatic hydrothorax including spontaneous bacterial empyema (SBEM), tuberculosis, adenocarcinoma, parapneumonic empyema, and undiagnosed exudates [82]. Hence both thoracentesis and paracentesis should be performed to ascertain that both fluids are similar in character [83].

The composition of pleural fluid from hepatic hydrothorax, is similar to that of ascitic fluid. However, ascitic and pleural fluid analysis may not be completely identical, perhaps due to the greater efficacy of water absorption by the pleural surface. The cell count is usually low, and the total protein, albumin, cholesterol, and total lipid levels may be marginally higher in the pleural fluid compared to ascitic fluid [84]. However, the serum-to-pleural fluid albumin gradient is usually greater than 1.1 g/dL although, this has not been studied extensively.

SBEM is the infection of a preexisting pleural effusion (hydrothorax) in a patient with cirrhosis. Its incidence is around 15% (similar to the incidence reported for spontaneous bacterial peritonitis; SBP) in cirrhotic patients with ascites [85].

Its pathogenesis is also similar to that of SBP. The diagnosis of SBEM is made if the pleural fluid (PF) cultures are positive and a polymorphonuclear (PMN) count is >250 cells/μL. If culture is negative (and compatible clinical course) the diagnosis is made with a pleural fluid PMN count >500 cells/μL and by excluding a parapneumonic infection [86].

The microorganisms responsible for SBEM appear similar to that of SBP. Patient can present with local symptoms such as dyspnea or pleuritic chest pain, or with systemic symptoms such as fever, shock, or encephalopathy. Up to 40% of SBEM cases may not be associated with SBP. The treatment of SBEM is similar to that of SBP [87]. Despite treatment, mortality remains high at approximately 20%. Albumin therapy at 1.5 g/kg on day 1 and 1.0 g/kg on day 3 in the setting of SBEM may be considered although albumin infusion has not been specifically studied in the setting of hepatic hydrothorax and SBEM.

10. Diagnosis

This entity is usually suspected in a patient of cirrhosis if patient presents with pulmonary symptoms or features suggestive of pleural effusion on examination or on routine chest radiographs. A computerized tomographic (CT) scan of the chest should be obtained to exclude any mediastinal, pulmonary, or pleural pathology.

Moreover, detailed information of the diaphragm may be obtained with a CT scan or a magnetic resonance imaging, permitting recognition of the small diaphragmatic defects [88].

Thoracoscopy may also reveal the defects, but this procedure is invasive and carries significant morbidity in patients with advanced liver disease and therefore is rarely performed. Echocardiography may be indicated if there is a suspicion of pericardial or a cardiac pathology. In difficult cases, specifically when ascites is not detected or the hydrothorax is present on the left side; an intraperitoneal injection of [99Tcm] sulphur colloid or [99Tcm]-human serum albumin may be helpful. Migration of the radioisotopes from the peritoneal cavity into the pleural space establishes a communication between both spaces and confirms that the ascites is the source of the effusion [89, 90]. Conversely, failure of the marker to show up in the pleural space indicates an alternate diagnosis for the pleural effusion. This test has been considered the gold standard for identification of hepatic hydrothorax due to its very high specificity (up to 100%). However, its sensitivity remains modest (approximately 71%). Fortunately, the sensitivity of the test can be greatly improved (up to 100%) by performing a thoracentesis prior to administration of radioisotopes in order to reduce pleural pressure [91].

11. Treatment

The first and most important aspect in the management of all patients with cirrhosis and ascites or hepatic hydrothorax is evaluation for candidacy for liver transplantation. Patients of hepatic hydrothorax can be managed by dietary, pharmacologic, and radiological interventions. In selective patients with refractory hydrothorax, surgical approaches aimed at repairing the diaphragmatic defects responsible for pleural fluid accumulation can be considered.

12. Diet and Pharmacological Management

It is similar to the therapy of ascites. Achieving a negative sodium balance is the primary goal of dietary and pharmacologic management. Dietary restriction of sodium intake to 2 g/d (88 mEq/d) is the simplest manner by which achieve a negative sodium balance can be achieved [92].

However, most patients with ascites, and almost all patients with hepatic hydrothorax require diuretics (spironolactone and/or furosemide) along with salt restriction. These diuretics are maintained at a ratio of 10 : 4 (spironolactone 100 mg: furosemide 40 mg) to avoid dyselectrolytemia and dosages are increased as needed to attain a goal of producing renal excretion of at least 120 mEq of sodium per day [93].

Patients not responding despite fluid and sodium restriction and use of maximal tolerable doses of diuretics are considered to have refractory hydrothorax. Approximately 10% of patients either do not respond to diuretic therapy or develop diuretic-induced complications that prevent the use of high doses of these drugs. These patients should be considered for orthotopic liver transplantation. Other agents such as terlipressin, octreotide, and midodrine have been used in small studies with moderate benefit [94–96]. These agents will reduce splanchnic blood flow and hence decrease peritoneal and pleural fluid accumulation. However, presently there is not enough evidence to recommend routine use of these agents.

13. Thoracocentesis

It is a simple and relatively safe procedure which can be performed in patients with dyspnea for immediate relief of symptoms. In patients with dyspnea and both hepatic hydrothorax and massive ascites, it is recommended to drain the ascites prior to performing a thoracocentesis. It is recommended that no more than 2 liters of fluid should be removed during the first therapeutic thoracocentesis, in order to minimize the risk of unilateral pulmonary edema and/or hypotension [97]. The utility of concomitant albumin infusion has not been established. However, given the relatively small volume of fluid removed at thoracentesis, intravenous albumin to avoid circulatory dysfunction unlike its routine use with large volume paracentesis seems unnecessary. The major risk of thoracocentesis is development of pneumothorax. Usually diagnostic thoracocentesis carries a low risk (1%) of pneumothorax, compared to therapeutic thoracocentesis where the incidence is nearly 9% [82].

However, when thoracocentesis is required too frequently (<every 2-3 weeks) in patients on maximal sodium restriction and optimal diuretics, alternative treatment options must be considered.

14. Radiologic Interventions: Transjugular Intrahepatic Portosystemic Shunts (TIPS)

It is a nonselective side-to-side portosystemic shunt which decreases the sinusoidal hypertension that leads to ascites formation—an essential step for pleural fluid accumulation. In a study by Gordon et al. 24 Child class B and C cirrhosis patients following TIPS placement were evaluated. Fourteen out of twenty-four (58.3%) had complete resolution of symptoms following TIPS and did not require further thoracocentesis. Another 5 (20.8%) required fewer number of thoracentesis. But, despite this superior efficacy, 6 patients (25%) died of either postprocedure complications (1/6) or liver failure (5/6), and 9 (37.5%) developed transient hepatic encephalopathy [98]. Other groups have also showed symptomatic improvement in many patients, but with associated complications and did not improve the overall prognosis. A recent study has shown that severity of liver dysfunction is directly related to nonresponsiveness and higher one-year mortality after TIPS placement for refractory HH [99].

Thus, it should be considered in selected patients who reaccumulate their effusions rapidly (despite medical treatment) with a Child-Pugh score of less than 10, are younger than 60 and do not have hepatic encephalopathy or severe pulmonary hypertension.

15. Surgery

Pleurodesis: Falchuk et al. first described the use of tetracycline-induced pleurodesis in 2 patients with recurrent hepatic hydrothorax. In that study, one patient remained free of effusion at 6-month followup while the other died of variceal hemorrhage 3 weeks after the pleurodesis [100]. Chemical pleurodesis is not always successful and has a modest risk of complications such as fever, chest pain, empyema, incomplete reexpansion, pneumonia, and wound infection. Hence pleurodesis by itself is rarely performed and is reserved for patients in whom no other options exist.

Interestingly, the use of continuous positive airway pressure (CPAP) appears effective in keeping the pleural cavity dry after chemical pleurodesis. The underlying mechanism postulated is that CPAP will decrease the negative pleural pressure and thus prevent the shift of fluid form the peritoneal to the pleural space [101]. Further studies are needed before this can be routinely recommended.

Chest Tube Placement. It leads to massive fluid shifts, protein, and electrolyte depletion. Hence, chest tube insertion is considered a relative contraindication for the treatment of hepatic hydrothorax [102].

Repair of Diaphragmatic Defects. Thoracoscopy to repair diaphragmatic defects with/without sclerosing the pleural membranes is a good alternative in patients with refractory hepatic hydrothorax who are not candidates for TIPS. Thoracoscopy appears to be more likely to be effective if diaphragmatic defects can be identified. In a study by Mouroux et al. using video-assisted thoracoscopy (VATS) to close large defects using sutures and biologic glue in combination with talc pleurodesis in 8 patients. None of the patients (6/8) with repaired defects developed recurrent hydrothorax despite the recurrence of ascites [103]. Two other studies (15 and 41 patients each) showed almost 75% success rate with VATS-assisted talc pleurodesis without resorting to diaphragmatic repairs. Thus it may be considered a palliative alternative not only to patients requiring frequent thoracentesis, but also an alternative to TIPS [104, 105].

Peritoneovenous Shunts. A peritoneovenous shunt (Le Veen shunt) to divert ascitic fluid has been used in the past in refractory cases. However, the shunt is rendered ineffective over time as the intrathoracic pressure is lower than the central venous pressure resulting in fluid flow towards the pleural space [106]. Because of this reason and frequent complications associated with LeVeen shunt (infection, coagulopathy, and bleeding in compromised host), this procedure has become almost obsolete.

Liver Transplantation. It is the only option available when all other therapies fail and is curative for most patients with this complication. The short-term and long-term prognosis in patients undergoing liver transplantation for refractory hepatic hydrothorax appears similar to other groups [107].

References

[1] W. H. Abelmann, "Hyperdynamic circulation in cirrhosis: a historical perspective," *Hepatology*, vol. 20, no. 5, pp. 1356–1358, 1994.

[2] S. Moller, F. Bendtsen, and J. H. Henriksen, "Vasoactive substances in the circulatory dysfunction of cirrhosis," *Scandinavian Journal of Clinical and Laboratory Investigation*, vol. 61, no. 6, pp. 421–429, 2001.

[3] D. E. Newby and P. C. Hayes, "Hyperdynamic circulation in liver cirrhosis: not peripheral vasodilatation but "splanchnic steal"," *Quarterly Journal of Medicine*, vol. 95, no. 12, pp. 827–830, 2002.

[4] R. D. Grose, J. Nolan, J. F. Dillon et al., "Exercise-induced left ventricular dysfunction in alcoholic and non-alcoholic cirrhosis," *Journal of Hepatology*, vol. 22, no. 3, pp. 326–332, 1995.

[5] S. Moller and J. H. Henriksen, "Cirrhotic cardiomyopathy: a pathophysiological review of circulatory dysfunction in liver disease," *Heart*, vol. 87, no. 1, pp. 9–15, 2002.

[6] Z. Ma, A. Miyamoto, and S. S. Lee, "Role of adrenoceptor signal transduction in the pathogenesis of cirrhotic cardiomyopathy in rats," *Gastroenterology*, vol. 110, no. 4, pp. 1191–1198, 1996.

[7] C. A. Ward, H. Liu, and S. S. Lee, "Altered cellular calcium regulatory systems in a rat model of cirrhotic cardiomyopathy," *Gastroenterology*, vol. 121, no. 5, pp. 1209–1218, 2001.

[8] Z. Ma, S. S. Lee, and J. B. Meddings, "Effects of altered cardiac membrane fluidity on adrenergic receptor signalling in rats with cirrhotic cardiomyopathy," *Journal of Hepatology*, vol. 26, no. 4, pp. 904–912, 1997.

[9] J. Garcia-Estan, M. C. Ortiz, and S. S. Lee, "Nitric oxide and renal and cardiac dysfunction in cirrhosis," *Clinical Science*, vol. 102, no. 2, pp. 213–222, 2002.

[10] H. Liu and S. S. Lee, "Possible role of heme oxygenase enzymes in a rat model of cirrhotic cardiomyopathy," *Hepatology*, vol. 30, Article ID 326A, 1999.

[11] C. P. Day, O. F. James, T. J. Butler, and R. W. Campbell, "QT prolongation and sudden cardiac death in patients with alcoholic liver disease," *The Lancet*, vol. 341, no. 8858, pp. 1423–1428, 1993.

[12] R. Mochamad, P. R. Forsey, M. K. Davies, and J. M. Neuberger, "Effect of liver transplantation on QT interval prolongation and autonomic dysfunction in end-stage liver disease," *Hepatology*, vol. 23, no. 5, pp. 1128–1134, 1996.

[13] R. P. Myers and S. S. Lee, "Cirrhotic cardiomyopathy and liver transplantation," *Liver Transplantation*, vol. 6, no. 4, supplement 1, pp. S44–S52, 2000.

[14] T. C. Kennedy and R. J. Knudson, "Exercise-aggravated hypoxemia and orthodeoxia in cirrhosis," *Chest*, vol. 72, no. 3, pp. 305–309, 1977.

[15] M. J. Krowka and D. A. Cortese, "Pulmonary aspects of liver disease and liver transplantation," *Clinics in Chest Medicine*, vol. 10, no. 4, pp. 593–616, 1989.

[16] R. Rodriguez-Roisin, J. Roca, A. G. Agusti, R. Mastai, P. D. Wagner, and J. Bosch, "Gas exchange and pulmonary vascular reactivity in patients with liver cirrhosis," *American*

Review of Respiratory Disease, vol. 135, no. 5, pp. 1085–1092, 1987.

[17] M. J. Krowka, E. R. Dickson, and D. A. Cortese, "Hepatopulmonary syndrome: clinical observations and lack of therapeutic response to somatostatin analogue," *Chest*, vol. 104, no. 2, pp. 515–521, 1993.

[18] M. Altman and E. D. Robin, "Platypnea (diffuse zone I phenomenon?)," *New England Journal of Medicine*, vol. 281, no. 24, pp. 1347–1348, 1969.

[19] E. D. Robin, D. Laman, B. R. Horn, and J. Theodore, "Platypnea related to orthodeoxia caused by true vascular lung shunts," *New England Journal of Medicine*, vol. 294, no. 17, pp. 941–943, 1976.

[20] E. D. Robin, B. Horn, M. L. Goris et al., "Detection, quantitation and pathophysiology of lung spiders," *Transactions of the Association of American Physicians*, vol. 88, pp. 202–216, 1975.

[21] M. J. Krowka and D. A. Cortese, "Pulmonary aspects of chronic liver disease and liver transplantation," *Mayo Clinic Proceedings*, vol. 60, no. 6, pp. 407–418, 1985.

[22] D. T. Palma and M. B. Fallon, "The hepatopulmonary syndrome," *Journal of Hepatology*, vol. 45, no. 4, pp. 617–625, 2006.

[23] M. B. Fallon, "Mechanisms of pulmonary vascular complications of liver disease: hepatopulmonory syndrome," *Journal of Clinical Gastroenterology*, vol. 39, supplement 4, pp. S138–S142, 2005.

[24] M. J. Krowka and D. A. Cortese, "Hepatopulmonary syndrome: an evolving perspective in the era of liver transplantation," *Hepatology*, vol. 11, no. 1, pp. 138–142, 1990.

[25] B. Luo, L. Liu, L. Tang et al., "ET-1 and TNF-aplha in HPS: analysis in prehepatic portal hypertension and biliary and nonbiliary cirrhosis in rats," *American Journal of Physiology*, vol. 286, no. 2, pp. G294–G303, 2004.

[26] P. Schenk, M. Schoniger-Hekele, V. Fuhrmann et al., "Prognostic significance of the hepatopulmonary syndrome in patients with cirrhosis," *Gastroenterology*, vol. 125, no. 4, pp. 1042–1052, 2003.

[27] G. A. Abrams, M. K. Sanders, and M. B. Fallon, "Utility of pulse oximetry in the detection of arterial hypoxemia in liver transplant candidates," *Liver Transplantation*, vol. 8, no. 4, pp. 391–396, 2002.

[28] M. Castro and M. J. Krowka, "Hepatopulmonary syndrome: a pulmonary vascular complication of liver disease," *Clinics in Chest Medicine*, vol. 17, no. 1, pp. 35–48, 1996.

[29] R. S. Meltzer, E. G. Tickner, and R. L. Popp, "Why do the lungs clear ultrasonic contrast?" *Ultrasound in Medicine and Biology*, vol. 6, no. 3, pp. 263–269, 1980.

[30] J. M. Vedrinne, S. Duperret, T. Bizollon et al., "Comparison of transesophageal and transthoracic contrast echocardiography for detection of an intrapulmonary shunt in liver disease," *Chest*, vol. 111, no. 5, pp. 1236–1240, 1997.

[31] M. Zamirian, A. Aslani, and S. Shahrzad, "Left atrial volume: a novel predictor of hepatopulmonary syndrome," *American Journal of Gastroenterology*, vol. 102, no. 7, pp. 1392–1396, 2007.

[32] A. Karabulut, K. Iltumur, K. Yalcin et al., "Hepatopulmonary syndrome and right ventricular diastolic functions: an echocardiographic examination," *Echocardiography*, vol. 23, no. 4, pp. 271–278, 2006.

[33] B. L. Lima, A. V. Franca, A. Pazin-Filho et al., "Frequency, clinical characteristics, and respiratory parameters of hepatopulmonary syndrome," *Mayo Clinic Proceedings*, vol. 79, no. 1, pp. 42–48, 2004.

[34] G. Abrams, N. Nanda, E. Dubovsky, M. J. Krowka, and M. Fallon, "Use of macroaggregated albumin lung perfusion scan to diagnose hepatopulmonary syndrome: a new approach," *Gastroenterology*, vol. 114, no. 2, pp. 305–310, 1998.

[35] M. J. Krowka and D. A. Cortese, "Pulmonary aspects of liver disease and liver transplantation," *Clinics in Chest Medicine*, vol. 10, no. 4, pp. 593–616, 1989.

[36] K. N. Lee, H. J. Lee, W. W. Shin, and W. R. Webb, "Hypoxemia and liver cirrhosis (hepatopulmonary syndrome) in eight patients: comparison of the central and peripheral pulmonary vasculature," *Radiology*, vol. 211, no. 2, pp. 549–553, 1999.

[37] Y. Katsuta, H. Honma, X. Zhang et al., "Pulmonary blood transit time and impaired arterial oxygenation in patients with chronic liver disease," *Journal of Gastroenterology*, vol. 40, no. 1, pp. 57–63, 2005.

[38] P. A. Lange and J. K. Stoller, "The hepatopulmonary syndrome: effect of liver transplantation," *Clinics in Chest Medicine*, vol. 17, no. 1, pp. 115–123, 1996.

[39] F. Philit, T. Wiesendanger, D. Gille, O. Boillot, and J. Cordier, "Late resolution of hepatopulmonary syndrome after liver transplantation," *Respiration*, vol. 64, no. 2, pp. 173–175, 1997.

[40] M. S. Mandell, B. M. Groves, and J. Duke, "Progressive plexogenic pulmonary hypertension following liver transplantation," *Transplantation*, vol. 59, no. 10, pp. 1488–1490, 1995.

[41] G. A. Abrams, K. Rose, M. B. Fallon et al., "Hepatopulmonary syndrome and venous emboli causing intracerebral hemorrhages after liver transplantation: a case report," *Transplantation*, vol. 68, no. 11, pp. 1809–1811, 1999.

[42] V. Scott, A. Mira, Y. Kang et al., "Reversibility of the hepatopulmonary syndrome by orthotopic liver transplantation," *Transplantation Proceedings*, vol. 25, no. 2, pp. 1787–1788, 1993.

[43] J. Henrion, M. Schapira, R. Luwaert, L. Colin, A. Delannoy, and F. R. Heller, "Hypoxic hepatitis: clinical and hemodynamic study in 142 consecutive cases," *Medicine*, vol. 82, no. 6, pp. 392–406, 2003.

[44] H. Hortnagel, E. A. Singer, and K. Lenz, "Substance-P is markedly increased in plasma of patients with hepatic coma," *The Lancet*, vol. 1, no. 8375, pp. 480–483, 1984.

[45] G. A. Abrams and M. B. Fallon, "Treatment of hepatopulmonary syndrome with Allium sativum (garlic): a pilot trial," *Journal of Clinical Gastroenterology*, vol. 27, no. 3, pp. 232–235, 1998.

[46] L. Brussino, C. Bucca, M. Morello, E. Scappaticci, M. Mauro, and G. Rolla, "Effect on dyspnoea and hypoxaemia of inhaled NG-nitro-Larginine methyl ester in hepatopulmonary syndrome," *The Lancet*, vol. 362, no. 9377, pp. 43–44, 2003.

[47] R. M. Anel and J. N. Sheagren, "Novel presentation and approach to management of hepatopulmonary syndrome with use of antimicrobial agents," *Clinical Infectious Diseases*, vol. 32, no. 10, pp. E131–136, 2001.

[48] G. Martinez-Palli, B. B. Drake, J. C. Garcia-Pagan et al., "Effect of transjugular intrahepatic portosystemic shunt on pulmonary gas exchange in patients with portal hypertension and hepatopulmonary syndrome," *World Journal of Gastroenterology*, vol. 11, no. 43, pp. 6858–6862, 2005.

[49] J. J. Poterucha, M. J. Krowka, E. R. Dickson et al., "Failure of hepatopulmonary syndrome to resolve after liver transplantation and successful treatment with embolotherapy," *Hepatology*, vol. 21, no. 1, pp. 96–100, 1995.

[50] N. E. A. Saad, D. E. Lee, D. L. Waldman et al., "Pulmonary arterial coil embolization for the management of persistent type 1 hepatopulmonary syndrome after liver transplantation," *Journal of Vascular and Interventional Radiology*, vol. 18, no. 12, pp. 1576–1580, 2007.

[51] F. A. Mantz Jr. and E. Craige, "Portal axis thrombosis with spontaneous portacaval shunt and resultant cor pulmonale," *A. M. A. Archives of Pathology*, vol. 52, no. 1, pp. 91–97, 1951.

[52] M. M. Hoeper, M. J. Krowka, and C. P. Strassburg, "Portopulmonary hypertension and hepatopulmonary syndrome," *The Lancet*, vol. 363, no. 9419, pp. 1461–1468, 2004.

[53] M. Castro, M. J. Krowka, D. R. Schroeder et al., "Frequency and clinical implications of increased pulmonary artery pressures in liver transplant patients," *Mayo Clinic Proceedings*, vol. 71, no. 6, pp. 543–551, 1996.

[54] P. J. McDonnell, P. A. Toye, and G. M. Hutchins, "Primary pulmonary hypertension and cirrhosis: are they related?" *American Review of Respiratory Disease*, vol. 127, no. 4, pp. 437–441, 1983.

[55] A. Hadengue, M. K. Benhayoun, D. Lebrec et al., "Pulmonary hypertension complicating portal hypertension: prevalence and relation to splanchnic hemodynamics," *Gastroenterology*, vol. 100, no. 2, pp. 520–528, 1991.

[56] D. Plevak, M. Krowka, S. Rettke et al., "Successful liver transplantation in patients with mild to moderate pulmonary hypertension," *Transplantation Proceedings*, vol. 25, no. 2, p. 1840, 1993.

[57] F. S. Benjaminov, M. Prentice, K. W. Sniderman et al., "Portopulmonary hypertension in decompensated cirrhosis with refractory ascites," *Gut*, vol. 52, no. 9, pp. 1355–1362, 2003.

[58] M. S. Mandell and B. M. Groves, "Pulmonary hypertension in chronic liver disease," *Clinics in Chest Medicine*, vol. 17, no. 1, pp. 17–33, 1996.

[59] S. M. Kawut, D. B. Taichman, V. N. Ahya et al., "Hemodynamics and survival of patients with portopulmonary hypertension," *Liver Transplantation*, vol. 11, no. 9, pp. 1107–1111, 2005.

[60] K. L. Swanson, R. H. Wiesner, and M. Krowka, "Survival in portopulmonary hypertension and orthotopic liver transplantation," *Liver Transplantation*, vol. 11, Article ID c71, 2005.

[61] J. M. Golbin and M. J. Krowka, "Portopulmonary hypertension," *Clinics in Chest Medicine*, vol. 28, no. 1, pp. 203–218, 2007.

[62] R. Budhiraja and P. M. Hassoun, "Portopulmonary hypertension: a tale of two circulations," *Chest*, vol. 123, no. 2, pp. 562–576, 2003.

[63] R. J. Panos and S. K. Baker, "Mediators, cytokines, and growth factors in liver-lung interactions," *Clinics in Chest Medicine*, vol. 17, no. 1, pp. 151–170, 1996.

[64] D. C. Rockey, "Vascular mediators in the injured liver," *Hepatology*, vol. 37, no. 1, pp. 4–12, 2003.

[65] B. D. Robalino and D. S. Moodie, "Association between primary pulmonary hypertension and portal hypertension: analysis of its pathophysiology and clinical, laboratory and hemodynamic manifestations," *Journal of the American College of Cardiology*, vol. 17, no. 2, pp. 492–498, 1991.

[66] M. J. Krowka, M. K. Porayko, D. J. Plevak et al., "Hepatopulmonary syndrome with progressive hypoxemia as an indication for liver transplantation: case reports and literature review," *Mayo Clinic Proceedings*, vol. 72, no. 1, pp. 44–53, 1997.

[67] C. L. Cotton, S. Gandhi, P. T. Vaitkus et al., "Role of echocardiography in detecting portopulmonary hypertension in liver transplant candidates," *Liver Transplantation*, vol. 8, no. 11, pp. 1051–1054, 2002.

[68] R. Rodriguez-Roisin, M. J. Krowka, P. Herve, and M. B. Fallon, "Pulmonary-hepatic vascular disorders: a task force report," *European Respiratory Journal*, vol. 24, no. 5, pp. 861–880, 2004.

[69] J. Lewis, M. D. Rubin, B. David et al., "Bosentan therapy for pulmonary arterial hypertension," *New England Journal of Medicine*, vol. 346, no. 12, pp. 896–903, 2002.

[70] R. Chua, A. Keogh, and M. Miyashita, "Novel use of sildenafil in the treatment of portopulmonary hypertension," *Journal of Heart and Lung Transplantation*, vol. 24, no. 4, pp. 498–500, 2005.

[71] S. M. Shapiro, R. J. Oudiz, T. Cao et al., "Primary pulmonary hypertension: improved long-term effects and survival with continuous intravenous epoprostenol infusion," *Journal of the American College of Cardiology*, vol. 30, no. 2, pp. 343–349, 1997.

[72] R. J. Barst, L. J. Rubin, W. A. Long et al., "A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension," *New England Journal of Medicine*, vol. 334, no. 5, pp. 296–300, 1996.

[73] R. J. Barst, L. J. Rubin, W. A. Long et al., "The Primary Pulmonary Hypertension Study Group," *New England Journal of Medicine*, vol. 334, no. 5, pp. 296–302, 1996.

[74] S. Minder, M. Fischler, B. Muellhaupt et al., "Intravenous iloprost bridging to orthotopic liver transplantation in portopulmonary hypertension," *European Respiratory Journal*, vol. 24, no. 4, pp. 703–707, 2004.

[75] L. Karen, D. O. Swanson, and M. J. Krowka, "Screen for portopulmonary hypertension, especially in liver transplant candidates," *Cleveland Clinic Journal of Medicine*, vol. 75, no. 2, pp. 121–136, 2008.

[76] W. M. Alberts, A. J. Salem, D. A. Solomon, and G. Boyce, "Hepatic hydrothorax: cause and management," *Archives of Internal Medicine*, vol. 151, no. 12, pp. 2383–2388, 1991.

[77] K. N. Lazaridis, J. W. Frank, M. J. Krowka, and P. S. Kamath, "Hepatic hydrothorax: pathogenesis, diagnosis, and management," *American Journal of Medicine*, vol. 107, no. 3, pp. 262–267, 1999.

[78] F. L. Lieberman, R. Hidemura, R. L. Peters, and T. B. Reynolds, "Pathogenesis and treatment of hydrothorax complicating cirrhosis with ascites," *Annals of Internal Medicine*, vol. 64, no. 2, pp. 341–351, 1966.

[79] B. R. Mittal, A. Maini, and B. K. Das, "Peritoneopleural communication associated with cirrhotic ascites: scintigraphic demonstration," *Abdominal Imaging*, vol. 21, no. 1, pp. 69–70, 1996.

[80] A. Benet, F. Vidal, R. Toda, R. Siurana, C. M. De Virgala, and C. Richart, "Diagnosis of hepatic hydrothorax in the absence of ascites by intraperitoneal injection of 99 m-Tc-Fluor colloid," *Postgraduate Medical Journal*, vol. 68, no. 796, p. 153, 1992.

[81] K. B. Nolop, "Massive hydrothorax complicating occult cirrhosis," *Southern Medical Journal*, vol. 78, no. 2, pp. 214–215, 1985.

[82] X. Xiol, J. Castellote, R. Cortes-Beut, M. Delgado, J. Guardiola, and S. Sese, "Usefulness and complications of thoracentesis in cirrhotic patients," *American Journal of Medicine*, vol. 111, no. 1, pp. 67–69, 2001.

[83] W. M. Alberts, A. J. Salem, D. A. Solomon, and G. Boyce, "Hepatic hydrothorax: cause and management," *Archives of Internal Medicine*, vol. 151, no. 12, pp. 2383–2388, 1991.

[84] S. A. Sahn, "The pleura," *American Review of Respiratory Disease*, vol. 138, no. 1, pp. 184–234, 1988.

[85] X. Xiol, J. M. Castellvi, J. Guardiola et al., "Spontaneous bacterial empyema in cirrhotic patients: a prospective study," *Hepatology*, vol. 23, no. 4, pp. 719–723, 1996.

[86] X. Xiol, J. Castellote, C. Baliellas et al., "Spontaneous bacterial empyema in cirrhotic patients: analysis of eleven cases," *Hepatology*, vol. 11, no. 3, pp. 365–370, 1990.

[87] B. A. Runyon, E. A. Akriviadis, F. R. Sattler, and J. Cohen, "Ascitic fluid and serum cefotaxime and desacetyl cefotaxime levels in patients treated for bacterial peritonitis," *Digestive Diseases and Sciences*, vol. 36, no. 12, pp. 1782–1786, 1991.

[88] T. Zenda, S. Miyamoto, S. Murata, and H. Mabuchi, "Detection of diaphragmatic defect as the cause of severe hepatic hydrothorax with magnetic resonance imaging," *American Journal of Gastroenterology*, vol. 93, no. 11, pp. 2288–2289, 1998.

[89] D. Rubinstein, I. E. McInnes, and F. J. Dudley, "Hepatic hydrothorax in the absence of clinical ascites: diagnosis and management," *Gastroenterology*, vol. 88, no. 1, pp. 188–191, 1985.

[90] A. Benet, F. Vidal, R. Toda, R. Siurana, C. M. De Virgala, and C. Richart, "Diagnosis of hepatic hydrothorax in the absence of ascites by intraperitoneal injection of 99 m-Tc-Fluor colloid," *Postgraduate Medical Journal*, vol. 68, no. 796, p. 153, 1992.

[91] C. A. Stewart, G. L. Hung, Z. Ackerman, and D. M. Applebaum, "Radionuclide determination of peritoneopleural communication in hydrothorax," *Journal of Nuclear Medicine*, vol. 32, p. 924, 1991.

[92] N. Garcia Jr. and A. J. Sanyal, "Minimizing ascites: complication of cirrhosis signals clinical deterioration," *Postgraduate Medicine*, vol. 109, no. 2, pp. 91–103, 2001.

[93] L. R. Roberts and P. S. Kamath, "Ascites and hepatorenal syndrome: pathophysiology and management," *Mayo Clinic Proceedings*, vol. 71, no. 9, pp. 874–881, 1996.

[94] D. Ibrisim, Y. Cakaloglu, F. Akyuz et al., "Treatment of hepatic hydrothorax with terlipressin in a cirrhotic patient," *Scandinavian Journal of Gastroenterology*, vol. 41, no. 7, pp. 862–865, 2006.

[95] R. Pfammatter, C. Quattropani, J. Reichen, B. Goke, and A. C. Wagner, "Treatment of hepatic hydrothorax and reduction of chest tube output with octreotide," *European Journal of Gastroenterology and Hepatology*, vol. 13, no. 8, pp. 977–980, 2001.

[96] G. Kalambokis, A. Fotopoulos, M. Economou, and E. V. Tsianos, "Beneficial haemodynamic and renal sodium handling effects of combined midodrine and octreotide treatment in a cirrhotic patient with large hepatic hydrothorax and mild ascites," *Nephrology Dialysis Transplantation*, vol. 20, no. 11, p. 2583, 2005.

[97] B. J. Heller and K. Grathwohl, "Contralateral reexpansion pulmonary edema," *Southern Medical Journal*, vol. 93, no. 8, pp. 828–831, 2000.

[98] F. D. Gordon, H. T. Anastopoulos, W. Crenshaw et al., "The successful treatment of symptomatic, refractory hepatic hydrothorax with transjugular intrahepatic portosystemic shunt," *Hepatology*, vol. 25, no. 6, pp. 1366–1369, 1997.

[99] J. Y. Wilputte, P. Goffette, F. Zech, A. Godoy-Gepert, and A. Geubel, "The outcome after transjugular intrahepatic portosystemic Shunt (TIPS) for hepatic hydrothorax is closely related to liver dysfunction: a long-term study in 28 patients," *Acta Gastro-Enterologica Belgica*, vol. 70, no. 1, pp. 6–10, 2007.

[100] K. R. Falchuk, I. Jacoby, W. S. Colucci, and M. E. Rybak, "Tetracycline induced pleural symphysis for recurrent hydrothorax complicating cirrhosis. A new approach to treatment," *Gastroenterology*, vol. 72, no. 2, pp. 319–321, 1977.

[101] F. Drouhin, D. Fischer, J. D. Law Koune, R. Boiteau, A. Tenaillon, and D. Labayle, "Treatment of hydrothorax in liver cirrhosis with chemical pleurodesis and continuous positive airway pressure ventilation. Preliminary results," *Gastroenterologie Clinique et Biologique*, vol. 15, no. 3, pp. 271–272, 1991.

[102] B. A. Runyon, M. Greenblatt, and R. H. C. Ming, "Hepatic hydrothorax is a relative contraindication to chest tube insertion," *American Journal of Gastroenterology*, vol. 81, no. 7, pp. 566–567, 1986.

[103] J. Mouroux, C. Perrin, N. Venissac, B. Blaive, and H. Richelme, "Management of pleural effusion of cirrhotic origin," *Chest*, vol. 109, no. 4, pp. 1093–1096, 1996.

[104] D. Ferrante, M. R. Arguedas, R. J. Cerfolio, B. G. Collins, and D. J. van Leeuwen, "Video-assisted thoracoscopic surgery with talc pleurodesis in the management of symptomatic hepatic hydrothorax," *American Journal of Gastroenterology*, vol. 97, no. 12, pp. 3172–3175, 2002.

[105] R. J. Cerfolio and A. S. Bryant, "Efficacy of video-assisted thoracoscopic surgery with talc pleurodesis for porous diaphragm syndrome in patients with refractory hepatic hydrothorax," *Annals of Thoracic Surgery*, vol. 82, no. 2, pp. 457–459, 2006.

[106] R. W. Ikard and J. L. Sawyers, "Persistent hepatic hydrothorax after peritoneojugular shunt," *Archives of Surgery*, vol. 115, no. 9, pp. 1125–1127, 1980.

[107] X. Xiol, G. Tremosa, J. Castellote et al., "Liver transplantation in patients with hepatic hydrothorax," *Transplant International*, vol. 18, no. 6, pp. 672–675, 2005.

SAGE-Hindawi Access to Research
International Journal of Hepatology
Volume 2011, Article ID 695470, 5 pages
doi:10.4061/2011/695470

Review Article

Management of Coagulopathy in Patients with Decompensated Liver Cirrhosis

Pooja D. Amarapurkar[1] and Deepak N. Amarapurkar[2]

[1] *Department of Gastroenterology, Bombay Hospital and Medical Research Centre, Mumbai 400 020, India*
[2] *Ameya Co-Op Housing Society, New Prabhadevi Road, Prabhadevi, Mumbai 400 025, India*

Correspondence should be addressed to Deepak N. Amarapurkar, amarapurkar@gmail.com

Received 19 July 2011; Accepted 27 September 2011

Academic Editor: Richard Guan

Patients with decompensated liver cirrhosis have significantly impaired synthetic function. Many proteins involved in the coagulation process are synthesized in the liver. Routinely performed tests of the coagulation are abnormal in patients with decompensated liver cirrhosis. This has led to the widespread belief that decompensated liver cirrhosis is prototype of acquired hemorrhagic coagulopathy. If prothrombin time is prolonged more than 3 seconds over control, invasive procedures like liver biopsy, splenoportogram, percutaneous cholangiography, or surgery were associated with increased risk of bleeding, and coagulopathy should be corrected with infusion of fresh frozen plasma. These practices were without any scientific evidence and were associated with significant hazards of fresh frozen plasma transfusion. Now, it is realized that coagulation is a complex process involving the interaction of procoagulation and anticoagulation factors and the fibrinolytic system. As there is reduction in both anti and procoagulant factors, global tests of coagulation are normal in patients with acute and chronic liver disease indicating that coagulopathy in liver disease is more of a myth than a reality. In the last few years, surgical techniques have substantially improved, and complex procedures like liver transplantation can be done without the use of blood or blood products. Patients with liver cirrhosis may also be at increased risk of thrombosis. In this paper, we will discuss coagulopathy, increased risk of thrombosis, and their management in decompensated liver cirrhosis.

1. Introduction

Traditionally decompensated liver cirrhosis has been considered as a prototype of hemorrhagic coagulopathy. Routinely performed coagulation profile is abnormal in the majority of these patients [1]. If prothrombin time is prolonged more than 3 seconds over control, invasive procedures like liver biopsy, splenoportogram, percutaneous cholangiography, or surgery were associated with increased risk of bleeding [2]. For years, it was evident that haemostasis tests performed in peripheral blood correlated poorly with the actual duration of bleeding and the amount of blood loss measured directly at laparoscopy from biopsy puncture. Abnormal bleeding after liver biopsy is a random event which cannot be predicted by currently used coagulation tests. Abnormal coagulation tests also did not correlate with development of soft tissue hematomas, variceal bleeding, and other bleeding episodes in cirrhotic patients [3–6].

In the recent years, surgical techniques have improved remarkably, and even liver transplantation can be performed without using blood or blood products [7]. It has been realized that thrombin plug formation is a dynamic process, and coagulation tests suggest that prothrombin time (PT) and activated partial thromboplastin time (APTT) explore only early phase of thrombin formation [8]. Thrombin formation is globally measured by using a thrombin generation assay modified by addition of thrombomodulin, and hence it is sensitive not only to the low plasma level of coagulation factors but also to the reduced levels of naturally occurring coagulation inhibitors in patients with liver disease. Patients with cirrhosis do form thrombin in amounts similar to healthy individuals [9]. Two single-theme conferences have

been organized to address the issue of coagulation in patients with liver cirrhosis, and the reports of both meetings have been published [10, 11].

Both these reports suggest that coagulopathy in liver cirrhosis is a complex issue, and optimal strategies for prediction and prevention of bleeding episodes cannot be done by currently used coagulation tests and infusion of fresh frozen plasma. Strategies to treat bleeding complications in decompensated liver cirrhotic patients are not clear and require further clinical studies [10, 11]. The proper management of coagulopathy in patients with decompensated liver cirrhosis is highly debatable, and a major area of interest in the field of hepatology in this paper, the physiology of normal coagulation, the limitations of coagulation tests, and a reasonable approach to the management of coagulation disorders in patients with decompensated liver disease will be discussed.

2. Coagulation and Haemostatic Abnormalities in Context of Decompensated Liver Cirrhosis

Coagulation and heamostasis is a dynamic process with interplay between primary heamostasis, coagulation, and fibrinolysis. Majority of plasma clotting factors and proteins of the fibrinolytic and anticoagulants are synthesized in the liver, while cell surface factors (surface factor is a transmembrane protein that acts as a receptor and cofactor for FVII) responsible for heamostasis are not synthesized by liver. Normal coagulation system has been conceptualized as Y shape pathway with separate intrinsic and extrinsic component initiated factor XII or factor VIIa/tissue factors leading to a common pathway of factor Xa/factor Va. In patients with severe liver disease, heamostasis is affected due to diminished synthesis of factors II, V, VI, IX, X, XI, XIII, fibrinogen, protein C, protein S, Vitamin K deficiency due to malabsorption or malnutrition, dysfibrinogenemia, enhanced fibrinolysis, diffuse intravascular coagulation, thrombocytopenia, impaired clearance of activated clotting factors, plasminogen activators, and fibrinogen degradation products. Clinical consequences of this may lead to abnormal bleeding test, bleeding, and thrombosis. Coagulation in patients with decompensated liver cirrhosis can also be affected by other factors like infections, endogenous heparinoids, renal failure, and endothelial dysfunction [10–12]. Endogenous heparinoids have effect on coagulopathy in patients with cirrhosis. This has been demonstrated by thromboelastography with addition of heparinase 1 in patients who have recent variceal bleed or infection. Effect of endogenous heparinoids has also been seen after reperfusion of liver undergoing liver transplant patient [12].

Current concept of heamostasis is cell based. Primary heamostasis initiates from the adhesions of circulating platelets to the subendothelium at the site of injury through the mediation of the adhesive protein von Willebrand factor (VWF) and specific platelet receptors. Elevated levels of VWF seen in patients with cirrhosis are due to thrombocytopenia and decreased VWF protein, cleaving protease ADAMTS13 [13, 14]. After the adhesions, platelet aggregation due to fibrinogen or VWF with substances secreted by platelets themselves act as agonist. Activated platelets express their cell surface phosphatidylserine (P-serine) that promotes the conversion of factor II to thrombin by means of factor Xa, Va, and calcium. This is the initiating phase of a chain of events leading to thrombin generation and final conversion of fibrinogen to fibrin. Fibrin is stabilized factor XIII, and fibrinolysis is responsible for degradation of fibrin through a complex mechanism of pro- and antiactivators which regulates the generation of plasmin. Majority of the factors involved in heamostasis, coagulation, fibrinolysis, and anticoagulation are synthesized in the liver. In normal individuals, these systems are in a balance. In patients with cirrhosis, VWF plays a key role together with factor IX and negatively charged phospholipids of activated platelets to boost thrombin generation. Protein C activation by thrombin in complex with its endothelial receptor thrombomodulin acts as a powerful thrombin quenching protease by inhibiting the activated form of factor V and VIII. Patients with cirrhosis have increased levels of factor VIII and decreased levels of protein C and antithrombin. Elevation in factor VIII levels is due to decreased clearance from the circulation [8]. There are patients with isolated factor deficiencies like hemophilia and patients present with bleeding in contrast to patients with liver disease who have decreased levels of procoagulants and anticoagulants leading to a balance in the heamostasis without increasing the risk of bleeding, but this balance is precarious and may be tipped off either towards the bleeding or thrombosis by external factors like infection, renal failure, and so forth [11, 15].

Another important factor in coagulation in patients with decompensated liver cirrhosis is platelets. Patients with decompensated liver cirrhosis have thrombocytopenia and thrombocytopathy. This can be due to platelets sequestration, thrombopoietin deficiency, (myelosuppression due to hepatitis C, folate deficiency, and ethanol toxicity) autoantibodies, and low-grade disseminated intravascular coagulation (DIC) [16–18]. Standard diagnostic tests of platelet functions are of little use to predict the bleeding risk in patients with liver disease. Decrease in platelet function in cirrhosis is compensated by high plasma levels of VWF which compensates for platelet capacity to provide surface for thrombin generation. Platelet count beyond 50,000/mmq is adequate enough for a normal heamostasis. Prophylactic role of platelet transfusion is highly questionable [9].

2.1. Fibrinolysis and Liver Disease. Cirrhosis is considered to be a hyperfibrinolytic state. The fibrinolytic system consists of plasminogen which is converted to plasmin via intrinsic activation with factor XIIa, kallikrein, tissue plasminogen activator (tPA), and urokinase. All these factors are synthesized by the liver. Recent work has suggested that thrombin-activated fibrinolysis inhibitor (TAFI) is decreased in liver cirrhosis. Decrease in TAFI is counterbalanced by the concomitant decrease in profibrinolytic factors, and excessive fibrinolysis does not occur in patients with liver disease. Various tests are available for assessing fibrinolysis, and these include (1) clot lysis time, (2) euglobulin lysis time, (3) D-dimer assay, (4) fibrinogen degradation product assay,

Table 1: Therapeutic options in coagulopathy in decompensated liver cirrhosis.

Agent	Utility in specific situations	Comment
Red blood cell transfusion	Bleeding patients	Transfusion should be minimum, not allowing Hb to exceed 8 to 9 mg%
Vitamin K	Every patient	May not be useful if patient has no deficiency
Fresh frozen plasma	Questionable in bleeding patients	May be used in bleeding patients when volume expansion is not a concern
Platelets	Count less than 50.000	Limited data
Cryoprecipitate	In bleeding patients	Limited data
Prothrombin complex concentrate	In bleeding patients	Limited data
Desmopressin	In bleeding patients	Efficacy unproved
Aprotinin, transexamine acid, and epsilon amino caprioric acid	Patients with hypofibrinogenemia Fibrinogen less than 100/dL	Can induce thrombosis
Recombinant factor VII	In placing ICP devices, bleeding after surgery, massive variceal bleed	Can induce thrombosis
Topical agents—cyanoacrylates, fibrin glue, and thrombin	Topical heamostasis and localized bleeding	Extremely expensive and limited data
Reduction in the portal pressure, maintaining low CVP by volume contraction (phlebotomy/diuresis)		
Surgical techniques—vascular clamping, ultrasonic/hydrojet dissectors, and thermal techniques (aarton plasma coagulator, radio frequency ablators)		

(5) tPA assay, and (6) thromboelastogram clot lysis index. Majority of these tests have high interindividual variability and low specificity. Except for thromboelastogram, no commercial test evaluates global fibrinolysis. Measurement of individual components of the fibrinolytic pathway is unlikely to help in assessing and managing bleeding risk of cirrhosis [19].

2.2. Clinical Tests for Coagulation in Liver Disease. A variety of coagulation of tests which include bleeding time, clotting time, prothrombin time, activated partial thromboplastin time, thrombin time, whole blood clot lysis, plasma fibrinogen, serum fibrinogen degradation product, plasma D-dimer, euglobulin lysis time, factor assays for F XIII, protein C, protein S, and antithrombin III. The literature evidence suggests that conventional coagulation tests are of little value in predicting bleeding risk in patients with cirrhosis and are of limited use in guiding decisions of the appropriate management of bleeding events in cirrhosis. For judging the risk of bleeding, we need tests for global evaluation of coagulation-like thrombin generation time, thromboelastography, sonorheometry, and national normalized ratio calibrated for cirrhosis (INRliver). Thrombin generation test is a global test in which coagulation cascade is activated with small amounts of tissue factor as a trigger and phospholipids acting as a platelets substitute. Thrombin generation measured in the presence of thrombomodulin and platelet-rich plasma is similar for patients with chronic liver disease and healthy subjects. The critical platelet count is 60,000/cumm [9, 20]. Thromboelastography measures clot formation, clot strength, and clot dissolution but does not measure vascular tone. It accesses global heamostasis. The modern thromboelastography which combines new computer technology with new materials and equipment is popular during surgical interventions like liver transplantation [21]. The INR liver is prothrombin time calibrated using plasma from patients with cirrhosis instead of vitamin K antagonists and may resolve variability of INR in these patients [22]. These tests have not been prospectively evaluated in patients with liver disease. Prothrombin time has been used traditionally in assessment of severity of liver disease in child pugh score or as a INR in MELD score. Prothrombin time expressed as an INR is highly variable and has never been standardized in patients with liver disease [20, 21]. Current controversies in patients with liver cirrhosis are which humoral or hematological test can predict risk of bleeding versus risk of thrombosis and which prophylactic intervention can be used effectively from both bleeding and thrombotic perspective. Recently, Tripodi et al. described a simple laboratory method which focuses on function of protein C deficiency which could promote clotting in patients of cirrhosis. This test is standardizable laboratory test which may determine the relative risk of clotting versus bleeding in patients with cirrhosis [23].

3. Management of Coagulopathy in Decompensated Liver Cirrhosis

Vitamin K deficiency is seen in decompensated liver cirrhosis secondary to various complex mechanisms which include bile salt deficiency, bile salt secretory failure, and use of broad spectrum antibiotics. 10 mg of vitamin K injections for three days is adequate enough to correct the vitamin K deficiency

and should be given to patients with decompensated liver cirrhosis. Oral vitamin K has no role [1]. Prophylactic correction of prothrombin time using fresh frozen plasma is not recommended [22]. Prothrombin times more than 4 seconds over control are unlikely to get corrected with fresh frozen plasma. Fresh frozen plasma has unpredictable response in patients with decompensated liver cirrhosis and is associated with significant side effects like volume overload, exacerbation of portal hypertension, risk of infections, and risk of transfusion-related acute liver injury [7].

4. Management of Bleeding Episodes

Patients with bleeding should be investigated for superimposed causes of coagulopathy like infections, renal failure, and so forth. Superimposed insults should be corrected aggressively. Other therapeutic options are as shown in Table 1. Use of vitamin K has already been discussed. Platelet transfusion may be considered if platelet count is less than 50,000/mm^3. Target platelet count to be achieved is more than 70,000/mm^3. Fresh frozen plasma contains all coagulation factors, inhibitors of coagulation, and fibrinolytic factors. Fresh frozen plasma should be solvent detergent-treated plasma or donor-retested plasma. Therapeutic improvement is transient and may be associated with adverse reactions as mentioned above. Hypofibrinogenemia (fibrinogen <10 mg/dL) should be treated with cryoprecipitate till normal fibrinogen levels are reached. Other agents used in the treatment of fibrinolysis in patients with decompensated liver cirrhosis are aprotinin, transexaminc acid, and epsilon amino caproic acid. These agents play a major role in treating local bleeding but also carry a risk of thrombotic complications. Their use has not been well studied in clinical trials. Desmopressin (DDAVP) is an analogue of anti diuretic hormone vasopressin. DDAVP releases vWf and factor VIII. It shortens the bleeding time, and peak response is achieved in 30–60 minutes after intravenous administration. Unfortunately, no benefit of DDAVP administration is seen in patients with variceal bleeding and liver surgery. Recombinant activated factor VIIa is shown to improve prothrombin time and clot formation without enhanced fibrinolysis. The effect is immediate but transient. Repeated dosing is required and is extremely expensive. Recombinant factor VIIa though clearly corrects in vitro coagulation abnormalities was not shown to be effective in patients with variceal bleeding. Some advantage was shown in child C cirrhosis. The most efficient use of this product is in intracranial pressure monitor placement. It may have efficient role in controlling active variceal bleeding when there is no clear endoscopic view. Caveats with use of recombinant factor Va are thrombotic complications, high cost of the therapy, and limited outcome data. Control of bleeding can be achieved with topical haemostatic agents like fibrin glue, cyanoacrylates, thrombin, and suture supports. Surgical and anesthesiological methods used to reduce the blood loss during liver surgery in patients with cirrhosis are vascular clamping techniques, dissection devices like ultrasonic dissection, hydro jet dissection, thermal devises like argon plasma coagulator and radio frequency ablator, and topical haemostatic agents. Maintaining low central venous pressure and reducing the portal pressure may also be of help in controlling the bleeding during surgery [7, 8, 11].

Deep vein thrombosis, pulmonary embolism, and acute portal vein thrombosis can be treated with anticoagulants with special care [10]. Anticoagulation may prove to be safe and effective in patients with cirrhosis. Currently, anticoagulation has been used in patients with portal vein thrombosis and if thrombosis has extended to superior mesenteric vein. These patients are not suitable for liver transplantation. A recent randomized control trial has shown that low-molecular-weight heparin can prevent portal vein thrombosis and cirrhosis [24, 25].

In summary, heamostasis in patients with decompensated liver disease is a complex issue with counteracting forces which are in dynamic equilibrium and are affected by extraneous factors like infection and renal function. Currently, available tests for coagulation have a poor predictability for bleeding or thrombosis in patients with cirrhosis. New tests like TEG, thrombin tests, and so forth may give a better picture but need prospective studies. Role of specific intervention like platelet transfusion, antifibrinolytics and recombinant factors, anticoagulant need to be defined clearly.

References

[1] S. Sherlock and J. Dooly, "Haematology of liver disease," in *Diseases of Liver and Biliary System*, S. Sherlock and J. Dooly, Eds., pp. 43–62, Blackwell Science, London, UK, 10th edition, 1997.

[2] A. Grant and J. Neuberger, "Guidelines on the use of liver biopsy in clinical practice," *British Society of Gastroenterology Gut*, vol. 43, supplement 4, pp. IV1–IV11, 1999.

[3] K. Ewe, "Bleeding after liver biopsy does not correlate with indices of peripheral coagulation," *Digestive Diseases and Sciences*, vol. 26, no. 5, pp. 388–393, 1981.

[4] V. L. Ng, "Liver disease, coagulation testing and heamostasis," *Clinics in Laboratory Medicine*, vol. 29, no. 2, pp. 265–282, 2009.

[5] A. L. Boks, E. J. Brommer, S. W. Schalm, and H. H. van Vliet, "Hemostasis and fibrinolysis in severe liver failure and their relation to hemorrhage," *Hepatology*, vol. 6, no. 1, pp. 79–86, 1986.

[6] P. A. McVay and P. T. Toy, "Lack of increased bleeding after liver biopsy in patients with mild hemostatic abnormalities," *American Journal of Clinical Pathology*, vol. 94, no. 6, pp. 747–753, 1990.

[7] P. M. Mannucci, "Abnormalities of heamostasis tests in chronic liver disease: clinically relevant?" in *Portal Hypertension*, I. V. Bavino and R. D. Franchis, Eds., pp. 40–46, Blackwell Publishing, Oxford, Uk, 2006.

[8] A. Tripodi, M. Primignani, and P. M. Mannucci, "Abnormalities of hemostasis and bleeding in chronic liver disease: the paradigm is challenged," *Internal and Emergency Medicine*, vol. 5, no. 1, pp. 7–12, 2010.

[9] A. Tripodi, F. Salerno, V. Chantarangkul et al., "Evidence of normal thrombin generation in cirrhosis despite abnormal

conventional coagulation tests," *Hepatology*, vol. 41, no. 3, pp. 553–558, 2005.

[10] S. H. Caldwell, M. Hoffman, T. Lisman et al., "Coagulation Disorder and heamostasis in liver disease: pathophysiology and critical assessment of current management," *Hepatology*, vol. 44, pp. 1039–1046, 2006.

[11] T. Lisman, S. H. Caldwell, A. K. Burroughs et al., "Hemostasis and thrombosis in patients with liver disease: the ups and downs," *Journal of Hepatology*, vol. 53, no. 2, pp. 362–371, 2010.

[12] M. Senzolo, E. Cholongitas, U. Thalheimer et al., "Heparin-like effect in liver disease and liver transplantation," *Clinics in Liver Disease*, vol. 13, no. 1, pp. 43–53, 2009.

[13] T. Lisman and R. J. Porte, "Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences," *Blood*, vol. 116, no. 6, pp. 878–885, 2010.

[14] T. Lisman, T. Bongers, J. Adelmeijer et al., "Elevated levels of von Willebrand factor in cirrhosis support platelet adhesion despite reduced functional capacity," *Hepatology*, vol. 44, no. 1, pp. 53–61, 2006.

[15] J. H. Smalberg and F. W. G. Leebeek, "Superimposed coagulopathic conditions in cirrhosis: infection and endogenous heparinoids, renal failure, and endothelial dysfunction," *Clinics in Liver Disease*, vol. 13, no. 1, pp. 33–42, 2009.

[16] A. Ordinas, G. Escolar, I. Cirera et al., "Existence of a platelet-adhesion defect in patients with cirrhosis independent of hematocrit: studies under flow conditions," *Hepatology*, vol. 24, no. 5, pp. 1137–1142, 1996.

[17] P. A. Cahill, E. M. Redmond, and J. V. Sitzmann, "Endothelial dysfunction in cirrhosis and portal hypertension," *Pharmacology and Therapeutics*, vol. 89, no. 3, pp. 273–293, 2001.

[18] G. G. C. Hugenholtz, R. J. Porte, and T. Lisman, "The platelet and platelet function testing in liver disease," *Clinics in Liver Disease*, vol. 13, no. 1, pp. 11–20, 2009.

[19] D. Ferro, A. Celestini, and F. Violi, "Hyperfibrinolysis in liver disease," *Clinics in Liver Disease*, vol. 13, no. 1, pp. 21–31, 2009.

[20] A. Tripodi, "Tests of coagulation in liver disease," *Clinics in Liver Disease*, vol. 13, no. 1, pp. 55–61, 2009.

[21] M. B. Koh and B. J. Hunt, "The management of perioperative bleeding," *Blood Reviews*, vol. 17, no. 3, pp. 179–185, 2003.

[22] A. Tripodi, V. Chantarangkul, M. Primignani et al., "The international normalized ratio calibrated for cirrhosis (INRlier) normalizes prothrombin time results for model for end-stage liver disease calculation," *Hepatology*, vol. 46, no. 2, pp. 520–527, 2007.

[23] A. Tripodi, M. Primignani, L. Lemma et al., "Detection of the imbalance of procoagulant versus anticoagulant factors in cirrhosis by a simple laboratory method," *Hepatology*, vol. 52, no. 1, pp. 249–255, 2010.

[24] E. A. Tsochatzis, M. Senzolo, G. Germani, A. Gatt, and A. K. Burroughs, "Systemic review portal vein thrombosis in cirrhosis," *Alimentary Pharmacology & Therapeutics*, vol. 31, pp. 366–374, 2010.

[25] R. Zecchini, A. Ferrari, and V. Bemabucci, "Anticoagulant therapy is safe and effective n preventing portal vein thrombosis (PVT) in advanced cirrhotic patients : a prospective randomized controlled study," *Journal of Hepatology*, vol. 52, p. S460, 2010.

SAGE-Hindawi Access to Research
International Journal of Hepatology
Volume 2011, Article ID 759047, 12 pages
doi:10.4061/2011/759047

Review Article

Determination of ADAMTS13 and Its Clinical Significance for ADAMTS13 Supplementation Therapy to Improve the Survival of Patients with Decompensated Liver Cirrhosis

Masahito Uemura,[1] Yoshihiro Fujimura,[2] Saiho Ko,[3] Masanori Matsumoto,[2] Yoshiyuki Nakajima,[3] and Hiroshi Fukui[1]

[1] *Third Department of Internal Medicine, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan*
[2] *Department of Blood Transfusion Medicine, Nara Medical University, Kashihara, Nara 634-8522, Japan*
[3] *Department of Surgery, Nara Medical University, Kashihara, Nara 634-8522, Japan*

Correspondence should be addressed to Masahito Uemura, muemura@naramed-u.ac.jp

Received 25 February 2011; Accepted 8 April 2011

Academic Editor: Deepak Amarapurkar

The liver plays a central role in hemostasis by synthesizing clotting factors, coagulation inhibitors, and fibrinolytic proteins. Liver cirrhosis (LC), therefore, impacts on both primary and secondary hemostatic mechanisms. ADAMTS13 is a metalloproteinase, produced exclusively in hepatic stellate cells, and specifically cleaves unusually large von Willebrand factor multimers (UL-VWFM). Deficiency of ADAMTS13 results in accumulation of UL-VWFM, which induces platelet clumping or thrombi under high shear stress, followed by sinusoidal microcirculatory disturbances and subsequent progression of liver injuries, eventually leading to multiorgan failure. The marked imbalance between decreased ADAMTS13 activity (ADAMTS13 : AC) and increased production of UL-VWFM indicating a high-risk state of platelet microthrombi formation was closely related to functional liver capacity, hepatic encephalopathy, hepatorenal syndrome, and intractable ascites in advanced LC. Some end-stage LC patients with extremely low ADAMTS13 : AC and its IgG inhibitor may reflect conditions similar to thrombotic thrombocytopenic purpura (TTP) or may reflect "subclinical TTP." Hence, cirrhotic patients with severe to moderate deficiency of ADAMTS13 : AC may be candidates for FFP infusion as a source of ADAMTS13 or for recombinant ADAMTS13 supplementation. Such treatments may improve the survival of patients with decompensated LC.

1. Introduction

The liver is a major source of clotting and fibrinolytic proteins and plays a central role in thromboregulation [1–4]. Liver diseases, hence, impact on both primary and secondary hemostatic mechanisms. Because the hemostatic system is normally in a delicate balance between pro-hemostatic and antihemostatic processes, advanced liver cirrhosis (LC) patients experience multiple changes in the hemostatic system that may lead to either bleeding or thrombosis [1–4]. Despite clinical evidence of increasing bleeding tendency in LC patients, many facts indicate local and systemic hypercoagulability including portal or hepatic vein thrombosis, pulmonary embolism, and deep vein thrombosis, which are closely related to microcirculatory disturbances [4]. Deficiency of anticoagulant proteins and high levels of several procoagulant factors may favor hypercoagulability [4], but the mechanisms underlying this disorder have not been fully elucidated.

ADAMTS13 (**a** **d**isintegrin-like **a**nd **m**etalloproteinase with **t**hrombo**s**pondin type-1 motifs **13**) is a metalloproteinase that specifically cleaves multimeric von Willebrand factor (VWF) between Tyr1605 and Met1606 residues in the A2 domain [5, 6]. In the absence of ADAMTS13 activity (ADAMTS13 : AC), unusually large VWF multimers (UL-VWFMs) are released from vascular endothelial cells (ECs) and improperly cleaved, causing them to accumulate and to induce the formation of platelet thrombi in the microvasculature under conditions of high shear stress. Currently, a severe deficiency in ADAMTS13 : AC, which results either

from genetic mutations in the *ADAMTS13* gene (Upshaw-Schulman syndrome, (USS)) [5–8] or acquired autoantibodies against ADAMTS13 [9, 10], is thought to be a specific feature of thrombotic thrombocytopenic purpura (TTP) [5–12].

In 2000, we demonstrated that a decreased plasma ADAMTS13 : AC in patients with cirrhotic biliary atresia can be fully restored after liver transplantation, indicating that the liver is the main organ producing ADAMTS13 [13]. One year later, northern blot analysis showed that the 4.6-kilobase ADAMTS13 mRNA was highly expressed in the liver [7, 14, 15], and subsequently both *in situ* hybridization and immunohistochemistry clearly indicated that ADAMTS13 is produced exclusively in hepatic stellate cells (HSCs) [16]. Platelets [17], vascular ECs [18], and kidney podocytes [19] have also been implicated as ADAMTS13-producing cells, but the amount produced by these cell types in the liver appears to be far less than that produced by HSC.

Mannucci et al. [20] originally reported a reduction of the ADAMTS13 : AC in advanced LC. Since HSCs were shown to be the major producing cells in the liver [16], much attention has been paid to the potential role of ADAMTS13 in the pathophysiology of liver diseases associated with sinusoidal and/or systemic microcirculatory disturbance [21–35]. ADAMTS13 : AC significantly decreased in patients with hepatic veno-occlusive disease (VOD) [22, 23], alcoholic hepatitis [24–27], liver cirrhosis [29, 30], and those undergoing living-donor-related liver transplantation [31–33] and partial hepatectomy [34]. Furthermore, hepatitis C virus- (HCV-) related LC patients with ADAMTS13 inhibitor (ADAMTS13 : INH) typically developed TTP [35]. Once patients with LC develop a decompensated condition, the risk of early mortality sharply increases for specific life-threatening complications such as ascites, hepatic encephalopathy, sepsis, hepatorenal syndrome, or hepatopulmonary syndrome [36].

In this paper, we will focus on the importance of ADAMTS13 determination for a better understanding of pathophysiology and/or for possible therapeutic approaches of ADAMTS13 supplementation to improve survival in patients with advanced LC.

2. Hepatic Microcirculation and Hypercoagulable State in LC

Hepatic microcirculation compromises a unique system of capillaries, called sinusoids, which are lined by three different cell types: sinusoidal endothelial cells (SECs), HSC, and Kupffer cells [37]. The SEC modulates microcirculation between hepatocytes and the sinusoidal space through the sinusoidal endothelial fenestration. The SEC has tremendous endocytic capacity, including VWF and the extracellular matrix, and secretes many vasoactive substances [37]. The HSC is located in the space of Disse adjacent to the SEC and regulates sinusoidal blood flow by contraction or relaxation induced by vasoactive substances [38]. Kupffer cells are intrasinusoidally located tissue macrophages and secrete potent inflammatory mediators during the early phase of liver inflammation [37]. Intimate cell-to-cell interaction has been found between these sinusoidal cells and hepatocytes [37, 38]. In LC, a sinusoidal microcirculatory disturbance occurs when the normal hepatic structure is disrupted by fibrin deposition [39] or by impaired balance between the action of vasoconstrictors and vasodilators in hepatic vascular circulation [37]. Studies have shown that cirrhotic liver exhibits a hyperresponse to vasoconstrictors, including catecholamine, endothelin, and leukotrienes D_4 [37].

Vascular endothelial cells play a pivotal role in hemostasis and thrombosis [5, 6]. VWF is a marker of endothelial cell activation (damage) and plays an essential role in hemostasis [5, 6]. In the normal state, VWF immunostaining is usually positive in large vessels but negative in the SEC [40]. On the occurrence of liver injury accompanied by a necroinflammatory process, the SEC becomes positive for VWF, presumably in association with the capillarization of hepatic sinusoids [39]. Subsequently, platelets adhere to subendothelial tissue mediated by UL-VWFM [5, 6]. ADAMTS13 then cleaves UL-VWFM into smaller VWF multimers [5, 6]. This interaction of ADAMTS13 and UL-VWFM is, indeed, the initial step in hemostasis [5, 6].

In patients with LC, circulating plasma VWF levels are extremely high [41, 42]. In liver tissue from cirrhotics [43] and even from the early stages of alcoholic liver diseases [44], VWF immunostaining shows positive cells predominantly at the scar-parenchyma interface, within the septum, and in the sinusoidal lining cells. Actually, portal or hepatic vein thrombosis is often observed in advanced LC routinely screened with Doppler ultrasound [45], and, in cirrhotic liver removed at transplantation, intimal fibrosis suggesting hepatic and portal vein thrombosis was frequently observed [46]. An autopsy series revealed microthrombi in one or multiple organs in one-half of cirrhotics [47]. Such a hypercoagulable state in liver diseases may be involved in hepatic parenchymal destruction, the acceleration of liver fibrosis and disease progression [4], leading to hepatorenal syndrome, portopulmonary hypertension, and spontaneous bacterial peritonitis [48].

Systemically, deficiency of anticoagulant proteins (antithrombin, protein C, and protein S) and the high levels of several procoagulant factors (factor VIII and VWF) may contribute to hypercoagulability in patients with LC [4]. Locally, the SEC dysfunction could lead to the development of a hypercoagulable state at the hepatic sinusoids corresponding to the site of liver injury, even in the face of a systemic hypocoagulable state [4]. Considering that ADAMTS13 is synthesized in HSC and its substrate, UL-VWFM, is produced in transformed SEC during liver injury, decreased plasma ADAMTS13 : AC may involve not only sinusoidal microcirculatory disturbances, but also subsequent progression of liver diseases, finally leading to multiorgan failure. Based on these findings, it is of particular interest to evaluate the activity of plasma ADAMTS13 : AC in LC patients.

3. Cleavage of UL-VWFM by ADAMTS13

Although the mechanism by which TTP develops in the absence of ADAMTS13 : AC has not been fully elucidated,

accumulating evidence has provided a hypothesis as illustrated in Figure 1 [49]. UL-VWFMs are produced exclusively in vascular ECs and stored in an intracellular organelle termed Weidel-palade bodies (WPBs) and then released into the circulation upon stimulation. Under physiological conditions, epinephrine acts as an endogenous stimulus, but under nonphysiological conditions, DDAVP (1-deamino-8-D-arginine vasopressin), hypoxia, and several cytokines such as interleukin IL-2, IL-6, IL-8, and tumor necrosis factor- (TNF-) α act as stimuli that upregulate VWF release. Once ECs are stimulated, UL-VWFMs and P-selectin, both stored in WPBs, move to the membrane surface of ECs, where P-selectin anchors UL-VWFMs on the ECs surface [50]. Under these circumstances, high shear stress generated in the microvasculature induces a change in the UL-VWFM from a globular to an extended form [51]. The ADAMTS13 protease efficiently cleaves the active extended form of UL-VWFM between the Tyr1605 and Met1606 residues in the A2 domain [52]. In this context, it has been postulated that multiple exocites within the disintegrin-like/TSP1/cysteine-rich/spacer (DTCS) domains of ADAMTS13 play an important role in interacting with the unfolded VWF-A2 domain [53]. ADAMTS13 may more efficiently cleave newly released UL-VWFMs that exist as solid-phase enzymes anchored to the vascular EC surface by binding to CD36, because CD36 is a receptor for TSP1, which is a repeated domain within the ADAMTS13 molecule [54]. When ADAMTS13 activity is reduced, UL-VWFM interacts more intensively with platelet GPIb and generates signals that further accelerate platelet activation [5, 6]. A series of these reactions leads to platelet microaggregates and thrombocytopenia. However, little information has been available on the cleavage of the UL-VWFMs by ADAMTS13 in the sinusoidal microcirculation in LC.

4. Assays for Plasma ADAMTS13 : AC and ADAMTS13 : INH

ADAMTS13 : AC was determined with a classic VWFM assay in the presence of 1.5 mol/L urea using purified plasma-derived VWF as a substrate according to the method described by Furlan et al. [55], and the detection limit of this assay was 3% of the normal control in our laboratory [56]. In 2005, we developed a novel chromogenic ADAMTS13-act-ELISA using both an N- and C-terminal tagged recombinant VWF substrate (termed GST-VWF73-His). This assay was highly sensitive, and the detection limit was 0.5% of the normal control [57]. Plasma ADAMTS13 : AC levels highly correlated between VWFM assay and ADAMTS13-act-ELISA (mean ± SD, 102 ± 23% versus 99.1 ± 21.5%, $r^2 = 0.72$, $P < .01$) [57]. No interference of the ADAMTS13-act-ELISA occurred even in the presence of hemoglobin, bilirubin, or chylomicrons in the samples, thus enabling distinction from the FRETS-VWF73 assay [58]. Because of its high sensitivity, easy handling, and lack of interference from plasma components, the ADAMTS13-act-ELISA would be recommended for routine laboratory use.

The ADAMTS13 : INH has also been evaluated with the chromogenic act-ELISA by means of the Bethesda method [59]. Prior to the assay, the test samples were heat-treated at 56°C for 60 min to eliminate endogenous enzyme activity, mixed with an equal volume of intact normal pooled plasma, and incubated for 2 hours at 37°C. The residual enzyme activity is measured after incubation. One Bethesda unit is defined as the amount of inhibitor that reduces activity by 50% of the control value, and values greater than 0.5 U/mL are significant.

5. Thrombocytopenia, Determination of ADAMTS13 : AC, and Its Clinical Significance in LC

5.1. Thrombocytopenia. It is well accepted that thrombocytopenia gradually progresses as functional liver capacity decreases [30, 60] (Figure 2(a)). The pathogenesis of thrombocytopenia in LC includes splenic sequestration in portal hypertension [61], impaired platelet production due to decreased synthesis of thrombopoietin in the liver [62] or due to myelosupression resulting from HCV infection [63], folic acid deficiency, or ethanol chronic consumption [64], which has a negative effect on megacaryocytopoiesis. However, our recent studies have provided evidence that in patients with advanced LC, elevated plasma levels of UL-VWFM enhance high-shear stress-induced platelet aggregation, resulting in thrombocytopenia [30].

5.2. ADAMTS13 : AC. Our study showed that ADAMTS13 : AC decreased with increasing severity of cirrhosis [30] (Figure 2(b)). The values determined by act-ELISA correlated well with those of the classical VWFM assay and also closely correlated with ADAMTS13 antigen de-termined by the antigen-ELISA. These results confirmed that both ADAMTS13 activity and antigen decreased with increasing cirrhosis severity [30] (Figures 2(b) and 2(c)), which are consistent with findings described by Feys et al. [29]. In contrast, Lisman et al. showed that both ADAMTS13 activity and antigen levels were highly variable; however, they did not distinguish between patients with varying degrees of cirrhosis [28]. It is unclear why they reached different conclusions from ours. One possible explanation relates to different etiologies: a majority of our patients developed cirrhosis secondary to HCV infection, whereas in their study one-half of the patients suffered from alcohol abuse-related cirrhosis. Further, the techniques used to determine ADAMTS13 : AC differed between our study [55–57] and theirs [65]. It is assumed that the collagen binding assay they used can be highly influenced by the increased amount of VWF : Ag in tested cirrhotic plasmas [29], because the substrate in this assay is intact multimeric VWF. In this regard, our act-ELISA is performed using VWF73-based fusion protein, termed GST-VWF73-His, which is readily cleaved by ADAMTS13 without any protein denaturant, and therefore the increased amount of VWF : Ag in tested plasmas does not interfere with the assays [57].

As shown in Figure 3, ADAMTS13 : ACs were significantly lower in LC patients with hepatic encephalopathy (Figure 3(a)), hepatorenal syndrome (Figure 3(b)), and

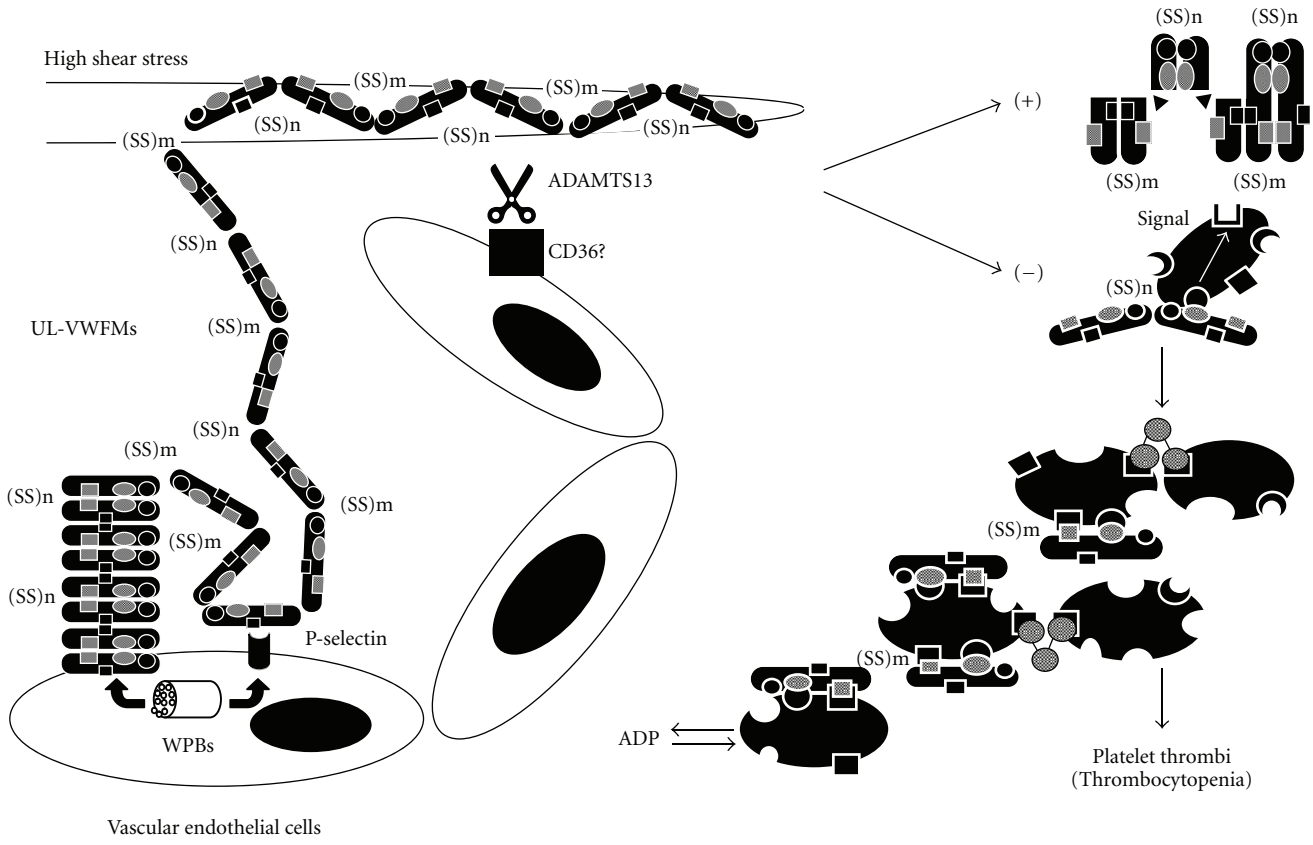


Figure 1: Proposed mechanism of platelet thrombi under high shear stress in the absence of ADAMTS13 : AC. Unusually large von Willebrand factor multimers (UL-VWFMs) are produced in vascular endothelial cells (ECs) and stored in Weidel-palade bodies (WPBs). UL-VWFMs are released from WPBs into the circulation upon stimulation by cytokines, hypoxia, DDAVP, and epinephrine. P-selectin that comigrates from WPBs anchors UL-VWFMs on the vascular EC surface. Under these circumstances, high shear stress changed the molecular conformation of UL-VWFMs from a globular to an extended form, allowing ADAMTS13 to access this molecule. In the absence of ADAMTS13 : AC, UL-VWFMs remain uncleaved, allowing them to excessively interact with platelet glycoprotein (GP)Ibα and activate platelets via intraplatelet signaling, which result in the formation of platelet thrombi. (Partially modified from Fujimura et al., [49]).

severe esophageal varices than those without [30]. Moreover, patients with refractory ascites had lower ADAMTS13 : AC levels than patients without ascites or those with easily mobilized ascites (Figure 3(c)). A multivariate analysis using all significant baseline parameters determined by the univariate analysis, excluding the Child-Pugh score, showed spleen volume, blood ammonia, and serum creatinine independently correlated with ADAMTS13 : AC. As a second step, the three parameters that contribute to the Child-Pugh classification (total bilirubin, albumin, and prothrombin time) were replaced by the Child-Pugh score. As a result, the Child-Pugh score and spleen volume were independently selected, indicating that ADAMTS13 : AC is closely related to the severity of liver disease and splenomegaly in cirrhotic patients [30].

5.3. VWF : Ag and VWF Multimer Patterns. Plasma levels of VWF : Ag substantially increase as liver diseases progress (Figure 2(d)) [30], as previously reported [41, 42]. This is presumably attributed to sinusoidal and/or extrahepatic endothelial damage induced by endotoxin and cytokines [41, 42, 66, 67]. The VWF : RCo was higher (Figure 2(e)) [30], but the ratio of VWF : RCo/VWF : Ag was lower in LC patients than that in healthy subjects. These findings suggest that increased VWF : Ag appears less functional in LC patients [30], which are consistent with previous reports [28]. Nevertheless, our study has clearly shown that the ratio of VWF : RCo/ADAMTS13 : AC progressively increases with the worsening of chronic liver diseases (Figure 2(f)), further intensifying an enhanced thrombogenesis with the progression of liver dysfunction and thrombocytopenia [30].

With regard to VWF multimers, the higher molecular weight multimer showed greater degradation than in healthy controls, thus maintaining normal enzyme-to-substrate (ADAMTS13/UL-VWFMs) ratio to maintain blood fluidity [29]. We showed that there were three different VWFM patterns in LC patients with lower ADAMTS13 : AC (<50 % of controls): normal-VWFM was detected in 53%, degraded-VWFM in 31%, and UL-VWFM in 16% (Table 1) [30]. UL-VWFM-positive patients showed the lowest ADAMTS13 : AC and the highest values of serum creatinine, blood urea nitrogen, and blood ammonia. In addition, LC patients with UL- and normal-VWFM had higher levels of VWF : RCo

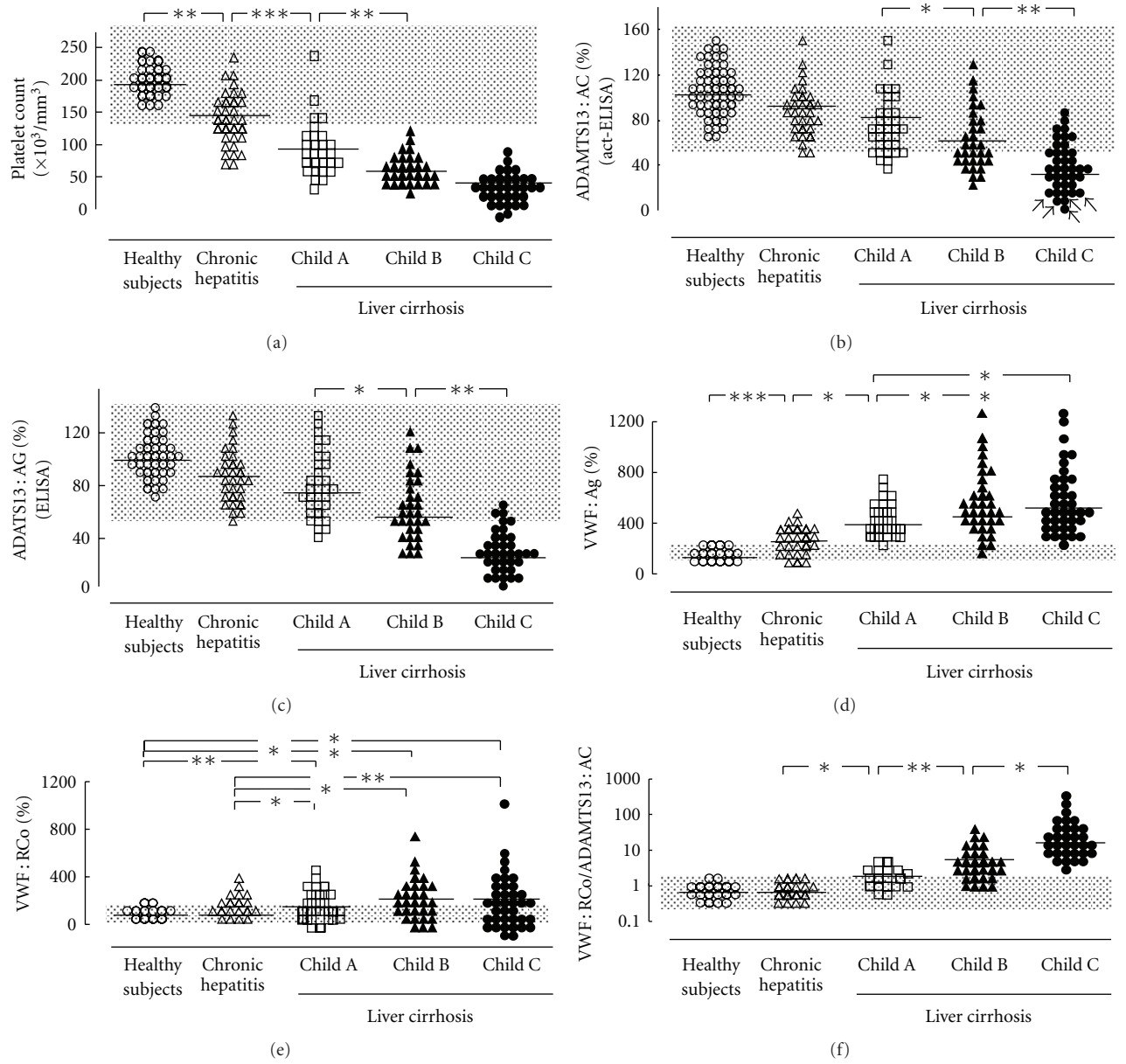


Figure 2: Platelet counts and plasma levels of ADAMTS13 : AC and its related parameters in patients with chronic liver diseases. Platelet counts decreased with the severity of chronic liver diseases, but no difference was found between Child B and C (a). Plasma ADAMTS13 : AC determined by ELISA progressively decreased with worsening cirrhosis (b). Arrows indicate patients whose plasma ADAMTS13 : AC was extremely low (< 3% of normal control by VWFM assay). The ADAMTS13 : AG levels determined by ELISA also decreased with increasing cirrhosis severity (c), which highly correlated with ADAMTS13 : AC measured by the act-ELISA ($r = 0.715$, $P < .001$). The VWF : Ag increased with the progression of chronic liver diseases, but the difference between Child B and C did not reach statistical significance (d). The VWF : RCo is higher in liver cirrhosis patients than that in patients with chronic hepatitis and healthy subjects, but it did not differ among subgroups within liver cirrhosis (e). The VWF : RCo relative to ADAMTS13 : AC progressively increased with worsening chronic liver disease (f). Open circles: normal controls; open triangles: chronic hepatitis; open squares: cirrhosis with Child A; closed triangles: cirrhosis with Child B; closed circles: cirrhosis with Child C. Shaded area shows normal range. ADAMTS13 : AC : ADAMTS13 activity, ADAMTS13 : AG = ADAMTS13 antigen. VWF : Ag = von Willebrand factor antigen, VWF : RCo = von Willebrand factor ristocetin cofactor activity; $^{*}P < .05$, $^{**}P < .01$, and $^{***}P < .001$ significantly different between the two groups. (Partially modified from Uemura et al., [30]).

and Child-Pugh score and lower values of cholinesterase and hemoglobin than those with degraded-VWFM [30] (Table 1). The pattern, therefore, appears to shift from degraded- to normal-VWFM, and finally to UL-VWFM as functional liver capacity and renal function deteriorates, indicating that advanced LC may be a predisposing state toward platelet microthrombi formation, even in the absence of clinically overt thrombotic events [30].

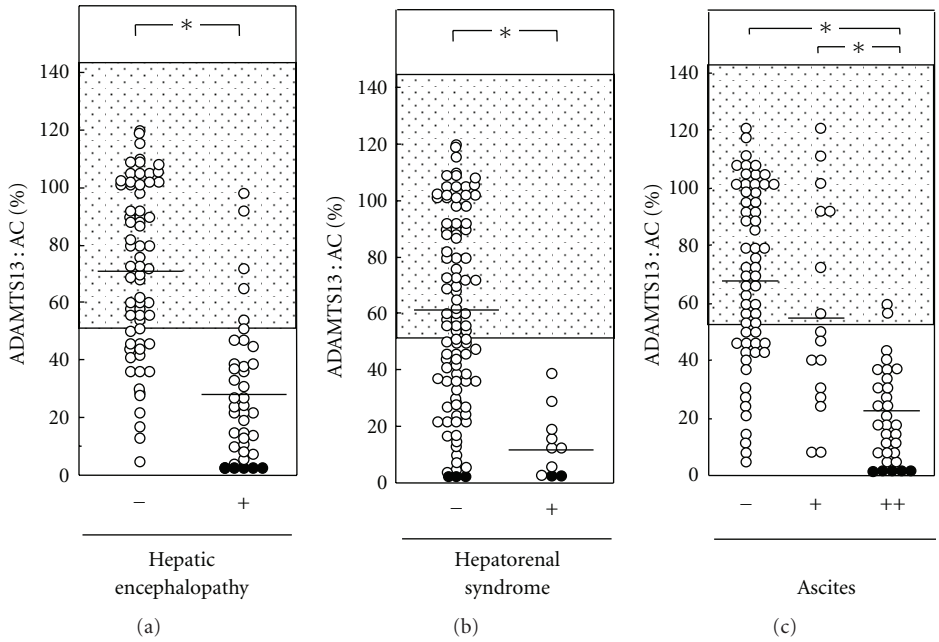


Figure 3: Relationship of ADAMTS13 : AC to the presence or absence of hepatic encephalopathy, hepatorenal syndrome, and ascites in patients with liver cirrhosis. The ADAMTS13 : AC was significantly lower in LC patients with hepatic encephalopathy (a) and hepatorenal syndrome (b) than that those without. Moreover, patients with refractory ascites had lower ADAMTS13 : AC than those without ascites or those with easily mobilized ascites (c). Closed circles indicate patients whose plasma ADAMTS13 : AC was extremely low (< 3% of normal control by VWFM assay). ADAMTS13 : AC: ADAMTS13 activity; $^*P < .001$ significantly different between the two groups. (Partially modified from Uemura et al., [30]).

Table 1: Comparison of clinical parameters among cirrhotic patients according to VWF multimer patterns.

Variables	VWF multimer pattrens			a versus b	a versus c	b versus c
	Degraded[a] ($n = 15$)	Normal[b] ($n = 26$)	Unusually large[c] ($n = 8$)			
ADAMTS13 : AC (%) (ELISA)	47 ± 24	44 ± 13	26 ± 14	n.s.	$P < .05$	$P < .01$
VWF : RCo (%)	110 ± 92	196 ± 134	216 ± 110	$P < .05$	$P < .05$	n.s.
Child-Pugh score	8.6 ± 2.5	10.9 ± 2.1	12.4 ± 1.7	$P < .01$	$P < .005$	n.s.
Serum albumin (g/dL)	3.07 ± 0.54	2.85 ± 0.54	2.59 ± 0.25	n.s.	$P < .05$	n.s.
Cholinesterase (IU/L)	126 ± 62	78 ± 64	60 ± 36	$P < .05$	$P < .02$	n.s.
Total cholesterol (mg/dL)	142 ± 51	93 ± 45	88 ± 40	$P < .01$	$P < .03$	n.s.
Hemoglobin (g/dL)	11.0 ± 1.7	9.3 ± 2.0	8.9 ± 1.7	$P < .02$	$P < .02$	n.s.
Serum creatinine (mg/dL)	1.06 ± 0.72	1.11 ± 0.79	2.43 ± 2.16	n.s.	$P < .05$	$P < .03$
Blood urea nitrogen (mg/dL)	22 ± 17	30 ± 21	74 ± 62	n.s.	$P < .01$	$P < .01$
Blood ammonia (μg/dL)	87 ± 50	100 ± 39	144 ± 53	n.s.	$P < .05$	$P < .05$

VWF: von Willebrand factor; ADAMTS13 : AC : ADAMTS13 activity; ELISA : enzyme-linked immunosorbent assay; VWF : RCo: VWF ristocetin cofactor activity; n.s.: not significant. (Partially modified from Uemura et al., [30]).

6. Mechanism of Decreased ADAMTS13 : AC in LC Patients

The mechanism responsible for the decrease in ADAMTS13 : AC in advanced LC may include enhanced consumption due to the degradation of large quantities of VWF : AG [20], inflammatory cytokines [68, 69], and/or ADAMTS13 plasma inhibitor [9, 10]. It is controversial whether ADAMTS13 deficiency is caused by decreased production in the liver; Kume et al. reported that HSC apoptosis plays an essential role in decreased ADAMTS13 : AC using dimethylnitrosamine-treated rats, but not carbon tetrachloride- (CCl_4-) treated

animals [70], whereas Niiya et al. found upregulation of ADAMTS13 antigen and proteolytic activity in liver tissue using rats with CCl_4-induced liver fibrosis [71]. We observed the inhibitor of ADAMTS13 in 83% of patients with severe to moderate ADAMTS13 deficiency, but its inhibitory activity was in a marginal zone between 0.5 and 1.0 BU/mL in most cases except in cases of a TTP patient (2.0 BU/mL) and a patient with severe ADAMTS13 deficiency (3.0 BU/mL) [30]. Interestingly, IgG-type autoantibodies specific to purified plasma derived-ADAMTS13 were detected by Western blotting only in five end-stage cirrhotics with severe ADAMTS13 deficiency (<3%) corresponding to TTP [30]. One patient showed an apparent TTP [35], while the other four cirrhotics did not show apparent clinical features of TTP but had complications of hepatorenal syndrome, spontaneous bacterial peritonitis (SBP), marked inflammation together with cytokinemia, and advanced hepatocellular carcinoma (HCC) [30]. Various clinical conditions, including infection, malignancies, and certain drugs, can lead to acquired TTP [72]. In advanced LC patients, endotoxemia is frequently detected [42, 73], and SBP sometimes occurs [74]. HCC is highly complicated as the cirrhotic stage progresses [75], suggesting a high-risk state of platelet microthrombi formation. Some end-stage LC patients with extremely low ADAMTS13 : AC and its IgG inhibitor may reflect conditions similar to TTP or may reflect "subclinical TTP" [21]. Further studies will be necessary to clarify whether inhibitors other than the IgG inhibitor might be involved in cirrhotics with lower ADAMTS13 : AC.

Alternatively, cytokinemia [25, 68, 69, 76] and endotoxemia [25, 77] are additional potential candidates for decreasing plasma ADAMTS13 : AC. Recent investigations demonstrated that IL-6 inhibited the action of ADAMTS13 under flow conditions and both IL-8 and TNF-α stimulated the release of UL-VWFM in human umbilical vein endothelial cells *in vitro* [68]. It remains to be clarified whether IL-6 directly hampers the cleavage of UL-VWFM or downregulates gene expression of ADAMTS13 with modification of promoter activity. IFN-γ, IL-4, and TNF-α also inhibit ADAMTS13 synthesis and activity in rat primary HSC [69]. In addition, ADAMTS13 deficiency associated with inflammation promoted formation of UL-VWFM [78], and intravenous infusion of endotoxin to healthy volunteers caused a decrease in plasma ADAMTS13 : AC together with the appearance of UL-VWFM [77]. In patients with alcoholic hepatitis, especially in severe cases complicated by LC, ADAMTS13 : AC concomitantly decreased, and VWF : Ag progressively increased with increasing concentrations of these cytokines from normal range to over 100 pg/mL [25]. Plasma endotoxin concentration inversely correlated with ADAMTS13 activity and was higher in patients with UL-VWFM than that those without [25]. From these results as well as our own, marked cytokinemia and/or enhanced endotoxemia may be closely related to decreased ADAMTS13 : AC and the appearance of UL-VWFM [25]. It will be necessary to clarify what types of inhibitor may be involved in association with inflammatory cytokines and endotoxin.

7. Typical TTP in Patients with Liver Diseases

We previously encountered a patient with HCV-related LC who was compromised by fatal TTP [35]. This case showed advanced LC and rigid ascites. As reported in the literature, since 1979, there have been 13 patients with liver diseases who developed TTP [35, 79–90]. Five of them were treated with IFN therapy, but the remaining 8 were not. Three of them showed evidence of autoimmune hepatitis, one of which was complicated by systemic lupus erythematosus (SLE). The remaining 4 patients had HCV-related LC, hepatitis B virus- (HBV-) related LC, alcoholic LC, or haemochromatosis. IFN may be able to induce autoimmune reactions, resulting in the generation of autoantibodies against ADAMTS13, although this phenomenon has yet to be confirmed. On the other hand, irrespective of IFN therapy, HCV infection and/or advanced LC itself may contribute to the development of TTP.

There is general consensus that the overall prevalence of serum non-organ-specific autoantibodies is significantly higher in patients with HCV (about one third of all cases) than that in both healthy subjects and patients with HBV [91–93], but not alcoholic liver injury. In addition, HCV infection was confirmed in five of 10 patients (50%) who developed thrombotic microangiopathy (TMA) after living-donor liver transplantation [94]. In our study, the etiology of our five end-stage LC patients with IgG-type autoantibodies was HCV in 2, HBV in 1, PBC in 1, and cryptogenic in 1, but none of the patients displayed alcohol-abuse-related cirrhosis [30]. Nevertheless, the diagnosis of TTP may be hampered by clinical features accompanying hepatic failure similar to the pentad of typical TTP (fever, thrombocytopenia, renal failure, fluctuating neurological signs, and microangiopathic hemolytic anemia) [11, 12].

8. Possible Therapeutic Approaches of ADAMTS13 Supplementation for Patients with Decompensated LC

Fresh frozen plasma (FFP) infusion is commonly used to correct the prolonged prothrombin time in patients with advanced chronic liver disease, but exact indication for its use has not been clearly defined [95]. The aim of FFP infusions is usually either to improve the coagulopathy before invasive procedures or to control ongoing bleeding from various sites in patients with vitamin K-unresponsiveness prolonged prothrombin time. The mean prothrombin time was improved by the infusion of 2–6 units of FFP, but only 12.5% of the retrospective study group and 10% of the prospective study groups showed reversal of their coagulopathy, and higher volume (6 or more units) may be more effective but rarely is employed [96]. However, attention should be directed to complications including the risk of infection, allergic reaction, and acute volume expansion leading to heart failure or pulmonary edema [95, 96].

With regard to FFP infusion as a unique source of ADAMTS13, we clearly showed that preexisting UL-VWFMs

in the plasma of USS patients began to diminish within 1 hour and completely diminished 24 hours after ADAMTS13 was replenished with infusions of FFP [97]. Retrospectively, these results indicated that exogenous ADAMTS13 could efficiently cleave both UL-VWFMs that preexisted in the circulation and the newly produced molecules at the ECs surface. Advanced LC is known to be a predisposing state toward platelet microthrombi formation, even in the absence of clinically overt thrombi [30]. In our study, UL-VWFM-positive patients showed the lowest ADAMTS13 : AC and the highest values of serum creatinine, blood urea nitrogen, and blood ammonia, and the VWFM patterns appeared to shift from degraded to normal VWFM and finally to UL-VWFM as functional liver capacity and renal function deteriorated (Table 1). From these results, it may be reasonable to assume that advanced LC patients with severe to moderate deficiency of ADAMTS13 : AC (<3% to ~25% of normal control) could be candidates for FFP infusion as a source of ADAMTS13. It is necessary to evaluate the effectiveness of FFP administration to patients with ADAMTS13 : AC levels from 25% to 50%.

Alternatively, our recent study demonstrated that plasma ADAMTS13 : AC is reduced in VOD patients after stem cell transplantation (SCT) (12–32% of normal) compared to non-VOD patients (57–78% of normal), even before any conditioning regimen and throughout SCT, and that the activity might thus be a predictor for the development of hepatic VOD [22]. A multicenter, prospective, randomized controlled study revealed that prophylactic FFP infusion may be instrumental in preventing the development of hepatic VOD after SCT [23]. The imbalance caused by decreased ADAMTS13 : AC versus increased production of VWF : Ag before and during the early stage after SCT would contribute to a microcirculatory disturbance that could ultimately lead to VOD [23]. The supplementation of ADAMTS13 by prophylactic FFP infusion may suppress the increase in VWF : AG that is extensively released from damaged SEC. Furthermore, we first reported in 2006 that a significant reduction of ADAMTS13 : AC with a concomitant appearance of UL-VWFM was consistently observed in patient plasma soon after liver transplantation [31]. These changes were closely related to liver-graft dysfunction, ischemia-reperfusion injury, and acute rejection. The ADAMTS13 : AC often decreased to less than 10% of normal controls, concurrent with severe thrombocytopenia. The organ dysfunction appeared to be restricted to the liver graft, indicating that a decrease of plasma ADAMTS13 : AC coupled with the appearance of UL-VWFM was attributed to a mechanism of "local TTP" within the liver graft [21, 31]. It is, therefore, extremely important to monitor plasma ADAMTS13 : AC in the treatment of thrombocytopenia associated with allograft dysfunction after liver transplantation. This is because the infusions of platelet concentrate under conditions of an imbalance of decreased ADAMTS13 : AC to enhanced UL-VWFM production might further exacerbate the formation of platelet aggregates mediated by uncleaved UL-VWFM, leading to graft failure via the "local TTP" mechanism [21, 31]. FFP infusion as ADAMTS13 replacement therapy may improve both liver dysfunction and thrombocytopenia in liver transplant patients. From this point of view, we are particularly interested in conducting clinical trials with recombinant ADAMTS13 preparations not only in patients with advanced LC but also in patients with VOD and liver transplantations.

9. Conclusion and Future Perspectives

The introduction of ADAMTS13 to the field of hepatology not only enabled us to confirm the diagnosis of TTP early but also provided novel insight into the pathophysiology of liver diseases. Some diseases were shown to be TTP itself, but others did not show any apparent clinical features of TTP, even in the presence of extremely decreased ADAMTS13 : AC and increased UL-VWFM corresponding to TTP. Such TTP-like states, but without disseminated intravascular coagulation, might be "subclinical TTP" as seen in advanced liver cirrhotics [30] and SAH patients [24–27] or "local TTP" as shown in patients with hepatic VOD after SCT [22, 23] and patients with adverse events after living-donor liver transplantation [31, 32]. Essentially, one would be unable to detect such TTP-like phenomena without the determination of ADAMTS13 : AC, because the interaction of ADAMTS13 and UL-VWFM is the initial step in hemostasis, and their abnormalities do occur in the absence of apparent imbalance in other hemostatic factors and/or irrespective of the presence or absence of abnormal conventional hemostatic factors. The origin of VWF, the substrate of ADAMS13, indeed may be transformed hepatic sinusoidal and/or extrahepatic endothelial cells, but not hepatocytes. The procoagulant and anticoagulant proteins synthesized in hepatocytes decrease as liver disease progresses, whereas VWF markedly increases. Under such circumstances, ADAMTS13 deficiency may lead to a microcirculatory disturbance not only in the liver, but also in the systemic circulation. The determination of ADAMTS13 and its related parameters thus will be quite useful for improved understanding of the pathophysiology and for providing appropriate treatments especially in severe liver disease patients. It will be necessary to measure ADAMTS13 : AC when patients with unexplained thrombocytopenia are encountered in the course of liver disease. When "subclinical or local TTP" status would be confirmed, FFP infusion as ADAMTS13 replacement therapy may improve both liver dysfunction and thrombocytopenia. Further investigation will be necessary to define candidates for ADAMTS13 supplementation therapy and to evaluate its potential therapeutic efficacy in advanced LC patients.

Acknowledgments

The authors sincerely thank Hiromichi Ishizashi, Ayami Isonishi, Seiji Kato, Tomomi Matsuyama, Chie Morioka, and Masatoshi Ishikawa for their great help in the assay of ADAMTS13 activity, VWF antigen, and UL-VWFM. This work was supported in part by research grants from the Japanese Ministry of Education, Culture, Science (to M. Uemura, Y. Fujimura, S. Ko, and M. Matsumoto) and from

the Ministry of Health, Labour and Welfare of Japan for Blood Coagulation Abnormalities (to Y. Fujimura).

References

[1] L. N. Roberts, R. K. Patel, and R. Arya, "Haemostasis and thrombosis in liver disease," *British Journal of Haematology*, vol. 148, no. 4, pp. 507–521, 2010.

[2] A. Tripodi, M. Primignani, and P. M. Mannucci, "Abnormalities of hemostasis and bleeding in chronic liver disease: the paradigm is challenged," *Internal and Emergency Medicine*, vol. 5, no. 1, pp. 7–12, 2010.

[3] T. Lisman and R. J. Porte, "Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences," *Blood*, vol. 116, no. 6, pp. 878–885, 2010.

[4] P. G. Northup, V. Sundaram, M. B. Fallon et al., "Hypercoagulation and thrombophilia in liver disease," *Journal of Thrombosis and Haemostasis*, vol. 6, pp. 2–9, 2008.

[5] J. L. Moake, "Thrombotic microangiopathies," *New England Journal of Medicine*, vol. 347, no. 8, pp. 589–600, 2002.

[6] Y. Fujimura, M. Matsumoto, H. Yagi, A. Yoshioka, T. Matsui, and K. Titani, "Von Willebrand factor-cleaving protease and Upshaw-Schulman syndrome," *International Journal of Hematology*, vol. 75, no. 1, pp. 25–34, 2002.

[7] G. G. Levy, W. C. Nichols, E. C. Lian et al., "Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura," *Nature*, vol. 413, pp. 488–494, 2001.

[8] K. Kokame, M. Matsumoto, K. Soejima et al., "Mutations and common polymorphisms in ADAMTS13 gene responsible for von Willebrand factor-cleaving protease activity," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 99, no. 18, pp. 11902–11907, 2002.

[9] M. Furlan, R. Robles, M. Galbusera et al., "Von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome," *New England Journal of Medicine*, vol. 339, no. 22, pp. 1578–1584, 1998.

[10] H. M. Tsai and E. C. Lian, "Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura," *New England Journal of Medicine*, vol. 339, no. 22, pp. 1585–1594, 1998.

[11] E. Moschcowitz, "Hyaline thrombosis of the terminal arterioles and capillaries: a hitherto undescribed disease," *Proceeding New York Pathological Society*, vol. 24, pp. 21–24, 1924.

[12] E. L. Amorosi and J. E. Ultmann, "Thrombotic thrombocytopenic purpura: report of 16 cases and review of the literature," *Medicine*, vol. 45, pp. 139–159, 1966.

[13] M. Matsumoto, H. Chisuwa, Y. Nakazawa et al., "Living-related liver transplantation rescues reduced vWF-cleaving protease activity in patients with cirrhotic biliary atresia," *Blood*, vol. 96, p. 636a, 2000.

[14] X. Zheng, D. Chung, T. K. Takayama, E. M. Majerus, J. E. Sadler, and K. Fujikawa, "Structure of von Willebrand factor-cleaving protease (ADAMTS13), a metalloprotease involved in thrombotic thrombocytopenic purpura," *Journal of Biological Chemistry*, vol. 276, no. 44, pp. 41059–41063, 2001.

[15] K. Soejima, N. Mimura, M. Hirashima et al., "A novel human metalloprotease synthesized in the liver and secreted into the blood: possibly, the von Willebrand factor-cleaving protease?" *Journal of Biochemistry*, vol. 130, no. 4, pp. 475–480, 2001.

[16] M. Uemura, K. Tatsumi, M. Matsumoto et al., "Localization of ADAMTS13 to the stellate cells of human liver," *Blood*, vol. 106, no. 3, pp. 922–924, 2005.

[17] M. Suzuki, M. Murata, Y. Matsubara et al., "von Willebrand factor-cleaving protease (ADAMTS-13) in human platelets," *Biochemical and Biophysical Research Communications*, vol. 313, no. 1, pp. 212–216, 2004.

[18] N. Turner, L. Nolasco, Z. Tao, J. F. Dong, and J. Moake, "Human endothelial cells synthesize and release ADAMTS-13," *Journal of Thrombosis and Haemostasis*, vol. 4, no. 6, pp. 1396–1404, 2006.

[19] M. Manea, A. Kristoffersson, R. Schneppenheim et al., "Podocytes express ADAMTS13 in normal renal cortex and in patients with thrombotic thrombocytopenic purpura," *British Journal of Haematology*, vol. 138, no. 5, pp. 651–662, 2007.

[20] P. M. Mannucci, M. T. Canciani, I. Forza, F. Lussana, A. Lattuada, and E. Rossi, "Changes in health and disease of the metalloprotease that cleaves von Willebrand factor," *Blood*, vol. 98, no. 9, pp. 2730–2735, 2001.

[21] M. Uemura, Y. Fujimura, S. Ko, M. Matsumoto, Y. Nakajima, and H. Fukui, "Pivotal role of ADAMTS13 function in liver diseases," *International Journal of Hematology*, vol. 91, no. 1, pp. 20–29, 2010.

[22] Y. D. Park, A. Yoshioka, K. Kawa et al., "Impaired activity of plasma von Willebrand factor-cleaving protease may predict the occurrence of hepatic veno-occlusive disease after stem cell transplantation," *Bone Marrow Transplantation*, vol. 29, no. 9, pp. 789–794, 2002.

[23] M. Matsumoto, K. Kawa, M. Uemura et al., "Prophylactic fresh frozen plasma may prevent development of hepatic VOD after stem cell transplantation via ADAMTS13-mediated restoration of von Willebrand factor plasma levels," *Bone Marrow Transplantation*, vol. 40, pp. 251–259, 2007.

[24] M. Uemura, Y. Fujimura, T. Matsuyama et al., "Potential role of ADAMTS13 in the progression of alcoholic hepatitis," *Current Drug Abuse Reviews*, vol. 1, no. 2, pp. 188–196, 2008.

[25] M. Ishikawa, M. Uemura, T. Matsuyama et al., "Potential role of enhanced cytokinemia and plasma inhibitor on the decreased activity of plasma ADAMTS13 in patients with alcoholic hepatitis: relationship to endotoxemia," *Alcoholism: Clinical and Experimental Research*, vol. 34, supplement 1, pp. S25–S33, 2010.

[26] T. Matsuyama, M. Uemura, M. Ishikawa et al., "Increased von Willebrand factor over decreased ADAMTS13 activity may contribute to the development of liver disturbance and multiorgan failure in patients with alcoholic hepatitis," *Alcoholism: Clinical and Experimental Research*, vol. 31, supplement 1, pp. S27–S35, 2007.

[27] M. Uemura, T. Matsuyama, M. Ishikawa et al., "Decreased activity of plasma ADAMTS13 may contribute to the development of liver disturbance and multiorgan failure in patients with alcoholic hepatitis," *Alcoholism: Clinical and Experimental Research*, vol. 29, no. 12, supplement 3, pp. 264S–271S, 2005.

[28] T. Lisman, T. N. Bongers, J. Adelmeijer et al., "Elevated levels of von Willebrand factor in cirrhosis support platelet adhesion despite reduced functional capacity," *Hepatology*, vol. 44, no. 1, pp. 53–61, 2006.

[29] H. B. Feys, M. T. Canciani, F. Peyvandi, H. Deckmyn, K. Vanhoorelbeke, and P. M. Mannucci, "ADAMTS13 activity to antigen ratio in physiological and pathological conditions associated with an increased risk of thrombosis," *British Journal of Haematology*, vol. 138, no. 4, pp. 534–540, 2007.

[30] M. Uemura, Y. Fujimura, M. Matsumoto et al., "Comprehensive analysis of ADAMTS13 in patients with liver cirrhosis," *Thrombosis and Haemostasis*, vol. 99, no. 6, pp. 1019–1029, 2008.

[31] S. Ko, E. Okano, H. Kanehiro et al., "Plasma ADAMTS13 activity may predict early adverse events in living donor liver transplantation: observations in 3 cases," *Liver Transplantation*, vol. 12, no. 5, pp. 859–869, 2006.

[32] T. Kobayashi, H. Wada, M. Usui et al., "Decreased ADAMTS13 levels in patients after living donor liver transplantation," *Thrombosis Research*, vol. 124, no. 5, pp. 541–545, 2009.

[33] I. T. A. Pereboom, J. Adelmeijer, Y. Van Leeuwen, H. G. D. Hendriks, R. J. Porte, and T. Lisman, "Development of a severe von Willebrand factor/ADAMTS13 dysbalance during orthotopic liver transplantation," *American Journal of Transplantation*, vol. 9, no. 5, pp. 1189–1196, 2009.

[34] E. Okano, S. Ko, H. Kanehiro, M. Matsumoto, Y. Fujimura, and Y. Nakajima, "ADAMTS13 activity decreases after hepatectomy, reflecting a postoperative liver dysfunction," *Hepato-Gastroenterology*, vol. 57, no. 98, pp. 316–320, 2010.

[35] M. Yagita, M. Uemura, T. Nakamura, A. Kunitomi, M. Matsumoto, and Y. Fujimura, "Development of ADAMTS13 inhibitor in a patient with hepatitis C virus-related liver cirrhosis causes thrombotic thrombocytopenic purpura," *Journal of Hepatology*, vol. 42, no. 3, pp. 420–421, 2005.

[36] F. Durand and D. Valla, "Assessment of prognosis of cirrhosis," *Seminars in Liver Disease*, vol. 28, no. 1, pp. 110–122, 2008.

[37] Z. Kmieć, "Cooperation of liver cells in health and disease," *Advances in Anatomy, Embryology, and Cell Biology*, vol. 161, pp. 1–151, 2001.

[38] D. C. Rockey, "Hepatic blood flow regulation by stellate cells in normal and injured liver," *Seminars in Liver Disease*, vol. 21, no. 3, pp. 337–350, 2001.

[39] F. Schaffner and H. Popper, "Capillarization of hepatic sinusoids in man," *Gastroenterology*, vol. 44, pp. 239–242, 1963.

[40] M. Hattori, Y. Fukuda, M. Imoto, Y. Koyama, I. Nakano, and F. Urano, "Histochemical properties of vascular and sinusoidal endothelial cells in liver diseases," *Gastroenterologia Japonica*, vol. 26, no. 3, pp. 336–343, 1991.

[41] L. Albornoz, D. Alvarez, J. C. Otaso et al., "Von Willebrand factor could be an index of endothelial dysfunction in patients with cirrhosis: relationship to degree of liver failure and nitric oxide levels," *Journal of Hepatology*, vol. 30, no. 3, pp. 451–455, 1999.

[42] D. Ferro, C. Quintarelli, A. Lattuada et al., "High plasma levels of von Willebrand factor as a marker of endothelial perturbation in cirrhosis: relationship to endotoxemia," *Hepatology*, vol. 23, no. 6, pp. 1377–1383, 1996.

[43] T. Knittel, K. Neubauer, T. Armbrust, and G. Ramadori, "Expression of von Willebrand factor in normal and diseased rat livers and in cultivated liver cells," *Hepatology*, vol. 21, no. 2, pp. 470–476, 1995.

[44] S. Urashima, M. Tsutsumi, K. Nakase, J. S. Wang, and A. Takada, "Studies on capillarization of the hepatic sinusoids in alcoholic liver disease," *Alcohol and Alcoholism*, vol. 1B, pp. 77–84, 1993.

[45] L. Amitrano, M. A. Guardascione, V. Brancaccio et al., "Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis," *Journal of Hepatology*, vol. 40, no. 5, pp. 736–741, 2004.

[46] I. R. Wanless, F. Wong, L. M. Blendis, P. Greig, E. J. Heathcote, and G. Levy, "Hepatic and portal vein thrombosis in cirrhosis: possible role in development of parenchymal extinction and portal hypertension," *Hepatology*, vol. 21, no. 5, pp. 1238–1247, 1995.

[47] K. Oka and K. Tanaka, "Intravascular coagulation in autopsy cases with liver diseases," *Thrombosis and Haemostasis*, vol. 42, no. 2, pp. 564–570, 1979.

[48] A. Pluta, K. Gutkowski, and M. Hartleb, "Coagulopathy in liver diseases," *Advanced Medical Science*, vol. 55, pp. 16–21, 2010.

[49] Y. Fujimura, M. Matsumoto, and H. Yagi, *Thrombotic Microangiopathy*, Springer, Tokyo, Japan, 2008.

[50] A. Padilla, J. L. Moake, A. Bernardo et al., "P-selectin anchors newly released ultralarge von Willebrand factor multimers to the endothelial cell surface," *Blood*, vol. 103, no. 6, pp. 2150–2156, 2004.

[51] C. A. Siedlecki, B. J. Lestini, K. K. Kottke-Marchant, S. J. Eppell, D. L. Wilson, and R. E. Marchant, "Shear-dependent changes in the three-dimensional structure of human von Willebrand factor," *Blood*, vol. 88, no. 8, pp. 2939–2950, 1996.

[52] J. A. Dent, S. D. Berkowitz, J. Ware, C. K. Kasper, and Z. M. Ruggeri, "Identification of a cleavage site directing the immunochemical detection of molecular abnormalities in type IIA von Willebrand factor," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 87, no. 16, pp. 6306–6310, 1990.

[53] M. Akiyama, S. Takeda, K. Kokame, J. Takagi, and T. Miyata, "Crystal structures of the noncatalytic domains of ADAMTS13 reveal multiple discontinuous exosites for von Willebrand factor," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 106, no. 46, pp. 19274–19279, 2009.

[54] A. K. Davis, R. S. Makar, C. P. Stowell, D. J. Kuter, and W. H. Dzik, "ADAMTS13 binds to CD36: a potential mechanism for platelet and endothelial localization of ADAMTS13," *Transfusion*, vol. 49, no. 2, pp. 206–213, 2009.

[55] M. Furlan, R. Robles, and B. Lämmle, "Partial purification and characterization of a protease from human plasma cleaving von Willebrand factor to fragments produced by in vivo proteolysis," *Blood*, vol. 87, no. 10, pp. 4223–4234, 1996.

[56] S. Kinoshita, A. Yoshioka, Y. D. Park et al., "Upshaw-Schulman syndrome revisited: a concept of congenital thrombotic thrombocytopenic purpura," *International Journal of Hematology*, vol. 74, pp. 101–108, 2001.

[57] S. Kato, M. Matsumoto, T. Matsuyama, A. Isonishi, H. Hiura, and Y. Fujimura, "Novel monoclonal antibody-based enzyme immunoassay for determining plasma levels of ADAMTS13 activity," *Transfusion*, vol. 46, no. 8, pp. 1444–1452, 2006.

[58] S. C. Meyer, I. Sulzer, B. Lämmle, and J. A. Kremer Hovinga, "Hyperbilirubinemia interferes with ADAMTS-13 activity measurement by FRETS-VWF73 assay: diagnostic relevance in patients suffering from acute thrombotic microangiopathies," *Journal of Thrombosis and Haemostasis*, vol. 5, no. 4, pp. 866–867, 2007.

[59] C. K. Kasper, L. Aledort, D. Aronson et al., "A more uniform measurement of factor VIII inhibitors," *Thrombosis et Diathesis Haemorrhagica*, vol. 34, no. 2, pp. 869–872, 1975.

[60] N. Afdhal, J. McHutchison, R. Brown et al., "Thrombocytopenia associated with chronic liver disease," *Journal of Hepatology*, vol. 48, no. 6, pp. 1000–1007, 2008.

[61] R. H. Aster, "Pooling of platelets in the spleen: role in the pathogenesis of "hypersplenic" thrombocytopenia," *Journal of Clinical Investigation*, vol. 45, no. 5, pp. 645–657, 1966.

[62] M. Peck-Radosavljevic, M. Wichlas, J. Zacherl et al., "Thrombopoietin induces rapid resolution of thrombocytopenia after orthotopic liver transplantation through increased platelet production," *Blood*, vol. 95, no. 3, pp. 795–801, 2000.

[63] J. García-Suárez, C. Burgaleta, N. Hernanz, F. Albarran, P. Tobaruela, and M. Alvarez-Mon, "HCV-associated thrombocytopenia: clinical characteristics and platelet response after recombinant alpha2b-interferon therapy," *British Journal of Haematology*, vol. 110, no. 1, pp. 98–103, 2000.

[64] H. S. Ballard, "Hematological complications of alcoholism," *Alcoholism: Clinical and Experimental Research*, vol. 13, no. 5, pp. 706–720, 1989.

[65] H. E. Gerritsen, P. L. Turecek, H. P. Schwarz, B. Lämmle, and M. Furlan, "Assay of von Willebrand factor (vWF)-cleaving protease based on decreased collagen binding affinity of degraded vWF. A tool for the diagnosis of thrombotic thrombocytopenic purpura (TTP)," *Thrombosis and Haemostasis*, vol. 82, no. 5, pp. 1386–1389, 1999.

[66] A. E. Schorer, C. F. Moldow, and M. E. Rick, "Interleukin 1 or endotoxin increases the release of von Willebrand factor from human endothelial cells," *British Journal of Haematology*, vol. 67, no. 2, pp. 193–197, 1987.

[67] I. Tornai, J. Hársfalvi, Z. Boda, M. Udvardy, G. Pfliegler, and K. Rak, "Endothelium releases more von Willebrand factor and tissue-type plasminogen activator upon venous occlusion in patients with liver cirrhosis than in normals," *Haemostasis*, vol. 23, no. 1, pp. 58–64, 1993.

[68] A. Bernardo, C. Ball, L. Nolasco, J. F. Moake, and J. F. Dong, "Effects of inflammatory cytokines on the release and cleavage of the endothelial cell-derived ultralarge von Willebrand-factor multimers under flow," *Blood*, vol. 104, no. 1, pp. 100–106, 2004.

[69] W. J. Cao, M. Niiya, X. W. Zheng, D. Z. Shang, and X. L. Zheng, "Inflammatory cytokines inhibit ADAMTS13 synthesis in hepatic stellate cells and endothelial cells," *Journal of Thrombosis and Haemostasis*, vol. 6, no. 7, pp. 1233–1235, 2008.

[70] Y. Kume, H. Ikeda, M. Inoue et al., "Hepatic stellate cell damage may lead to decreased plasma ADAMTS13 activity in rats," *FEBS Letters*, vol. 581, no. 8, pp. 1631–1634, 2007.

[71] M. Niiya, M. Uemura, X. W. Zheng et al., "Increased ADAMTS-13 proteolytic activity in rat hepatic stellate cells upon activation in vitro and in vivo," *Journal of Thrombosis and Haemostasis*, vol. 4, no. 5, pp. 1063–1070, 2006.

[72] Y. Fujimura and M. Matsumoto, "Registry of 919 patients with thrombotic microangiopathies across Japan: database of Nara Medical University during 1998–2008," *Internal Medicine*, vol. 49, no. 1, pp. 7–15, 2010.

[73] H. Fukui, B. Brauner, J. C. Bode, and C. Bode, "Plasma endotoxin concentrations in patients with alcoholic and non-alcoholic liver disease: reevaluation with an improved chromogenic assay," *Journal of Hepatology*, vol. 12, no. 2, pp. 162–169, 1991.

[74] P. Tandon and G. Garcia-Tsao, "Bacterial infections, sepsis, and multiorgan failure in cirrhosis," *Seminars in Liver Disease*, vol. 28, no. 1, pp. 26–42, 2008.

[75] M. Sala, A. Forner, M. Varela, and J. Bruix, "Prognostic prediction in patients with hepatocellular carcinoma," *Seminars in Liver Disease*, vol. 25, no. 2, pp. 171–180, 2005.

[76] R. A. Claus, C. L. Bockmeyer, M. Sossdorf, and W. Lösche, "The balance between von-Willebrand factor and its cleaving protease ADAMTS13: biomarker in systemic inflammation and development of organ failure?" *Current Molecular Medicine*, vol. 10, no. 2, pp. 236–248, 2010.

[77] R. A. Reiter, K. Varadi, P. L. Turecek, B. Jilma, and P. Knöbl, "Changes in ADAMTS13 (von-Willebrand-factor-cleaving protease) activity after induced release of von Willebrand factor during acute systemic inflammation," *Thrombosis and Haemostasis*, vol. 93, no. 3, pp. 554–558, 2005.

[78] C. L. Bockmeyer, R. A. Claus, U. Budde et al., "Inflammation-associated ADAMTS13 deficiency promotes formation of ultra-large von Willebrand factor," *Haematologica*, vol. 93, no. 1, pp. 137–140, 2008.

[79] K. Iyoda, M. Kato, T. Nakagawa et al., "Thrombotic thrombocytopenic purpura developed suddenly during interferon treatment for chronic hepatitis C," *Journal of Gastroenterology*, vol. 33, no. 4, pp. 588–592, 1998.

[80] A. Hori, M. Kami, T. Hamaki et al., "Thrombotic thrombocytopenic purpura without any evidence of thrombotic lesions at autopsy," *Annals of Hematology*, vol. 80, no. 8, pp. 496–498, 2001.

[81] A. Shibuya, A. Satomichi, S. Nagaba, H. Endoh, S. Kuwao, and K. Saigenji, "Thrombotic thrombocytopenic purpura in autoimmune hepatitis," *Journal of Gastroenterology*, vol. 36, no. 8, pp. 569–573, 2001.

[82] J. V. Nally and E. N. Metz, "Acute thrombotic thrombocytopenic purpura. Another cause for hemolytic anemia and thrombocytopenia in cirrhosis," *Archives of Internal Medicine*, vol. 139, no. 6, pp. 711–712, 1979.

[83] S. Killick, S. Jeffery, M. Otter, C. Rist, and D. Bevan, "Thrombotic thrombocytopenic purpura in a patient with genetic haemochromatosis, liver cirrhosis and an iron-free focus," *British Journal of Haematology*, vol. 99, no. 4, pp. 839–841, 1997.

[84] K. Kitano, Y. Gibo, A. Kamijo et al., "Thrombotic thrombocytopenic purpura associated with pegylated-interferon alpha-2a by an ADAMTS13 inhibitor in a patient with chronic hepatitis C," *Haematologica*, vol. 91, article ECR34, supplement 8, 2006.

[85] F. Lambot, B. Hanson, and B. Sztern, "Thrombotic thrombocytopenic purpura mediated by an ADAMTS13-inhibitor related to a treatment with pegylated-interferon alpha-2a and ribavirine in a patient with chronic hepatitis C," *Presse Medicale*, vol. 39, pp. 1207–1210, 2010.

[86] M. Deutsch, E. K. Manesis, E. Hadziyannis, D. Vassilopoulos, and A. J. Archimandritis, "Thrombotic thrombocytopenic purpura with fatal outcome in a patient with chronic hepatitis C treated with pegylated interferon-a/2b," *Scandinavian Journal of Gastroenterology*, vol. 42, no. 3, pp. 408–409, 2007.

[87] M. Sallée, E. Crétel, R. Jean et al., "Thrombotic thrombocytopenic purpura complicating interferon therapy in chronic C hepatitis," *Gastroenterologie Clinique et Biologique*, vol. 32, no. 2, pp. 145–146, 2008.

[88] M. Shimizu, S. Nomura, K. Ishii et al., "The significance of ADAMTSI3 in a patient with thrombotic thrombocytopenic purpura complicated autoimmune hepatitis," *Thrombosis and Haemostasis*, vol. 101, no. 3, pp. 599–600, 2009.

[89] K. Sonomoto, T. Miyamura, H. Watanabe et al., "A case of systemic lupus erythematosus complicated with autoimmune hepatitis and thrombotic thrombocytic purpura," *Japanese Journal of Clinical Immunology*, vol. 32, no. 2, pp. 110–115, 2009.

[90] Y. Usta, F. Gurakan, Z. Akcoren, and S. Ozen, "An overlap syndrome involving autoimmune hepatitis and systemic lupus erythematosus in childhood," *World Journal of Gastroenterology*, vol. 13, no. 19, pp. 2764–2767, 2007.

[91] M. Lenzi, S. Bellentani, G. Saccoccio et al., "Prevalence of non-organ-specific autoantibodies and chronic liver disease in the general population: a nested case-control study of the Dionysos cohort," *Gut*, vol. 45, no. 3, pp. 435–441, 1999.

[92] M. Y. Hsieh, C. Y. Dai, L. P. Lee et al., "Antinuclear antibody is associated with a more advanced fibrosis and lower RNA levels of hepatitis C virus in patients with chronic hepatitis C," *Journal of Clinical Pathology*, vol. 61, no. 3, pp. 333–337, 2008.

[93] S. Tamura, Y. Sugawara, Y. Matsui et al., "Thrombotic microangiopathy in living-donor liver transplantation," *Transplantation*, vol. 80, no. 2, pp. 169–175, 2005.

[94] B. D. Clifford, D. Donahue, L. Smith et al., "High prevalence of serological markers of autoimmunity in patients with chronic hepatitis C," *Hepatology*, vol. 21, no. 3, pp. 613–619, 1995.

[95] A. Iorio, M. Basileo, E. Marchesini et al., "The good use of plasma. A critical analysis of five international guidelines," *Blood Transfusion*, vol. 6, no. 1, pp. 18–24, 2008.

[96] W. I. Youssef, F. Salazar, S. Dasarathy, T. Beddow, and K. D. Mullen, "Role of fresh frozen plasma infusion in correction of coagulopathy of chronic liver disease: a dual phase study," *American Journal of Gastroenterology*, vol. 98, no. 6, pp. 1391–1394, 2003.

[97] H. Yagi, M. Konno, S. Kinoshita et al., "Plasma of patients with Upshaw-Schulman syndrome, a congenital deficiency of von Willebrand factor-cleaving protease activity, enhances the aggregation of normal platelets under high shear stress," *British Journal of Haematology*, vol. 115, no. 4, pp. 991–997, 2001.

SAGE-Hindawi Access to Research
International Journal of Hepatology
Volume 2011, Article ID 918017, 11 pages
doi:10.4061/2011/918017

Review Article

Treatment of Hepatitis B in Decompensated Liver Cirrhosis

Richard Guan[1] and Hock Foong Lui[2]

[1] *Mount Elizabeth Hospital and Medical Centre, Singapore 228510*
[2] *Gleneagles Hospital and Medical Centre, Singapore 258500*

Correspondence should be addressed to Richard Guan, rgyc5@singnet.com.sg

Received 15 February 2011; Accepted 19 April 2011

Academic Editor: Deepak Amarapurkar

Chronic hepatitis B infection progresses from an asymptomatic persistently infected state to chronic hepatitis, cirrhosis, decompensated liver disease, and/or hepatocellular carcinoma. About 3% of patients with chronic hepatitis develop cirrhosis yearly, and about 5% of individuals with hepatitis B cirrhosis become decompensated annually. The outcome for patients with decompensated cirrhosis is bleak. Lamivudine, the first oral antiviral agent available for hepatitis B treatment is safe and effective and can improve or stabilize liver disease in patients with advanced cirrhosis and viraemia. Viral resistance restricts its prolonged use. Entecavir and tenofovir are newer agents with excellent resistance profile to date. These and some other antiviral agents are being investigated for optimal use in this rather challenging patient group.

1. Introduction

Chronic hepatitis B virus (HBV) infection is a major global public health problem with an estimated 1 million deaths yearly worldwide from complications of liver cirrhosis namely, liver failure and hepatocellular cancer (HCC) [1, 2]. Up to 40% patients with chronic hepatitis B virus infection develop serious complications during their lifetime. Up to 12% of patients with HBV cirrhosis die of liver failure, and up to 10% perish from liver cancer [3, 4]. The prognosis for patients with decompensated HBV cirrhosis is poor, with a 5-year survival of only 14% compared with 84% in patients with compensated HBV cirrhosis [3]. The ultimate cure for end stage liver disease is liver transplantation. Many patients with advanced hepatitis B worldwide do not have access to or are not eligible for this treatment modality [1, 5]. This article briefly review the epidemiology and natural progression of chronic hepatitis B infection and provides an update on the medical management of patients with decompensated HBV cirrhosis with particular emphasis on the use of available antiviral agents.

2. Prevalence of Hepatitis B Infection

Hepatitis B virus (HBV) infection is endemic in the Asia Pacific region and in Africa. Up to 62% of the population in China, up to 98% of the people in sub-Saharan Africa and up to 80% of the populations in some Pacific islands have markers of HBV infection [6]. Chronic or persistent HBV infection is defined as the presence of hepatitis B surface antigen (HBsAg) in the serum for longer than 6 months. It is estimated that there are 350 million people with chronic HBV infection worldwide (more than 5% of the world population). More than 75% of these chronically infected people live in Asia and a further 12%, (approximately 50 million) live in Africa. In many countries in the Asia Pacific region, 8–20% of the populations have chronic HBV infection [7].

3. Disease Progression in Chronic Hepatitis B Infection

Chronic HBV infection can lead to chronic liver disease, with a broad range of symptoms [8, 9]. The early phase of the infection is typically asymptomatic with active virus replication (HBVDNA > 20,000 IU/mL) and very little liver necroinflammation. Hepatitis B antigen (HBeAg) is present. This phase, also called the immune-tolerant phase, can last for several decades before the appearance of hepatitis symptoms. Persistent or episodic hepatic necroinflammation (chronic hepatitis), with elevated serum alanine

aminotransferase (ALT) levels, characterizes this phase of immune elimination of HBV. During this stage, HBeAg and HBV DNA levels may progressively decrease and seroconversion from HBeAg to HBe antibody (anti-HBe) may occur [10, 11]. The longer this period of active liver disease lasts, the higher the risk of irreversible liver damage. Patients enter the third (inactive carrier) phase when HBV replication is no longer detected and liver histology usually stabilizes [10]. However low levels of the virus (HBVDNA < 2000 IU/mL) can stillbe detected in the majority of patients, and reactivation of HBV replication with exacerbation of disease can occur [12–14]. Some patients may progress to cirrhosis and HCC during this phase of apparent inactivity.

In the Asia-Pacific region, the annual incidence of chronic hepatitis in asymptomatic, persistently infected individuals ranged from 0.84 to 2.7%. The annual incidence of cirrhosis among patients with chronic hepatitis B was reported to be approximately 1.0–2.4%. The annual rates of progression from compensated cirrhosis to decompensated cirrhosis were around 4.6% [15, 16]. The annual incidence of HCC ranged from 0.02–0.65% in asymptomatic persistently infected individuals, 0.27–1.0% in patients with chronic hepatitis B and 3.0–6.6% in compensated HBV cirrhosis [6]. The annual progression rate from decompensated HBV cirrhosis to HCC was around 7.1%. The 5-year mortality rate from decompensated cirrhosis was from 41% to 67% [17, 18].

Factors associated with rapid disease progression in HBV infected patients include the male gender, increasing age, viraemia with repeated hepatic flares or prolonged periods of liver necroinflammation, and alcohol use; confection with other viruses such as hepatitis C, hepatitis D, and human immunodeficiency virus (HIV); use of immunosuppressive agents, platelets less than 150,000/mL and serum bilirubin more than 1.1 mg/dL (18.8 umol/L) [19–26]. Patients with HBV cirrhosis and active viral replication are at increased risk of developing progressive liver disease and death [4, 27]. Loss of HBeAg and seroconversion to HBe antibody (anti-HBe) with reduction in HBVDNA levels have been associated with a 55% reduction in the risk of death [3]. Suppression of HBV replication with loss of HBeAg and or HBsAg is therefore an important event in the natural history and treatment of chronic HBV infection.

4. Liver Cirrhosis and Decompensation

The mean age of onset of cirrhosis in chronic HBV infection acquired during childhood, is about 40 years and complications become clinically evident 3 to 5 years later. It is estimated that the annual rate of hepatic decompensation is 4% in cirrhotic patients with viraemia and 1% in those without viraemia [14]. The development of jaundice, ascites, hepatic encephalopathy (HE) or bleeding oesophageal varices signals decompensation. Acute decompensation is usually secondary to a hepatitis flare or spontaneous bacterial infection which further impairs the already decreased hepatic reserve. The other form is a gradually developing end-stage event. As mentioned previously, the outlook for decompensated cirrhosis is rather bleak with a 5-year survival of 14% compared with 84% in patients with compensated cirrhosis [3].

5. General Management of Patients with Decompensated Liver Cirrhosis

5.1. Assessment of Disease Severity. Clinical examination and measurement of blood parameters like serum albumin, bilirubin, creatinine and prothrombin time can help determine the severity and progression of liver disease.The Child-Turcotte-Pugh (CTP) score and Model for End Stage Liver Disease (MELD) score are two indices that are usually used to determine the severity of liver disease in patients with cirrhosis [28] (Table 1). The CTP score was developed to determine preoperative risk of patients with cirrhosis for portal-systemic shunt surgery. It is calculated by adding the individual scores assigned to ranges of serum albumin level, serumbilirubin level, prothrombin time, the presence and degree of ascites and hepatic encephalopathy. The CTP score is easily calculated at the patient's bedside. The MELD score was initially developed to predict short-term mortality following transjugular intrahepatic portosystemic shunt (TIPS) placement. It was later modified to predict short-term mortality in patients with different causes of cirrhosis [28] and is now being used to predict waiting list mortality of patients listed for liver transplantation. The MELD score uses objective and standardized laboratory parameters (i.e., serum bilirubin, prothrombin time (international normalized ratio, INR), and creatinine) over a broader range of possible values to provide a more dynamic assessment of liver disease severity. Calculating the MELD score needs a calculator and cannot be easily done at the patient's bedside.

5.2. Prevent Further Liver Damage. Alcohol, potentially hepatotoxic drugs including medications that may increase the risk of gastrointestinal bleeding (nonsteroidal anti-inflammatory agents), or renal insufficiency should be avoided. Patients with decompensated HBV cirrhosis should be vaccinated against hepatitis A if not already immune as superimposed hepatitis A infection could be fatal [29, 30]. As mentioned, the presence of HBeAg or HBV DNA indicates continuing viral replication. International guidelines suggest treating patients with chronic hepatitis B cirrhosis if serum HBV DNA present (EASL) or more than 2,000 IU/mL (AASLD/APASL). The threshold for antiviral therapy is usually lower for decompensated liver disease [31–33].

5.3. Prevent and Treat Complications of Cirrhosis. Gastroscopy should be performed on initial presentation and every two years afterwards in patients with liver cirrhosis to look for oesophageal and gastric varices [34]. If these are found, appropriate treatment should be instituted. Variceal bleeding can be prevented in grade 3 and 4 varices by oral beta blockers and endoscopicvariceal ligation [35]. Treatment of variceal bleeding should include antibiotics to prevent spontaneous septicaemia. Transjugular intrahepatic portosystemic stent (TIPS) placement may be required in patients with uncontrolled or recurrent variceal bleeding

Table 1: Assessing liver disease severity in decompensated HBV cirrhosis.

Scale (range)	Mild	Moderate	Severe	Ref.
CTP (5 to 15)	5-6 (A)	7–9 (B)	10–15 (C)	Keeffe, 2001 [43]
MELD (6–40)	6–10	11–24	25–40	Kamath et al., 2001 [28]

[36]. TIPS may also be considered in patients with refractory ascites if their liver function is not severely impaired, if they are less than 70 years old, and if hepatic encephalopathy is absent [37]. Spontaneous bacterial peritonitis (SBP) and other spontaneous infections should be treated straight away with broad spectrum antibiotics, (e.g., cephalosporins or amoxicillin/clavulanate) and albumin to prevent the hepatorenal syndrome [38]. Prophylactic antibiotics should be given to patients with a history of SBP [39].

Hepatic encephalopathy is a severe complication of cirrhosis and is related to the effect of ammonia. Recent evidence suggests that the effect of ammonia on the brain is triggered by inflammation caused by spontaneous infections. The mainstay of therapy is antibiotics (neomycin, rifaximin, vancomycin) and nonabsorbable disaccharides. Protein restriction is no longer recommended and can worsen the nutritional status if maintained [40]. The development of HE in patients with cirrhosis is associated with a less than 50% survival at 1 year. Liver transplant should be considered. Hepatorenal syndrome (HRS) is a potentially lethal complication and is usually triggered by infections. Besides antibiotics, it can be effectively treated with vasoconstrictors associated with intravenous albumin, TIPS, and albumin dialysis [41] .

5.4. HCC Surveillance. Patients should undergo HCC surveillance by determining serum alpha-fetoprotein (AFP) levels and liver ultrasound every 6 months [32] (Table 2). Early stage HCC can be successfully managed by loco-regional ablative therapy [42] and may change the priority for transplantation [43].

6. Liver Transplantation

Liver transplantation is a well-established modality for treating patients with advanced irreversible liver failure for which there are no alternative treatments [43]. Approximately 5% of liver transplants performed in the United States annually are for hepatitis B [44], and the proportion is higher in the Asia Pacific region [33]. All cirrhotic patients with a CTP score of more than 7 and a complication of portal hypertension such as ascites, encephalopathy, or variceal bleeding should be referred for liver transplant evaluation [43]. Selected patients with unresectable HCC that is less than 5 cm in maximal diameter should also be referred for liver transplant evaluation.

Immunoprophylaxis using prolonged high-dose hepatitis B immunoglobulin (HBIG) has resulted in excellent patient and graft survival rates for patients with decompensated HBV cirrhosis who were viraemic pretransplant [5, 45]. Up to 40% of patients with pretransplant viraemia who received HBIG alone developed recurrent HBV infection [5]. This risk of posttransplant HBV recurrence can be reduced by antiviral suppression of HBV replication prior to transplantation and maintenance of antiviral therapy after transplantation [33]. Liver transplantation is not available to many patients with decompensated HBV infection in the Asia Pacific region, and the only recourse for these patients is antiviral therapy.

7. Antiviral Treatment

Suppression of HBV replication has resulted in reduction of hepatic necroinflammation and improvement of liver function in patients with CHB cirrhosis and liver decompensation. Patients with decompensated HBV-cirrhosis should be considered for antiviral therapy irrespective of HBVDNA levels.

7.1. Interferon-Alpha. Interferon-alpha or its pegylated version is safe and effective in patients with chronic hepatitis B and in selected patients with compensated HBV cirrhosis [46, 47]. It has been associated with life-threatening hepatitis flares (up to 50%) and infectious complications (28%) in prospective trials of patients with decompensated HBV cirrhosis even when used in very low doses [48, 49]. It is generally discouraged in patients with decompensated HBV cirrhosis.

7.2. Oral Antiviral Agents. Most practice guidelines recommend prescribing an oral nucleos(t)ide analogue (and not interferon) for patients with decompensated HBV cirrhosis independent of the patients serum ALT, HBV DNA level, and HBeAg status [31–33]. These recommendations are largely based upon open-label studies of lamivudine and adefovir in this group of patients. These studies reported that antiviral therapy was associated with improved outcomes including a delay or prevention in the need for liver transplantation (Table 1) [50–53]. A biphasic survival pattern was noted with most deaths occurring within the first 6 months of treatment; patients with higher pretreatment bilirubin, creatinine, and HBV DNA levels were at greatest risk for early death while early suppression of HBV replication was not associated with more favorable outcomes [51].

8. Lamivudine

Lamivudine is an orally administered nucleoside analogue that inhibits HBVDNA synthesis by incorporating active triphosphate (3TC-TP) into growing DNA chains. It suppressed serum HBV DNA to undetectable levels (using hybridization assays) in more than 90% of patients with compensated chronic hepatitis B. This was associated with improved serum ALT levels as well as liver histology at 12 months [54, 55]. It is generally safe and well tolerated with a side effect profile similar to that of placebo [54], making it the preferred treatment compared to IFN for patients with

Table 2: General Recommendations in Decompensated HBV Cirrhosis.

Assess disease severity	Clinical, liver biochemistry, creatinine, INR CTP score, MELD score
Prevent further liver damage	Avoid alcohol
	Avoid hepatotoxic drugs
	Avoid Immunosuppression. Antiviral prophylaxis if necessary
	Avoid Aspirin/NSAIDS
	Hepatitis A vaccination in nonimmune
Prevent and treat	Laboratory and clinical assessment 3 to 6 monthly
Complications	Endoscopy at presentation and treat varices accordingly
	Be aware of spontaneous infections and treat appropriately
	Salt and fluid restriction in ascites control, TIPS
	Albumin and terlipressin in hepatorenal syndrome
	Antibiotics and nonabsorbable disaccharides in hepatic encephalopathy
	Low-protein diet not essential
	Regular AFP measurement and ultrasound examination
Antiviral therapy	Entecavir
	Lamivudine. Replace with entecavir monotherapy, Tenofovir monotherapy, or add on adefovir in cases of lamivudine resistance
	Tenofovir
	Telbivudine
	Adefovir
Liver transplantation	Pretransplant antiviral therapy in viraemic subjects and immunoprophylaxis using HBIG after transplant

decompensated HBV cirrhosis. Hepatitis flares during treatment usually indicate the occurrence of resistant mutations. The recommended dose of lamivudine is 100 mg daily. Dose modification is necessary in renal impairment (reduction) and in patients with HIV coinfection (increment). Once treatment is initiated, it should be maintained indefinitely even in patients who appear to have dramatic clinical improvement and in those undergoing liver transplantation.

Development of lamivudine resistance begins after 6 months of treatment, and up to 70% of patients become lamivudine resistant after 5 years of continuous therapy [32]. Resistance to lamivudine is manifested by the reappearance of HBV DNA after its initial suppression with a variable increase in serum ALT levels [55, 56]. The most common mutation involves the YMDD motif of the HBV polymerase gene (M204V/I) and is frequently accompanied by another mutation in an upstream region (L180M) [57]. Diagnostic assays for lamivudine-resistant mutants are commercially available. Hepatitis flares are not uncommon with the emergence of YMDD mutants resulting in progressive worsening of liver disease [58, 59] and can be fatal in patients with decompensated disease.

Lamivudine resulted in a rapid suppression of HBV DNA to undetectable levels (non-PCR-based assays) and improvement in biochemical and clinical parameters in both controlled and uncontrolled studies of patients with decompensated HBV cirrhosis [51, 60–65]. Twenty-three out of 35 decompensated HBV patients treated by Villeneuve and colleagues showed a slow but marked improvement in biochemical parameters and CTP scores [60]. Seven patients underwent liver transplantation, and 5 patients died within the first 6 months of lamivudine treatment. Two of these 23 patients later perished (from SBP and HCC, resp.) and 3 developed lamivudine resistance.

Significant improvement in CTP scores (8.3 versus 6.7) and ALT levels (111 versus 58 IU/L) were also noted in 18 Indians with decompensated HBV cirrhosis after a mean treatment duration of 18 months using lamivudine [61]. Yao and Bass reported similar CTP score improvement in 13 patients with Child's C cirrhosis given lamivudine and 5 of the patients were eventually taken off the liver transplant waiting list [62]. Similar findings were also noted in 30 Greek patients with decompensated HBV cirrhosis given lamivudine [63].

More than 80% of 154 patients with decompensated HBV cirrhosis had suppression of HBV DNA to undetectable levels by the branched-chain DNA (bDNA) assay within 8 weeks of initiating lamivudine treatment by Fontana and coworkers [51]. HBeAg loss was seen in 35% patients and HBeAg seroconversion to anti-HBe occurred in 20% of patients. The actuarial 3-year survival was 72% for all patients and 88% for patients who survived beyond the first 6 months of treatment.

In a study involving 77 HBsAg-positive liver transplant candidates, Perrillo et al. reported stabilization or improvement in liver disease severity with lamivudine in 27 patients without transplants who were treated with lamivudine for a median of 28 months [64]. The actuarial survival in these patients appeared to be better than the survival in untreated historical controls with decompensated HBV cirrhosis and

similar to that of patients with untreated compensated HBV cirrhosis from an earlier observation [3].

Yao et al. noted that transplant candidates receiving lamivudine were less likely to undergo transplantation than untreated historical controls who were matched for age, gender, and illness severity at the time of listing (35% versus 74%, $P = .04$) [65]. A significantly greater proportion of the lamivudine-treated patients experienced an improvement ≥3 points in their CTP scores compared with the untreated historical controls (61% versus 0%, $P = .0001$). In a retrospective analysis of 309 North American HBsAg positive liver transplant candidates, Fontana and his colleagues compared the outcomes of 162 lamivudine-treated patients and 147 untreated patients [66]. The two groups were comparable in liver disease severity before treatment. Treated patientswere more likely to have evidence of active HBV replication. Overall, the actuarial pretransplant and transplant-free survival was similar in the two groups and lamivudine had no apparent effect on liver disease severity in patients who underwent transplantation. However, among the patients who were still awaiting transplantation, lamivudine appeared to stabilize or improve liver disease severity.

Earlier studies using lamivudine in decompensated HBV cirrhosis were not controlled, and control cohorts used in later studies were either historical or non-randomised. Inclusion criteria and therapeutic endpoints were also inhomogeneous. It was unclear whether patients in some of the studies had acute hepatic decompensation secondary to a recent hepatitis flare as improvement upon viral suppression is more likely in group than in patients with hepatic decompensation secondary to end-stage liver disease [60, 61]. Other interventions that may have prolonged transplant-free survival (e.g., TIPS, use of prophylactic antibiotics) may have contributed to the observed improvements in clinical outcomes. In spite of all these inadequacies, lamivudine was found to be safe in patients with decompensated HBV cirrhosis although not all patients benefited from it [67]. Clinical improvement usually occurs between 3 to 6 months of therapy and improvement might not occur if treatment is started late. Pretreatment severity of liver disease (increased bilirubin, low albumin, prolonged PT and raised creatinine) is a more important predictor of early mortality than antiviral response in this group of patients [51, 66]. Careful monitoring is mandatory in patients with decompensated liver disease treated with lamivudine as a hepatitis flare from resistant mutants can be fatal. Should molecular resistance be detected add on therapy with adefovir dipivoxil or substitution therapy with tenofovir or entecavir is advised. Patients with initial clinical improvement can develop complications of cirrhosis and HCC even in the absence of lamivudine-resistance.

9. Adefovir Dipivoxil

Adefovir dipivoxil is a prodrug of adefovir, an acyclic nucleotide analog of adenosine monophosphate. Adefovir is phosphorylated to the active metabolite, adefovir diphosphate, by cellular kinases. Adefovir diphosphate inhibits HBV DNA polymerase (reverse transcriptase) by competing with the natural substrate deoxyadenosine triphosphate and by causing DNA chain termination after its incorporation into viral DNA [33]. It has a high genetic barrier to resistance and has the ability to suppress most lamivudine-resistant mutants. Renal toxicity is rare with the dose of 10 mg daily (Table 3). Adefovir dipivoxil has been available for the treatment of chronic hepatitis B since 2003 but has not been evaluated as a primary treatment for patients with decompensated cirrhosis.

In a compassionate use study involving 128 patients with decompensated cirrhosis and 196 patients with recurrent hepatitis B after liver transplant, addition of adefovir resulted in a 3-4 log10 reduction in serum HBVDNA levels, which was sustained throughout the course of treatment [52]. After 48 weeks of treatment, undetectable HBV DNA by PCR and normal ALT was noted in 81% and 76% of the pretransplant and 34% and 49% of the posttransplant patients, respectively. More than 90% of the pretransplant patients had improvement in their CTP scores, and 1-year survival was 84% for the pre- and 93% for the posttransplant patients. Follow-up data on 226 pretransplant patients showed that viral suppression was maintained in 65% of patients after 96 weeks of treatment with accompanying improvement in CTP and MELD scores. Fourteen percent of patients died within the first year and at least 33% required liver transplantation for long-term survival [53].

A recent interim report showed no difference in mortality rates after 24 weeks of treatment in 195 patients with decompensated HBV cirrhosis randomized to adefovir or entecavir. This study is in progress [68].

Although antiviral drug resistance is substantially less common with adefovir monotherapy compared to lamivudine, concerns remain regarding the slow rate of suppressing HBV replication with adefovir as well as the potential for dose-dependent nephrotoxicity in decompensated HBV patients (up to 28% of patients had an increase in serum creatinine ≥0.5 mg/dL after 48 weeks of treatment [69, 70]. Until more data becomes available, adefovir should not be recommended as first-line treatment in patients with decompensated HBV-cirrhosis. However, for patients with worsening liver disease secondary to lamivudine resistance, use of adefovir as a salvage therapy is an option.

10. Telbivudine

Telbivudine, a synthetic thymidine nucleoside analogue, is active against HBV. It undergoes phosphorylation by cellular enzymes to form the active metabolite, telbivudine triphosphate which incorporates into viral DNA competing with the natural substrate, thymidine triphosphate, and causing DNA chain termination, resulting in inhibition of HBV replication. It has demonstrated potent activity against hepatitis B with a significantly higher rate of response and superior viral suppression compared with lamivudine and adefovir [71]. It is generally well tolerated with a low adverse effect. It was approved by the FDA in late 2006. HBV strains with reduced susceptibility to telbivudine have emerged during therapy with the drug. Cross-resistance may

Table 3: Antiviral Agents with Activity against Wild Type and Lamivudine resistant HBV.

Agent	Daily dose	Side effects	Comments
Adefovir	10 mg	Dose-dependant nephrotoxicity	Drug resistance after 12 months
Entecavir	1 mg	No major side effects to date	Drug resistance eventually in lamivudine-resistant mutants
Tenofovir	300 mg	Neuropathy, nausea, CPK elevations, Fanconi syndrome	No drug resistance up to 4 years

occur among some nucleoside analogues active against HBV. Lamivudine-resistant HBV with reduced susceptibility to telbivudine has been observed. Some adefovir-resistant HBV are also resistant to telbivudine.

Gane and colleagues conducted a double blind trial on 195 patients (70% Asians) with decompensated HBV liver disease [72]. Patients were randomly assigned to receive 600 mg telbivudine or 100 mg lamivudine for 104 weeks. About three-quarters were men, with a mean age of 52 years and 57% were HBeAg negative. In a 2-year intent-to-treat analysis, more patients appeared to have undetectable HBV DNA (<300 copies/mL; 47% versus 36%, $P = .15$) and ALT normalization (58% versus 50%, $P = .25$) in the telbivudine treatment arm than in the lamivudine arm. Using a composite endpoint of undetectable HBV DNA and ALT normalization, however, telbivudine performed significantly better than lamivudine (34% versus 24%, resp.; $P = .004$). 29% of telbivudine recipients experienced viral breakthrough while on therapy, compared with 39% of lamivudine recipients ($P = .16$). At the end of treatment, about 75% of patients in both arms had stabilized or improved liver disease, as indicated by changes from baseline in CTP scores. Kidney function (indicated by glomerular filtration rate) modestly improved in the telbivudine arm, while worsening in the lamivudine arm. Early (week 24) survival rates were similar in the 2 study arms, 96% with telbivudine and 92% with lamivudine. Long-term (week 104) survival rates were 96% and 83%, respectively, with a trend toward statistical significance. Serious adverse events were common, consistent with advanced liver disease, and they occurred with similar frequency in both arms (55% of telbivudine recipients versus 61% of lamivudine recipients). No cases of rhabdomyolysis or lactic acidosis were reported. The investigators concluded that telbivudine was well tolerated with stabilization of liver function and had comparable tolerability to lamivudine.

11. Entecavir

Entecavir is a cyclopentyl guanosine analogue with potent selective inhibition of the priming, DNA-dependent synthesis, and reverse transcription functions of HBV polymerase. It has demonstrated activity against both wildtype HBV and, to a lesser extent, lamivudine-resistant HBV [73, 74]. It suppresses HBV replication more rapidly and effectively than lamivudine or adefovir in patients with compensated chronic HBV [75, 76]. It has an excellent resistance profile after 5 years in nuycleosid(t)e naïve patients and does not have any reported nephrotoxicity [77], It has been used to rescue a small number of liver transplant recipients with lamivudine-resistant HBV successfully [78].

Shim et al. demonstrated that 0.5 mg entecavir daily was effective in treating 70 nucleoside naïve decompensated HBV patients with nearly 90% achieving undetectable HBV DNA (PCR) at 1 year [79]. The virological responses in 55 decompensated HBV patients treated for at least 1 year were compared to 144 compensated patients treated with entecavir from the same center. The mean MELD (11.5 versus 7) and CTP scores (8.1 versus 5.3) were significantly higher in the decompensated patients. The proportion of HBeAg positive patients and mean HBV DNA levels were similar in the two groups. Overall, the 1-year transplant-free survival rate was 87% in the decompensated patients. As seen previously with lamivudine, the majority of adverse outcomes occurred during the first 6 months of therapy with the nine patients having more severe liver failure at entry. Baseline HBV DNA levels, HBe antigenaemia and response to therapy were similar in both survivors and non-survivors or those who underwent transplant. Nearly 50% of the entecavir treated patients had a clinically significant decrease in their CTP score of >2 points at 1-year. HBeAg loss in both the decompensated and compensated patients was remarkably high at 1 year (48% vs 41%). HBV DNA suppression was maintained during followup with no instances of viral rebound or entecavir-resistant HBV. Not all decompensated patients improved with entecavir therapy. Twelve patients (22%) showed no change in their CTP score at 1-year (4 patients had aggravation or their liver disease with worsening CTP scores). Five patients developed HCC during followup.

A retrospective analysis of 107 decompensated patients (mean age 53 years; 70.1% men; 42% HBeAg positive) treated with lamivudine or entecavir showed significantly lower serum HBV DNA levels and prevalence of patients with undetectable HBV DNA (PCR) at 3, 6, 9, and 12 months after treatment in entecavir-treated patients than in the lamivudine group. Serum ALT levels, CTP and MELD score, and the prevalence of patients with improved CTP scores at 3, 6, 9, and 12 months did not differ between two groups. The prevalence of HBeAg seroconversion and HCC and mortality also did not differ between two groups while that of viral breakthrough was significantly more frequent in the lamivudine-treated patients [80].

Liaw et al. randomized 195 patients with decompensated HBV to entecavir (1.0 mg per day) or aderovir (10 mg per day) [68], One-third (34%) of patients had lamivudine-resistant HBV. Interim results at week 24 demonstrated a significantly greater reduction in HBV DNA and serum ALT levels in the entecavir treated patients. The 24 week mortality rates were similar in both treatment arms. Entecavir was well tolerated and safety results were comparable in both treatment groups. Continued followup is needed since the rate of

entecavir-resistant HBV can substantially increase over time in lamivudine-resistant HBV infection and potentially fatal flares may develop [81].

Entecavir was recently compared with tenofovir + emtricitabine combination and tenofovir singly in an ongoing multicentre study [82]. Improvements in CTP and MELD scores as well as frequency of undetectable HBV DNA at week 48 were similar in the three treatment arms.

Severe lactic acidosis with entecavir has been reported in patients with decompensated liver [83].

12. Tenofovir

Tenofovir is an acyclic nucleotide analog with a molecular structure similar to that of adefovir. It is approved for the treatment of HIV infection and has in vitro activity against both wild type and lamivudine-resistant HBV [84]. It is administered as the prodrug tenofovir disoproxil fumarate (TDF), and it is converted to tenofovir by plasmaesterases. Tenofovir is phosphorylated to the active metabolite which works as a chain terminator if incorporated into the DNA chain and is a competitive inhibitor of natural deoxyadenosine 50-triphosphate. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. It is a significantly more potent suppressor of HBV replication than adefovir and no drug-resistant variants have been reported with 4 years of continuous treatment in compensated HBV patients [85].

In the ongoing study reported in the previous section [84], on 112 decompensated HBV patients given tenofovir, tenofovir + emtricitabine, or entecavir, there were more undetectable HBV DNA at week 48 in the tenofovir containing treatment arms (71%) than in the entecavir treatment arm (33%) in patients with lamivudine resistant HBV. HBeAg seroconversion was seen in 21 % and 13% of the tenofovir and tenofovir/emtricitabine arms, respectively, but not in the entecavir arm. Rates of nephrotoxicity, tolerability and patient mortality were similar in the three treatment arms through week 48. Continued follow-up of these patients is needed to determine which of the newer antiviral agents can offer the best risk-benefit ratio in this challenging patient population.

Although a tenofovir-based regimen may be preferred in decompensated patients with lamivudine-resistant HBV, there are concerns regarding the long-term safety of tenofovirin some HBV patients including nephrotoxicity and metabolic bone disease [86, 87]. Patients with decompensated cirrhosis are frequently malnourished and may have low vitamin D levels. Prospective studies of bone density and metabolic parameters during prolonged tenofovir treatment are warranted as well as potential calcium and vitamin D supplementation [88].

13. Summary

The availability of safe, orally administered antiviral agents has revolutionized the management of chronic HBV and opened up new treatment options for the large number of patients with decompensated HBV cirrhosis worldwide who previously had a dismal prognosis. These drugs can improve or stabilize liver disease in patients who are not transplant candidates or have no access to liver transplantation. For these patients, the oral HBV antivirals may represent the only hope for better quality or longer duration of survival and reduced utilization of health care resources. The aim of treatment in transplant candidates is to improve their functional status such that they eventually might be removed from the transplantation list. All patients with decompensated cirrhosis, regardless of their serum HBV DNA level, should be considered for treatment. Decompensated patients with evidence of active HBV replication (i.e., presence of HBe antigenemia and HBV DNA > 2000 iu/mL,) are more likely to derive benefit from antiviral therapy.

Clinical studies have confirmed that oral antivirals are generally safe and effective in suppressing HBV replication in decompensated HBV cirrhosis with resultant stabilization or improvement in liver disease. Clinical improvement is slow and takes 3 to 6 months. It is not certain if starting treatment earlier will improve the rate of response. Recent efficacy and safety data supports the use of entecavir as a first-line treatment option for nucleos(t)ide naive patients with decompensated HBV cirrhosis [89]. Lamivudine and telbivudine are also safe agents, but the risk of resistance with prolonged therapy is ever present with potential for worsening liver disease and increased risk of HBV recurrence after transplantation and vigilance is important. Tenofovir or entecavir monotherapy or adefovir add-on therapy are possible rescue options should resistance occur. Studies evaluating tenofovir monotherapy and combination therapy in patients with decompensated cirrhosis are in progress. However, continued follow-up from these ongoing studies including long-term efficacy, safety, and resistance data are needed. Further studies are also needed to identify the optimal agent(s) for patients with decompensated lamivudine-resistant HBV cirrhosis. Decompensated HBV patients receiving oral nucleos(t)lde analogues must undergo frequent clinical and laboratory assessment to insure medication compliance and surveillance for vIrological and clinical response as well as drug side effects, drug resistance, and HCC. As it is not possible to identify which patients with high CTP or MELD scores will have poor short term prognosis, it is advisable to refer all decompensated HBV patients for liver transplant evaluation at presentation if available.

Antiviral therapy should be given to all potential liver transplant candidates with decompensated HBV cirrhosis and detectable HBV-DNA. Lamivudine resistance will result in HBV recurrence in the posttransplant period [33]. Adefovir and entecavir can be given to rescue lamivudine resistance, and initial use of these agents may minimize drug resistance. Lamivudine plus low-dose intramuscular HBIg (400–800 U daily for 1 week, then monthly) is as effective as lamivudine plus high-dose intravenous HBIg in preventing recurrent HBV infection resulting in a 5-year graft survival of up to 85% at 10% of the cost [90]. Substituting HBIg with adefovir 12 months posttransplant also prevent late HBV recurrence and costs much less [91]. Lamivudine plus adefovir combination from the time of listing has been shown to be well tolerated, prevent lamivudine resistance

prior to transplant, rescued some patients from the need for transplantation, and prevented recurrent HBV infection following liver transplantation, regardless of baseline HBV-DNA status [92]. Patients who were HBV-DNA negative prior to transplant and those with sustained protective levels of anti-HBs following posttransplant vaccination can be safely given lamivudine or entecavir monotherapy 12 months after transplant. Antiviral prophylaxis should also be given in patients who have received an anti-HBc(+) liver to prevent de novo HBV infection.

Although the outlook for decompensated HBV patients is bright with the advent of these oral antivirals, emphasis should be placed on effective treatment of patients with chronic HBV infection to prevent them from progressing to the decompensated state.

References

[1] E. E. Mast, M. J. Alter, and H. S. Margolis, "Strategies to prevent and control hepatitis B and C virus infections: a global perspectiveStrategies to prevent and control hepatitis B and C virus infections: a global perspective," *Vaccine*, vol. 17, no. 13-14, pp. 1730–1733, 1999.

[2] G. M. McQuillan, P. J. Coleman, D. Kruszon-Moran, L. A. Moyer, S. B. Lambert, and H. S. Margolis, "Prevalence of hepatitis B virus infection in the United States: the National Health and Nutrition examination surveys, 1976 through 1994," *American Journal of Public Health*, vol. 89, no. 1, pp. 14–18, 1999.

[3] F. E. De Jongh, H. L. A. Janssen, R. A. De Man, W. C. J. Hop, S. W. Schalm, and M. Van Blankenstein, "Survival and prognostic indicators in hepatitis B surface antigen-positive cirrhosis of the liver," *Gastroenterology*, vol. 103, no. 5, pp. 1630–1635, 1992.

[4] G. Fattovich, L. Brollo, G. Giustina et al., "Natural history and prognostic factors for chronic hepatitis B," *Gut*, vol. 32, no. 3, pp. 294–298, 1991.

[5] D. Samuel, R. Muller, G. Alexander et al., "Liver transplantation in European patients with the hepatitis B surface antigen," *New England Journal of Medicine*, vol. 329, no. 25, pp. 1842–1847, 1993.

[6] X. M. Lin, N. Robinson, M. Thursz et al., "Chronic hepatitis B virus infection in the Asia-Pacific region and Africa: review of disease progression," *Journal of Gastroenterology and Hepatology*, vol. 20, pp. 833–843, 2005.

[7] I. D. Gust, "Epidemiology of hepatitis B infection in the Western Pacific and South East Asia," *Gut*, vol. 38, supplement 2, no. 2, pp. S18–S23, 1996.

[8] A. S. Lok, "Natural history and control of perinatally acquired hepatitis B virus infection," *Digestive Diseases*, vol. 10, no. 1, pp. 46–52, 1992.

[9] D. S. Chen, "Natural history of chronic hepatitis B virusinfection: new light on an old story," *Journal of Gastroenterology and Hepatology*, vol. 8, pp. 470–475, 1993.

[10] C. M. Chu, P. Karayiannis, and M. J. F. Fowler, "Natural history of chronic hepatitis B virus infection in Taiwan: studies of hepatitis B virus DNA in serum," *Hepatology*, vol. 5, no. 3, pp. 431–434, 1985.

[11] E. R. Schiff, M. F. Sorrell, and W. C. Maddrey, *Diseases of the Liver*, Lippincott Williams &Wilkins, Haggerstown, Md, USA, 8th edition, 1999.

[12] P. Marcellin, M. Martinot-Peignoux, M. A. Loriot et al., "Persistence of hepatitis B virus DNA demonstrated by polymerase chain reaction in serum and liver after loss of HBsAg induced by antiviral therapy," *Annals of Internal Medicine*, vol. 112, no. 3, pp. 227–228, 1990.

[13] S. Kaneko, R. H. Miller, A. M. Di Bisceglie, S. M. Feinstone, J. H. Hoofnagle, and R. H. Purcell, "Detection of hepatitis B virus DNA in serum by polymerase chain reaction: application for clinical diagnosis," *Gastroenterology*, vol. 99, no. 3, pp. 799–804, 1990.

[14] C. M. Chu and Y. F. Liaw, "Hepatitis B virus-related cirrhosis: natural history and treatment," *Seminars in Liver Disease*, vol. 26, no. 2, pp. 142–152, 2006.

[15] B. Xu, D. C. Hu, D. M. Rosenberg et al., "Chronic Hepatitis B—a long term retrospective cohort study of disease progression in Shanghai, China," *Journal of Gastroenterology and Hepatology*, vol. 18, no. 12, pp. 1345–1352, 2003.

[16] Y. F. Liaw, D. Y. Lin, T. J. Chen, and C. M. Chu, "Natural course after the development of cirrhosis in patients with chronic type B hepatitis: a prospective study," *Liver*, vol. 9, no. 4, pp. 235–241, 1989.

[17] I. Okazaki, K. Maruyama, and K. Funatsu, "Ten year survival rate of 131 patients with liver cirrhosis excluded the association of liver carcinoma at the establishment of diagnosis," *Gastroenterologia Japonica*, vol. 15, no. 4, pp. 350–354, 1980.

[18] A. Y. Hui, H. L. Y. Chan, N. W. Y. Leung, L. C. T. Hung, F. L. Chan, and J. J. Y. Sung, "Survival and prognostic indicators in patients with hepatitis B virus-related cirrhosis after onset of hepatic decompensation," *Journal of Clinical Gastroenterology*, vol. 34, no. 5, pp. 569–572, 2002.

[19] F. Donato, A. Tagger, R. Chiesa et al., "Hepatitis B and C virus infection, alcohol drinking, and hepatocellular carcinoma: a case-control study in Italy," *Hepatology*, vol. 26, no. 3, pp. 579–584, 1997.

[20] K. Krogsgaard, B. O. Lindhardt, and J. O. Nielsen, "The influence of HTLV-III infection on the natural history of hepatitis B virus infection in male homosexual HBsAg carriers," *Hepatology*, vol. 7, no. 1, pp. 37–41, 1987.

[21] V. K. Rustgi, J. H. Hoofnagle, and J. L. Gerin, "Hepatitis B virus infection in the acquired immunodeficiency syndrome," *Annals of Internal Medicine*, vol. 101, no. 6, pp. 795–797, 1984.

[22] Y. F. Liaw, "Role of hepatitis C virus in dual and triple hepatitis virus infection," *Hepatology*, vol. 22, no. 4 I, pp. 1101–1108, 1995.

[23] L. Benvegnu, G. Fattovich, F. Noventa et al., "Concurrent hepatitis B and C virus infection and risk of hepatocellular carcinoma in cirrhosis: a prospective study," *Cancer*, vol. 74, no. 9, pp. 2442–2448, 1994.

[24] G. Fattovich, G. Giustina, E. Christensen et al., "Influence of hepatitis delta virus infection on morbidity and mortality in compensated cirrhosis type B," *Gut*, vol. 46, no. 3, pp. 420–426, 2000.

[25] R. Tur-Kaspa, Y. Shaul, D. D. Moore et al., "The glucocorticoid receptor recognizes a specific nucleotide sequence in hepatitis B virus DNA causing increased activity of the HBV enhancer," *Virology*, vol. 167, no. 2, pp. 630–633, 1988.

[26] J. S. McMillan, T. Shaw, P. W. Angus, and S. A. Locarnini, "Effect of immunosuppressive and antiviral agents on hepatitis B virus replication in vitro," *Hepatology*, vol. 22, no. 1, pp. 36–43, 1995.

[27] Y. F. Liaw, D. I. Tai, C. M. Chu, and T. J. Chen, "The development of cirrhosis in patients with chronic type B hepatitis: a prospective study," *Hepatology*, vol. 8, no. 3, pp. 493–496, 1988.

[28] P. S. Kamath, R. H. Wiesner, M. Malinchoc et al., "A model to predict survival in patients with end-stage liver disease," *Hepatology*, vol. 33, no. 2, pp. 464–470, 2001.

[29] E. B. Keeffe, "Is hepatitis A more severe in patients with chronic hepatitis B and other chronic liver diseases?" *American Journal of Gastroenterology*, vol. 90, no. 2, pp. 201–205, 1995.

[30] Centers for Disease Control and Prevention, "Prevention of hepatitis A through active or passive immunization: recommendations of the advisory committee on immunization practices (ACIP)," *The MMWR Recommendations and Reports*, vol. 45, pp. 1–30, 1996.

[31] European Association for the Study of the Liver, "EASL clinical practice guide lines: management of chronic hepatitis B," *Journal of Hepatology*, vol. 10, no. 2, pp. 227–242, 2009.

[32] A. S. F. Lok and B. J. McMahon, "Chronic hepatitis B: update 2009," *Hepatology*, vol. 50, no. 3, pp. 661–662, 2009.

[33] Y. F. Liaw, N. Leung, J. H. Kao et al., "Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update," *Hepatology International*, vol. 2, no. 3, pp. 263–283, 2008.

[34] J. C. Teran, T. F. Imperiale, K. D. Mullen, A. S. Tavill, and A. J. McCullough, "Primary prophylaxis of variceal bleeding in cirrhotics: a cost-effectiveness analysis," *Gastroenterology*, vol. 112, no. 2, pp. 473–482, 1997.

[35] A. I. Sharara and D. C. Rockey, "Gastroesophageal variceal hemorrhage," *New England Journal of Medicine*, vol. 345, no. 9, pp. 669–681, 2001.

[36] A. Luca, G. D'Amico, R. La Galla, M. Midiri, A. Morabito, and L. Pagliaro, "TIPS for prevention of recurrent bleeding in patients with cirrhosis: meta-analysis of randomized clinical trials," *Radiology*, vol. 212, no. 2, pp. 411–421, 1999.

[37] P. Ginès and A. Cárdenas, "The management of ascites and hyponatremia in cirrhosis," *Seminars in Liver Disease*, vol. 28, no. 1, pp. 43–58, 2008.

[38] P. Tandon and G. Garcia-Tsao, "Bacterial infections, sepsis, and multiorgan failure in cirrhosis," *Seminars in Liver Disease*, vol. 28, no. 1, pp. 26–42, 2008.

[39] M. Rössle, A. Ochs, V. Gülberg et al., "A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites," *New England Journal of Medicine*, vol. 342, no. 23, pp. 1701–1707, 2000.

[40] J. Córdoba and B. Mínguez, "Hepatic encephalopathy," *Seminars in Liver Disease*, vol. 28, no. 1, pp. 70–80, 2008.

[41] V. Arroyo, J. Fernandez, and P. Ginès, "Pathogenesis and treatment of hepatorenal syndrome," *Seminars in Liver Disease*, vol. 28, no. 1, pp. 81–95, 2008.

[42] M. Sherman, K. M. Peltekian, and C. Lee, "Screening for hepatocellular carcinoma in chronic carriers of hepatitis B virus: incidence and prevalence of hepatocellular carcinoma in a North American urban population," *Hepatology*, vol. 22, no. 2, pp. 432–438, 1995.

[43] E. B. Keeffe, "Liver transplantation: current status and novel approaches to liver replacement," *Gastroenterology*, vol. 120, no. 3, pp. 749–762, 2001.

[44] E. C. Seaberg, S. H. Belle, K. C. Beringer, J. L. Schivins, and K. M. Detre, "Liver transplantation in the United States from 1987–998: updated results from the PITT-UNOS liver transplant registry," in *Clinical Transplants 1998*, J. M. Cecka and P. I. Terasaki, Eds., pp. 17–37, UCLA Tissue Typing Laboratory, Los Angeles, Calif, USA, 1999.

[45] D. Shouval and D. Samuel, "Hepatitis B immune globulin to prevent hepatitis B virus graft reinfection following liver transplantation: a concise review," *Hepatology*, vol. 32, no. 6, pp. 1189–1195, 2000.

[46] R. P. Perrillo, E. R. Schiff, G. L. Davis et al., "A randomized, controlled trial of interferon alfa-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B," *New England Journal of Medicine*, vol. 323, no. 5, pp. 295–301, 1990.

[47] D. K. H. Wong, A. M. Cheung, K. O'Rourke, C. D. Naylor, A. S. Detsky, and J. Heathcote, "Effect of alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B: a meta-analysis," *Annals of Internal Medicine*, vol. 119, no. 4, pp. 312–323, 1993.

[48] J. H. Hoofnagle, A. M. Di Bisceglie, J. G. Waggoner, and Y. Park, "Interferon alfa for patients with clinically apparent cirrhosis due to chronic hepatitis B," *Gastroenterology*, vol. 104, no. 4, pp. 1116–1121, 1993.

[49] R. Perrillo, C. Tamburro, F. Regenstein et al., "Low-dose, titratable interferon alfa in decompensated liver disease caused by chronic infection with hepatitis B virus," *Gastroenterology*, vol. 109, no. 3, pp. 908–916, 1995.

[50] R. J. Fontana, "Management of patients with decompensated HBV cirrhosis," *Seminars in Liver Disease*, vol. 23, no. 1, pp. 89–100, 2003.

[51] R. Fontana, H. W. L. Hann, R. P. Perrillo et al., "Determinants of early mortality in patients with decompensated chronic hepatitis B treated with antiviral therapy," *Gastroenterology*, vol. 123, no. 3, pp. 719–727, 2002.

[52] E. R. Schiff, C. L. Lai, S. Hadziyannis et al., "Adefovir dipivoxil therapy for lamivudine-resistant hepatitis B in pre- and post-liver transplantation patients," *Hepatology*, vol. 38, no. 6, pp. 1419–1427, 2003.

[53] E. Schiff, C. L. Lai, S. Hadziyannis et al., "Adefovir dipivoxil for wait-listed and post-liver transplantation patients with lamivudine-resistant hepatitis B: final long-term results," *Liver Transplantation*, vol. 13, no. 3, pp. 349–360, 2007.

[54] J. L. Dienstag, E. R. Schiff, T. L. Wright et al., "Lamivudine as initial treatment for chronic hepatitis B in the United States," *New England Journal of Medicine*, vol. 341, no. 17, pp. 1256–1263, 1999.

[55] C. L. Lai, R. N. Chien, N. W. Y. Leung et al., "A one-year trial of lamivudine for chronic hepatitis B," *New England Journal of Medicine*, vol. 339, no. 2, pp. 61–68, 1998.

[56] N. W. Y. Leung, C. L. Lai, T. T. Chang et al., "Extended lamivudine treatment in patients with chronic hepatitis B enhances hepatitis B e antigen seroconversion rates: results after 3 years of therapy," *Hepatology*, vol. 33, no. 6, pp. 1527–1532, 2001.

[57] M. I. Allen, M. Deslauriers, C. Webster Andrews et al., "Identification and characterization of mutations in hepatitis B virus resistant to lamivudine," *Hepatology*, vol. 27, no. 6, pp. 1670–1677, 1998.

[58] M. Melegari, P. P. Scaglioni, and J. R. Wands, "Hepatitis B virus mutants associated with 3TC and Famciclovir administration are replication defective," *Hepatology*, vol. 27, no. 2, pp. 628–633, 1998.

[59] Y. F. Liaw, R. N. Chien, C. T. Yeh, S. L. Tsai, and C. M. Chu, "Acute exacerbation and hepatitis B virus clearance after emergence of YMDD motif mutation during lamivudine therapy," *Hepatology*, vol. 30, no. 2, pp. 567–572, 1999.

[60] J. P. Villeneuve, L. D. Condreay, B. Willems et al., "Lamivudine treatment for decompensated cirrhosis resulting from chronic hepatitis B," *Hepatology*, vol. 31, no. 1, pp. 207–210, 2000.

[61] D. Kapoor, R. C. Guptan, S. M. Wakil et al., "Beneficial effects of lamivudine in hepatitis b virus-related decompensated cirrhosis," *Journal of Hepatology*, vol. 33, no. 2, pp. 308–312, 2000.

[62] F. Y. Yao and N. M. Bass, "Lamivudine treatment in patients with severely decompensated cirrhosis due to replicating hepatitis b infection," *Journal of Hepatology*, vol. 33, no. 2, pp. 301–307, 2000.

[63] S. Manolakopoulos, S. Karatapanis, T. Elefsiniotis et al., "Clinical course of lamivudine monotherapy in patients with decompensated cirrhosis due to hepatitis BeAg negative chronic HBV infection," *American Journal of Gastroenterology*, vol. 99, pp. 57–63, 2003.

[64] R. P. Perrillo, T. Wright, J. Rakela et al., "A multicenter United States-Canadian trial to assess lamivudine monotherapy before and after liver transplantation for chronic hepatitis B," *Hepatology*, vol. 33, no. 2, pp. 424–432, 2001.

[65] F. Y. Yao, N. A. Terrault, C. Freise, L. Maslow, and N. M. Bass, "Lamivudine treatment is beneficial in patients with severely decompensated cirrhosis and actively replicating hepatitis B infection awaiting liver transplantation: a comparative study using a matched, untreated cohort," *Hepatology*, vol. 34, no. 2, pp. 411–416, 2001.

[66] R. J. Fontana, E. B. Keeffe, W. Carey et al., "Effect of lamivudine treatment on survival of 309 North American patients awaiting liver transplantation for chronic hepatitis B," *Liver Transplantation*, vol. 8, no. 5, pp. 433–439, 2002.

[67] Y. Kitay-Cohen, Z. Ben-Ari, R. Tur-Kaspa, H. Fainguelernt, and M. Lishner, "Extension of transplantation free time by lamivudine in patients with hepatitis B-induced decompensated cirrhosis," *Transplantation*, vol. 69, no. 11, pp. 2382–2383, 2000.

[68] Y. F. Liaw, M. Raprapoulou-Glgi, H. Chemquer, S. K. Sann, T. Tanwandee, N. Leung et al., "Efficacy, safety of entecavir versus adefovir In chronic hepatitis B patients with evidence of hepatic decompensation ," *Journal of Hepatology*, vol. 50, p. 505A, 2009.

[69] S. J. Hadziyannis, N. C. Tassopoulos, E. J. Heathcote et al., "Long-tern therapy With adefovir dipivoxil in HBeAg-negative chronic hepatitis B for up to 5 years," *Gastroenterology*, vol. 131, no. 6, pp. 1743–1751, 2006.

[70] H. Izzedine, V. Launay-Vacher, and G. Deray, "Antiviral drug-induced nephrotoxicity," *American Journal of Kidney Diseases*, vol. 45, no. 5, pp. 804–817, 2005.

[71] C. L. Lai, N. Leung, E. K. Teo et al., "A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B," *Gastroenterology*, vol. 129, no. 2, pp. 528–536, 2005.

[72] E. J. Gane, H. L. Chan, G. Choudhuri et al., "Treatment of decompensated HBV-cirrhosis: results from 2-years randomized trial with telbivudine or lamivudine," *Journal of Hepatology*, vol. 52, supplement 1, p. S4, 2010.

[73] R. A. De Man, L. M. M. Wolters, F. Nevens et al., "Safety and efficacy of oral entecavir given for 28 days in patients with chronic hepatitis B virus infection," *Hepatology*, vol. 34, no. 3, pp. 578–582, 2001.

[74] S. Levine, D. Hernandez, G. Yamanaka et al., "Efficacies of entecavir against lamivudine-resistant hepatitis B virus replication and recombinant polymerases in vitro," *Antimicrobial Agents and Chemotherapy*, vol. 46, no. 8, pp. 2525–2532, 2002.

[75] I. T. Chang, R. G. Gish, R. DcMan et al., "A comparison of entecavir and lamivudine tor HBeAg-positive chronic hepatitis B," *New England Journal of Medicine*, vol. 345, pp. 1001–1010, 2006.

[76] N. Leung, C. Y. Peng, H. W. Hann et al., "Early hepatitis B virus DNA reduction in hepatitis B e antigen-positive patients with chronic hepatitis B: a randomized international study of entecavir versus adefovir," *Hepatology*, vol. 49, no. 1, pp. 72–79, 2009.

[77] D. J. Tenney, R. E. Rose, C. J. Baldick et al., "Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naïve patients is rare through 5 years-of therapy," *Hepatology*, vol. 49, no. 5, pp. 1503–1514, 2009.

[78] A. O. Shakil, L. Lilly, P. Angus et al., "Entecavir reduces viral load in liver transplant patients who failed prophylaxis or treatment for hepatitis B," *Journal of Hepatology*, vol. 34, abstract 619A, 2001.

[79] J. H. Shim, H. C. Lee, K. M. Kim et al., "Efficacy of entecavir in treatment-naïve patients with hepatitis B virus-related decompensated cirrhosis," *Journal of Hepatology*, vol. 52, no. 2, pp. 176–182, 2010.

[80] Y. S. Seo, F. S. Jung, J. H. Kim et al., "Lamivudine versus entecavir in patients with hepatitis B virus related decompensated liver cirrhosis," *Journal of Hepatology*, vol. 50, abstract 550A, 2010.

[81] A. M. Peilirelli, G. Barbarim, M. Romano, C. Furlan, A. Paffettl, and R. Villam, "Entecavlr therapy tor lamlvudme resistant HBV cirrhotic patients waiting tor OLT: viral, biochemical outcomes at one year," *Journal of Hepatology*, vol. 50, abstract S14A, 2009.

[82] Y. F. Liaw, C. Lee, U. S. Akarc, P. V. George, F. Wong et al., "Interim results of a double-blind, randomized phase 2 study of the safety of tenofovir disoproxil fumarate, emtricitabine plus tenofovir disoproxil fumarate, and entecavir in the treatment of chronic hepatitis B subjects with decompensated Liver disease," *Hepatology*, vol. 50, abstract 222, 2009.

[83] C. M. Lange, J. Bojunga, W. P. Hofmann et al., "Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function," *Hepatology*, vol. 50, no. 6, pp. 2001–2006, 2009.

[84] J. S. James, "Tenofovir approved: broad indication," *AIDS Treatment News*, no. 373, pp. 2–3, 2001.

[85] J. Heathcote, E. J. Gane, R. A. De Man et al., "Long term (4 year) efficacy and safety of tenofovir disoproxil fumarate (TDF) treatment in HBeAg positive patients with chronic hepatitis B (Study 103): a preliminary analysis," *Hepatology*, vol. 50, abstract 556A, 2010.

[86] J. Gallant, E. S. Staszewski, A. L. Pozniak, E. Dejesus, M. Sulellnan, M. D. Millel et al., "Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial," *Journal of the American Medical Association*, vol. 292, no. 2, pp. 191–201, 2004.

[87] J. G. Rajinders, T. Vries-Slulls, B. E. Hansen, H. L. Zaaijer, M. Prinsj, M. Schumen et al., "Five-year tenotovii therapy is associated with maintained virologic response but significant decline in renal function in HIV-HBV infected patients," *Hepatology*, vol. 50, abstract 506A, 2009.

[88] C. Constable, K. Childs, M. L. Bachon, D. C. Camero, M. R. Mullen, and D. T. Dieterich, "Does tenofovlr increase the risk of abnormal bone and calcium metabolism?" *Hepatology*, vol. 51, abstract 518, 2009.

[89] E. B. Keeffe, D. T. Dieterich, S. H. B. Han et al., "A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 update," *Clinical Gastroenterology and Hepatology*, vol. 6, no. 12, pp. 1315–1341, 2008.

[90] E. J. Gane, P. W. Angus, S. Strasser et al., "Lamivudine plus low-dose hepatitis B immunoglobulin to prevent recurrent hepatitis B following liver transplantation," *Gastroenterology*, vol. 132, no. 3, pp. 931–937, 2007.

[91] P. Angus, S. Strasser, S. Patterson, G. McCaughan, and E. Gane, "A randomized study to assess the safety and efficacy of adefovir dipivoxil ," *Hepatology*, vol. 46, abstract 238A, 2007.

[92] E. Gane, S. Strasser, S. Patterson, G. McCaughan, and P. Angus, "A prospective study on the safety and efficacy of lamivudine and adefovir prophylaxis in HBsAg positive liver transplantation candidates," *Hepatology*, vol. 46, abstract 479A, 2007.

SAGE-Hindawi Access to Research
International Journal of Hepatology
Volume 2011, Article ID 219238, 7 pages
doi:10.4061/2011/219238

Review Article

Treatment of Decompensated Alcoholic Liver Disease

John Menachery and Ajay Duseja

Department of Hepatology, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India

Correspondence should be addressed to Ajay Duseja, ajayduseja@yahoo.co.in

Received 22 February 2011; Accepted 12 May 2011

Academic Editor: Deepak Amarapurkar

Alcoholic liver disease (ALD) is a spectrum ranging from simple hepatic steatosis to alcoholic hepatitis and cirrhosis. Patients with severe alcoholic hepatitis can have clinical presentation almost similar to those with decompensated cirrhosis. Scoring with models like Maddrey discriminant function, a model for end-stage liver disease, Glasgow alcoholic hepatitis score, and Lille model are helpful in prognosticating patients with ALD. One of the first therapeutic goals in ALD is to induce alcohol withdrawal with psychotherapy or drugs. Most studies have shown that nutritional therapy improves liver function and histology in patients with ALD. The rationale for using glucocorticoids is to block cytotoxic and inflammatory pathways in patients with severe alcoholic hepatitis. Pentoxifylline, a tumor necrosis factor alpha (TNFα) suppressor, and infliximab, an anti-TNFα mouse/human chimeric antibody, has been extensively studied in patients with alcoholic hepatitis. Liver transplantation remains the definitive therapy for decompensated cirrhosis/alcoholic hepatitis despite the issues of recidivism, poor compliance with postoperative care, and being a self-inflicted disease.

1. Introduction

Alcohol is a major risk factor for chronic disease burden all over the world. Alcohol abusers and patients with alcoholic liver disease (ALD) usually suffer negative consequences from drinking such as significant financial burden, unemployment, loss of family, accidental injury, or death [1]. Alcoholism is a physical dependence that includes impaired control, craving, development of tolerance, and development of withdrawal symptoms on abstinence.

ALD is a spectrum that ranges from fatty liver to alcoholic steatohepatitis (ASH) and eventually cirrhosis. Simple hepatic steatosis is the commonest histological finding and occurs in 90% of heavy drinkers but is rapidly reversible with abstinence. Alcoholic hepatitis or ASH occurs in up to 35% of heavy drinkers and is usually a precursor of cirrhosis [2].

Epidemiological data suggest that a threshold of 80 g of daily alcohol in a male and 20–40 g in a female for an average of 10 to 12 years is necessary for causing significant alcohol-induced liver injury [3, 4]. However, only a minority of individuals who consume alcohol in excess develop significant ALD. Synergistic factors such as chronic hepatitis C, obesity, and genetic factors may accelerate the development of ALD even at lower doses of alcohol consumption.

ASH is a clinic-pathological syndrome that denotes hepatocellular necrosis and inflammation. The clinical spectrum can range from being asymptomatic to developing overt liver failure. There may be low-grade fever, jaundice, leukocytosis, and mild elevation of transaminases. Histological features of ASH include the presence of parenchymal necrosis, Mallory bodies, and a perivenular neutrophilic infiltrate. Other features that are commonly present include bridging necrosis, fatty changes, bile duct proliferation, cholestasis, and perivenular fibrosis. Liver biopsy as a means of prognostication in alcoholic hepatitis has mostly been replaced with less invasive scoring systems. Patients with severe alcoholic hepatitis can have clinical presentation almost similar to those with decompensated cirrhosis, and it may become difficult to establish if such patients have associated cirrhosis or not. But histologically, the majority of patients with severe alcoholic hepatitis have either significant fibrosis or cirrhosis liver. And alcoholic hepatitis with underlying cirrhosis is one of the most important causes of acute on chronic liver failure (ACLF) [5].

2. Prognostic Models in Patients with Alcoholic Liver Disease

2.1. Discriminant Function. The Maddrey discriminant function (DF) score remains the most commonly used predictive model and was developed to facilitate the assessment of response in a clinical trial of corticosteroids in patients with alcoholic hepatitis [6]. Modified DF is calculated as = 4.6 × (prolongation of prothrombin time in seconds) + Serum bilirubin (mg/dL). A modified DF score >32 in the presence of hepatic encephalopathy predicts >50% mortality within 28 days in patients with alcoholic hepatitis [7, 8]. However, fatal outcomes have also been known to occur in patients with modified DF score <32, and this low specificity has suggested a need for alternative scoring systems.

2.2. Model for End-Stage Liver Disease (MELD). MELD score was initially developed to predict survival in patients with cirrhosis undergoing transjugular intrahepatic portosystemic shunting (TIPSS). However, it has been found to predict mortality in ASH, and a MELD score ≥21 (within 24 hours of presentation) is a good predictor of 90-day mortality in these patients [9]. MELD and modified DF scores (calculated within 24 hours of presentation) are equivalent in predicting 30- and 90-day mortality in patients with alcoholic hepatitis [10].

2.3. Glasgow Alcoholic Hepatitis Score (GAHS). GAHS was developed in an effort to overcome the low specificity of the Maddrey DF and lack of an optimal predictive cutoff point for the MELD score. GAHS is a composite scoring system based on age, serum bilirubin, blood urea nitrogen, PT, and the peripheral leucocyte count. GAHS ≥9 is a predictor of mortality and is more accurate than DF in predicting both 28- and 84-day mortality but is equivalent to MELD in predicting 28-day mortality [11].

2.4. Lille Model. The Lille model incorporates age, renal insufficiency, albumin, PT, bilirubin, and the evolution of bilirubin on day 7 to predict 6-month mortality in patients with severe alcoholic hepatitis who have received corticosteroid therapy [12].

A recent study showed that among the various prognostic scores for acute alcoholic hepatitis (Lille, Glasgow, and Maddrey scores) and cirrhosis (MELD, MELD-Na, and Child-Turcotte-Pugh) in ALD patients treated with corticosteroids, Lille score ≥0.45 and GAHS ≥9 were the most accurate models for the prediction of mortality [13]. Although the components may be different in each of these scores, they help the physicians to identify a subset of patients with higher mortality and requiring aggressive management.

3. Treatment of Alcoholic Liver Disease

3.1. General Management. One of the first therapeutic goals of patient management in patients with ALD is to induce alcohol withdrawal. The administration of fluid, calories, vitamins, and minerals is usually required. However, overhydration should be avoided, as this can worsen ascites and can precipitate variceal bleed. Vitamin K is usually administered to patients who have a prolonged prothrombin time, even though this regimen is typically ineffective because coagulopathy reflects severity of underlying liver disease. Correction of the coagulopathy with fresh frozen plasma is not recommended in the absence of active hemorrhage, because this treatment might increase the risk of variceal hemorrhage in a patient with portal hypertension. Admission to a critical care unit should be considered for unstable patients, and airway protection should be assured in a patient with hepatic encephalopathy.

3.2. Abstinence. Abstinence is the cornerstone of therapy in the management of ALD. Ideally, this includes rehabilitation with a multidisciplinary approach. If abstinence is achieved, clinical and histological improvement occurs, even if the patient is already cirrhotic [14–17]. Both psychological and pharmacological approaches can be used to treat alcohol dependence. Psychological interventions involve strategies to educate and inform patients about the nature of their problem and provide them with advice on how to change their behavior. Psychosocial treatments such as cognitive behavioral therapy and motivational enhancement therapy have been shown to reduce alcohol intake in alcohol-dependent patients [18].

As an addition to psychological therapies, many patients might benefit from pharmacological therapy. Both acamprosate and naltrexone have been demonstrated to reduce the number of drinking days and increase abstinence rates in randomized controlled trials [19]. Acamprosate, unlike naltrexone, is well tolerated except in patients with Child C cirrhosis and its benefit seems to persist for at least 1 year after treatment withdrawal. Disulfiram, an inhibitor of acetaldehyde dehydrogenase, has been used for many years in the management of alcohol-dependent patients, although with conflicting results.

3.3. Nutrition. Patients with ALD are malnourished for a number of reasons, including malabsorption, the induction of a catabolic state, and the replacement of calories with alcohol. Protein-caloric malnutrition has also been demonstrated to correlate with short-term and long-term mortality in alcoholics. Hence, malnutrition should be actively sought in such patients, and replacement should be commenced accordingly. The efficacy of nutritional therapy in ASH has been evaluated in numerous clinical trials. Although various results have been reported, most studies have shown that nutritional therapy improves liver function and histology. Enteral feeding is preferred to parenteral nutrition. Although protein ingestion is a theoretical risk factor for the development of hepatic encephalopathy, protein feeding is well tolerated, and protein should not be routinely restricted in patients with ASH.

Two randomized controlled trials have looked at the effects of nutritional therapy. The first study compared enteral tube feeding of an energy-dense formula (>2,000 kcal daily) with an isocaloric standard oral diet in 35 randomly

allocated, severely malnourished, cirrhotic patients. In-hospital mortality was significantly lower in the enteral group (12% versus 47%) [20]. The second study which compared enteral feeding with steroids in 71 patients with acute, severe ASH found that there was no difference in mortality between the groups during the 28-day treatment period. However, the mortality rate was lower in the enterally fed group in the year following treatment [21]. In summary, nutritional supplementation could have a role in the improvement of medium-term to long-term survival in patients with severe ASH. The American College of Gastroenterology guidelines recommend 1.2 to 1.5 g/kg of protein and 35 to 40 kcal/kg of body weight for patients with ALD [22].

3.4. Glucocorticoids. Glucocorticoids are the most intensely studied and yet most hotly debated treatment for acute alcoholic hepatitis. The rationale for glucocorticoid use is to block cytotoxic and inflammatory pathways in alcoholic hepatitis. Glucocorticoids have been shown to decrease proinflammatory cytokines and intercellular cell adhesion molecule 1 expression and inhibit neutrophil activation and have demonstrated short-term histological improvement in patients with alcoholic hepatitis.

Results from trials of glucocorticoids for ALD are variable and depend on the nature of the trial and the group of patients recruited as the study population. Even among glucocorticoids trials with beneficial results, enrolled subjects were heterogeneous with variable definitions of randomization and blinding and without homogeneous inclusion or exclusion criteria. Different types of steroids for different durations and different criteria were used for treatment. Steroid use in alcoholic hepatitis raises the risk of infection in an already immunocompromised host. Some trials have demonstrated higher mortality in the glucocorticoid group compared to the placebo group [23–26]. Associated with this higher mortality, a greater incidence of fungal infections among patients receiving glucocorticoids has been reported by some authors [25]. A meta-analysis on this subject, published in 1990, demonstrated a protective effect of glucocorticoids in high quality trials. This was especially so in studies that excluded patients with gastrointestinal bleeding but included those with hepatic encephalopathy [27]. But another meta-analysis by Christensen and Gluud found no benefit once they attempted to control for confounders [28]. A subsequent reanalysis of the same 3 randomized, controlled trials in Christiansen and Gluud's meta-analysis, which pooled raw data from more than 200 patients with modified DF $\geq$32, found a 28-day survival benefit of glucocorticoids (85%) versus placebo (65%). In patients with modified DF $\geq$32, treatment with glucocorticoids improved short-term (28-day) survival, with mortality decreasing from 35% in controls to 15% with steroids. Conversely, patients with modified DF <32 had a >90% survival rate without steroids. The number of patients who needed to be treated to save 1 patient was 5 [29]. Another meta-analysis of 15 trials with 721 randomized patients reported that the evidence in favor of glucocorticoids was based on heterogeneous trials of low quality [30]. Recently using individual patient data from more than 400 patients, Mathurin et al. demonstrated improved survival with corticosteroid treatment. Patients were classified as complete responders (Lille score $\leq$0.16; $\leq$35th percentile), partial responders (Lille score 0.16–0.56; 35th–70th percentile), and null responders (Lille $\geq$0.56; $\geq$70th percentile). 28-day survival was strongly associated with these groupings (91% versus 79% versus 53%, $P < 0.0001$). Corticosteroids had a significant effect on 28-day survival in complete responders and in partial responders but not in null responders [31]. The long-term benefit of steroids is difficult to assess as the various trials had differing follow-up periods, and unless the patient abstains from alcohol completely, alcoholic hepatitis is likely to recur. The survival benefit of corticosteroid therapy has not been found to persist beyond 1 year.

Despite having 13 randomized controlled trials and 6 meta-analyses of steroids as a treatment for ASH, concerns over their use continue. Although corticosteroids are probably beneficial in patients with severe disease, mortality on treatment remains high, particularly when renal impairment is present, and treatment is contraindicated in a relatively large number of patients with concomitant infection and gastrointestinal bleeding.

3.5. Antitumor Necrosis Factor Alpha Treatment

3.5.1. Pentoxifylline. Elevated tumor necrosis factor alpha (TNFα) levels have been found to be predictive of poor survival in patients with alcoholic hepatitis. Pentoxifylline is a nonselective phosphor-di-esterase inhibitor and a TNFα suppressor. In 1991, a study of pentoxifylline for severe alcoholic hepatitis (DF $\geq$ 32) reported a reduction in the development of hepatorenal syndrome and mortality in comparison with placebo [32]. A subsequent study of 101 patients from the same center supported the earlier findings, demonstrating a 40% reduction in mortality in comparison with placebo. The number needed to treat to prevent 1 death was 4.7. However, in this study, there was no demonstrable improvement in routine liver function tests or liver histology and the better survival was predominantly due to decreased incidence of hepatorenal syndrome [33].

In another study, 29 patients who did not respond to corticosteroids (identified by an absence of an early decline in bilirubin) were switched to pentoxifylline for 28 days and compared to 58 other matched patients who persisted with corticosteroid therapy. No survival benefit was observed with pentoxifylline at 2 months [34]. Thus, although some data suggest a benefit with pentoxifylline in alcoholic hepatitis, it is unclear whether its benefit extends beyond possibly preventing hepatorenal syndrome.

3.5.2. Infliximab. Infliximab is an anti-TNFα mouse/human chimeric antibody and has been extensively studied in alcoholic hepatitis. Early reports were encouraging, demonstrating improved survival rates, improved Maddrey scores, or improved laboratory parameters. However, the largest randomized, controlled trial to date, which enrolled 36 patients and compared a combination of prednisolone

(40 mg/day) and infliximab (10 mg/kg 3 times per week in weeks 0, 2, and 4) to prednisolone and placebo in alcoholic hepatitis was terminated prematurely [35]. More deaths had occurred in the group treated with prednisolone and infliximab. Whether this risk was related to the higher doses of infliximab used, more ill patients being recruited in this trial in comparison with earlier studies, the combined use of prednisolone and infliximab, or the possible unsuitability of infliximab for the treatment of alcoholic hepatitis is still debatable.

3.5.3. Etanercept. A small, uncontrolled study evaluated the use of etanercept in 13 patients with moderate to severe alcoholic hepatitis. Two patients died within 32 days, and 3 developed serious adverse events (infection, gastrointestinal bleeding, and hepatorenal syndrome) mandating withdrawal of the drug [36]. A more recent multicenter, randomized, double-blind, placebo-controlled study of etanercept in 48 patients with severe alcoholic hepatitis (defined as MELD $\geq$15) found no difference in the 1-month mortality rates in the 2 groups on an intention-to-treat analysis [37]. Alarmingly, the 6-month mortality in the etanercept group was significantly higher in comparison with the controls. Rates of serious adverse infectious events were also significantly higher in the etanercept group. These results have considerably dampened the enthusiasm for using anti-TNFα agents in patients with severe ASH.

3.6. Antioxidant Cocktails. Antioxidants have been tried in alcoholic hepatitis as oxidative stress is a key factor in its pathogenesis. However, results have failed to show any convincing benefit from their use. Phillips et al., who compared corticosteroids to an antioxidant cocktail (β-carotene, vitamins C and E, selenium, methionine, allopurinol, desferrioxamine, and *N*-acetylcysteine), reported inferior survival rates in comparison with corticosteroids at 30 days [38]. Another study stratified patients with severe alcoholic hepatitis by gender and corticosteroid treatment. The active group received a loading dose of *N*-acetylcysteine (150 mg/kg followed by 100 mg/kg/day for 1 week) and daily doses of vitamins A and E, biotin, selenium, zinc, manganese, copper, magnesium, folic acid, and coenzyme Q for 6 months. Antioxidant therapy showed no benefit, either alone or in combination with corticosteroids [39]. A more recent study of 87 patients with severe alcoholic hepatitis (defined as modified Maddrey DF $\geq$32) randomized patients to receive either corticosteroids with *N*-acetylcysteine infusion for 5 days or corticosteroids alone [40]. Although patients in the *N*-acetylcysteine group had better 1-month survivals, this effect did not persist at 3 and 6 months.

3.7. S-Adenosyl Methionine. *S*-Adenosyl methionine (SAMe) is a precursor of glutathione that theoretically might be protective in alcohol-induced liver injury. In a Cochrane database review of 9 randomized trials that combined a heterogeneous sample of 434 patients with ALD, SAMe failed to show a survival benefit [41]. Only 1 trial of 62 patients deemed to have adequate methodology and outcome reporting and good quality suggested benefit (improved survival and delay to liver transplantation) with 2 years of SAMe treatment for Child's class A and B alcoholic cirrhosis [42].

3.8. Treatment of Hepatorenal Syndrome Associated with Alcoholic Hepatitis. In patients with severe ASH, the development of renal failure is associated with a survival of less than 10% even with intensive management. The most significant advance in the management of patients with advanced liver disease over the past decade has been the introduction of albumin infusions combined with splanchnic vasoconstrictor agents for patients with hepatorenal syndrome. Although no randomized trials have specifically examined this form of therapy in patients with ASH, the previously reported high mortality in ASH patients with hepatorenal syndrome suggests that albumin infusions combined with splanchnic vasoconstrictor agents would have a significant and beneficial effect on patient survival. The usefulness of pentoxyfylline in this clinical setting has been mentioned earlier.

3.9. Liver Transplantation in ALD. Orthotopic liver transplantation (OLT) remains the definitive therapy for decompensated cirrhosis due to ALD despite continued alcohol abstinence. Short-term (1- to 7-year) graft survival and patient survival remain at par with, if not superior to, survival with non-ALD if the patient remains abstinent. Bellamy et al. reported that in 123 patients who were transplanted, patient survival at 1, 5, and 7 years was 84%, 72%, and 64%, respectively. Graft survival was 81%, 66%, and 50%, respectively, over the same period [43]. The 1- and 5-year patient and graft survival rates for all patients with cirrhosis were 86.9%/73.4% and 82.4%/67.4%, respectively [44].

However, OLT for ALD patients continues to fuel controversy, including issues of recidivism, potentially poor compliance with postoperative care, and inherent biases against alcoholics, such as concern about using scarce organs for what is often perceived to be a self-inflicted disease.

DiMartini et al.'s prospective study of alcoholic recipients found that 22% had used some alcohol by the end of the first year post-OLT and 42% had by 5 years, of whom 26% had a binge drinking pattern [45]. Such a wide range of relapse rates may stem from varying definitions of recidivism and methods of eliciting alcohol consumption data. Most studies addressing recidivism in the past 20 years have used the "any use" definition of alcohol relapse. However, a return to drinking does not necessarily mean excessive drinking. Furthermore, Fabrega et al.'s report of patients who had returned to drinking revealed no decreased compliance with other medical care, including immunosuppressant therapy [46]. Pfitzmann et al. stratified relapsers into slips and harmful drinking, revealing significantly worse 5- and 10-year survival rates (69.5% and 20%) among "harmful" drinkers versus abstainers (90.3% and 81.5%) [47].

A major focus in determining candidacy for liver transplantation in ALD has been identifying factors to

predict posttransplant recidivism. Pretransplant duration of abstinence from alcohol was the first predictive factor analyzed. Other medical and social variables can be associated with high relapse rates, including tobacco consumption, noncompliance to follow-up clinic visits, and mental illness. A 2008 meta-analysis of 50 studies looking at predictors of recidivism found 3 significant, albeit modest, variables: a poor social support system, a family history of alcohol abuse/dependence, and pretransplant abstinence of 6 months or less [48].

Pre-OLT abstinence, especially the 6-month rule, remains contentious. Studies over the years have provided convincing data for and against the 6-month abstinence requirement. Lucey et al. suggested that this 6-month period of abstinence would allow the native liver to recover with medical management and possibly obviate transplantation [49]. However, this minimal period of abstinence is sometimes waived if the patient is deemed too ill to survive beyond 6 months without a liver transplant. One study showed that recovery in decompensated alcoholic cirrhosis by alcohol abstinence can be predicted within 3 months of abstinence by the monitoring of clinical signs via the Child-Pugh scoring system (serum bilirubin, albumin, international normalized ratio, ascites, and hepatic encephalopathy) [50]. This study by Veldt et al. found that although such improvement in liver function can take place within 3 months of abstinence, some abstinent patients die within 6 months; this has led some authors to suggest reducing the period of abstinence from 6 to 3 months. Yet, abstinence less than 12 months was recently identified as a significant risk factor for relapse in a large retrospective study of OLT recipients [50].

Finally, an increasing concern of late is the high risk for de novo malignancies in long-term survivors transplanted for ALD. Although posttransplantation lymphoproliferative disorder and nonmelanoma skin cancer remain the most common malignancies after liver transplantation, the incidence of esophageal cancer is significantly increased in patients with alcohol as the etiology of end-stage liver disease. Duvoux et al.'s prospective study showed a significantly higher incidence of malignancies in patients with ALD compared to those with non-ALD etiologies [51]. They also detected squamous cell carcinoma of the oropharynx or esophagus only in recipients transplanted for ALD. Risk factors undoubtedly include the cumulative effects of alcohol and, in most cases, smoking with posttransplant immunosuppression. Thus, regular ear, nose, and throat examinations appear justified in patients transplanted for ALD.

References

[1] H. Singh, B. Masih, S. K. Satpathy, A. Duseja, and Y. Chawla, "Financial burden of alcohol abuse in patients with alcoholic liver disease," *Tropical Gastroenterology*, vol. 22, no. 3, p. 172, 2001.

[2] M. Adachi and D. A. Brenner, "Clinical syndromes of alcoholic liver disease," *Digestive Diseases*, vol. 23, no. 3-4, pp. 255–263, 2005.

[3] W. Lelbach, "Epidemiology of alcoholic liver disease," in *Progress in Liver Disease*, H. Popper and F. Schaffner, Eds., vol. 5, pp. 494–515, Grune and Stratton, New York, NY, USA, 1976.

[4] W. Lelbach, "Quantitative aspects of drinking in alcoholic liver cirrhosis," in *Alcoholic Liver Pathology*, H. M. Khanna, Y. Israel, and H. Kalant, Eds., pp. 1–18, Toronto Addiction Research Foundation of Ontario, Toronto, Canada, 1975.

[5] A. Duseja, Y. K. Chawla, R. K. Dhiman, A. Kumar, N. Choudhary, and S. Taneja, "Non-hepatic insults are common acute precipitants in patients with acute on chronic liver failure (ACLF)," *Digestive Diseases and Sciences*, vol. 55, pp. 3188–3192, 2010.

[6] W. C. Maddrey, J. K. Boitnott, M. S. Bedine, F. L. Weber Jr., E. Mezey, and R. I. White Jr., "Corticosteroid therapy of alcoholic hepatitis," *Gastroenterology*, vol. 75, pp. 193–199, 1978.

[7] R. L. Carithers Jr., H. F. Herlong, A. M. Diehl et al., "Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicenter trial," *Annals of Internal Medicine*, vol. 110, no. 9, pp. 685–690, 1989.

[8] M. J. Ramond, T. Poynard, B. Rueff et al., "A randomized trial of prednisolone in patients with severe alcoholic hepatitis," *The New England Journal of Medicine*, vol. 326, no. 8, pp. 507–512, 1992.

[9] W. Dunn, L. H. Jamil, L. S. Brown et al., "MELD accurately predicts mortality in patients with alcoholic hepatitis," *Hepatology*, vol. 41, no. 2, pp. 353–358, 2005.

[10] W. Srikureja, N. L. Kyulo, B. A. Runyon, and K. Q. Hu, "MELD score is a better prognostic model than Child-Turcotte-Pugh score or Discriminant Function score in patients with alcoholic hepatitis," *Journal of Hepatology*, vol. 42, no. 5, pp. 700–706, 2005.

[11] E. H. Forrest, C. D. Evans, S. Stewart et al., "Analysis of factors predictive of mortality in alcoholic hepatitis and derivation and validation of the Glasgow alcoholic hepatitis score," *Gut*, vol. 54, no. 8, pp. 1174–1179, 2005.

[12] A. Louvet, S. Naveau, M. Abdelnour et al., "The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids," *Hepatology*, vol. 45, no. 6, pp. 1348–1354, 2007.

[13] J. Boursier, M. Demy, V. Moal et al., "Prediction of outcome in patients with severe acute alcoholic hepatitis treated by corticosteroids," *Hepatology*, vol. 48, p. S636A, 2008.

[14] T. B. Reynolds, H. M. Geller, O. T. Kuzma, and A. G. Redeker, "Spontaneous decrease in portal pressure with clinical improvement in cirrhosis," *The New England Journal of Medicine*, vol. 263, pp. 734–739, 1960.

[15] J. F. Alexander, M. W. Lischner, and J. T. Galambos, "Natural history of alcoholic hepatitis. II. The long-term prognosis," *The American Journal of Gastroenterology*, vol. 56, no. 6, pp. 515–525, 1971.

[16] W. J. Powell Jr. and G. Klatskin, "Duration of survival in patients with Laennec's cirrhosis. Influence of alcohol withdrawal, and possible effects of recent changes in general management of the disease," *The American Journal of Medicine*, vol. 44, no. 3, pp. 406–420, 1968.

[17] O. Niemela, J. Risteli, J. E. Blake, L. Risteli, K. V. Compton, and H. Orrego, "Markers of fibrogenesis and basement membrane formation in alcoholic liver disease. Relation to severity, presence of hepatitis, and alcohol intake," *Gastroenterology*, vol. 98, no. 6, pp. 1612–1619, 1990.

[18] A. Moyer, J. W. Finney, C. E. Swearingen, and P. Vergun, "Brief interventions for alcohol problems: a meta-analytic review of controlled investigations in treatment-seeking and non-treatment-seeking populations," *Addiction*, vol. 97, no. 3, pp.

279–292, 2002.

[19] J. C. Garbutt, S. L. West, T. S. Carey, K. N. Lohr, and F. T. Crews, "Pharmacological treatment of alcohol dependence: a review of the evidence," *Journal of the American Medical Association*, vol. 281, no. 14, pp. 1318–1325, 1999.

[20] E. Cabre, F. Gonzalez-Huix, A. Abad-Lacruz et al., "Effect of total enteral nutrition on the short-term outcome of severely malnourished cirrhotics. A randomized controlled trial," *Gastroenterology*, vol. 98, no. 3, pp. 715–720, 1990.

[21] E. Cabré, P. Rodríguez-Iglesias, J. Caballería et al., "Short- and long-term outcome of severe alcohol-induced hepatitis treated with steroids or enteral nutrition: a multicenter randomized trial," *Hepatology*, vol. 32, no. 1, pp. 36–42, 2000.

[22] A. J. McCullough and J. F. O'Connor, "Alcoholic liver disease: proposed recommendations for the American College of Gastroenterology," *The American Journal of Gastroenterology*, vol. 93, no. 11, pp. 2022–2036, 1998.

[23] C. L. Mendenhall, S. Anderson, P. Garcia-Pont et al., "Short-term and long-term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone," *The New England Journal of Medicine*, vol. 311, no. 23, pp. 1464–1470, 1984.

[24] J. B. Shumaker, R. H. Resnick, J. T. Galambos et al., "A controlled trial of 6-methyl-prednisolone in acute alcoholic hepatitis. With a note on published results in encephalopathic patients," *The American Journal of Gastroenterology*, vol. 69, pp. 443–449, 1978.

[25] B. L. Blitzer, M. G. Mutchnick, P. H. Joshi et al., "Adrenocorticosteroid therapy in alcoholic hepatitis. A prospective, double blind randomized study," *The American Journal of Digestive Diseases*, vol. 22, no. 6, pp. 477–484, 1977.

[26] A. Theodossi, A. L. Eddleston, and R. Williams, "Controlled trial of methylprednisolone therapy in severe acute alcoholic hepatitis," *Gut*, vol. 23, no. 1, pp. 75–79, 1982.

[27] T. F. Imperiale and A. J. McCullough, "Do corticosteroids reduce mortality from alcoholic hepatitis? A meta-analysis of the randomized trials," *Annals of Internal Medicine*, vol. 113, no. 4, pp. 299–307, 1990.

[28] E. Christensen and C. Gluud, "Glucocorticoids are ineffective in alcoholic hepatitis: a meta-analysis adjusting for confounding variables," *Gut*, vol. 37, no. 1, pp. 113–118, 1995.

[29] P. Mathurin, C. L. Mendenhall, R. L. Carithers Jr. et al., "Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis (AH): individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH," *Journal of Hepatology*, vol. 36, no. 4, pp. 480–487, 2002.

[30] A. Rambaldi, H. H. Saconato, E. Christensen, K. Thorlund, J. Wetterslev, and C. Gluud, "Systematic review: glucocorticosteroids for alcoholic hepatitis—a Cochrane Hepato-Biliary Group systematic review with meta-analyses and trial sequential analyses of randomized clinical trials," *Alimentary Pharmacology and Therapeutics*, vol. 27, no. 12, pp. 1167–1178, 2008.

[31] P. Mathurin, J. O'Grady, R. L. Carithers et al., "Corticosteroids improve 28-day survival in patients with severe alcoholic hepatitis: meta analysis of individual patient data," *Gut*, vol. 60, pp. 255–260, 2011.

[32] J. G. McHutchison, B. A. Runyon, J. O. Draguesku et al., "Pentoxifylline may prevent renal impairment (hepatorenal syndrome) in severe acute alcoholic hepatitis," *Hepatology*, vol. 14, p. S96A, 1991.

[33] E. Akriviadis, R. Botla, W. Briggs, S. Han, T. Reynolds, and O. Shakil, "Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial," *Gastroenterology*, vol. 119, no. 6, pp. 1637–1648, 2000.

[34] A. Louvet, E. Diaz, S. Dharancy et al., "Early switch to pentoxifylline in patients with severe alcoholic hepatitis is inefficient in non-responders to corticosteroids," *Journal of Hepatology*, vol. 48, no. 3, pp. 465–470, 2008.

[35] S. Naveau, S. Chollet-Martin, S. Dharancy et al., "A double-blind randomized controlled trial of infliximab associated with prednisolone in acute alcoholic hepatitis," *Hepatology*, vol. 39, no. 5, pp. 1390–1397, 2004.

[36] K. V. Menon, L. Stadheim, P. S. Kamath et al., "A pilot study of the safety and tolerability of etanercept in patients with alcoholic hepatitis," *The American Journal of Gastroenterology*, vol. 99, no. 2, pp. 255–260, 2004.

[37] N. C. Boetticher, C. J. Peine, P. Kwo et al., "A randomized, double-blinded, placebo-controlled multicenter trial of etanercept in the treatment of alcoholic hepatitis," *Gastroenterology*, vol. 135, no. 6, pp. 1953–1960, 2008.

[38] M. Phillips, H. Curtis, B. Portmann, N. Donaldson, A. Bomford, and J. O'Grady, "Antioxidants versus corticosteroids in the treatment of severe alcoholic hepatitis—a randomised clinical trial," *Journal of Hepatology*, vol. 44, no. 4, pp. 784–790, 2006.

[39] S. Stewart, M. Prince, M. Bassendine et al., "A randomized trial of antioxidant therapy alone or with corticosteroids in acute alcoholic hepatitis," *Journal of Hepatology*, vol. 47, no. 2, pp. 277–283, 2007.

[40] E. Nguyen-Khac, T. Thevenot, M. Piquet et al., "Treatment of severe alcoholic hepatitis with corticosteroids plus N-acetylcysteine versus corticoids: planned interim analysis of a multicenter, controlled, randomized trial," *Hepatology*, vol. 48, p. S634A, 2008.

[41] A. Rambaldi and C. Gluud, "S-adenosyl-L-methionine for alcoholic liver diseases," *Cochrane Database of Systematic Reviews*, no. 2, article CD002235, 2006.

[42] J. M. Mato, J. Camara, J. Fernandez de Paz et al., "S-adenosylmethionine in alcoholic liver cirrhosis: a randomized, placebo-controlled, double-blind, multicenter clinical trial," *Journal of Hepatology*, vol. 30, pp. 1081–1089, 1999.

[43] C. O. Bellamy, A. M. DiMartini, K. Ruppert et al., "Liver transplantation for alcoholic cirrhosis: long term follow-up and impact of disease recurrence," *Transplantation*, vol. 72, no. 4, pp. 619–626, 2001.

[44] "OPTN/SRTR Annual Report, 2008," http://optn.transplant.hrsa.gov/ar2008/Chapter_IV_AR_CD.htm?cp=5.

[45] A. DiMartini, N. Day, M. A. Dew et al., "Alcohol consumption patterns and predictors of use following liver transplantation for alcoholic liver disease," *Liver Transplantation*, vol. 12, no. 5, pp. 813–820, 2006.

[46] E. Fabrega, J. Crespo, F. Casafont et al., "Alcoholic recidivism after liver transplantation for alcoholic cirrhosis," *Journal of Clinical Gastroenterology*, vol. 26, pp. 204–206, 1998.

[47] R. Pfitzmann, J. Schwenzer, N. Rayes, D. Seehofer, R. Neuhaus, and N. C. Nüssler, "Long-term survival and predictors of relapse after orthotopic liver transplantation for alcoholic liver disease," *Liver Transplantation*, vol. 13, no. 2, pp. 197–205, 2007.

[48] M. A. Dew, A. F. DiMartini, J. Steel et al., "Meta-analysis of risk for relapse to susbtance use after transplantation of the liver or other solid organs," *Liver Transplantation*, vol. 14, no. 2, pp. 159–172, 2008.

[49] M. R. Lucey, K. A. Brown, G. T. Everson et al., "Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized

by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases," *Liver Transplantation and Surgery*, vol. 3, no. 6, pp. 628–637, 1997.

[50] B. J. Veldt, F. Lainé, A. Guillygomarch et al., "Indication of liver transplantation in severe alcoholic liver cirrhosis: quantitative evaluation and optimal timing," *Journal of Hepatology*, vol. 36, no. 1, pp. 93–98, 2002.

[51] C. Duvoux, I. Delacroix, J. P. Richardet et al., "Increased incidence of oropharyngeal squamous cell carcinomas after liver transplantation for alcoholic cirrhosis," *Transplantation*, vol. 67, pp. 418–421, 1999.

SAGE-Hindawi Access to Research
International Journal of Hepatology
Volume 2011, Article ID 519526, 5 pages
doi:10.4061/2011/519526

Review Article

Prescribing Medications in Patients with Decompensated Liver Cirrhosis

Deepak N. Amarapurkar

Department of Gastroenterology, Bombay Hospital and Medical Research Centre, New Prabhadevi Road, Prabhadevi, Mumbai 400 025, India

Correspondence should be addressed to Deepak N. Amarapurkar, amarapurkar@gmail.com

Received 21 February 2011; Accepted 24 May 2011

Academic Editor: Richard Guan

Patients with decompensated liver cirrhosis have various serious complications which require multiple drugs for therapeutic or prophylactic use. Majority of the drugs are primarily metabolized and excreted by hepatobiliary system; hence, liver cell necrosis contributes to impaired drug handling in liver failure while portosystemic shunt can alter drug action in cirrhosis. Hence, in order to decide drug dosing in liver failure, 3 important factors need to be considered (1) pharmacokinetic alterations of drugs, (2) pharmacodynamic alteration of drugs, and (3) increased susceptibility of patients to adverse events particularly hepatotoxicity. Though there is no predictable test which can be used to determine drug dosage in patients with decompensated liver cirrhosis, drugs with first pass metabolism require reduction in oral dosages, for high clearance drugs both loading and maintenance dosages need adjustment, for low clearance drugs maintenance dose needs adjustment, whenever possible measuring drug level in the blood and monitoring of adverse events frequently should be done. No evidence-based guidelines exist for the use of medication in patients' with liver cirrhosis. There are hardly any prospective studies on the safety of drugs in cirrhotic patients. According to the experts opinion, most of the drugs can be used safely in patients with cirrhosis, but drug-induced hepatotoxicity may be poorly tolerated by patients with cirrhosis; hence, potential hepatotoxins should be avoided in patients with liver cirrhosis. Potentially hepatotoxic drugs may be used in patients with liver cirrhosis based on the clinical needs and when there are no alternatives available. Caveat for the prescribing medications in patients with cirrhosis the drug dosing should be individualized depending on a number of factors like nutritional status, renal function, adherence, and drug interaction. Monitoring of the liver function at frequent intervals is highly recommended.

1. Introduction

Liver is a primary site of drug metabolism. Various steps in the drug biotransformation in the liver are entry of the drug in the liver, uptaken by the liver cells, phase I reaction, for example, hydrolysis, hydroxylation, oxidation, reduction, demethylation and phase II reactions conjugation with glycine, glucuronide sulphate, hippurate, and others. These steps are dependent on two factors, hepatic blood flow and metabolic capacity of the liver. In patients with liver cirrhosis impaired drug handling is due to (1) liver cell necrosis, (2) shunting of the blood through porta systemic colaterals, (3) reduction in the concentration of drug-binding proteins, (4) abnormal drug volume distribution, (5) altered drug elimination, (6) altered drug metabolism, (7) altered pharmaco dynamics, (8) associated renal failure, and (9) drug-drug interaction. The impairment of drug metabolism is proportional to the liver dysfunction. Patients with well-compensated cirrhosis and near-normal synthetic function will have a lesser extent of impaired drug metabolism as compared to patients with decompensated cirrhosis with significant synthetic dysfunction and portal hypertension [1, 2]. Though various tests like liver function test, indocyanine green clearance, megaxx, Child Pugh score, and meld score are used for prediction of impaired liver function, still no tests can determine drug dosing in these patients. Drugs with first pass metabolism require reduction in oral dosages, for high clearance drugs both loading and maintenance dosage need adjustment, for clearance drugs maintenance dose needs adjustment (Figure 1). Whenever

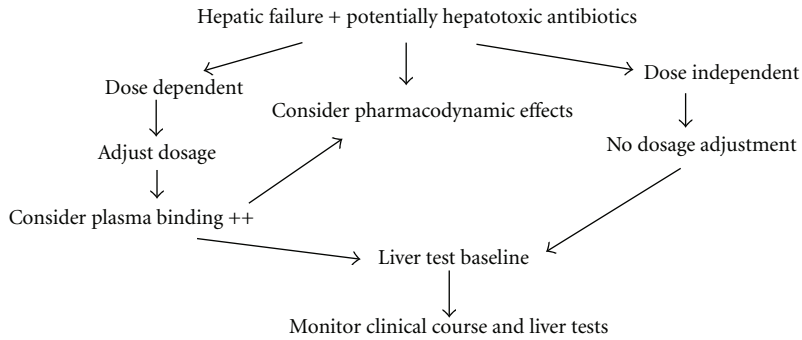


Figure 1: Algorithm for drug dosing in liver failure. Possibly avoids drugs which are metabolized by liver and/or have potential hepatotoxicity.

possible, measuring drug level in the blood and monitoring of adverse events frequently should be done. No evidence-based guidelines exist for the use of medication in patients with liver cirrhosis [3–5]. There are hardly any prospective studies on the safety of drugs in cirrhotic patients. Drug-induced liver injury (DILI) is the commonest cause of drug withdrawal from further development and from the market [6]. Almost 50% of the drugs are associated with some sort of liver injury [7]. Nearly 100 drugs are known to cause fulminant hepatic failure, and 10% of all adverse drug reaction are hepatotoxicity [8, 9]. Approximately 1000 drugs and several herbal remedies have been shown to be causing DILI. Because of this drugs associated with liver toxicity are usually contraindicated in patients with chronic liver disease; still most of the drugs can be used safely in patients with chronic liver disease according to the expert opinion [10–13].

According to the experts' opinion most of the drugs can be used safely in patients with cirrhosis, but drug-induced hepatotoxicity may be poorly tolerated by patients with cirrhosis; hence, potential hepatotoxins should be avoided in patients with liver cirrhosis [14]. Potentially hepatotoxic drugs may be used in patients with liver cirrhosis based on the clinical needs and when there are no alternatives available. Caveat for the prescribing medications in patients with cirrhosis the drug dosing should be individualized depending on a number of factors like nutritional status, renal function, adherence, and drug-drug interaction. Monitoring of the liver function at frequent intervals is highly recommended [14, 15]. In spite of these recommendations, monitoring of drug-induced liver injury by alanine transaminase is inconvenient and not followed by both patients and physicians [4]. We as clinicians should educate our patients about the warning signs of drug-induced liver injury like abdominal pain, nausea, and jaundice for stopping the drugs and seeking urgent medical attention.

In this paper after extensive literature search and expert opinions, I will discuss rational use of various drugs in patients with cirrhosis.

2. Antibiotic Dosing in Cirrhosis

Liver is an important site of removal of blood bone bacteria. Hepatic destruction of bacteria and reticular endothelial system-related phagocytosis are impaired in patients with cirrhosis. In cirrhotic patients serum bactericidal opsonic activity and neutrophil function are defective. This leads to 5 to 7 fold increase in bacteremia in these patients requiring antibiotics for therapeutic or prophylactic purpose [16]. Extensive literature search was done to identify the antibiotics that need dosage alteration in patients with liver cirrhosis. Macrolide antibiotics like erythromycin, azithromycin, chloramphenicol, lincomycine, and clindamycin which are excreted and detoxified by liver should be used with cautions in these patients. Tetracycline, Isoniazid and Rifampin have prolonged half life in patients with liver cirrhosis. Metronidazole ketocanozole, miconazole, fluconazole, itraconazole, and nitrofurantoin pyrazinamide should be used with caution. Beta-lactum antibiotics can cause leucopenia, while amino glycosides can increase susceptibility to renal failure. Vancomycin can cause increased toxicity in patients with liver failure. Antibiotics which can produce hepatitis or cholestasis should be avoided or used with caution. Tuberculosis was more common in alcoholic and Child class C cirrhosis (Table 1). Antituberculosis therapy (ATT) is associated with hepatotoxicity in 10%. Hepatotoxicity requires withdrawal, modification, and sequential reintroduction to achieve cure of tuberculosis. Using such hepatotoxic drugs in presence of cirrhosis or advanced liver disease is a challenge. Cirrhotic patients with tuberculosis have significantly lower completion of Rifamipicin + Isoniazid based ATT, higher hepatotoxicity, and higher mortality. Recommended ATT in Child class A cirrhosis is the same as a noncirrhotic population but strict followup is required. Pyrazinamide may be avoided. In Child class B Pyrazinamide should be avoided,

Table 1: Antibiotics to be avoided in liver disease.

Chloramphenicol—higher risk of bone marrow suppression (markedly increased half life)
Erythromycin estolate: causes cholestasis
Tetracycline—dose related hepatotoxicity
Antituberculous therapy in combinations, pyrazinamide
Griseofulvin—contraindicated
Nalidixic acid
Nitrofurantoin prolonged use

Table 2: Antibiotics which need to be used with extra caution in patients with liver failure.

Piperacillin	Nalidixic acid	Azithromycin
Ceftazidime	Pefloxacin	Tetracycline
Ceftriaxone	Gatifloxacin	Cotrimoxazole + Trimethoprim
Cefoperazone	Erythromycin	Metronidazole
Cefoperazone + Sulbactam Cefetamet	Roxithromycin	Ketoconazole & other fluconozoles

Table 3: Antibiotics causing hepatotoxicity.

Hepatocellular injury	Cholestatic injury	Fulminant hepatic failure
Chloramphenicol, Clindamycin	Cephalosporins, Erythromycin	Sulfonamides, Trimethoprim—Sulfomethoxazole
Penicillin G, Amoxicillin	Penicillin G, Oxacillin, Cloxacillin	Ketoconazole, PAS, Trovafloxacin
Trimethoprim—Sulfomethoxazole	Floxacillin, Augmentin, Clarithromycin	
Amphotericin, Hydroxystilbamidine	Nitrofurantoin, Trimethoprim—Sulfomethoxazole	
Ketoconazole, Itraconazole	5-fluorocytosine, Griseofulvin	
INH, Trovafloxacin, Oxacillin	Trovafloxacin, Thiabendazole	

Isoniazid with rifamipicin may be avoided. Isoniazid or rifamipicin with ethambutol and quinolone can be used for 12 to 18 months. In Child Class C ethambutol, quinolone, and one second line agent may be used for 12 to 18 months [2, 14, 17–19].

Antifungal drugs like Ketocanozole and miconazole though hepatotoxic can be used in patients with cirrhosis but monitor drug concentration in serum is recommended. Metronidazole reduce dose by 50% in patients with severe cirrhosis and/or associated renal insufficiency. There is no information of safe use of nitrofurntoin, chloramaphenicol, sodium fusidate and pyrazinamide but they are poentially toxic hence avoid their use in liver disease [14] (Tables 2 and 3).

3. Sedation, Anesthesia and Analgesia in Patients with Liver Cirrhosis

Endoscopic procedures are often necessary in patients with cirrhosis who may need sedation or short anesthesia. Benzodiazepines like midazolam administered in single dose have minimal impact in patients with compensated cirrhosis. Benzodiazepines can be cautiously used in decompensated cirrhosis. Flumazenil can be used to reverse the effect of benzodiazepine. Fentanyl (opioid) elimination is near normal in cirrhotics and can be used for sedation. Patients with opioid toxicity can be treated with nalaxone; propofol is preferred to benzodiazepines or opioids for endoscopic sedation for patients with decompensated cirrhosis due to its short half life and lower risk of inducing encephalopathy. In patients without extrahepatic high risk, the gastroenterologist directed propofol is safe. The adverse effects of propofol are hypotension, tachycardia, hypoventilation, and prolongation of QT interval [1, 20–22].

4. Anesthetic Agents

General Anesthesia can reduce the hepatic blood flow resulting into decompensation. Volatile agents and halothane should be avoided. The new agents like isoflurane, desflurane are not significantly metabolized by the liver; hence, are safe. Combination of agents like fentanyl may greatly reduce the need of anesthetic agents. Propofol is also a good agent for combination anesthesia [14, 23].

5. Analgesics

Pain management in cirrhosis is a challenging task as use of analgesic agents is associated with severe complications like gastrointestinal bleeding, hepatic encephalopathy, hepatorenal syndrome, and mortality. Nonsteroid anti-inflammatory agents are contraindicated as they can induce GI bleed and renal failure. Opioid analgesic should be used with caution as it can precipitate encephalopathy. Acetaminophen at a dose less than 2 gm/day is a reasonably safe option. Patients with cirrhosis having visceral or musculoskeletal pain should be treated with acetaminophen less than 2-3 gms/day [24, 25]. In case of inadequate pain relief, tramadol 25 mg every 8 hours can be used. For intractable pain hydromorphone orally or fentanyl topical patch can be used. Combination of these drugs with tramadol should not be done. Neuropathic pain can be treated with nortriptyline, desipramine, and gabapentin, pregabalin with or without acetaminophen. Analgesic choice in patients with cirrhosis should be individualized depending on etiology of cirrhosis, nutritional status, adherence, renal function, liver transplant candidacy, and drug-drug interaction [14, 20, 22].

6. Anticonvulsants

Phenytoin, Carbamazapin, and valproate can be hepatotoxic. All the drugs can be used in patients with decompensated

liver disease with caution. The newer anticonvulsants like lamotrigine, topiramate also need lowering of the dosage in cirrhotic patients. Antidepressant, (selective serotonin reuptake inhibitors) like fluvoxamine, paroxetine, and fluoxetine need dose modification in patients with cirrhosis [14].

Antiemetic metoclopramide and ondansetron require significant dose reduction in patients with cirrhosis. As antiulcer agents proton pump inhibitors are preferred over H2 receptor blockers but they still need half the dosage [14].

7. Cardiovascular Drug Therapy

Patients of nonalcoholic steatosis-related cirrhosis have increased incidence of dyslipidemia, hypertension, and coronary artery disease. Drugs like labatolol and methyldopa can cause severe hepatotoxicity and need frequent monitoring and should be used only when there are no other choices. Captopril, Amiodarone, and ticlopidine can cause hepatotoxicity and should be used with caution. The details of dose adjustments on alpha blockers, ACE inhibitors, angiotensin II receptor antagonist, and other drugs used in cardiovascular diseases have been reviewed in the recent past [26]. Satins appear to be remarkably safe in patients with liver cirrhosis [27].

Drug-induced liver injury has been reported almost in 50% drugs in the physicians' desk reference. More than 100 drugs are incriminated in causing fulminant hepatic failure. The drugs that have been mentioned to be contraindicated in the patients with liver disease are methotrexate, niacin, Naltrexone, Metformin, Novastatin, Felbamate, Ticklopidine, Clonazipam, Gemfibrizil, valproic acid, and estrogens in the physicians' desk reference, but some of them are used in clinical practice under strict supervision. Metformin can be used in patients with liver cirrhosis without renal insufficiency. Other antidiabetics like second-generation sulfonylurea like Glipizide, Glimepride may be the drug of choice in patients with liver cirrhosis. Thiazolidinediones can cause drug hepatitis but can be used in reduced dosage with strict monitoring [14, 15].

In conclusion prescribing medicines in patients with liver disease is a challenging task. There are no clear tests which can identify altered drug metabolism in these patients. Medications should be individualized depending upon various factors. Surveillance using liver enzymes though recommended routinely the use of INH can lead to acute liver failure despite the surveillance. The enhanced Nephrotoxicity of radio contrast agents Aminoglycosides and NSAID may be a more frequent and dangerous challenge than hepatotoxicity.

References

[1] V. Rodighiero, "Effects of liver disease on pharmacokinetics. An update," *Clinical Pharmacokinetics*, vol. 37, no. 5, pp. 399–431, 1999.

[2] F. Delcò, L. Tchambaz, R. Schlienger, J. Drewe, and S. Krähenbühl, "Dose adjustment in patients with liver disease," *Drug Safety*, vol. 28, no. 6, pp. 529–545, 2005.

[3] S. Verma and N. Kaplowitz, "Diagnosis, management and prevention of drug-induced liver injury," *Gut*, vol. 58, no. 11, pp. 1555–1564, 2009.

[4] J. R. Senior, "Monitoring for hepatotoxicity: what is the predictive value of liver "function" tests?" *Clinical Pharmacology and Therapeutics*, vol. 85, no. 3, pp. 331–334, 2009.

[5] G. Abboud and N. Kaplowitz, "Drug-induced liver injury," *Drug Safety*, vol. 30, no. 4, pp. 277–294, 2007.

[6] http://www.fda.gov/cder/livertox/prevention/m0093/rfld002.htm.

[7] *Physicians' Desk Reference*, Medical Economics Inc., Montvale, NJ, USA, 56th edition, 2002.

[8] C. Lammert, E. Bjornsson, A. Niklasson, and N. Chalasani, "Oral medications with significant hepatic metabolism at higher risk for hepatic adverse events," *Hepatology*, vol. 51, no. 2, pp. 615–620, 2010.

[9] D. Larrey, "Epidemiology and individual susceptibility to adverse drug reactions affecting the liver," *Seminars in Liver Disease*, vol. 22, no. 2, pp. 145–155, 2002.

[10] R. A. Nathwani and N. Kaplowitz, "Drug Hepatotoxicity," *Clinics in Liver Disease*, vol. 10, no. 2, pp. 207–217, 2006.

[11] G. C. Farrell, *Drug Induced Liver Disease*, Churchill Livingstone, London, UK, 1994.

[12] G. Marino, H. J. Zimmerman, and J. H. Lewis, "Management of drug-induced liver disease," *Current Gastroenterology Reports*, vol. 3, no. 1, pp. 38–48, 2001.

[13] J. H. Lewis, "Drug-induced liver disease," *Medical Clinics of North America*, vol. 84, no. 5, pp. 1275–1311, 2000.

[14] J. H. Lewis, "The rational use of potentially hepatotoxic medications in patients with underlying liver disease," *Expert Opin Drug Saf*, vol. 1, no. 2, pp. 159–172, 2002.

[15] H. J. Zimmerman, *Hepatotoxicity. The Adverse Effects of Drugs and Other Chemical on the Liver*, Lippincot Williams & Wilkins, Philadelpha, Pa, USA, 2nd edition, 1999.

[16] N. Rolando, J. Philpott-Howard, and R. Williams, "Bacterial and fungal infection in acute liver failure," *Seminars in Liver Disease*, vol. 16, no. 4, pp. 389–402, 1996.

[17] J. Reichen, "Prescribing in liver disease," *Journal of Hepatology*, vol. 26, no. 1, pp. 36–40, 1997.

[18] B. E. Senousy, S. I. Belal, and P. V. Draganov, "Hepatotoxic effects of therapies for tuberculosis," *Nature Reviews Gastroenterology and Hepatology*, vol. 7, no. 10, pp. 543–556, 2010.

[19] S. Agal, R. Baijal, S. Pramanik et al., "Monitoring and management of antituberculosis drug induced hepatotoxicity," *Journal of Gastroenterology and Hepatology*, vol. 20, no. 11, pp. 1745–1752, 2005.

[20] I. Tegeder, J. Lötsch, and G. Geisslinger, "Pharmacokinetics of opiods in liver disease," *Clinical Pharmacokinetics*, vol. 37, no. 1, pp. 17–40, 1999.

[21] N. Bamji and L. B. Cohen, "Endoscopic sedation of patients with chronic liver disease," *Clinics in Liver Disease*, vol. 14, no. 2, pp. 185–194, 2010.

[22] N. Chandok and K. D. S. Watt, "Pain management in the cirrhotic patient: the clinical challenge," *Mayo Clinic Proceedings*, vol. 85, no. 5, pp. 451–458, 2010.

[23] O. Picker, C. Beck, and B. Pannen, "Liver protection in the perioperative setting," *Best Practice and Research: Clinical Anaesthesiology*, vol. 22, no. 1, pp. 209–224, 2008.

[24] S. Rossi, D. N. Assis, M. Awsare et al., "Use of over-the-counter analgesics in patients with chronic liver disease: physicians' recommendations," *Drug Safety*, vol. 31, no. 3, pp. 261–270, 2008.

[25] S. K. Khalid, J. Lane, V. Navarro, and G. Garcia-Tsao, "Use of over-the-counter analgesics is not associated with acute decompensation in patients with cirrhosis," *Clinical Gastroenterology and Hepatology*, vol. 7, no. 9, pp. 994–999, 2009.

[26] S. I. Sokol, A. Cheng, W. H. Frishman, and C. S. Kaza, "Cardiovascular drug therapy in patients with hepatic diseases and patients with congestive heart failure," *Journal of Clinical Pharmacology*, vol. 40, no. 1, pp. 11–30, 2000.

[27] R. Vuppalanchi and N. Chalasani, "Statins for hyperlipidemia in patients with chronic liver disease: are they safe?" *Clinical Gastroenterology and Hepatology*, vol. 4, no. 7, pp. 838–839, 2006.

SAGE-Hindawi Access to Research
International Journal of Hepatology
Volume 2011, Article ID 363151, 4 pages
doi:10.4061/2011/363151

Review Article

Screening for Hepatocellular Carcinoma

Hock-Foong Lui[1, 2]

[1] *Gleneagles Hospital, 6A Napier Road, Singapore 258500*
[2] *Singapore General Hospital, Outram Road, Singapore 169608*

Correspondence should be addressed to Hock-Foong Lui, drluiclinic@gmail.com

Received 16 March 2011; Accepted 19 July 2011

Academic Editor: Deepak Amarapurkar

Hepatocellular carcinoma is one of the most serious complications of chronic liver disease and is the third most lethal cancer worldwide. Symptoms emerge very late in the course of its natural history with an attendant poor outcome. Screening is of paramount importance in a successful strategy to treat hepatocellular carcinoma. A successful screening program rests the availability of an at-risk population, reliable diagnostics tests that are able to diagnose a condition at a stage where effective, and relatively simple and acceptable treatments are available. In hepatocellular carcinoma, all patients with liver cirrhosis or chronic hepatitis B virus infection are at risk. Six monthly ultrasound and alpha-foetoprotein determination form the backbone of the screening program. Newer modalities and tests show promise but have not supplanted the standard tests.

1. Introduction

One of the most serious complications of chronic liver disease is hepatocellular carcinoma. Across the world, it is the 4th most common cancer (age standardised rate of 16 per 100,000) and the 3rd most common cause (age standardised rate of 14.6 per 100,000) of deaths from all cancers, accounting for 700,000 deaths per annum [1]. Although a global cancer, it is especially prevalent in the Asia Pacific and sub-Saharan Africa.

The outcome of a patient after the discovery of hepatocellular carcinoma, like many malignancies, very much depends on the stage of the disease at the time of diagnosis. Curative treatment can be offered to 30% of cases if diagnosed at BCLC stage 0 or A and carries a 5-year survival of 40% to 70%. If diagnosed at stages B or C, the median survival with treatment is 11–20 months. At stage D, only symptomatic treatment is possible and survival does not exceed 3 months [2]. Unfortunately, the lack of symptoms for most part of the natural history of hepatocellular carcinoma is such that many cases are discovered at late stages, limiting the survival of these cases. It is the leading cause of mortality in patients with compensated liver cirrhosis [3].

One of the main strategies for prolonging survival in patients with chronic liver disease therefore lies in the diagnosing hepatocellular carcinoma in the early stages so that effective therapy can be offered. In this regard, screening for hepatocellular carcinoma, that is, detection before the onset of symptoms, forms the backbone of such a strategy.

2. Screening for Diseases

Screening refers to the detection of a condition whilst it is still without sign or symptom. The repeated application of screening is termed surveillance. The primary aim of screening is to pick up a disease at a stage where treatment is more effective and the outcome, usually measured as survival, is better compared with a later stage of discovery of the condition. The World Health Organisation in 1968 published the following desirable criteria for a condition to be screened [4].

(1) The condition should be an important health problem.

(2) There should be treatment for the condition.

(3) Facilities for diagnosis and treatment should be available.

(4) There should be a test or examination for the condition.

(5) The test should be acceptable to the population.

(6) The natural history of the condition should be adequately understood.

(7) There should be an agreed policy on who to treat.

(8) The total cost of finding the case should be economically balanced in relation to medical expenditure as a whole.

(9) Case finding should be a continuous process, not just a "once and for all" project.

Paraphrasing the above, the ideal screening programme should meet the following criteria:

(1) a sufficiently high prevalence of the disease in the population to be screened;

(2) a reliable method for screening, that is, it should have a high true positive rate or low false negative rate (high sensitivity) and a high true negative rate or low false positive rate (high specificity);

(3) the method of screening should also be easily available, inexpensive, and carries little or no risk of harm to the individual screened;

(4) an effective treatment should be available for the disease to positively impact on the survival of the individual.

Currently the hepatocellular carcinoma screening programmes advocated by various expert bodies have a high degree of concurrence. The ensuing discussion will review the merits of hepatocellular carcinoma screening vis-à-vis the desired characteristics of an ideal screening programme as listed above.

3. Prevalence of Hepatocellular Carcinoma

Hepatocellular carcinoma develops almost exclusively in the setting of chronic liver disease. The risk of developing hepatocellular carcinoma in this group is over 200 times that of the general population [5]. The risk factors are liver cirrhosis (where the repeated inflammation-necrosis-regeneration cycle increases the risk of carcinogenesis) and chronic hepatitis B virus infection (where the incorporation of hepatitis B virus genome into the hepatocyte DNA increases the risk of carcinogenesis). The risk of hepatocellular carcinoma development varies across these conditions and depends on several factors: age, gender, presence of family history of hepatocellular carcinoma, exposure to environmental factors such as aflatoxins, and aetiology of cirrhosis [6]. Hepatitis C-related cirrhosis appears to be associated with the highest risk of hepatocellular carcinoma, with a 5-year cumulative risk of 17–30%. Haemochromatosis-related cirrhosis carries a 5-year cumulative incidence of 21% whereas hepatitis B-related cirrhosis has a 5-year cumulative incidence of 10–15% depending on endemicity. The corresponding figures for alcoholic cirrhosis and advanced primary biliary cirrhosis are 8% and 4%, respectively [3]. Individuals with chronic hepatitis B virus infections without cirrhosis have a 0.5% annual risk of hepatocellular carcinoma. In this group the risk is higher with advancing age, in men and in those with a family history of hepatocellular carcinoma. Women are at lower risk but the risk is increased in women above the age of 50 years old [7, 8]. Chronic hepatitis B patients with liver cirrhosis have an annual risk of hepatocellular carcinoma of 3–8%. In patients with liver cirrhosis caused by hepatitis C virus infection or advanced primary biliary cirrhosis (stage 4), the annual risk of hepatocellular carcinoma is also high at 3–8%. Cirrhosis caused by other aetiologies such as genetic haemochromatosis and alpha-1-antitrypsin deficiency carry with it a lower annual risk of hepatocellular carcinoma of around 1.5% [9–13]. It is clear that hepatocellular carcinoma can develop from cirrhosis arising from nonalcoholic fatty liver disorder. However the incidence is not clear [14, 15].

The effectiveness of a screening strategy can be measured by improvement in survival against the cost incurred to achieve this outcome (cost for each year of life gained). Other outcome measures such as quality of life gained, years of economically viable life gained are important but are more difficult to assess. The thresholds for each of these measures will vary according to cultures, individual outlook, and economic status of a country and are arbitrary.

Utilising the principles of decision analysis and costeffectiveness, the generally accepted threshold for life gain is 3 months, achieved at a cost of less than US $50,000 per year of life gained. Applying this to decide on the threshold for screening hepatocellular carcinoma, the annual incidence for screening noncirrhotic patients is to be 0.2% and above, and for cirrhotic patients, this translates to an annual risk of 1.5% and above. The difference in the threshold incidences between noncirrhosis and cirrhosis lies in the lower quantum of life gain when hepatocellular carcinoma is diagnosed in an individual with liver cirrhosis.

Based on the above assumptions and thresholds, there is no justification for population-wide screening of hepatocellular carcinoma. Current screening strategies centre on selecting high risk groups for screening [16]. The at-risk groups meeting the above cost-effective criteria for hepatocellular carcinoma screening are

(1) patients with liver cirrhosis;

(2) male patients with chronic hepatitis B virus infection without cirrhosis who are above the age of 40 years;

(3) female patients with chronic hepatitis B virus infection without cirrhosis who are above the age of 50 years;

(4) patients with chronic hepatitis B virus infection who have a family history of hepatocellular carcinoma.

For younger individuals with chronic hepatitis B virus infection, the annual risk of hepatocellular carcinoma development is lower than the threshold of 0.2%, but the disease is often more aggressive [17]. Whether the above thresholds should be used to decide if screening should be recommended for this group should be discussed. Whilst not "costeffective", the discovery of an early tumour in this age group brings about the greatest potential gain in terms of survival and also economically useful years gained, not to mention the less tangible but no less important benefit of

averting the trauma for the patient and family of coming to terms with a fatal cancer in a young individual.

The risk of HCC in patients with chronic HBV infection can also be further stratified using prognostic variables—age, gender, indices of necroinflammation—alanine transaminase level, and HBV DNA load. A prognostic scoring system was developed and validated in a large Asian population with chronic HBV and gives the risk of HCC development at 3, 5, and 10 years [18]. This scoring system has the potential to be applied to refine the decision-making process with respect to screening in less clear-cut situations, for example, in the group discussed above.

4. Reliable Method of Screening

Currently available methods to diagnose hepatocellular carcinoma comprise blood tests to detect elevation of "tumour markers" and imaging modalities. Blood tests that are elevated with hepatocellular carcinoma include AFP (alpha-fetoprotein), the more specific AFP-L3 (L3 subfraction of AFP), and DCP (descarboxy prothrombin) [19–21]. AFP is released by regenerating hepatocytes, malignant hepatocytes, and also extrahepatic sources such as placental cells and germ cells. Among the nonmalignant causes that cause elevated AFP are inflammatory liver conditions, pregnancy, and molar pregnancy. The AFP-L3 is the glycosylated subfraction of AFP and is specific to malignant hepatocytes. It is useful in discriminating between AFP elevation arising from a benign condition against that arising from hepatocellular carcinoma. However its sensitivity is low in cases where the AFP is not markedly elevated.

DCP is also specific to hepatocellular carcinoma; it is found especially elevated when there is invasion of vascular structures and is a marker of more advanced hepatocellular carcinoma, and therefore may not be a suitable screening tool.

AFP, taken at a level of 20 ng/mL, has a sensitivity of 66% and a specificity of 82% for hepatocellular carcinoma. AFP-L3 has not been studied adequately for screening of hepatocellular carcinoma. Whilst specific, it will likely suffer from decreased sensitivity and is not recommended as a general screening tool. More recently the highly sensitive AFP-L3 (hs-AFP-L3) was evaluated in individuals whose AFP was <20 ng/mL [22]. It was found to increase the sensitivity of detecting HCC from 7% with AFP-L3 to 41.5% with hs-AFP-L3. In addition, it also predicted poorer outcomes in patients with HCC. At present AFP-L3 and hs-AFP-L3 remain adjunctive tools in further evaluation in cases of raised AFP and is not in a position to supplant the use of AFP as a screening tool. As it stands, the present accepted blood test for screening is AFP.

Liver imaging modalities that have proven effective in detecting hepatocellular carcinoma are ultrasound, CT scan, and MRI scan of the liver. In trained operators, ultrasound reliably detects liver nodules above the dimensions of 5 mm. Hepatocellular carcinoma may appear hypoechoic but may be isoechoic or hyperechoic. Other pathological conditions may share similar ultrasonic characteristics. Ultrasound has a sensitivity of 65–80% and a specificity of 90% [16]. It is a test that is generally reproducible, does not carry any adverse effects, and is economical. One limitation of ultrasonography is the difficulty in obtaining a good study in obese patients.

CT scan of the liver and MRI of the liver provide diagnostic details superior to ultrasound. CT scan is now widely available. Its cost has decreased with economies of scale. However, the radiation exposure is significant, raising the risk of carcinogenesis if used repeatedly [17]. Whilst advocated by some for screening of hepatocellular carcinoma, it is still not yet accepted and therefore not recommended for screening. MRI offers superior resolution. Whilst it does not have the drawback of radiation danger, it is an expensive test, and the acquisition time for one study is considerable, limiting its use as a screening test. At present the use of wither MRI or CT scan of the liver lies in the diagnosis of hepatocellular carcinoma where the screening tests (either ultrasound or AFP) have flagged up suspicion.

At present the combined use of AFP and ultrasound is the recommended mode for screening. The interval of screening should be such that the growth of cancer should be picked up between 2 screening. Too short an interval is a waste of healthcare resources and inconveniences the patient. Too long an interval, in the other hand, runs the risk of allowing the cancer to grow to a later stage, thereby compromising the effectiveness of the whole screening process. The determinant of this interval is the rate of growth or doubling time of the cancer. Studies involving HCV patients suggest that 12-month screening interval brings about survival improvement and is not different from screening at 6-monht intervals [23, 24]. In studies of HBV patients, 6-month screening resulted in improved survival compared to 12-month screening [25].

5. Availability of Effective Therapy

The last 10–15 years have witnessed the advent of newer treatment options for hepatocellular carcinoma, and with it, some measure improvement in outcomes. With early diagnosis, cure is possible in 30% of cases, and in the rest, effective control is achievable. Surgical resection and local ablation are effective in the treatment of an early, localised hepatocellular carcinoma, and achieving 5-year survival of up to 70%. Liver transplant in well-selected patients can bring about a 5-year survival in the order of 80% [26, 27]. Recent data indicates that RFA is comparable to surgical resection for early hepatocellular carcinoma in terms of survival outcomes and has the advantage of being less invasive [28, 29]. Transarterial chemoembolisation is an option proven to prolong survival in cases of nonresectable, nontransplantable cases of nonmetastatic hepatocellular carcinoma.

6. Summary

Surveillance of hepatocellular carcinoma is justified in groups at risk of hepatocellular carcinoma. It allows for its detection at earlier stages. This in turn translates to more effective treatment options resulting in improved survival. HCC screening therefore is an important part of the strategy in improving survival in patients with advanced liver disease.

Present screening method is that of AFP and ultrasound performed at 6–12-month intervals.

References

[1] International Agency for Cancer Reseach, "GLOBOCAN 2008".

[2] J. M. Llovet, A. M. Di Bisceglie, J. Bruix et al., "Design and endpoints of clinical trials in hepatocellular carcinoma," *Journal of the National Cancer Institute*, vol. 100, no. 10, pp. 698–711, 2008.

[3] G. Fattovich, T. Stroffolini, I. Zagni, and F. Donato, "Hepatocellular carcinoma in cirrhosis: incidence and risk factors," *Gastroenterology*, vol. 127, no. 5 supplement 1, pp. S35–S50, 2004.

[4] J. M. G. Wilson and G. Jungner, "Principles and practice of screening for disease," Public Health Papers number 34, pp. 22–473, WHO Chronicle Geneva: World Health Organization, 1968.

[5] G. Fattovich, T. Stroffolini, I. Zagni, and F. Donato, "Hepatocellular carcinoma in cirrhosis: incidence and risk factors," *Gastroenterology*, vol. 127, pp. S35–S50, 2004.

[6] S. N. Zaman, W. M. Melia, R. D. Johnson, B. C. Portmann, P. J. Johnson, and R. Williams, "Risk factors in development of hepatocellular carcinoma in cirrhosis: prospective study of 613 patients," *The Lancet*, vol. 15, no. 1, pp. 1357–1360, 1985.

[7] J. P. Villeneuve, M. Desrochers, C. Infante-Rivard et al., "A long-term follow-up study of asymptomatic hepatitis B surface antigen-positive carriers in Montreal," *Gastroenterology*, vol. 106, no. 4, pp. 1000–1005, 1994.

[8] G. Fattovich, L. Brollo, G. Giustina et al., "Natural history and prognostic factors for chronic hepatitis type B," *Gut*, vol. 32, no. 3, pp. 294–298, 1991.

[9] R. Befrits, M. Hedman, L. Blomquist et al., "Chronic hepatitis C in alcoholic patients: prevalence, genotypes, and correlation to liver disease," *Scandinavian Journal of Gastroenterology*, vol. 30, no. 11, pp. 1113–1118, 1995.

[10] M. M. Hassan, L. Y. Hwang, C. J. Hatten et al., "Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus," *Hepatology*, vol. 36, no. 5, pp. 1206–1213, 2002.

[11] M. Elmberg, R. Hultcrantz, A. Ekbom et al., "Cancer risk in patients with hereditary hemochromatosis and in their first-degree relatives," *Gastroenterology*, vol. 125, no. 6, pp. 1733–1741, 2003.

[12] L. Caballeria, A. Pares, A. Castells, A. Gines, C. Bru, and J. Rodes, "Hepatocellular carcinoma in primary biliary cirrhosis: similar incidence to that in hepatitis C virus-related cirrhosis," *The American Journal of Gastroenterology*, vol. 96, pp. 1160–1163, 2001.

[13] S. Eriksson, J. Carlson, and R. Velez, "Risk of cirrhosis and primary liver cancer in alpha 1-antitrypsin deficiency," *The New England Journal of Medicine*, vol. 314, no. 12, pp. 736–739, 1986.

[14] E. Bugianesi, N. Leone, E. Vanni et al., "Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma," *Gastroenterology*, vol. 123, no. 1, pp. 134–140, 2002.

[15] M. Shimada, E. Hashimoto, M. Taniai et al., "Hepatocellular carcinoma in patients with non-alcoholic steatohepatitis," *Journal of Hepatology*, vol. 37, no. 1, pp. 154–160, 2002.

[16] J. Bruix and M. Sherman, "Practice guidelines committee, American association for the study of liver diseases. Management of hepatocellular carcinoma," *Hepatology*, vol. 42, pp. 1208–1236, 2005.

[17] P. E. Chang, W. C. Ong, H. F. Lui, and C. K. Tan, "Is the prognosis of young patients with hepatocellular carcinoma poorer than the prognosis of older patients? A comparative analysis of clinical characteristics, prognostic features, and survival outcome," *Journal of Gastroenterology*, vol. 43, no. 11, pp. 881–888, 2008.

[18] H. I. Yang, M. F. Yuen, H. L. Chan et al., "Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score," *The Lancet Oncology*, vol. 12, pp. 568–574, 2011.

[19] A. B. de González and S. Darby, "Risk of cancer from diagnostic X-rays: estimates for the UK and 14 other countries," *The Lancet*, vol. 363, no. 9406, pp. 345–351, 2004.

[20] F. Trevisani, P. E. D'Intino, A. M. Morselli-Labate et al., "Serum α-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease: influence of HBsAg and anti-HCV status," *Journal of Hepatology*, vol. 34, no. 4, pp. 570–575, 2001.

[21] K. Izuno, S. Fujiyama, K. Yamasaki, M. Sato, and T. Sato, "Early detection of hepatocellular carcinoma associated with cirrhosis by combined assay of des-γ-carboxy prothrombin and α-fetoprotein: a prospective study," *Hepato-Gastroenterology*, vol. 42, no. 4, pp. 387–393, 1995.

[22] H. Toyoda, T. Kumada, T. Tada et al., "Clinical utility of highly sensitive Lens culinaris agglutinin-reactive alpha-fetoprotein in hepatocellular carcinoma patients with alpha-fetoprotein <20 ng/mL," *Cancer Science*, vol. 102, pp. 1025–1031, 2011.

[23] K. Shiraki, K. Takase, Y. Tameda, M. Hamada, Y. Kosaka, and T. Nakano, "A clinical study of lectin-reactive alpha-fetoprotein as an early indicator of hepatocellular carcinoma in the follow-up of cirrhotic patients," *Hepatology*, vol. 22, no. 3, pp. 802–807, 1995.

[24] L. Bolondi, S. Sofia, S. Siringo et al., "Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis," *Gut*, vol. 48, no. 2, pp. 251–259, 2001.

[25] F. Trevisani, S. De Notariis, G. Rapaccini et al., "Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience)," *The American Journal of Gastroenterology*, vol. 97, no. 3, pp. 734–744, 2002.

[26] E. Santagostino, M. Colombo, M. Rivi et al., "A 6-month versus a 12-month surveillance for hepatocellular carcinoma in 559 hemophiliacs infected with the hepatitis C virus," *Blood*, vol. 102, no. 1, pp. 78–82, 2003.

[27] D. Y. Kim, K.-H. Han, S. H. Ahn et al., "Semiannual surveillance for hepatocellular carcinoma improved patient survival compared to annual surveillance (Korean experience)," *Hepatology*, vol. 46, p. 403A, 2007.

[28] S. M. Lin, C. J. Lin, C. C. Lin, C. W. Hsu, and Y. C. Chen, "Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma $\leq$4 cm," *Gastroenterology*, vol. 127, no. 6, pp. 1714–1723, 2004.

[29] S. Shiina, T. Teratani, S. Obi et al., "A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma," *Gastroenterology*, vol. 129, no. 1, pp. 122–130, 2005.

SAGE-Hindawi Access to Research
International Journal of Hepatology
Volume 2011, Article ID 121862, 9 pages
doi:10.4061/2011/121862

Review Article

Indications and Contraindications for Liver Transplantation

Vibha Varma, Naimish Mehta, Vinay Kumaran, and Samiran Nundy

Department of Surgical Gastroenterology and Liver Transplantation, Sir Ganga Ram Hospital Room No. 2221, SSR Block, Rajinder Nagar, New Delhi 110060, India

Correspondence should be addressed to Samiran Nundy, snundy@hotmail.com

Received 14 March 2011; Accepted 10 August 2011

Academic Editor: Richard Guan

Patients with chronic liver disease and certain patients with acute liver failure require liver transplantation as a life-saving measure. Liver transplantation has undergone major improvements, with better selection of candidates for transplantation and allocation of scarce deceased donor organs (according to more objective criteria). Living donor liver transplantation came into existence to overcome the shortage of donor organs especially in countries where there was virtually no deceased donor programme. Advances in the technical aspects of the procedure, the intraoperative and postoperative care of both recipients and donors, coupled with the introduction of better immunosuppression protocols, have led to graft and patient survivals of over 90% in most high volume centres. Controversial areas like transplantation in alcoholic liver disease without abstinence, acute alcoholic hepatitis, and retransplantation for recurrent hepatitis C virus infection require continuing discussion.

1. Introduction

Liver transplantation is a life-saving procedure for patients with chronic end stage liver disease and selected patients with acute liver failure (ALF) [1–3]. Over the years, the technique of the operation has undergone major changes. Together with this, there has been an improvement in the understanding of pre- and posttransplantation physiology and the introduction of newer and more effective immunosuppressive drugs and strategies for preventing posttransplantation infections so that, in the United States, the one year patient survival has now reached 87.6% and graft survival 82.4% [4].

Liver grafts for transplantation can be obtained either from deceased donors (DDs) or living donors (LDs). Living donor liver transplantation (LDLT) was introduced because of the increasing demand for donor organs and the widening gap between the resource (deceased donor) and demand (recipient). It is very important to prioritize the patients for organ allocation in a deceased donor liver transplantation (DDLT) programme. This is, however, different in a programme which is based mainly on LDLT where the prospective donor is usually a close relation. However, in both the situations, a measure such as a scoring system is important in prognosticating the outcome following transplantation. There has to be a balance between the patient's medical reserves to withstand a major operation like liver transplantation and its probable outcome.

For DDLT organ, allocation was initially based on the location of the patient (at home, in hospital or in an intensive care unit) and the time on the waiting list (United Network for Organ Sharing-UNOS status). However, with the use of more objective mathematical models, based on certain selected risk factors such as the model for end-stage liver disease (MELD) score, the system of allocation has probably improved. The MELD and PELD (for paediatric recipients) scores are systems for assessing a patient's need for transplantation or for the likelihood of requiring transplantation in the future [5–7].

The older Child-Turcotte-Pugh (CTP) classification system and its variations have also been used to stratify patients with chronic liver disease to predict the mortality and morbidity. However, because it relies on many subjective criteria, its use has been superseded by the MELD and PELD scores. These are mathematical regression models which objectively assess the need for liver transplantation and more accurately predict the short-term mortality while on the transplantation waiting list. Their purpose is to help physicians select those patients who might benefit most from

Table 1: United network for organ-sharing (UNOS) liver status classification.

Status 1	Fulminant liver failure with life expectancy <7 days (i) Fulminant hepatic failure as traditionally defined (ii) Primary graft nonfunction <7 days of transplantation (iii) Hepatic artery thrombosis <7 days of transplantation (iv) Acute decompensated Wilson's disease
Status 2a	Hospitalized in ICU for chronic liver failure with life expectancy <7 days, with a Child-Pugh score of ≥10 and one of the following: (i) unresponsive active variceal hemorrhage (ii) hepatorenal syndrome (iii) refractory ascites/hepatic hydrothorax, (iv) Stage 3 or 4 hepatic encephalopathy
Status 2B	Requiring continuous medical care, with a Child-Pugh score of ≥10, or a Child-Pugh score ≥7 and one of the following: (i) unresponsive active variceal hemorrhage (ii) hepatorenal syndrome (iii) spontaneous bacterial peritonitis (iv) refractory ascites/hepatic hydrothorax, or presence of hepatocellular carcinoma
Status 3	Requiring continuous medical care, with a Child-Pugh score of ≥7, but not meeting criteria for Status 2B
Status 7	Temporary inactive

From http://www.unos.org/ initially implemented in July 1997 later modified in January 1998 and August 1998.

the transplantation. The MELD score is calculated using the patient's international normalized ratio (INR), bilirubin, and creatinine according to the formula given below [8, 9].

MELD score = 10{0.957 log(serum creatinine) + 0.378 log(total bilirubin) + 1.12 log(INR) + 0.643}

If the MELD score is ≥30 the patient's UNOS listing status (Table 1) is 2a, if it is 24–29, it is 2b, and if it is less than 24, it is 3.

The PELD score includes parameters like albumin, bilirubin, INR, age (<1 year, >1 year), and the presence of growth failure to stratify children with liver disease on the waiting list.

2. Timing of Referral

Patients with a MELD score of >10 and/CTP score of >7 are referred for transplantation [10]. Other criteria to take into consideration are those with decompensated chronic liver disease in the form of intractable ascites, spontaneous bacterial peritonitis, variceal bleeding, encephalopathy, jaundice as well as health-related quality of life issues such as severe itching and recurrent cholangitis. Conditions which are not included in the scoring system and influence allocation are hepatocellular carcinoma, hepatopulmonary syndrome, and portopulmonary hypertension (Tables 2 and 3). Organ allocation is according to the status of the patient (UNOS status) and the MELD/PELD score. A Status 1 (Table 1) patient is given priority following which those with a MELD/PELD score ≥15 and later those having a score of ≤14.

3. Indications for Liver Transplantation

The list of indications for liver transplantation includes all the causes of end stage liver disease which are irreversible and curable by the procedure (Tables 2 and 3). In 1997 the American Society of Transplant Physicians and the American Association for the Study of the Liver Disease put forward the minimal listing criteria for patients with end stage liver disease. To qualify for the listing, the patient's expected survival should be ≤90% within 1 year without transplantation. Liver transplantation should lead to prolonged survival and an improved quality of life [10]. The outcome following liver transplantation is better for those with chronic cholestatic liver disease (including primary biliary cirrhosis and primary sclerosing cholangitis) compared with those who have hepatocellular carcinoma.

3.1. Acute Liver Failure (ALF). Fulminant hepatic failure (ALF and subfulminant hepatic failure) is characterized by encephalopathy, jaundice, and coagulopathy. It accounts for 5-6% of all patients undergoing liver transplantation [4]. In the West, acetaminophen toxicity is the leading cause of ALF, and hepatitis A, E, B and seronegative hepatitis are the other common aetiological factors. The major cause of subfulminant hepatic failure is idiosyncratic drug induced liver injury [11]. Patients who meet the King's College Criteria for urgent transplantation provide a very small window for action, and they need to undergo transplantation, as soon as possible. There is a 100% percent mortality if these selected patients do not undergo transplantation and this is either due to liver

Table 2: Indications for liver transplantation.

Acute liver failure
Hepatitis A, acetaminophen, autoimmune hepatitis
Hepatitis B
Hepatitis C, cryptogenic
Drugs, hepatitis D
Wilson's disease, Budd-Chiari syndrome
Fatty infiltration—acute fatty liver of pregnancy, Reye's syndrome
Cirrhosis from chronic liver disease
Chronic hepatitis B virus infection
Chronic hepatitis C virus infection
Alcoholic liver disease
Autoimmune hepatitis
Cryptogenic liver disease
Nonalcoholic fatty liver disease
Malignant diseases of the liver
Hepatocellular carcinoma
Carcinoid tumor
Islet cell tumor
Epithelioid hemangioendothelioma
Cholangiocarcinoma
Metabolic liver disease
Wilson's disease
Hereditary hemochromatosis
Alpha-1 antitrypsin deficiency
Glycogen storage disease
Cystic fibrosis
Glycogen storage disease I and IV
Crigler-Najjar syndrome
Galactosemia
Type 1 hyperoxaluria
Familial homozygous hypercholesterolemia
Hemophilia A and B
Vascular diseases of the liver
Budd-Chiari syndrome
Veno-occlusive disease
Cholestatic liver diseases
Primary biliary cirrhosis
Primary sclerosing cholangitis
Secondary biliary cirrhosis
Biliary atresia
Alagille syndrome
Byler's disease
Miscellaneous
Adult polycystic liver disease
Nodular regenerative hyperplasia
Caroli's disease
Severe graft-versus-host disease
Amyloidosis
Sarcoidosis
Hepatic trauma

Table 3: Variant syndromes requiring liver transplantation.

Intractable ascites
Diuretic resistant, Nonresponsive to TIPS or, TIPS contraindicated
Hepatopulmonary Syndrome
Shunt fraction >8%, pulmonary vascular dilatation
Chronic hepatic encephalopathy
Persistent and intractable pruritus

failure *per se* or because of sepsis and multiorgan failure [11]. Patients with subacute failure have a poor outcome with almost universal mortality if not transplanted; these patients might require transjugular liver biopsy to establish the presence of massive or submassive liver cell necrosis. Timely referral is important in these patients because in the absence of transplantation death may occur from sepsis and cerebral oedema. There are several scoring systems for listing a patient for urgent liver transplantation: King's College criteria, UK Blood and Transplant criteria, Clichy criteria (acute viral hepatitis), and Wilson's prognostic index/revised Wilson's prognostic index (Wilson's disease with fulminant hepatitis) [12–16]. (Tables 4 and 5).

3.2. Chronic Liver Disease. Patients who have a projected 1-year mortality of 10% without liver transplantation get entry into the waiting list. Apart from their CTP and MELD scores, the UK Liver Transplant Units have developed a new scoring system to predict the mortality of such patients. This is the United Kingdom model for end-stage liver disease (UKELD) score—which is calculated by using the patient's serum bilirubin, INR, creatinine, and sodium levels [17]. Patients with a UKELD score of more than 49 fall into the criteria for listing. This score is dynamic and is reassessed over a period of time.

3.3. Alcoholic Liver Disease (ALD). A patient with ALD who is abstinent for a period of at least 3–6 months and who has had an evaluation with a psychiatrist is listed for transplantation if he has a CTP score of ≥7, portal hypertensive bleed, or an episode of spontaneous bacterial peritonitis [18]. These patients may have a concurrent infection with hepatitis B or C virus which needs evaluation. They are also more prone to develop hepatocellular carcinoma. A period of abstinence is mandatory to ensure that they do not relapse and also to give a trial of an alcohol-free period during which the liver function might recover. The period of abstinence is not uniform, however, but presently a 6-month rule of abstinence is generally followed in US and European liver transplant programmes [19].

Acute alcoholic hepatitis (AAH) is a contra-indication for liver transplantation as the required period of abstinence is lacking, and there is very little and mixed experience of liver transplantation in this situation. The severity of AAH is assessed using the Maddrey discriminant function (DF) score which predicts the risk of early death. Patients with a DF score of ≥32 are put on medical therapy [20, 21]. There

Table 4: UK blood and transplant criteria for registration as a super-urgent transplant.

	Paracetamol poisoning
Category 1	pH < 7.25 more than 24 hours after overdose and fluid resuscitation
Category 2	Coexisting prothrombin time >100 s or INR > 6.5 and serum creatinine >300 μmol/L or anuria, and grade 3-4 en encephalopathy
Category 3	Serum Lactate >24 hours after overdose > 3.5 mmol/L on admission or >3 mmol/L after fluid resuscitation
Category 4	Two of the three criteria from category 2 with clinical evidence of deterioration (e.g. increased ICP, Fi02 > 50%, increasing inotrope requirement) in the absence of clinical sepsis
	Seronegative hepatitis, hepatitis A, B, or an idiosyncratic drug reaction
Category 5	Prothrombin time >100 s or INR > 6.5, and any grade of encephalopathy
Category 6	Any grade of encephalopathy, and any three from the following: unfavourable aetiology (idiosyncratic drug reaction, seronegative hepatitis), age > 40 years jaundice encephalopathy interval >7 days, serum bilirubin >300 μmol/L, prothrombin time >50 s or INR > 3.5
Category 7	Acute presentation of Wilson's disease, or Budd-Chiari syndrome. A combination of coagulopathy, and any grade of encephalopathy
Category 8	Hepatic artery thrombosis on days 0 to 21 days after liver transplantation
Category 9	Early graft dysfunction on days 0 to 7 after liver transplantation with at least 2 of the following: AST > 10,000 IU/L, INR > 3.0, serum lactate > 3 mmol/L, absence of bile production
Category 10	Any patient who has been a live donor who develops severe liver failure within 4 weeks of the donor operation

Table 5: Criteria for liver transplantation in acute liver failure (ALF).

(a) King's College Criteria

Acetaminophen-induced ALF	**Nonacetaminophen ALF**
(1) Arterial pH < 7.3 *irrespective* of grade of encephalopathy	(1) INR > 6.5 (PT > 100 sec), *irrespective* of grade of encephalopathy
OR	OR any 3 of the following:
(1) PT > 100 sec	(1) INR > 3.5 (PT > 50 sec)
(2) Serum creatinine >3.4 mg/dL	(2) Age < 10 or >40 years
(3) Stage 3 or 4 encephalopathy	(3) Serum bilirubin >18 mg/dL
	(4) Jaundice to encephalopathy interval >7 days
	(5) Non-A, non-B hepatitis, idiosyncratic drug reaction

(b) Prognostic index in fulminant Wilsons hepatitis (WPI) [14]

Score	0	1	2	3	4
Serum bilirubin (reference range 3–20 mmol/L)	<100	100–150	151–200	201–300	>300
Serum aspartate transaminase (reference range 7–40 IU/L)	<100	100–150	151–200	201–300	>300
Prothrombin time prolongation (seconds)	<4	4–8	9–12	13–20	>30
Patients with a WPI score ≥7 need urgent liver transplantation					

(c) Revised Wilson prognostic index (RWPI) [15]

Score	Bilirubin (μmol/L)	INR	AST (IU/L)	WCC (10^9/L)	Albumin (g/L)
0	0–100	0–1.29	0–100	0–6.7	>45
1	101–150	1.3–1.6	101–150	6.8–8.3	34–44
2	151–200	1.7–1.9	151–300	8.4–10.3	25–33
3	201–300	2.0–2.4	301–400	10.4–15.3	21–24
4	≥301	>2.5	>401	>15.4	<20
Patients with a RWPI ≥11 needed urgent liver transplantation					

(d) Clichy criteria (Hospital Paul-Brousse, Villejuif [16])

Hepatic encephalopathy, and factor V level:
<20% in patients <30 years of age, or
<30% in patients ≥30 years of age

have been recent reports from France where transplantation is being proposed for patients with AAH; however, it is still not accepted as an indication elsewhere [22].

3.4. Viral Hepatitis. Hepatitis C virus (HCV)-related chronic liver disease is the commonest indication for liver transplantation in the United States [23]. It is important to know the pretransplant viral load and genotype; this helps in predicting the prognosis after transplantation. Patients with decompensated HCV-related chronic liver disease do not tolerate interferon therapy, and those with high viral loads have a high chance of recurrence in the new graft. According to the International Liver Transplantation Society (ILTS) guidelines patients with a child's score of 8–11 may be considered for antiviral treatment while they are listed for transplantation; however, there are very high chances of adverse events [24]. Posttransplantation serological recurrence is universal in patients who have viraemia at the time of transplantation. Patient survival is adversely affected by the pretransplant viral load and cytomegalovirus status, advanced recipient age, hyperbilirubinaemia, a raised INR, and advanced donor age [25]. Retransplantation in these patients with recurrent HCV infection and cirrhosis is controversial in the setting of DDLT. The efficacy of antiviral therapy in the presence of a recurrence is questionable. Patients with early (within one year) aggressive recurrence and graft failure have a poor outcome following retransplantation.

Hepatitis B virus-related chronic liver disease is another common indication for transplantation, and this was previously also associated with a high prevalence of recurrent infection in the graft. However, the availability of hepatitis B immunoglobulin (HBIG) and oral nucleoside or nucleotide therapy reinfection of the graft and recurrent hepatitis B disease is rare. The duration of HBIG therapy and oral antiviral therapy is still controversial; a few programmes give HBIG for one year while others are using it life long [26].

3.5. Cholestatic Liver Disease. The severity of cholestatic liver diseases such as primary biliary cirrhosis(PBC) and primary sclerosing cholangitis (PSC) is taken into consideration apart from using the child's score ($\geq$7) and the Mayo models for PSC and PBC with a risk score predicting > than 10% mortality at one year without transplantation [10]. Quality of life issues like recurrent cholangitis requiring repeated drainage procedures (endoscopic or percutaneous), intractable itching, xanthomatous neuropathy, and severe metabolic bone disease are some of the other indications for transplantation.

In paediatric patients, biliary atresia and sclerosing cholangitis are the commonest cholestatic disorders requiring transplantation, with biliary atresia being the foremost cause (60–70%) in those undergoing liver transplantation [27]. Liver transplantation is required in most patients with biliary atresia irrespective of a previous Kasai's procedure. Other cholestatic disorders which can lead to cirrhosis and decompensation requiring transplantation are the Alagille syndrome and Byler's disease.

3.6. Hepatic Malignancy. Cirrhosis is associated with a 2 to 8% annual incidence of hepatocellular carcinoma [28]. Liver transplantation has become the mainstay of treatment for HCC in the early stages, as it offers the advantage of not only being curative, thus, minimizing the risk of recurrence; it also takes care of the complications associated with the underlying cirrhosis. There have been several criteria for listing these patients for transplantation. They have been modified over a period of time so as to include as many patients who would benefit from transplantation and who would have a 5-year survival of >50%. The Milan criteria defines early stage HCC as those with a single lesion < 5 cm, or no more than 3 lesions, with none > than 3 cm, in the absence of vascular invasion and metastases [29]. However, using the University of California, San Francisco, (UCSF) criteria (a single lesion $\leq$6.5 cm or 3 or fewer lesions with the largest being $\leq$4.5 cm and a total tumour burden of 8 cm or less), patients had a similar outcome following transplantation compared to those within the Milan criteria [30]. The MELD score in patients with HCC might be low, and this might prevent these patients from being given priority or even being listed in spite of the fact that their disease is fatal if left untreated. Because this these patients are prioritized depending upon the stage of the tumour, those with T1 lesions are given a score of 20, and T2 lesions a score of 24 [31]. While waiting for transplantation, they usually undergo either transarterial chemoembolisation or radiofrequency ablation as a "bridge" to more definitive therapy.

Other uncommon primary malignancies of the liver which are indications for transplantation are epitheloid haemangioendothelioma and hepatoblastoma. Metastatic lesions of the liver have a poor prognosis; hence, they do not form an indication for transplantation; however, neuroendocrine tumors after the removal of the primary may have a good outcome following the procedure.

3.7. Metabolic Liver Disease. Metabolic liver diseases which cause decompensation and irreversible damage are indications for transplantation. These include Wilson's disease, hereditary haemochromatosis, and α_1-antitrypsin disease. They also affect other organ systems; hence, pretransplant evaluation includes assessment of the concerned system to rule out systemic disease which would otherwise preclude transplantation. Other metabolic disorders, which affect extrahepatic organs while the synthetic liver functions are intact like Type-1 hyperoxaluria or familial homozygous hypercholesterolaemia, are indications for transplantation as the concerned metabolic disorder gets corrected. In childhood, the metabolic disorders which form an indication for transplantation are the urea cycle defects, Criggler-Najjar syndrome, tyrosinaemia, and cystic fibrosis.

3.8. Vascular Disorders. The Budd-Chiari syndrome is characterized by obstruction to the hepatic venous outflow either at the level of the hepatic veins and/or the inferior vena cava. It is associated with myeloproliferative disorders (50%), malignancy (10%), hypercoagulable states (15%), webs in

the IVC, and paroxysmal nocturnal haemoglobinuria (5%). No cause is found in about 20% of patients. Indications for transplantation in these patients are established cirrhosis and acute decompensation. These patients generally require life-long anticoagulation after the transplant procedure [32].

3.9. Miscellaneous. Complicated polycystic liver disease (combined with or without kidney disease) with haemorrhage, infection, pain, massive cystic enlargement, portal hypertension, biliary obstruction, and rarely malignant transformation also forms an indication for liver transplantation. These patients might have well-preserved synthetic functions. Auto immune hepatitis (AIH) either alone or as an overlap syndrome with PSC/PBC is another indication for transplantation. It is important to identify the AIH as these patients require life-long low-dose steroids. Nonalcoholic steatohepatitis is another cause of cirrhosis which might require transplantation.

4. Contraindications to Liver Transplantation

4.1. Severe Cardiopulmonary Disease. Severe pulmonary hypertension or hypoxaemia resulting from the hepatopulmonary syndrome (HPS) poses an undue risk to patients at the time of transplantation (Table 6). A mean pulmonary arterial pressure (PAP) of $\geq$50 mmHg is an absolute contraindication for transplantation as the postprocedure mortality is 100%. Those with PAP between 35–50 mmHg have a 50% mortality after transplantation. Patients with mild pulmonary hypertension with a mean PAP of <35 mmHg are suitable candidates [33]. The mortality in patients with HPS increases to about 30% in the presence of arterial hypoxaemia (<50 mmHg PaO_2) [34]. Oxygen-dependent chronic obstructive airways disease and advanced pulmonary fibrosis are contraindications for transplantation, whereas reactive airway disease, hepatic hydrothorax, muscle wasting and infection, being reversible conditions, are only relative contraindications.

Symptomatic coronary artery disease, severe ventricular dysfunction, advanced cardiomyopathy, severe valvular heart disease, and aortic stenosis having poor ventricular function are absolute contraindications for transplantation. Following bypass surgery or revascularization and angioplasty wherein myocardial ischaemia is resolved, these patients could be listed for transplantation.

4.2. Active Alcohol and Substance Abuse. Active alcohol intake or substance abuse is absolute contraindication for transplantation. A pretransplant period of abstinence is a must for listing in most transplant programmes, but the period of abstinence is not well defined (6 months is generally required) [35]. This period of abstinence gives time for the acute insult on the liver to recover (if at all some recovery takes place); it also provides an opportunity for psychosocial assessment and preparation to minimize the chance of recidivism following transplantation. About 20–26% of patients resume heavy alcohol intake within 4.5 years of transplantation; this affects the graft survival adversely [36].

Table 6: Contraindications to liver transplantation.

Absolute contraindications
Severe cardiopulmonary disease
Extrahepatic malignancy (oncologic criteria for cure not met)
Active alcohol/substance abuse
Acute alcoholic hepatitis
Active infection/uncontrolled sepsis
Lack of psychosocial support/inability to comply with medical treatment
Brain death
Relative contraindications
Advanced age
Acquired immune deficiency syndrome
Cholangiocarcinoma
Diffuse portal vein thrombosis

Acute alcoholic hepatitis is a contraindication for transplantation in almost all programmes. There is insufficient data on the outcome of transplantation in these patients as there is no period of abstinence [20, 21].

It is essential to rule out drug or poly drug abuse (opiates, sedatives, and cannabinoids), active tobacco abuse, as they form a high-risk group requiring psychiatric assessment and treatment. These candidates have a relative contraindication to be listed for transplantation as long as the active abuse continues.

4.3. Psychosocial Support. Patients following transplantation require good social support, in the absence of which it is likely that there will be lack of compliance with the immunosuppressive medication leading ultimately to the loss of the graft.

4.4. Age. Advanced age is associated with cardiopulmonary risk factors. Older patients require extensive evaluation to rule out the absolute contraindications like severe cardiopulmonary disease and malignancy. Patients over the age of 60–65 have been shown to have lower survival rates at 1 year and 5 years than those who are younger [37]. However, many centres now accept 70 years as the cut off limit for transplantation and have shown good results with this policy [38].

4.5. Obesity. Morbidly obese patients (BMI > 40) have an increased 5-year mortality after transplantation because of the associated cardiovascular morbidity [39]. Recipients who have a BMI > 35 kg/m^2 require an individualized approach according to the policy of the centre.

4.6. HIV Infection. Patients with HIV infection have a better survival due to the effectiveness of highly active antiretroviral therapy (HAART). However they have other complications which may prove fatal, like chronic hepatitis C and cirrhosis.

Earlier HIV used to be an absolute contraindication for transplantation, due to the fear of progression of disease with immunosuppression; however, with the availability of highly effective antiretroviral drugs, virus control has improved and transplantation is now being offered selectively. The absolute contraindication to transplantation in these patients includes uncontrolled HIV disease with multi drugresistance, leukoencephalopathy, advanced malnutrition, life support requirement, and opportunistic infections [26]. Transplantation in these patients should be done in collaboration with experts in the management of HIV infections.

4.7. Other Infections. Pneumonia, sepsis, bacteraemia, osteomyelitis, and fungal infection should be treated adequately before transplantation and the ongoing presence of any of these is an absolute contra-indication.

4.8. Miscellaneous. Retransplantation for recurrent HCV infection, autoimmune hepatitis, alcoholic liver disease, non-alcoholic steatohepatitis, and hepatocellular carcinoma are some of the controversial areas though not contraindications in themselves. This is because the survival of both patient and graft is suboptimal in the long term. Previous abdominal surgery increases the length of operation, blood loss, and complications related to the transplantation procedure. Portal vein thrombosis, once considered to be a contraindication, is no longer so except in the presence of diffuse thrombosis [40]. Patients with extrahepatic malignancy require at least a 5-year tumour-free interval before being considered for transplantation [41]. Cholangiocarcinoma once an indication for liver transplantation is now a relative contraindication because of the poor outcome especially in those with advanced disease.

5. Delisting Criteria

While waiting for the graft, if the liver disease progresses to such an extent that the survival benefit from transplantation (50% 5 year survival) no longer holds, which generally occurs if the MELD score is >40, then it is probably better to delist the patient. However, there is no guideline as such for delisting candidates except in patients with HCC who develop metastatic disease and fall out of the listing criteria. Patients who resume alcohol intake or substance abuse should be delisted. Temporary deactivation is done for patients who have clinical deterioration in the form of mechanical ventilation, haemodialysis, and fungal or resistant bacterial infection.

6. Living Donor Liver Transplantation

The indications for liver transplantation and the criteria for listing generally remain the same (child's score ≥7, MELD >10). Patients with cholestatic liver disease who have lower MELD scores, but other issues like, recurrent cholangitis, recurrent encephalopathy, and severe itching, who might not get listed in a DDLT program may, however, gain entry into the list in an LDLT setting. These patients benefit from partial liver grafts as they have otherwise stable liver disease. Studies have revealed that the average MELD score in a patient having LDLT is less than the score of a DDLT recipient (14.8 versus 23.5) [8]. The risk of transplantation is increased compared with its benefit if the MELD score is <14 or more than 25 [8]. There are two situations where LDLT poses an added advantage over DDLT. The first is a patient with HCC who probably has a lower MELD score, the waiting period is reduced, and the outcome is equally good. Patients fulfilling the Milan or UCSF criteria, depending upon the programme, get transplanted earlier in an LDLT setting before metastases occur. The other patients who have low MELD scores and would benefit from LDLT are those with symptomatic benign liver lesions (haemangioma, haemagioendothelioma, and polycystic liver disease), metabolic disorders (familial amyloidosis, hyperoxaluria, tyrosinaemia, glycogen storage disease), or complicated cholestatic liver disease. These patients otherwise would have to wait for a longer period to get a deceased donor graft.

The advantages of LDLT are that almost all transplants are planned and elective (except for those with ALF), the recipient's functional status can be optimized before surgery, and the graft cold ischaemia time is reduced. There has been evolution in the donor and patient selection, along with improvement in the surgical technique in both the donor and recipient surgery in LDLT. This has led to improved 1-year graft and patient survival to 81 and 89%; the vascular and biliary complications have reduced (hepatic artery thrombosis <5%, biliary complications 5–20%) [42–45].

It is very important to ensure donor safety in an LDLT program, and so far the reported donor mortality is <0.2–0.5%, morbidity is between 10–15%, and donor biliary complication is <5% [42, 46].

7. Contraindications for LDLT

Apart from the contraindications already mentioned in the earlier section, the additional contraindications pertaining to the living donor are as stated below.

Absolute Contraindications.

(1) Donor having macrosteatosis (>20%) on liver biopsy are rejected.

(2) Remnant liver volume less than 25%. This is an issue especially when right lobe graft is big. It is never an issue when the left lateral segment is the proposed graft and is rarely an issue if the left lobe graft is taken.

(3) The Human Organ Transplantation Act, in India, does not allow unrelated donation; this is to prevent donation under any kind of coercion and to avoid any organ trade. However unrelated donation is acceptable in other countries like Hong Kong, Korea, China, Japan, and so forth.

(4) Living donor should be between 18 and 55 years of age. Lower limit is the age at which legal consent can be given.

Relative Contraindications.

(1) Body mass index >30 of the donor is generally associated with macrosteatosis, such donors are advised to reduce weight, and they need to have a liver biopsy to rule out >20% steatosis. If there are other potential donors in the family, they are rejected as liver donors.

(2) Liver attenuation index of <5 on plain CT scan is suggestive of steatosis; hence, such donors are either rejected or in the absence of other donors need to reduce weight and have a biopsy to rule out >20% macrosteatosis.

(3) Donors are rarely rejected on anatomical grounds. Double artery, double portal vein, or more than 2 hepatic veins can be easily tackled during implantation, and these no longer preclude donation. However, certain anatomical anomalies, for example, a Type E portal vein in the donor where there are multiple right-sided segmental portal vein tributaries draining into the left portal vein is a contraindication for LDLT [47].

(4) All types of biliary anatomy in the donor (as classified by Huang) is acceptable [48]. Very rarely if there are multiple ducts in the donor (more than 3 bile ducts) to be anastomosed, then the donor is rejected [45].

8. Summary

Survival after liver transplantation has progressively improved over the decades. This can be attributed to advances in the surgical technique, perioperative and post-transplant intensive care management, and the introduction of better immunosuppressive drugs. Thus, there has been a constant evolution in the indications and contraindications for liver transplantation. Better scoring systems have been introduced to select patients and allocate organs in DDLT programs. Living donor transplantation has been introduced to overcome the gap between the need and availability of deceased donor organs especially in countries where deceased organ donation is rare. It offers definite advantage in situations where the waiting period otherwise would be lengthy and where entry to the waiting list for a DDLT would be restricted.

References

[1] A. S. Yu and E. B. Keeffe, "Liver transplantation," in *Hepatology: A Textbook of Liver Disease*, D. Zakim and T. D. Boyer, Eds., pp. 1617–1656, Elsevier, Philadelphia, Pa, USA, 4th edition, 2003.

[2] K. F. Murray and R. L. Carithers, "AASLD practice guidelines: evaluation of the patient for liver transplantation," *Hepatology*, vol. 41, no. 6, pp. 1407–1432, 2005.

[3] Consensus Conference, "Consensus conference: indications for Liver Transplantation, January 19 and 20, 2005, Lyon-Palais Des Congrès: text of recommendations (long version)," *Liver Transplantation*, vol. 12, no. 6, pp. 988–1011, 2006.

[4] US Scientific Registry (UNOS). Richmond (VA): United Network for Organ Sharing, 2006, http://www.unos.org/.

[5] R. M. Merion, D. E. Schaubel, D. M. Dykstra, R. B. Freeman, F. K. Port, and R. A. Wolfe, "The survival benefit of liver transplantation," *American Journal of Transplantation*, vol. 5, no. 2, pp. 307–313, 2005.

[6] P. S. Kamath, R. H. Wiesner, M. Malinchoc et al., "A model to predict survival in patients with end-stage liver disease," *Hepatology*, vol. 33, no. 2, pp. 464–470, 2001.

[7] G. Longheval, P. Vereerstraeten, P. Thiry et al., "Predictive models of short- and long-term survival in patients with nonbiliary cirrhosis," *Liver Transplantation*, vol. 9, no. 3, pp. 260–267, 2003.

[8] R. B. Freeman, "Overview of the MELD/PELD system of liver allocation indications for liver transplantation in the MELD era: evidence-based patient selection," *Liver Transplantation*, vol. 10, no. 10, pp. S2–S3, 2004.

[9] K. M. Olthoff, R. S. Brown, F. L. Delmonico et al., "Summary report of a national conference: evolving concepts in liver allocation in the MELD and PELD Era," *Liver Transplantation*, vol. 10, no. 10, pp. A6–A22, 2004.

[10] M. R. Lucey, K. A. Brown, G. T. Everson et al., "Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases," *Liver Transplantation and Surgery*, vol. 3, no. 6, pp. 628–637, 1997.

[11] W. M. Lee, "Acute liver failure," *The New England Journal of Medicine*, vol. 329, no. 25, pp. 1862–1872, 1993.

[12] J. G. O'Grady, G. J. M. Alexander, K. M. Hayllar, and R. Williams, "Early indicators of prognosis in fulminant hepatic failure," *Gastroenterology*, vol. 97, no. 2, pp. 439–445, 1989.

[13] G. C. MacQuillan, M. S. Seyam, P. Nightingale, J. M. Neuberger, and N. Murphy, "Blood lactate but not serum phosphate levels can predict patient outcome in fulminant hepatic failure," *Liver Transplantation*, vol. 11, no. 9, pp. 1073–1079, 2005.

[14] H. Nazer, R. J. Ede, A. P. Mowat, and R. Williams, "Wilson's disease: clinical presentation and use of prognostic index," *Gut*, vol. 27, no. 11, pp. 1377–1381, 1986.

[15] A. Dhawan, R. M. Taylor, P. Cheeseman, P. De Silva, L. Katsiyiannakis, and G. Mieli-Vergani, "Wilson's disease in children: 37-year experience and revised King's for liver transplantation," *Liver Transplantation*, vol. 11, no. 4, pp. 441–448, 2005.

[16] J. Bernuau, D. Samuel, F. Durand et al., "Criteria for emergency liver transplantation in patients with acute viral hepatitis and factor V (FV) below 50% of normal: a prospective study (abstract)," *Hepatology*, vol. 14, article 49A, 1991.

[17] K. M. Barber, S. Pioli, J. E. Blackwell, D. Collett, J. M. Neuberger, and A. E. Gimson, "Development of a UK score for patients with end-stage liver disease," *Hepatology*, vol. 46, article 510A, 2007.

[18] J. Neuberger, K. H. Schulz, C. Day et al., "Transplantation for alcoholic liver disease," *Journal of Hepatology*, vol. 36, no. 1, pp. 130–137, 2002.

[19] J. E. Everhart and T. P. Beresford, "Liver transplantation for alcoholic liver disease: a survey of transplantation programs in the United States," *Liver Transplantation and Surgery*, vol. 3, no. 3, pp. 220–226, 1997.

[20] H. Bonet, R. Manez, D. Kramer et al., "Liver transplantation for alcoholic liver disease: survival of patients transplanted with alcoholic hepatitis plus cirrhosis as compared with those with cirrhosis alone," *Alcoholism*, vol. 17, no. 5, pp. 1102–1106, 1993.

[21] A. O. Shakil, A. Pinna, J. Demetris, R. G. Lee, J. J. Fung, and J. Rakela, "Survival and quality of life after liver transplantation for acute alcoholic hepatitis," *Liver Transplantation and Surgery*, vol. 3, no. 3, pp. 240–244, 1997.

[22] H. Castel, C. Moreno, T. Antonini, J. Duclos-Vallee, J. Dumortier, and V. Leroy, "Early transplantation improves survival of non-responders to steroids in severe alcoholic hepatitis: a challenge to the 6 month rule of abstinence," *Hepatology*, vol. 4, pp. 307A–308A, 2009.

[23] M. P. Curry, "Hepatitis B and hepatitis C viruses in liver transplantation," *Transplantation*, vol. 78, no. 7, pp. 955–963, 2004.

[24] R. H. Wiesner, M. Sorrell, F. Villamil et al., "Report of the first international liver transplantation society expert panel consensus conference on liver transplantation and hepatitis C," *Liver Transplantation*, vol. 9, no. 11, pp. S1–S9, 2003.

[25] M. Charlton, K. Ruppert, S. H. Belle et al., "Long-term results and modeling to predict outcomes in recipients with HCV infection: results of the NIDDK liver transplantation database," *Liver Transplantation*, vol. 10, no. 9, pp. 1120–1130, 2004.

[26] S. A. Fink and R. S. Brown, "Current indications, contraindications, delisting criteria, and timing for liver transplantation," in *Textbook on Liver Transplantation*, R. W. Busuttil and G. B. Klintmalm, Eds., chapter 7, pp. 95–113, Elsevier, New York, NY, USA, 2nd edition, 2009.

[27] UNOS Policy 3 Appendix 3B, 2011, http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_15.pdf.

[28] M. Sherman, "Hepatocellular carcinoma: epidemiology, risk factors, and screening," *Seminars in Liver Disease*, vol. 25, no. 2, pp. 143–154, 2005.

[29] V. Mazzaferro, E. Regalia, R. Doci et al., "Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis," *The New England Journal of Medicine*, vol. 334, no. 11, pp. 693–699, 1996.

[30] F. Y. Yao, L. Ferrell, N. M. Bass et al., "Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival," *Hepatology*, vol. 33, no. 6, pp. 1394–1403, 2001.

[31] R. H. Wiesner, S. V. McDiarmid, P. S. Kamath et al., "Meld and Peld: application of survival models to liver allocation," *Liver Transplantation*, vol. 7, no. 7, pp. 567–580, 2001.

[32] A. S. Klein, "Management of Budd-Chiari syndrome," *Liver Transplantation*, vol. 12, no. 11, pp. S23–S28, 2006.

[33] M. J. Krowka, D. J. Plevak, J. Y. Findlay, C. B. Rosen, R. H. Wiesner, and R. A. F. Krom, "Pulmonary hemodynamics and perioperative cardiopulmonary-related mortality in patients with portopulmonary hypertension undergoing liver transplantation," *Liver Transplantation*, vol. 6, no. 4, pp. 443–450, 2000.

[34] M. J. Krowka, M. K. Porayko, D. J. Plevak et al., "Hepatopulmonary syndrome with progressive hypoxemia as an indication for liver transplantation: case reports and literature review," *Mayo Clinic Proceedings*, vol. 72, no. 1, pp. 44–53, 1997.

[35] J. K. Lim and E. B. Keeffe, "Liver transplantation for alcoholic liver disease: current concepts and length of sobriety," *Liver Transplantation*, vol. 10, no. 10, pp. S31–S38, 2004.

[36] A. DiMartini, N. Day, M. A. Dew et al., "Alcohol consumption patterns and predictors of use following liver transplantation for alcoholic liver disease," *Liver Transplantation*, vol. 12, no. 5, pp. 813–820, 2006.

[37] R. N. Keswani, A. Ahmed, and E. B. Keeffe, "Older age and liver transplantation: a review," *Liver Transplantation*, vol. 10, no. 8, pp. 957–967, 2004.

[38] G. S. Lipshutz, J. Hiatt, R. M. Ghobrial et al., "Outcome of liver transplantation in septuagenarians: a single-center experience," *Archives of Surgery*, vol. 142, no. 8, pp. 775–781, 2007.

[39] S. Nair, S. Verma, and P. J. Thuluvath, "Obesity and its effect on survival in patients undergoing orthotopic liver transplantation in the United States," *Hepatology*, vol. 35, no. 1, pp. 105–109, 2002.

[40] G. Manzanet, F. Sanjuán, P. Orbis et al., "Liver transplantation in patients with portal vein thrombosis," *Liver Transplantation*, vol. 7, no. 2, pp. 125–131, 2001.

[41] A. Ahmed and E. B. Keeffe, "Current Indications and Contraindications for Liver Transplantation," *Clinics in Liver Disease*, vol. 11, no. 2, pp. 227–247, 2007.

[42] H. P. Tan, K. Patel-Tom, and A. Marcos, "Adult living donor liver transplantation: who is the ideal donor and recipient?" *Journal of Hepatology*, vol. 43, no. 1, pp. 13–17, 2005.

[43] G. E. Gondolesi, G. Varotti, S. S. Florman et al., "Biliary complications in 96 consecutive right lobe living donor transplant recipients," *Transplantation*, vol. 77, no. 12, pp. 1842–1848, 2004.

[44] A. Marcos, M. Killackey, M. S. Orloff, L. Mieles, A. Bozorgzadeh, and H. P. Tan, "Hepatic arterial reconstruction in 95 adult right lobe living donor liver transplants: evolution of anastomotic technique," *Liver Transplantation*, vol. 9, no. 6, pp. 570–574, 2003.

[45] A. S. Soin, V. Kumaran, A. N. Rastogi et al., "Evolution of a reliable biliary reconstructive technique in 400 consecutive living donor liver transplants," *Journal of the American College of Surgeons*, vol. 211, no. 1, pp. 24–32, 2010.

[46] C. M. Lo, S. T. Fan, C. L. Liu et al., "Lessons learned from one hundred right lobe living donor liver transplants," *Annals of Surgery*, vol. 240, no. 1, pp. 151–158, 2004.

[47] T. Nakamura, K. Tanaka, T. Kiuchi et al., "Anatomical variations and surgical strategies in right lobe living donor liver transplantation: lessons from 120 cases," *Transplantation*, vol. 73, no. 12, pp. 1896–1903, 2002.

[48] T. L. Huang, Y. F. Cheng, C. L. Chen, T. Y. Chen, and T. Y. Lee, "Variants of the bile ducts: clinical application in the potential donor of living-related hepatic transplantation," *Transplantation Proceedings*, vol. 28, no. 3, pp. 1669–1670, 1996.