Preventive Approaches in Chronic Liver Diseases Part II: Compensated Liver Cirrhosis

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The objective of this article is to provide evidence-based strategies to prevent or detect early complications of liver cirrhosis (LC). The clinical severity of LC should be assessed once the diagnosis has been made by the scoring systems described. Due to increased risk of perioperative complications or death, patients with LC should undergo elective surgery after careful consideration. Patients diagnosed with LC should undergo esophagogastroduodenoscopy screening to detect varices. Beta-blockers are the first choice for treating patients with esophageal varices to prevent bleeding. In patients not tolerating beta blockers, banding ligation is a valid option. Liver cancer screening with abdominal CT or US at least yearly and serum alpha-feto protein levels every six months is recommended. Other preventive measures like pneumoccocus vaccination, yearly influenza vaccine and osteoporosis screening should be considered in patients with LC. This manuscript is the second part of three articles dealing with preventive measures for liver disease.

INTRODUCTION

Liver cirrhosis (LC) is an irreversible stage of chronic liver disease progression. Depending on the etiology of the liver disease, chronic liver disease could take up to 20–30 years to develop into cirrhosis. Hepatitis C virus (HCV) is the most frequent cause of LC and the leading indication for liver transplantation (1). LC is a diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules (2). It is the fifth cause of death, in the United States, for individuals between ages 45-to-54 (3).

The gold standard test to diagnose cirrhosis is liver biopsy. It is far from being a perfect test given its invasive nature and only fair sensitivity for advanced liver fibrosis. As an invasive procedure, it has complications such as prolonged hospital stay (about 1%–5% of cases) and mortality rate (about 0.1%–0.01%) (4). There has been a persistent search for an alternative method to diagnose liver fibrosis, but these have not been able to achieve wide clinical acceptance. Some approaches are based on imaging modalities to observe the changes in the liver per se. These techniques have not shown promising results regarding differentiation between early versus late liver fibrosis (5).

Other methods used for the diagnosis of liver fibrosis include the non-invasive biochemical fibrosis markers. There has been a search for a perfect marker that could accurately reflect fibrosis in patient with variety of liver diseases. Some are based on matrix degradation products (N-terminal propeptide of type III collagen, collagen IV, prolyl hydroxylase, etc.) which have shown to be non-specific (6). Some researchers have focused their investigation on the combination of laboratory tests and patient characteristics (like age and sex). These have shown to be non-reproducible. Rosenberg, et al used a combination of nine surrogate markers for liver fibrosis including age, hyaluronic acid and

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Table 1
Modified Histological Activity Index scoring of liver biopsy (37)*

Piecemeal necrosis	*Score*	*Confluent necrosis*	*Score*	*Portal inflammation*	*Score*	*Focal lytic necrosis*	*Score*	*Fibrosis Score†*	*Score*
None	0	None	0	None	0	None	0	No fibrosis	0
Mild	1	Focal confluent necrosis	1	Mild	1	One focus or less per 10X objective	1	Fibrous portal expansion of some portal areas	1
Mild/ Moderate	2	Zone 3 necrosis in some areas	2	Moderate	2	Two to four foci	2	Fibrous portal expansion of most portal areas	2
Moderate (<50% of tracts or septa)	3	Zone 3 necrosis in most areas	3	Moderate/ Marked	3	Five to ten foci	3	Above with portal to portal bridging	3
Marked (>50% of tracts or septa)	4	Zone 3 necrosis and occasional portal central bridging	4	Marked	4	More than ten foci	4	Above with marked portal to portal and portal to central bridging	4
		Zone 3 necrosis and multiple bridging	5					Marked bridging with occasional nodules	5
		Panacinar or multiacinar necrosis	6					Cirrhosis	6

*The HAI score is measured out of total of 18 including the four columns on the left.
†The fibrosis score shown in the last column on the right is measured out of total of 6.

tissue inhibitor of matrix metalloproteinase 1 (TIMP-1) and concluded that "they may be used in conjunction with liver biopsy to assess a range of chronic liver disease (7)." Other commercially available fibrosis markers tests like Fibrotest or Actitest have not proven to replace liver biopsy at this time (6).

Several histologic classifications have been proposed to minimize uncertainties and provide standardization regarding histologic findings in liver biopsy. The most universal systems are the HAI score and the Metavir score (Tables 1 and 2 provide details of these classifications).

The clinical severity of LC should be assessed once the diagnosis has been made. The two most popular methods for this assessment are the MELD score (Model for End-stage Liver Disease) and the Modified Child-Turcotte-Pugh score. MELD consists of a complex equation taking in consideration the total bilirubin, the INR (international normalized ratio) and the serum creatinine (Figure 1). It predicts mortality in adult patients with end stage liver disease. MELD scores range from six-to-40 and is the system used by United Network for Organ Sharing (UNOS) to priori-

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Table 2
The Metavir scoring system (38)

Fibrosis Score	*Score*
No fibrosis	0
Portal Fibrosis with no septal involvement	1
Portal fibrosis with few septal involvement	2
Portal fibrosis with numerous septal involvement with no cirrhosis	3
Cirrhosis	4
Activity Score (intensity of necroinflammatory lesions)	*Score*
No activity	A0
Mild activity	A1
Moderate activity	A2
Severe activity	A3

Table 3
Modified Child-Turcotte-Pugh classification *

Parameters/Points	*One*	*Two*	*Three*
Albumin g/dL	3.5	2.8–3.5	<2.8
Total Bilirubin mg/dL	<2	2–3	>3
INR	<1.7	1.7–2.3	>2.3
Encephalopathy	None	Grade 1–2†	Grade 3–4‡
Ascites	None	Slight	Moderate

†Grade 1 includes impaired attention, depression, irritability, personality change, tremor, incoordination, apraxia. Grade 2 includes drowsiness, behavioral changes, poor memory, sleep disorders, asterixis, slurred speech, and ataxia.
‡Grade 3 includes confusion, disorientation, somnolence, amnesia, hypoactive reflexes, nystagmus, clonus, and muscular rigidity. Grade 4 includes stupor and coma, dilated pupils and decerebrate posturing; oculocephalic reflex; absence of respone to stimuli.
*When total score is between 5–6 is considered Child A. Scores between 7–9 is Child B and Child C is scores between 10–15

tize candidates with chronic liver failure for organ allocation (8).

Modified Child-Turcotte-Pugh score takes in consideration two signs and three laboratory values for the evaluation of cirrhotic patients (Table 3). Based on this evaluation, patients are classified in three groups (A, B, C). Patients belonging to Child A group could survive up to 20 years compared to survival of Child C patients which is less than three years (9).

LC is considered decompensated when patients develop at least one complication of the disease (hepatic encephalopathy, gastrointestinal bleeding due to portal hypertension, ascites, coagulopathies, hepatocellular carcinoma or severe infections). This is important because it has been shown that patients with compensated liver cirrhosis have a ten-year survival of about 50% versus 16% five-year survival in patients with decompensated disease. The only cure for decompensated liver cirrhosis is liver transplantation if the patient is a suitable candidate.

Our main objective in this article is to provide evidence-based strategies to prevent or detect early complications of liver cirrhosis which could maximize the time to transplantation or death by slowing further liver damage and alleviating co-morbid conditions. This manuscript is the second part of three articles dealing with preventive measure for liver disease by primary caregivers. All the recommendations in part I (chronic liver disease) are applicable to all patients in part II (compensated cirrhosis) and III (decompensated cirrhosis).

CIRRHOSIS AND RISK OF ELECTIVE SURGERY

Cirrhotic patients are at higher risk for postoperative complications than patients with intact liver function. This is true for both elective and emergency non-hepatic surgeries. Several studies have shown that the best predictor for these complications is the preopera-

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$$R = 9.6 \times \log_e(\text{Serum creatinine}\dagger) + 3.8 \times \log_e(\text{Serum Total bilirubin}\ddagger) + 11.20 \times \log_e(\text{INR}^*) + 6.4$$

†Creatinine units are mg/dl; ‡Total bilirubin units are mg/dl; *INR = International Normalized Ratio

Figure 1. The Equation of Model for End-Stage Liver Disease (MELD)

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tive Child score. In one study done by Del Olmo, et al it was shown that non-hepatic procedures in patients with cirrhosis are associated with a significant death rate (16.3%) compared to non-cirrhotics (3.5%). They also reported that about 20% of cirrhotics develop decompensation of their cirrhosis postoperatively. In the same study, it was observed that patients with Child A score have similar outcome patients with no liver disease and it is mainly Child B and C groups that have a higher mortality rate (31.7% and 54.5%, respectively) (10). Similar results have been reported by other authors (11,12). On the other hand, Mansour, et al showed that mortality rate for cirrhotic patients that undergo abdominal surgery could be as high as 82% for patients with Child C score (Child A 10% and Child B 30%) (13). This shows that patients with LC have a higher mortality rate when having abdominal surgery compared to other type of surgeries.

Ziser, et al did a retrospective study of surgical procedures done on 733 patients with liver cirrhosis and defined several factors that are associated with perioperative complications and mortality in these patients (14). These factors included male gender, higher Child score, cause of cirrhosis other than primary biliary cirrhosis, presence of ascites, elevated creatinine and occurrence of preoperative gastrointestinal bleeding.

Due to this increased risk of perioperative complications or death, patient with liver cirrhosis should only undergo elective surgery after a detailed examination and careful consideration. The medical team should evaluate in detail the risks and benefit of the surgery in these patients. It is advisable to assess these patients by calculating their Child score before the operation and their risk of bleeding by looking at coagulation parameters and varices. Detailed preoperative preparation aimed at correcting the abnormalities associated with advanced liver disease (including coagulopathies, metabolic abnormalities, minimizing preexisting encephalopathy, preventing sepsis, and optimizing renal function) may improve post surgical outcomes (15).

CIRRHOSIS AND PORTAL HYPERTENSION/VARICEAL BLEEDING

A fibrotic liver provides an increase resistance to portal system inflow causing sinusoidal portal hypertension; this leads to the development of esophageal varices. Portal pressure is defined as the product of portal venous inflow and resistance to outflow from the portal venous system. This portal pressure is increased in cirrhosis due not only to elevated resistance to outflow but also splenic arteriolar vasodilatation that enhances portal inflow. When the pressure gradient between the portal and hepatic vein becomes greater than 12 mm Hg, collateral vessels form at the junctures of the portal and systemic venous system (2). When these collaterals are formed in the distal esophagus and stomach, the usually small rudimentary left gastric vein dilates and varices develop. On endoscopic examination, varices are found in about 50%-60% of patients with LC. Patients with large varices have a risk of bleeding of about 40%–45% yearly. Each episode of variceal bleeding carries a risk of mortality as high as 50% (16). The pressure gradient between the portal and hepatic vein is among the most important prognostic indicators in cirrhosis (17).

Patients diagnosed with liver cirrhosis should undergo esophagogastroduodenoscopy (EGD) screening to detect varices. D'Amico, et al (2006) did a detailed review of literature regarding prevention of variceal bleeding and concluded that a reduction of pressure gradient between the portal and hepatic vein to <12 mm Hg or by >20% of baseline gradient does not only significantly reduce the first bleeding risk but also prevents rebleeding. Their conclusion also concluded that the reduction of this gradient by >20% of baseline is associated with a marked reduction of mortality (18). Tunes, et al (2006) showed, in another study, that the reduction of this venous gradient is correlated with a reduced risk of spontaneous bacterial peritonitis (SBP) and bacteremia in cirrhotic patients (19).

Nonselective beta blockers have been used as a first choice for primary prophylaxis against variceal bleeding. Propranolol and nadolol are the most commonly used beta blockers for this purpose. A meta-analysis done by D'Amico, et al (1999) showed that the risk of first bleeding is decreased by nearly 50% by continued propranolol or nadolol therapy over a median follow-up of 2 years (20). The dose of these medications varies depending on the response of patients. Patients are normally started on propranolol 10 mg three times a day or

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nadolol 20 mg twice daily and the doses are increased stepwise until reaching a reduction of 20%–25% of heart rate below baseline but maintaining a heart rate above 55 beats per minute or systolic blood pressures above 90 mmHg. The pulse reduction method in clinical practice is a practical marker for the more invasive pressure measurement techniques mentioned above. If varices increase in size despite beta blockers, then mono-nitrates can be added (21).

Several randomized control studies have been performed in recent years in order to compare variceal banding ligation and propranolol as a prophylaxis for first-time variceal bleeding. Schepke, et al (2004) showed that both are similarly effective for primary prophylaxis of variceal bleeding (22). Jutabha, et al (2005) showed, in a randomized study, that prophylactic propranolol has a higher failure rate compared to ligation regarding variceal bleeding in high-risk patients with esophageal varices (23). In a detailed analysis of this study, the population used was highly selected making the findings hard to generalize. Inadequate use of beta-blockers with respect to dosing and interval weakened the medication arm. Methods for assessment of dysphagia in patients after ligation may underestimate this complication. These concerns should raise questions regarding the application of this study to practice.

Khuroo, et al did a meta-analysis of eight trials comparing the traditional approach of using beta blockers versus banding ligation in prevention of first variceal bleeding. They concluded that, for moderate to large varices, ligation is more beneficial than pharmacotherapy for first bleeding episode but no changes in survival were observed between the two modalities (24).

On the other hand, Triantos, et al did a randomized trial comparing ligation to no treatment in patients unable to take beta-blockers. The study had to be stopped due to increased bleeding in the banding group due to iatrogenic manipulation (25). They also provided a detailed meta-analysis comparing banding versus no treatment. By using a funnel plot, they showed a publication bias against studies with complications (25).

The general consensus regarding usage of endoscopic ligation as a first treatment option for patients with esophageal varices for prevention of first episode of bleeding is controversial at the present time until stronger evidence is provided. At present, beta-blockers are the first choice for treating patient with esophageal varices to prevent a first bleeding episode. In patients not tolerating beta blockers, banding ligation is a valid option for preventing the first variceal bleeding. The side effect profile of banding has more potential serious consequences such as bleeding from gastric varices and dysphagia; therefore, this option is considered only if pharmacological approach is not possible.

CIRRHOSIS AND SCREENING FOR HEPATOCELLULAR CARCINOMA

Patients with LC are prone to develop complications. One such complication is tendency to develop hepatocellular carcinoma (HCC). In patients with cirrhosis caused by HCV, HCC develops at a yearly rate of 1.5%–8% (26). A study done by Chalasani, et al (1999) showed a cumulative 22.9-fold increased risk of HCC in patients with LC after three and one-half years (27). HCC is the leading cause of death in patients with LC (2). Once HCC becomes symptomatic, the average survival time is about six months (28). The early detection of HCC in the patient with LC provides a window of opportunity for the treatment of these patients. Options like tumor resection and liver transplantation are potentially curative. Chemoembolization or other local ablative methods are considered palliative but can prevent tumor growth while awaiting transplantation.

All patients with cirrhosis should be screened for HCC on a regular basis. The method of screening and its frequency have been debated in the past several years due to the development of advances in computerized tomography (CT) and magnetic resonance imaging (MRI). Several cost-effectiveness studies have been done in the past regarding the screening for HCC with different findings regarding the best method.

Alpha-feto-protein (AFP) is a fetal specific glycoprotein produced primarily by the fetal liver. After birth, AFP serum concentration falls and its synthesis is blocked in adult life. About 70% of HCC patients have been shown to have high AFP levels in their serum (29). A study performed by McMahon, et al in 2000 showed that in Alaskan natives infected with chronic hepatitis B, AFP measuring permitted the detection of HCC at an earlier and treatable stage. They also showed increased

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survival in this group compared to controls (30). AFP sensitivity and specificity depend on the cut-off value chosen. In cirrhotic patients, AFP sensitivity is only around 60% and positive predictive value ranges from 9% to 50% (depending on prevalence of HCC in the population) if a cut-off level of 20 ng/mL is considered (31). Farinati, et al showed that AFP has a poor diagnostic role with a sensitivity of 54% even considering higher cut-off levels (>400 ng/mL) (32).

Ultersound sonography (US) has been studied for the detection of HCC in patients with LC. Liver ultersound examination has shown to have a sensitivity of 59%–74% and a specificity of about 94% detecting HCC (33). Solmi, et al showed that in cirrhotic patients, US can diagnose tumors of 3 cm or less in a high percentage of cases (at a potentially curable stage) compared with the patients not regularly followed (34). One of the downsides to liver US is that its sensitivity and specificity is operator dependent.

The combination of AFP and US have been advocated and widely used as a routine screening method in patients with LC (27). The combination of these two methods is still far from being perfect. A cost-effective study done by Lin, et al showed that US performed yearly and AFP measured each six months is the most cost effective method for screening (35). Arguedas, et al showed that screening for HCC with CT in patients with HCV related cirrhosis could be as cost effective as using US, falling below the commonly used threshold of $50,000 per quality-adjusted life year (QALY) saved. The same study showed that using MRI imaging will increase this cost to up to $118,000 per QALY saved (35). MRI imaging at present time is not considered to be cost effective compared to the other modalities.

At this time, patients with LC should be screened with CT or US at least yearly and AFP measurement every six months.

CIRRHOSIS AND OTHER GENERAL RECOMMENDATIONS

Patients with LC should have preventive measures similar to patients with other common chronic diseases like diabetes or renal failure. These patients should have a pneumoccocus vaccine after the diagnosis of LC. Also, a yearly influenza vaccine is highly recommended.

Table 4
Summary of evidence-based recommendations for patients with compensated liver cirrhosis

1. Alcohol abstinence
2. Appropriate vaccination for:
   – Hepatitis A and B (see part I)
   – Pneumococcus
   – Yearly influenza virus
3. Avoidance of hepatotoxic medications specially NSAID's
4. Endoscopic examination to evaluate for esophageal varices
5. Screening for hepatocellular carcinoma with AFP measurement every six month and yearly US or CT scan of abdomen
6. Detailed medical evaluation including Child score calculation before any elective surgery in patients with liver cirrhosis
7. Screening for osteoporosis by DEXA scan
8. Periodic assessments of Child score with referral to liver transplant center when Child B liver disease occurs

Patients with LC are at high-risk of developing osteoporosis. It was shown that they have a bone fracture rate about twice as high as patients without liver disease (36). Vitamin D deficiency is a common finding in patients with chronic liver disease. Patients with LC should be screened for osteoporosis and preventive measures with oral calcium and vitamin D supplementation should be started if low-bone density is diagnosed (37). Before oral biphosphanates are used, variceal screening with endoscopy should take place. If varices are seen, intravenous biphosphanates can be utilized to prevent esophageal erosions.

Prevention of drug toxicity is very important in patients with LC. All the recommendations provided in Part I of these three articles are still applicable to patients with LC. A special emphasis should be placed on the usage of non-steroidal anti-inflammatory drugs (NSAID's). NSAID's are more toxic to patient with LC due to two mechanisms; patients with LC have coagulopathies and the use of NSAID's make bleeding more likely. Also, patients with LC are greatly dependent on prostaglandins for adequate renal blood flow.

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NSAID's block prostaglandins production and could decrease renal blood flow. This could lead to the development of acute renal failure. Tylenol is a safe alternative in doses less than 2 grams daily.

In summary, in patients with liver cirrhosis there is an opportunity to practice preventive care to reduce the development of complications and maximize the time to transplantation or death by slowing further liver damage. Table 4 provides a summary of the evidence-based preventive measures that are recommended in patients with compensated liver cirrhosis. This manuscript is the second part of three articles addressing preventive approaches to patient with liver diseases. All of the recommendations provided by the first manuscript apply to the patients with liver cirrhosis. ■

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