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Review on Liver Cirrhosis Complications and Treatment

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ABSTRACT

Background: cirrhosis is a late stage of scarring (fibrosis) of the liver caused by many forms of liver diseases and conditions, such as hepatitis and chronic alcoholism. The liver carries out several necessary functions, including detoxifying harmful substances in your body, cleaning your blood and making vital nutrients. Cirrhosis occurs in response to damage to your liver. Each time your liver is injured, it tries to repair itself. In the process, scar tissue forms. As cirrhosis progresses, more and more scar tissue forms, making it difficult for the liver to function.

Objective of the Study: review and evaluate the best practices in diagnosis, complications and management of cirrhosis, and novel clinical and scientific developments.

Methods: electronic search in the scientific database from 1966 to 2017– (Medline, Embase, the Cochrane Library as well as NHS center websites were searched for English Publications obtained from both reprint requests and by searching the database. Data extracted included authors, country, year of publication, age and sex of patients, epidemiology, geographical distribution, pathophysiology, risk factors, clinical manifestations, investigations and types of surgical treatment.

Results: there is sufficient body of evidence suggesting that cirrhosis is a pathological diagnosis with no laboratory cutoff values for the diagnosis of cirrhosis.

However, it can still be diagnosed clinically, by history, physical examination laboratory analyses and ancillary testing such as ultrasonography. Early diagnosis has proven to give relevantly better case management results while late detection can only hardly manage the symptoms accompanied with cirrhosis.

Conclusion: Screening for chronic liver disease is a key factor for early detection of signs for liver damage, which can be performed inexpensively and easily with clinical history-taking, measurement of transaminase concentrations, upper abdominal ultrasonography, and transient elastography (where available). Abnormal findings should prompt specific diagnostic testing to determine the etiology of the underlying disease. In most patients, the dynamic process of progressive fibrosis, which could ultimately lead to cirrhosis, can be interrupted by the timely recognition of the risk, followed by appropriate treatment.

Keywords: cirrhosis, progressive liver disease, ascites, chronic disease.

INTRODUCTION

Cirrhosis results from different mechanisms of liver injury that lead to necroinflammation and fibrogenesis; histologically it is characterized by diffuse nodular regeneration surrounded by dense fibrotic septa with subsequent parenchymal extinction and collapse of liver structures, together causing pronounced distortion of hepatic vascular architecture [(1)]. This distortion results in increased resistance to portal blood flow and hence in portal hypertension and in hepatic synthetic dysfunction. Clinically, cirrhosis has been regarded as an end-stage disease that invariably leads to death, unless liver transplantation is done, and the only preventive strategies have been screening for esophageal varices and hepatocellular carcinoma.

One-year mortality in cirrhosis varies widely, from 1% to 57%, depending on the occurrence of clinical decompensating events [(2)]. Histopathologists have proposed that the histological term cirrhosis should be substituted by advanced liver disease, to underline the dynamic processes and variable prognosis of the disorder [(3)]. Moreover, fibrosis, even in the cirrhotic range, regresses with specific therapy if available, such as antiviral treatment for chronic hepatitis B or C [(4)].

Cirrhosis isn't curable, but it’s treatable. Doctors have two main goals in treating this disease: stop the damage to your liver, and prevent complications. Alcohol abuse, hepatitis, and fatty liver disease are some of the main causes. Your doctor will

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personalize your treatment based on what caused your cirrhosis, and the amount of liver damage you have [5]. Cirrhosis can lead to a number of complications, including liver cancer. In some people, the symptoms of cirrhosis may be the first signs of liver disease.

In the present article, we review the current understanding of cirrhosis as a dynamic process and outline current therapeutic options for prevention and treatment of complications of cirrhosis, on the basis of the sub-classification in clinical prognostic stages.

The study was done according to the ethical board of King Faisal university.

STAGING OF CIRRHOSIS

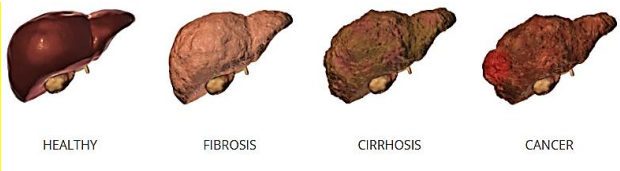

Figure 1: Stages of chronic liver diseases leading to live damage [6].

By combining data from two large natural history studies including 1649 patients [7] ,four clinical stages or status of cirrhosis can be identified, each with distinct clinical features and a markedly different prognosis. Each stage is defined by the presence or absence of complications of cirrhosis and was agreed upon in the recent Baveno IV consensus conference [8].

- Stage 1 is characterized by the absence of esophageal varices and of ascites. While patients remain in this status, the mortality rate is as low as 1% per year. Patients exit this status at a cumulative rate of 11.4% per year: 7% because of the development of varices and 4.4% because of the development of ascites (with or without varices).
- Stage 2 is characterized by the presence of esophageal varices without ascites and without bleeding. While patients remain in this status, the mortality rate is 3.4% per year. Patients leave this status by developing ascites (6.6% per year) or by developing variceal bleeding before or at the time of development of ascites (rate 4% per year).
- Stage 3 is characterized by ascites with or without esophageal varices in a patient that has never bled. While patients remain in this status, the mortality rate is 20% per year, significantly higher than in the two former states. Patients exit this stage by bleeding (7.6% per year).
- Stage 4 is characterized by GI bleeding with or without ascites. In this stage the one-year mortality rate is 57% (nearly half of these deaths occur within 6 weeks from the initial episode of bleeding).

Stages 1 and 2 correspond to patients with compensated cirrhosis while stages 3 and 4 refer to decompensated cirrhosis. HCC develops at a fairly constant rate of 3% per year and is associated with a worse outcome at whatever status it develop.

Prognostic models and staging systems are inevitable for adequate management of patients with liver cirrhosis, especially when it comes to selecting patients for liver transplantation [9]. Several classifications and prognostic models have been proposed in recent years of which the three most widely used staging systems are subsequently described briefly.

The Child-Pugh score was initially developed about 50 years ago to predict the prognosis after surgery for portal hypertension (portocaval shunting, transection of esophagus) in patients with liver cirrhosis[10]. The original score was slightly modified later on and since then includes the following five variables: grade of encephalopathy and ascites as well as serum bilirubin, albumin and prothrombin time (**table 1**) [11]. Sometimes prothrombin index or international normalized ratio (INR) are used instead of prothrombin time [9]. One to three points can be assigned for each variable and according to the sum of these points patients can be divided into three prognostic subgroups: Child-Pugh classes A (5–6 points), B (7–9 points), and C (10–15 points) [9,11]. The 1-year survival rate for the stages A, B and C is approximately 95%, 80% and 44%, respectively (**table 1**) [12]

Table 1: Child-Pugh score[12]

Variables			
Encephalopathy	None	Stage I–II	Stage III–IV
Ascites	Absent	Controlled	Refractory
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/L)	>35	28–35	<28
Prothrombin time (seconds)	<4	4–6	>6
Sum of points	5–6	7–9	10–15
Stage	A	B	C
1-year survival rate (%)	95	80	44

METHODS

Electronic search in the scientific database from 1960 to 2017.

Data source: Medline, Embase, the Cochrane Library as well as NHS centre websites were searched for English Publications were obtained from both reprint requests and by searching the database.

Data extracted included authors, country, year of publication, age and sex of patients, epidemiology, geographical distribution, pathophysiology, risk factors, clinical manifestations, investigations and types of treatment.

ETIOLOGY OF CIRRHOSIS

Alcoholic liver disease and hepatitis C are the most common causes in the Western world, while hepatitis B prevails in most parts of Asia and sub-Saharan Africa. After the identification of the hepatitis C virus in 1989 and of nonalcoholic steatohepatitis (NASH) in obese and diabetic subjects, the diagnosis of cirrhosis without an apparent cause (cryptogenic cirrhosis) is rarely made.

Many cases of cryptogenic cirrhosis appear to have resulted from nonalcoholic fatty liver disease (NAFLD). When cases of cryptogenic cirrhosis are reviewed, many patients have 1 or more of the classic risk factors for NAFLD: obesity, diabetes, and hypertriglyceridemia[13]. It is postulated that steatosis may regress in some patients as hepatic fibrosis progresses, making the histologic diagnosis of NAFLD difficult. Flavonoids have been reported to have positive effects on key pathophysiologic pathways in NAFLD (eg, lipid metabolism, insulin resistance, inflammation, oxidative stress) and may hold future potential for inclusion in NAFLD treatment [13].

It is important to know the etiology of cirrhosis, since it can predict complications and direct treatment decisions. It also allows the discussion of preventive measures, e.g., with family members of patients with alcoholic cirrhosis or chronic viral hepatitis, and consideration of (genetic) testing and preventive advice for relatives of patients with genetic diseases, such as hemochromatosis or Wilson's disease. Frequently multiple etiological factors contribute to the development of cirrhosis, as exemplified in epidemiological studies that identified regular (moderate) alcohol consumption, age above 50 years, and male gender as risk factors in chronic hepatitis C [14], or older age obesity, insulin resistance/type 2 diabetes, hypertension and hyperlipidemia (all features of the metabolic syndrome) in NASH

Table 2: Clinical features of cirrhosis

Author	Year of study	FINDINGS	Interpretation	ETIOLOGY
Epstein *et al.* [15]	1979	Hypertrophic osteoarthropathy/Finger clubbing	Painful proliferative osteoarthropathy of long bones	Hypoxemia due to right-to-left shunting, porto-pulmonary hypertension
Cattau *et al.* [16]	1982	Ascites	Proteinaceous fluid in abdominal cavity, clinically detected when ≥1.5 L	Portal hypertension
Van Thiel *et al.* [17]	1985	Gynecomastia, loss of male hair pattern	Benign proliferation of glandular male breast tissue	Enhanced conversion of androstenedione to estrone and estradiol, decreased estradiol degradation in liver
Attali *et al.* [18]	1987	Dupuytren's contracture	Fibrosis and contraction of the palmar fascia	Enhanced oxidative stress, elevated hypoxanthine (alcohol exposure or diabetes)
Pirovino *et al.* [19]	1988	Spider angiomata	Central arteriole with tiny radiating vessels, mainly on trunk and face	Elevated estradiol, decreased estradiol degradation in liver

Erlinger *et al.* [20]	1991	Cruveilhier Baumgarten syndrome	Epigastric vascular murmur	Shunts from portal vein to umbilical vein branches, can be present without Caput medusae
Tangerman *et al.* [21]	1994	Foetor hepaticus	Sweet, pungent smell	Volatile dimethylsulfide, especially in portosystemic shunting and liver failure
Bircher *et al.* [22]	1999	Jaundice	Yellow discoloration of skin, cornea and mucous membranes	Compromised hepatocyte excretory function, occurs when serum bilirubin >2mg/dl
		Hypogonadism	Mainly in alcoholic cirrhosis and hemochromatosis	Direct toxic effect of alcohol or iron
		Flapping tremor (asterixis)	Asynchronous flapping motions of dorsiflexed hands	Hepatic encephalopathy, disinhibition of motor neurons
Sherlock *et al.* [23]	2002	Caput medusae	Prominent veins radiating from umbilicus	Portal hypertension, reopening of the umbilical vein that shunts blood from the portal vein
		Nodular liver	Irregular, hard surface on palpation	Fibrosis, irregular regeneration
		Splenomegaly	Enlarged on palpation or in ultrasound	Portal hypertension, splenic congestion
Schiff ER *et al.* [24]	2003	Palmar erythema	Erythema sparing the central portion of the palm	Elevated estradiol, decreased estradiol degradation in liver
		Anorexia, fatigue, weight loss, muscle wasting	Occurs in >50% of cirrhotic	Catabolic metabolism by diseased liver, secondary to anorexia
		Type 2 diabetes	Occurs in 15-30% of cirrhotic	Disturbed glucose utilization and/or decreased insulin removal by the liver

DIAGNOSIS OF CIRRHOSIS

I. NONINVASIVE DIAGNOSIS OF CIRRHOSIS

A number of laboratory and ultrasound-based methods have been developed recently for the noninvasive diagnostic evaluation of cirrhosis.

These noninvasive methods often obviate the need for liver biopsy when the only question to be answered is the stage of fibrosis; nonetheless, the information they provide must always be considered in the light of the accompanying clinical findings [25].

1. Laboratory tests

Laboratory-based methods for estimating the extent of hepatic fibrosis can be divided into those based on routine liver function tests[26] and those based on particular laboratory values that are associated with fibrosis, such as the hyaluronic acid concentration [27] . The AST-to-platelet ratio index (APRI) is easily calculated as the quotient of the AST (GOT) and the platelet count and serves as a screening index for advanced fibrosis and cirrhosis[28].

Techniques for the measurement of liver stiffness and laboratory indices of hepatic fibrosis enable longitudinal assessment of the

progression and regression of fibrosis in patients with chronic liver disease.

ULTRASONOGRAPHY

Abdominal ultrasonography with Doppler is a noninvasive, widely available modality that provides valuable information regarding the gross appearance of the liver and blood flow in the portal and hepatic veins in patients suspected to have cirrhosis. Ultrasonography should be the first radiographic study performed in the evaluation of cirrhosis because it is the least expensive and does not pose a radiation exposure risk or involve intravenous contrast with the potential for nephrotoxicity as does computed tomography (CT). Nodularity, irregularity, increased echogenicity, and atrophy are ultrasonographic hallmarks of cirrhosis. In advanced disease, the gross liver appears small and multinodular, ascites may be detected, and Doppler flow can be significantly decreased in the portal circulation. The discovery of hepatic nodules via ultrasonography warrants further evaluation because benign and malignant nodules can have similar ultrasonographic appearances [(29)]. A study using high-resolution ultrasonography in patients with cirrhosis confirmed with biopsy or laparoscopy found a sensitivity and specificity for cirrhosis of 91.1 and 93.5 percent, respectively, and positive and negative predictive values of 93.2 and 91.5 percent, respectively [(30)].

The diagnostic evaluation of cirrhosis with ultrasonography is based on the direct relation between the extent of fibrosis and the ultrasonographically determined degree of liver stiffness. Transient elastography and the acoustic radiation force impulse (ARFI) technique are now well-established methods for the staging of fibrosis in various liver diseases[(31)]. These two techniques can be performed repeatedly on an outpatient basis, and they can also be combined[(25)].

Although ultrasonography can rule cirrhosis in or out in over 90% of cases[(31)], its findings are less than 100% specific because of occasional incorrect measurements and false-positive findings. There may be difficulty in interpreting values that do not cross the necessary thresholds for ruling advanced fibrosis, or cirrhosis, in or out; in such situations, the temporal course of the variable in question is its clinically relevant feature. It should also be borne in mind that the diagnostic threshold values vary depending on the underlying etiology of liver disease [(32)].

II. INVASIVE DIAGNOSIS OF CIRRHOSIS

1. CT AND MRI

CT and magnetic resonance imaging (MRI) generally are poor at detecting morphologic changes associated with early cirrhosis, but they can accurately demonstrate nodularity and lobar atrophic and hypertrophic changes, as well as ascites and varices in advanced disease. Although MRI sometimes differentiates among regenerating or dysplastic nodules and hepatocellular carcinoma, it is best used as a follow-up study to determine whether lesions have changed in appearance and size [(33)]. CT portal phase imaging can be used to assess portal vein patency, although flow volume and direction cannot be determined accurately [(34)].

Although used rarely, magnetic resonance angiography (MRA) can assess portal hypertensive changes including flow volume and direction, as well as portal vein thrombosis [(34)]. One study reported that MRI can accurately diagnose cirrhosis and provide correlation with its severity. Despite the potential of MRI and MRA in the diagnosis and evaluation of patients with cirrhosis, their widespread use is limited by their expense and by the ability of routine ultrasonography with Doppler to obtain adequate information for the diagnosis of cirrhosis and presence of complications.

2. Liver biopsy

Referral for liver biopsy should be considered after a thorough, noninvasive serologic and radiographic evaluation has failed to confirm a diagnosis of cirrhosis; the benefit of biopsy outweighs the risk; and it is postulated that biopsy will have a favorable impact on the treatment of chronic liver disease. The sensitivity and specificity for an accurate diagnosis of cirrhosis and its etiology range from 80 to 100 percent, depending on the number and size of the histologic samples and on the sampling method [(35)].

Liver biopsy is performed via percutaneous, transjugular, laparoscopic, open operative, or ultrasonography- or CT-guided fine-needle approaches. Before the procedure, a CBC with

platelets and prothrombin time measurement should be obtained. Patients should be advised to refrain from consumption of aspirin and nonsteroidal anti-inflammatory drugs for seven to 10 days before the biopsy to minimize the risk of bleeding [35].

General physical and laboratory signs that are frequently found in cirrhosis are summarized in **table** 3[36]

Table 3: Laboratory findings in cirrhosis [36]

Screening measures	Step 1: General laboratory testing	Step 2: Specific laboratory testing	Step 3: Molecular and invasive studies
History (identification of risk constellations)	ALT, AST, GGT, AP, bilirubin	Hepatitis serology (HBsAg, anti-HCV)	Ceruloplasmin, copper in 24-hour urine sample, genetic testing for Wilson disease
I. Physical examination	Complete blood count, platelet count, routine coagulation studies	Autoantibody testing (ANA, SMA, LKM, SLA, p-ANCA, AMA)	HFE mutation
Serum ALT and GGT	Total protein, albumin, serum electrophoresis	Quantitative immunoglobulins (IgA, IgG, IgM)	A1-antitrypsin genotype (PIZZ)
Ultrasonography	Cholesterol, triglycerides, glucose	Ferritin, transferrin saturation, iron	Liver biopsy, MRCP, ERC (for suspected PSC)

CIRRHOSIS TREATMENT

A. Pharmacologic treatment

Specific medical therapies may be applied to many liver diseases in order to alleviate symptoms and primarily to avoid or delay the development of cirrhosis. Examples include prednisone and azathioprine for autoimmune hepatitis, interferon and other antiviral agents for hepatitis B and C [37], phlebotomy for hemochromatosis, ursodeoxycholic acid for primary biliary cirrhosis, and trientine and zinc for Wilson disease.

These therapies become progressively less effective if chronic liver disease evolves into cirrhosis. Once cirrhosis develops, treatment is aimed at the management of complications as they arise. Certainly, variceal bleeding, ascites, and hepatic encephalopathy are among the most serious complications experienced by patients with cirrhosis. However, attention also must be paid to patients' chronic constitutional complaints.

With reference to an analysis of data from the TURQUOISE-II study, presented in October 2014 at the Annual Scientific Meeting of the American College of Gastroenterology (ACG), treatment with the combination of the protease inhibitor ABT-450 boosted with ritonavir, the NS5A inhibitor ombitasvir, and the non-nucleoside polymerase inhibitor dasabuvir plus ribavirin (3D + RBV) improved measures of liver function at 12 weeks in hepatitis C patients with cirrhosis [38].

Highly significant improvements from baseline were seen at 12 weeks for the liver enzymes alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase[38]. Among patients with elevated transaminase levels at baseline, levels normalized after 12 weeks in 70-90% of cases. Highly significant improvements were also observed in conjugated bilirubin and albumin levels and in prothrombin time at 12 weeks.

ASCITES

1. Treatment of uncomplicated ascites[39]

- The following interventions are recommended based on controlled and uncontrolled studies as well as expert opinion:
- salt restriction
- transparent image
- Spironolactone plus furosemide
- transparent image

- large-volume paracentesis plus albumin in hospitalized patients with tense ascites in whom other complications have been resolved
- transparent image
- short-term (7-day) antibiotic prophylaxis in cirrhotic patients with (or without) ascites admitted with GI hemorrhage
- transparent image
- the following interventions are not recommended, based on clinical trials demonstrating that other measures are either more effective or safe:
- Furosemide alone
- transparent image
- long-term antibiotic prophylaxis

2. Treatment of refractory ascites[39]

The following interventions are recommended based on randomized controlled studies:

- LVP plus albumin, associated with salt restriction and diuretics
- transparent image

In patients in whom <5 L is extracted, a synthetic plasma volume expander may be used instead of albumin or plasma volume expansion may not be necessary

- transparent image
- in patients requiring frequent LVP, TIPS is an option
- transparent image

As for patients with the need for frequent LVP, who are not TIPS or transplant candidates, PVS is an option

- transparent image
- the following intervention is not recommended based on controlled clinical trials demonstrating that other interventions are either more effective or safer:
- PVS or TIPS a s first-line therapy

HEPATIC ENCEPHALOTHERAPY[40]

Recommendation based on clinical trials and expert opinion:

- identification and treatment of precipitating event transparent image
- short-term protein restriction
- transparent image
- Lactulose by mouth or through nasogastric tube, adjusted to two to three bowel movements/day
- transparent image
- Lactulose enemas in patients who are unable to take it by mouth
- transparent image

For patients with chronic HE who cannot tolerate lactulose or do not respond to lactulose, treatment with laxatives plus neomycin can be considered

- transparent image

The following intervention is not recommended based on expert opinion:

- Long-term protein restriction
- transparent image

The following interventions are under evaluation and cannot be recommended until additional information is available:

- Flumazenil, ornithine aspartate, bromocriptine

Table 4. Treatment of hepatic Encephalotherapy [40]

Treatment Type	Recommendations	Comment
General Measures	**Identification and treatment of the precipitating cause(s)** **Avoidance of sedatives and tranquilizers** **Nutritional support**	• Protein from dairy or vegetable sources are preferable to animal protein
Acute Hepatic Encephalopathy	**Recommended therapy** Lactulose 45 cc PO every hour until bowel evacuation then adjust to a dose that will result in two to three bowel movements/day (usually 15-30 cc PO BID) **Alternative therapy** Neomycin 3-6 g PO every day in three doses plus milk of magnesia Metronidazole starting at 250 mg PO BID	Lactulose enemas (300 cc in 1 liter of water) in patients who are unable to take it by mouth. Short-term (<72 hours) protein restriction may be considered in severe HE
Chronic Hepatic Encephalopathy	**Recommended therapy** Lactulose dosage that produces two to three bowel movements/day, starting at 15-30 cc PO BID **Alternative therapy** Neomycin starting at 1-3 g PO QD (three divided doses) Metronidazole starting at 250 mg PO BID **Not recommended** Long-term protein restriction **Helicobacter pylori**eradication	• Patients on chronic antibiotics need to be monitored for nephrotoxicity, ototoxicity, and neurotoxicity • Protein from dairy or vegetable sources may be preferable to animal protein

PRURITUS [41]

Pruritus is a common complaint in cholestatic liver diseases (eg, primary biliary cirrhosis) and in noncholestatic chronic liver diseases (eg, hepatitis C). Although increased serum bile acid levels once were thought to be the cause of pruritus, endogenous opioids are more likely to be the culprit pruritogen. Mild itching complaints may respond to treatment with antihistamines and topical ammonium lactate.

Cholestyramine is the mainstay of therapy for the pruritus of liver disease. To avoid compromising GI absorption, care should be taken to avoid co-administration of this organic anion binder with any other medication.

Other medications that may provide relief against pruritus in addition to antihistamines (eg, diphenhydramine, hydroxyzine) and ammonium lactate 12% skin cream (Lac-Hydrin), include ursodeoxycholic acid, doxepin, and rifampin. Naltrexone may be effective but is often poorly tolerated. Gabapentin is an unreliable therapy. Patients with severe pruritus may require institution of ultraviolet light therapy or plasmapheresis.

HYPOGONADISM[41]

Some male patients suffer from hypogonadism. Patients with severe symptoms may undergo therapy with topical testosterone preparations, although their safety and efficacy is not well studied. Similarly, the utility and safety of growth hormone therapy remains unclear.

OSTEOPOROSIS[41]

Patients with cirrhosis may develop osteoporosis. Supplementation with calcium and vitamin D is important in patients at high risk for osteoporosis, especially patients with chronic cholestasis or primary biliary cirrhosis and patients receiving corticosteroids for autoimmune hepatitis. The discovery on bone densitometry studies of decreased bone mineralization may prompt the institution of therapy with an aminobisphosphonate (eg, alendronate sodium).

Zinc deficiency[41]

Zinc deficiency commonly is observed in patients with cirrhosis. Treatment with zinc sulfate at 220 mg orally twice daily may improve dysgeusia and can stimulate appetite. Furthermore, zinc is effective in the treatment of muscle cramps and is adjunctive therapy for hepatic encephalopathy.

Analgesics[42]

The choice of appropriate analgesic agents in patients with cirrhosis requires a thorough knowledge of their pharmacokinetics and side effect profiles.

Acetaminophen is an effective and safe analgesic for patients with chronic liver disease when used at low doses. For patients with ongoing alcohol ingestion and cirrhosis, acetaminophen may be used at a maximum of 2 grams per day, which is one-half of the recommended daily dose. Although some studies show 4 grams of acetaminophen per day to be safe in patients with cirrhosis who are not actively consuming alcohol, the authors recommend no more than 2 grams per day to stay well below toxicity levels. [42]

Many prescription and over the counter remedies are offered as combination preparations. Patients with cirrhosis need to be warned to read medication labels carefully before starting any new medicine to avoid accidental overdose.

NSAIDs are associated with an increased risk of variceal hemorrhage, impaired renal function, and the development of diuretic resistant ascites. Thus, NSAIDs (including aspirin) should generally be avoided in patients with cirrhosis.

Selective COX-2 inhibitors are effective analgesics, which are associated with a decreased incidence of gastrointestinal and renal toxicity and an increased incidence of cardiovascular events. Experience in patients with cirrhosis is limited. At present, we advise against using these agents. [42]

Opioids should be used cautiously in patients with cirrhosis. Fentanyl appears to be safe in patients with modest hepatic dysfunction. Morphine, oxycodone, and hydromorphone should be used at reduced doses and prolonged intervals of administration. Tramadol may be safe but experience is limited. The effects of codeine are difficult to predict and therefore alternatives should be considered.

Strong consideration should be given to referring patients who require long-term analgesics to a pain management program[42]

Table 5: Treatment of complications of cirrhosis

Author	IMPLICATION	TREATMENT	DOSAGE
Runyon [43]	Ascites	Sodium restriction	Maximum 2,000 mg per day3
		Spironolactone (Aldactone)	Start 100 mg orally per day; maximum 400 mg orally per day3
		Furosemide (Lasix)	Start 40 mg orally per day; maximum 160 mg orally per day3
		Albumin	8 to 10 g IV per liter of fluid (if greater than 5 L) removed for paracenteses3
		Fluid restriction	Recommended if serum sodium is less than 120 to 125 mEq per L (120 to 125 mmol per L)3
	Spontaneous bacterial peritonitis*†	Cefotaxime (Claforan)	2 g IV every eight hours3
		Albumin	1.5 g per kg IV within six hours of detection and 1 g per kg IV on day 33
		Norfloxacin (Noroxin)†	400 mg orally two times per day for treatment3
			400 mg orally two times per day for seven days with gastrointestinal hemorrhage3
			400 mg orally per day for prophylaxis3
		Trimethoprim/sulfamethoxazole	1 single-strength tablet orally per day for prophylaxis3
		(Bactrim, Septra)†	1 single-strength tablet orally two times per day for seven days with gastrointestinal hemorrhage3
Fitz [44]	Hepatic encephalopathy	Lactulose	30 to 45 mL syrup orally titrated up to three or four times per day or 300 mL retention enema until two to four bowel movements per day and mental status improvement7
Strauss E *et al.* [45]		Neomycin	4 to 12 g orally per day divided every six to eight hours; can be added to lactulose in patients who are refractory to lactulose alone[7,8]
Jalan and Hayes [46]	Portal hypertension and variceal bleeding	Propranolol (Inderal)	40 to 80 mg orally two times per day9
		Isosorbide mononitrate (Ismo)	20 mg orally two times per day9
Angeli P *et al.* [47]	Hepatorenal syndrome	Midodrine (ProAmatine) and octreotide (Sandostatin)	Dosed orally (midodrine) and IV (octreotide) to obtain a stable increase of at least 15 mm Hg mean arterial pressure10
		Dopamine	2 to 4 mcg per kg per minute IV (nonpressor dosing to produce renal vasodilatation)10

CONCLUSION

Screening for chronic liver disease is a key factor for early detection of signs for liver damage, which can be performed inexpensively and easily with clinical history-taking, measurement of transaminase concentrations, upper abdominal ultrasonography, and transient elastography (where available). Abnormal findings should prompt specific diagnostic testing to determine the etiology of the underlying disease. In most patients, the dynamic process of progressive fibrosis, which could ultimately lead to cirrhosis, can be interrupted by the timely recognition of the risk, followed by appropriate treatment.

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