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EDITORIAL

Management of liver cirrhosis between primary care and specialists

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Abstract

This article discusses a practical, evidence-based approach to the diagnosis and management of liver cirrhosis by focusing on etiology, severity, presence of complications, and potential home-managed treatments. Relevant literature from 1985 to 2010 (PubMed) was reviewed. The search criteria were peer-reviewed full papers published in English using the following MESH headings alone or in combination: "ascites", "liver fibrosis", "cirrhosis", "chronic hepatitis", "chronic liver disease", "decompensated cirrhosis", "hepatic encephalopathy", "hypertransaminasemia", "liver transplantation" and "portal hypertension". Forty-nine papers were selected based on the highest quality of evidence for each section and type (original, randomized controlled trial, guideline, and review article), with respect to specialist setting (Gastroenterology, Hepatology, and Internal Medicine) and primary care. Liver cirrhosis from any cause represents an emerging health issue due to the increasing prevalence of the disease and its complications worldwide. Primary care physicians play a key role in early identification of risk factors, in the management of patients for improving quality and length of life, and for preventing complications. Specialists, by contrast, should guide specific treatments, especially in the case of complications and for selecting patient candidates for liver transplantation. An integrated approach between specialists and primary care physicians is essential for providing better outcomes and appropriate home care for patients with liver cirrhosis.

Key words: Ascites; Family medicine; Hepatic encephalopathy; Hypertransaminasemia; Portal hypertension

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INTRODUCTION

Liver cirrhosis is defined in histology as a bridging fibrosis-a late stage of hepatic fibrosis-leading to deranged liver architecture and regenerative nodules. Liver cirrhosis is considered the end stage of a variety of chronic liver diseases, and is irreversible in its advanced stages[1]. Cirrhosis is characterized by poor life expectancy and is a leading cause of morbidity and mortality: in the United States liver cirrhosis is the 12th most common cause of death (9.5/100 000 individuals), while in Italy the incidence of liver cirrhosis is over 26 000 new cases each year, with a prevalence over 120 000 cases (7000 below 45 years), and 20 deaths/100 000 individuals[2,3]. Figures are likely to be even higher in Asia and Africa. Liver cirrhosis carries the

risk of life-threatening complications, partly due to a number of co-morbidities. Medical treatments that may halt the progression of compensated cirrhosis to decompensated cirrhosis are currently being developed[1]. Liver transplantation, however, is the only option in a selected subgroup of patients with end-stage disease. Because of the increasing prevalence of chronic viral hepatitis and (alcoholic-nonalcoholic) steatohepatitis and their high risk evolution toward liver cirrhosis and end-stage liver disease, preventive programs and early management of these conditions are considered an emerging health issue. It is essential that primary care physicians (PCPs) be optimally trained to identify patients with chronic liver disease as early as possible, and to properly manage those with liver cirrhosis[4]. A close interaction is therefore required between PCPs and specialists (i.e. gastroenterologists, hepatologists, and internists) who have a fundamental role as consultants and guides for specific treatments, i.e. in the case of complications and the management of patients approaching liver transplantation.

This article is based on a PubMed search to provide an updated view for comprehensive management of several aspects of liver cirrhosis in different settings.

DATA SOURCES

Full papers were searched on Medline (http://www.ncbi.nlm.nih.gov/PubMed) for guidelines, randomized controlled trials (RCTs), and authored review articles published in English-language journals in the past 25 years. The following MESH headings were used: "ascites", "liver fibrosis", "cirrhosis", "chronic hepatitis", "chronic liver disease", "decompensated cirrhosis", "hepatic encephalopathy", "hypertransaminasemia", "liver transplantation", and "portal hypertension". The reference list was updated as of November 2010. Authors independently assessed articles for relevance and study quality. For each section, evidence levels were scored as follows: (1) LEVEL I (at least one properly conducted RCT, systematic review, or meta-analysis); (2) LEVEL Ⅱ (other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study); and (3) LEVEL Ⅲ (expert opinion or consensus statements).

APPROACH TO PATIENTS WITH LIVER CIRRHOSIS

The clinical presentation of liver cirrhosis is often asymptomatic until complications appear. The presence of liver cirrhosis should be suspected in any patient with chronic liver disease and abnormal aminotransferases and/or alkaline phosphatase. Chronic liver disease stigmata should be searched for, and include vascular spiders, palmar erythema, and muscle wasting. Also, a palpable left lobe of the liver, hepatomegaly and splenomegaly are suggestive for liver cirrhosis. The diagnosis becomes much easier in the presence of signs of decompensation, namely jaundice, ascites, and asterixis. Additional laboratory tests include those exploring liver synthetic function, such as serum albumin and prothrombin time, while serum bilirubin investigates the ability of the liver to conjugate and excrete bilirubin. A low platelet count is suggestive of portal hypertension and hypersplenism. An AST/ALT ratio above 1 is indicative of liver cirrhosis, but its absence does not exclude cirrhosis (i.e. low specificity). The imaging studies include abdominal ultrasound, CT scan or magnetic resonance and might reveal a nodular liver and splenomegaly. The differential diagnosis of advanced chronic hepatitis relies on liver biopsy, which is still the gold standard for end-stage chronic liver disease. Percutaneous liver biopsy is not necessary in the presence of decompensated cirrhosis or when imaging studies have confirmed the presence of cirrhosis. Thus, liver biopsy is reserved for selected patients and can also be performed in out clinic settings[5,6]. Histology provides information on etiology, disease stage and grade of inflammation. Although the ultimate decision is not currently taken by PCPs, they should repeatedly check the patient with blood tests before referral for liver biopsy (at least two times and at least 2-3 mo apart). If abnormalities persist in spite of second step analyses and a liver ultrasonography has been inconclusive, the decision to perform a liver biopsy must be taken on an individual basis and rely on the patient's age and general health status, as well as the need for prognostic information (LEVEL Ⅲ)[7]. According to the American Association for the Study of Liver Disease (AASLD), liver biopsy has a major role in diagnosis, assessment of prognosis, assistance in therapeutic decisions, and reinforcement of the patient's compliance (LEVEL Ⅱ)[5]. Biopsy, however, is a costly procedure which is not free of potential side effects and risks, and is often refused by the patient. A French survey, which interviewed over one thousand PCPs, concluded that liver biopsy may be refused by up to 59% of patients with chronic hepatitis C and that 22% of PCPs share a similar concern[8].

Novel non-invasive methods might provide preliminary information with good diagnostic accuracy for further selection of patients at risk for progressive liver disease. For example, tests might help to evaluate the presence and extent of liver fibrosis, and to differentiate cirrhosis from chronic hepatitis (positive predictive values exceed 85%-90%)[9]. Such policy may be helpful in the primary care setting. Transient elastography (FibroScan®), for example, assesses liver stiffness, with some limitations in the case of morbid obesity, small intercostals spaces, and ascites[10]. Ongoing liver fibrosis is also predicted by using specific algorithms of surrogate serum markers or by the application of standardized procedures (e.g. APRI: the aspartate transaminase to platelets ratio index; FibroTest: haptoglobin, α2-macroglobulin, apolipoprotein A1, γGT, bilirubin: Hepascore: bilirubin, γGT, hyaluronic acid, α2-macroglobulin, age, gender; BARD: Body mass index (BMI), AST/ALT ratio, diabetes). A novel technique based upon ultrasound-based elastography (Fibroscan, Echosens, Paris, France) can assess mean hepatic tissue stiffness[11]. Results are expressed in kilopascals (kPa) and

Table 1 Diagnostic tests, suggested etiology, and current treatment for the most frequent forms of liver cirrhosis in adult patients

Abnormal test(s)	Etiology	Treatment
γGT (high), MCV (high)	Alcohol	Abstinence
HBsAg, HBV-DNA, HBc-IgM, HDV-RNA (positivity)	HBV + Delta virus infection	Interferon α-2b, nucleoside (Lamivudine, Telbivudine, Entecavir) and nucleotide (Adefovir, Tenofovir) analogues
HCV-RNA (positivity)	HCV infection	Interferon plus ribavirin
γGT (high), alkaline phosphatase (high), AMA (positivity)	Primary biliary cirrhosis	Ursodeoxycholate
ANA, ASMA, LKM (positivity)	Autoimmune hepatitis	Prednisone, azathioprine
Ferritin (high), transferring saturation index (> 45%), liver iron content (high), *HFE* gene mutation for hereditary hemochromatosis (C282Y, H63D)	Hemochromatosis	Phlebotomy, deferoxamine
Ceruloplasmin (low), serum (low) and 24 h urine copper excretion (high)	Wilson's disease	D-penicillamine, zinc
HDL-cholesterol (low), glucose (high), triglycerides (high)	NAFLD/NASH	Low caloric diet, exercise, drugs lowering insulin-resistance

AMA: Anti-mitochondrial antibody; ANA: Antinuclear antibody; ASMA: Anti-smooth-muscle antibody; γGT: γ- glutamyltransferase; HBV-DNA: Hepatitis B virus DNA; HCV-RNA: Hepatitis C virus RNA; HBsAg: Hepatitis B surface antigen; HDL: High density lipoprotein; HDV-RNA: Hepatitis delta virus RNA; LKM: Liver kidney microsomes; MCV: Mean corpuscular volume; NASH: Nonalcoholic steatohepatitis; NAFLD: Nonalcoholic fatty liver disease.

the harder or stiffer the tissue, the faster a shear wave propagates, as a marker of hepatic fibrosis. Similar results have been reported with magnetic resonance elastography (MRE)[12]. Likely, the combination of elastography with one of these indices will also help specialists to better select patients suitable for liver biopsy[9,10].

Life expectancy and quality of life in patients with advanced cirrhosis remains poor, despite diagnostic advancement. Patients experience fatigue, pruritus, ascites, bleeding and encephalopathy. Dyspepsia and malnutrition are common. Whereas liver transplantation has changed life expectation for a number of patients, many transplantable patients still die due to long waiting lists. Targeted therapy is crucial in slowing or even halting disease progression and to provide standard medical care. PCPs should identify and address alcohol abusers early, while conditions like nonalcoholic steatohepatitis (NASH), B and C hepatitis, autoimmune disorders, and hemochromatosis should be appropriately counseled and treated. Attention should be given to active immunization, nutrition, and general healthcare.

MANAGEMENT OF PERSISTENT ASYMPTOMATIC ELEVATION OF SERUM TRANSAMINASES

Measurement of serum ALT is part of standard laboratory tests in asymptomatic outpatients, and is a sensitive screening tool for chronic liver disease[13]. Between one and four percent of asymptomatic subjects may have elevated ALT (LEVEL Ⅲ)[7,14,15]. In a recent survey in the Mediterranean area, the most likely cause of elevated serum ALT was an excessive alcohol intake (45.6%), nonalcoholic fatty liver disease (NAFLD) (24%), and HCV infection (18.6%)[14].

Over 20% of subjects with elevated ALT show signs suggestive of relevant chronic liver disease[2]. PCPs are required to carefully investigate most common causes of elevated ALT and for early identification of treatable chronic liver diseases[16,17]. Patient histories should focus on the use of medications, herbal extracts, and alcohol consumption. The presence of diabetes and thyroid disease (hypothyroidism) must be considered. The problem, however, may be underestimated as about 38% of patients with occasional ALT elevation show normal values at next measurement[16]. Despite the very high number of subjects showing such liver test abnormality in family practice, only a few will need referral, i.e. those patients with doubtful diagnosis after initial evaluation and patients with established diagnosis requiring therapy (LEVEL Ⅲ)[18].

THE IMPORTANCE OF IDENTIFYING ETIOLOGY

The identification of the cause underlying liver cirrhosis is essential in starting preventive measures and designing specific intervention (LEVEL Ⅰ). Table 1 shows the most appropriate tests for etiologic diagnosis of cirrhosis. Anti-mitochondrial antibodies are specific for primary biliary cirrhosis, HBV-DNA or HCV-RNA positivity for hepatitis B or C, low serum ceruloplasmin levels for Wilson's disease, and high serum ferritin and transferrin saturation index for hereditary hemochromatosis. Of note, liver cirrhosis may result from coexisting etiologic factors (i.e. alcohol and viral infection, obesity and virus, *etc*.).

HOW TO SCORE AND DEFINE PROGNOSIS

Once the diagnosis of liver cirrhosis has been formulated, a further important step is to score the disease. However, neither physical findings nor transaminases are helpful for defining prognosis or scoring the disease. Other laboratory tests (bilirubin, albumin, and prothrombin time), combined with the presence and severity of encephalopathy and ascites, are included in the Child-Pugh score (Table 2), the traditional scale used by many clinicians for assessing the liver disease severity (LEVEL Ⅰ). Another scoring system is the model for end-stage liver disease (MELD, http://www.mdcalc.com/meld) which provides robust information on mortality in cirrhosis, and is used for prioritizing candidates for transplantation[19] (LEVEL Ⅰ). Both scores

Table 2 Child-Pugh scoring system for liver cirrhosis and related indication priority for transplantation[20]

Score	1	2	3
Bilirubin (mg/dL)	< 2	2-3	> 3
Prothrombin time (INR)	< 4 sec. (< 1.7)	4-6 sec. (1.7-2.3)	> 6 sec. (> 2.3)
Albumin (g/dL)	> 3.5	3.5-2.8	< 2.8
Ascites	Absent	Mild	Severe
Encephalopathy	Absent	Mild	Severe

The Child-Pugh score is given by the sum of the score (1 to 3) of each of the five parameters. A score of 6 or lower defines the patient as class A, 7 to 9 as class B, and 10 or higher as class C.

can also be easily applied in primary care. Regardless of the cause, once decompensation has occurred, mortality without transplantation is 85% over 5 years[1]. In general, one-year survival rates for patients with Child-Pugh score A, B and C are 100%, 80% and 45%, respectively[20]. MELD score provides a more accurate prediction[21]. The hepatic clearance of exogenous administered substances, which provides an indication of residual liver functional mass[22,23], are easy to perform and may also meet future applications in family practice.

SELECTION FOR LIVER TRANSPLANTATION

Liver transplantation is considered as a viable treatment option for patients with acute liver failure and end-stage liver disease. In liver cirrhosis, transplantation is generally considered when a patient has suffered from either a complication of portal hypertension or a manifestation of compromised hepatic synthetic function[24]. However, given the high costs, mortality rate, and the paucity of donor organs, transplantation is currently justified only in the case of long-term prognosis, and psychological, intellectual, financial and family support. Accordingly, patients may be considered as current, future or inappropriate candidates. Selection consists of a search for contraindications and PCPs are actively involved in this process (i.e. alcohol and drug use)[25]. Currently, patients are generally put on a waiting list once Child-Pugh class B or a MELD score of over 13 is reached[21]. Onset of complications may anticipate referral, but severely decompensated or debilitated patients are generally discarded. Current indications and relative and absolute contraindications to liver transplantation are reported in Table 3.

TREATMENTS TO BE SHARED BETWEEN PCPs AND SPECIALISTS

Assistance is based on disease stage, complications and grade of self-sufficiency. Stable (compensated) patients are generally self-sufficient and a six month check (blood tests and liver ultrasonography) is indicated. Complicated and decompensated forms require an integrated approach with referral centers. Home care reduces costs[26] and should focus on a chronic care model of patient education and

Table 3 Current indications and contraindications to orthotopic liver transplantation in adult patients with liver cirrhosis

Indications	Contraindications
Advanced chronic liver failure	Relative
Child-Pugh score > 7	HIV seropositivity
Qualifying MELD score	Methadone dependence
	Stage 3 hepatocellular carcinoma
Acute liver failure	Absolute
Drug, toxins or virus induced fulminant hepatitis	Extrahepatic malignant disease
	AIDS
	Cholangiocarcinoma
	Severe, uncontrolled systemic infection
	Multiorgan failure
	Advanced cardiopulmonary disease
	Active substance abuse
General	
No alternative available treatment	
No absolute contraindications	
Willingness to comply with follow-up care and family assistance	

AIDS: Acquired immunodeficiency syndrome; HIV: Human immunodeficiency virus; MELD: Model for end stage liver disease.

on empowering both the patient and the family to take responsibility for the care (Table 4)[17]. Several cirrhotic patients can benefit from treatments aimed to slow disease progression (Table 1)[27-31]. In particular, nucleoside (Lamivudine, Telbivudine, Entecavir) and nucleotide (Adefovir, Tenofovir) analogues have shown to be safe and effective in reducing the risk of decompensation and disease progression in patients with HBV infection, while interferon plus ribavirin is a therapeutic option for under-compensated liver cirrhotic patients with HCV infection.

SPECIFIC PROBLEMS

Monitoring alcohol and drug abuse

Alcohol abuse causes 25% of liver cirrhosis and contributes to another 25%-50% of cases. PCPs play a key role in the application of long-term detoxification programs, counseling, support, and monitoring. This step is crucial, since recovered abusers are considered for antiviral therapy or transplantation only after six months of continuous abstinence (LEVEL Ⅲ).

Ascites

Ascites is the most common complication and cause of hospitalization of cirrhotic patients, but it is also the complication which can be better treated at home. Portal hypertension, reduced albumin synthesis, decreased plasma oncotic pressure, and sodium retention are all determining factors. Paracentesis usually removes a transudative fluid (i.e. albumin < 1 g/dL; serum/ascites albumin gradient > 1.1). Patients exhibiting abdominal pain, tense ascites and fever may have a spontaneous bacterial peritonitis (SBP), a condition characterized by an ascitic granulocyte count exceeding

Table 4 Standard objectives for an efficient out clinic care of cirrhotic patients

1	Early diagnosis of chronic liver disease. Identification of etiology
2	Identification of patients with chronic liver disease at risk of cirrhosis
3	Evaluation of patient's general health status
4	Act on etiologic factors and on factors favoring disease progression. Identify treatment end-points and place the patient within his family and social setting
5	Promote family and cohabitants' participation to primary prevention for infective forms (health education), secondary prevention for inherited or metabolic disorders, support and surveillance for toxic forms (alcohol)
6	Suggest health-dietetic measures and therapeutic remedies
7	Check parameters of effectiveness and control side effects of specific treatments (antiviral, phlebotomy, immune-depressants, β-blockers, *etc.*)
8	Identify and treat associated conditions (diabetes, osteoporosis, malnutrition, *etc.*)
9	Avoid administration of hepatotoxic drugs, drugs promoting renal sodium retention and central nervous system depressants
10	Promote vaccination against flu and pneumonia, including transplanted patients, and against hepatitis A and B virus
11	Supervise for complications by promoting clinical, biochemical and instrumental follow-up
12	Assist specialists in identifying candidates for liver transplantation
13	Assist the patient requiring legal problems

250/mm^3. SBP can precipitate cirrhosis towards renal and liver failure. Therapy includes high doses of albumin to prevent renal failure and intravenous cefotaxime at doses of 2 g twice a day (LEVEL Ⅱ). Long term prophylaxis of SBP recurrence with norfloxacin is indicated in survived patients (LEVEL Ⅰ). Ascites is considered refractory if it persists despite the use of diuretic drugs at the maximum tolerable dose. Although some studies indicate the utility of bed rest as a remedy, no controlled trials have been performed in support to this practice. Therefore, initial treatment is dietary salt restriction[32,33] (LEVEL Ⅰ). Therapy starts with spironolactone at doses ranging from 100 to 400 mg/d. Furosemide may be added (40 to 160 mg/d) when spironolactone does not successfully improve fluid retention (LEVEL Ⅰ). Weight should be monitored daily and electrolytes should be frequently monitored. Albumin infusion is required to prevent post-paracentesis circulatory dysfunction[34] following large volume paracentesis[35]. Such treatments can be managed by PCPs or in an integrated care system with consultant specialists. Preventive measures include the avoidance of NSAIDs, since they promote sodium retention. In the case of recurrent or refractory ascites, before considering the patient for a transjugular intrahepatic portosystemic shunt (TIPS), large volume paracentesis is feasible at home. Paracentesis is safe and rarely precipitates hepatorenal syndrome (LEVEL Ⅱ). Patients with SBP or refractory ascites have a more advanced disease with a poorer prognosis, and so require hospitalization. Patients and their family have to be taught the importance of a daily body weight check, and to refer FD when it increases by 2-4 kg over a brief period of observation.

Hepatorenal syndrome (HRS) is a life-threatening complication in patients with refractory ascites. Diagnosis includes the following criteria: advanced chronic liver failure with portal hypertension; serum creatinine exceeding 1.5 mg/dL or a 24-h creatinine clearance of less than 40 mL/min; absence of shock, ongoing bacterial infection, or recent treatment with nephrotoxic drugs; no sustained improvement in renal function following diuretic withdrawal and the expansion of plasma volume with 1.5 L saline; less than 500 mg/dL proteinuria and no ultrasonographic evidence of obstructive uropathy or parenchymal kidney disease[36]. While awaiting transplantation, patients with HRS, eligible for transplantation, may improve with medications, namely albumin, terlipressin, and vasoactive drugs or TIPS[37].

Portal hypertension

Active variceal hemorrhage accounts for about one-third of all deaths related to cirrhosis. Steps related to the prevention and treatment of variceal hemorrhage includes: prediction of patients at risk, prophylaxis against a first bleed, treatment of an active bleed, and prevention of rebleeding. Diagnosing and treating portal hypertension is a way to prevent esophageal variceal bleeding, and PCPs may play an active role in this respect. Varices appearance should be checked by upper endoscopy every 2-3 years, with a follow-up after 2 years for low-risk bleeding or every year for high-risk bleeding. Non-selective β-blockers are effective in reducing the risk of bleeding by reducing the resting heart rate by 25% (LEVEL Ⅰ). Endoscopic band ligation is indicated for patients susceptible of high-risk bleeding and for those who have already bled[38] (LEVEL Ⅰ). TIPS is an alternative option for patients with previously failed treatments[39] (LEVEL Ⅱ). A recent study has shown that early use of TIPS is associated with significant reductions in treatment failure and mortality[40].

Hepatic encephalopathy

Hepatic encephalopathy is a chronically debilitating complication of hepatic cirrhosis and encompasses a wide spectrum of potentially reversible neuropsychiatric abnormalities seen in patients with liver dysfunction. This condition is deemed as the onset of brain dysfunction due to metabolic abnormalities, which occurs as a consequence of liver failure. Hepatic encephalopathy is mainly caused by a reduced clearance of gut-deriving neurotoxins, and is a potentially reversible condition ranging from subtle personality changes to coma, with flapping tremor as a frequent initial finding. PCPs should search for acid-base and electrolyte disturbances, constipation, infections, gastrointestinal bleeding, and inappropriate use of sedative medications. Treatment consists of identifying and correcting the precipitating factors, colon cleansing and acidification with lactulose (LEVEL Ⅱ). Dietary protein restriction is no longer advocated since it may facilitate malnutrition and the appearance of complications. Rifaximin, a minimally absorbed oral antibiotic, has an antimicrobial effect against enteric bacteria and has received approval from the United States Food and Drug Administration for reducing the risk of overt hepatic encephalopathy recurrence. In a randomized, double-blind, placebo-controlled trial, six-month rifaximin therapy at a dose of 550 mg twice daily was compared with a placebo

in patients with chronic liver disease who were in remission from recurrent hepatic encephalopathy. Rifaximin maintained remission more effectively than the placebo and also significantly reduced the risk of hospitalization for hepatic encephalopathy[41] (LEVEL Ⅰ). Venous infusion of branched-chain amino acids or flumazenil may be effective in the case of comas (LEVEL Ⅱ). Patients may be managed at home; admission to hospital is reserved for those who are non-responsive after 12 h treatment.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is a major complication of liver cirrhosis representing an increased cause of mortality; liver transplantation and cost management in most developed countries. As a consequence, screening for HCC is one of the most important tasks in patients with liver cirrhosis. American and European guidelines currently recommend at least one imaging screening/year for HCC (ultrasonography, triphasic CT). Serum alpha-fetoprotein has poor sensitivity and therefore is recommended only as an adjunctive screening marker[37,42]. Once HCC is detected, many treatment options are available, mainly depending on tumor size and number, and local expertise. Surgical resection can be effective; unfortunately most patients do not tolerate liver resection or have microscopic lesions, and so the best option for a cure remains liver transplantation. The Milan criteria are used as a guideline worldwide[43,44], and suggest that a four-year survival rate of 75 percent is achieved if liver transplantation is performed for either a single lesion of less than 5 cm in diameter, or up to 3 lesions with none larger than 3 cm. Outcomes are similar to the expected survival rates for patients undergoing transplantation for cirrhosis without HCC (LEVEL Ⅰ). Alternative treatments for patients who do not meet the criteria for resection or transplantation are ultrasound guided radiofrequency ablation, chemoembolization and alcohol ablation. These options are considered as a form of "bridging therapy" because it reduces tumor burden and delays tumor progression[45], and do not preclude future liver transplantation, if a donor organ becomes available.

Infections

Sepsis represents a high risk factor for mortality in cirrhotic patients which often do not present the typical signs and symptoms of infection (i.e. absence of leukocytosis due to severe leukopenia or even absence of fever). The active search for infections is important (cultures, X-ray, paracentesis, *etc.*). Most common infections concern the urinary tract (25%-55%), spontaneous bacterial peritonitis (10%-30%), and respiratory tract infection (20%). First line antibiotics include quinolones and cephalosporins[46] (LEVEL Ⅲ). Hospitalization is required for poor general health and/or the appearance of organ dysfunction.

SYSTEMIC PROBLEMS

Malnutrition

Malnutrition represents a negative prognostic factor for cirrhosis and consists of muscle wasting, hypoalbuminemia, decreased resistance to infections, and variceal bleeding. Causes include poor oral nutritional intake, malabsorption, ongoing alcohol use, chronic nausea, and early satiety due to abdominal compression from ascites. Nutritional status should be monitored in all cirrhotic patients; multivitamin supplementation is often indicated[47]. Nutritional support should be reserved only for severely malnourished patients scheduled for transplantation[48]. Oral supplementation with a branched chain amino acids has some utility by improving event-free survival in patients with decompensated liver cirrhosis[49]. Dental care is particularly important to allow adequate mastication.

Osteoporosis

In individuals with chronic liver disease, metabolic bone disease (hepatic osteodystrophy), is a potential complication of long-standing hepatic disease. It is therefore essential to prevent the development of fractures in individuals with advanced hepatic disease and those that have undergone liver transplantation[50]. In end-stage cirrhosis, vitamin D deficiency, hypoparathyroidism, and hypogonadism contribute to reduced bone formation. Osteopenia may occur early in patients with cholestasis or in those put on antiviral drugs[51]. This is also the case in patients after orthotopic liver transplantation[52]. Bisphosphonates, together with calcium and vitamin D_3, are effective in improving bone mineral density[53] (LEVEL Ⅱ).

Diabetes

Diabetes and cirrhosis are strictly interrelated, the first occurring with increased frequency in patients with NASH, hepatitis C or hemochromatosis. In a multivariate analysis, diabetes was an independent negative factor for liver disease evolution[54]. No controlled studies have tested the benefit of different regimens for cirrhotic patients with diabetes. Diet remains the first line remedy to control hyperglycemia. In the case of dietary failure, metformin is generally the first choice. Sulphonylureas can be used, but mindful of the risk of hypoglycemia. Glitazones are a new alternative, although no studies in liver cirrhosis have been performed. In any case, oral anti-diabetic drugs are not indicated in decompensated patients. Insulin represents the best approach, although this requires good self-monitoring (LEVEL Ⅲ).

PREVENTION

Primary prevention

The role of PCPs is important for this issue. The most attractive form of protection for liver cirrhosis is to prevent or slow the evolution of several risk factors triggering the hepatitis-fibrosis sequence. Mass infant vaccination has proven extremely effective in preventing hepatitis B infection. Screening blood donors effectively reduces hepatitis C transmission (LEVEL Ⅰ).

Secondary prevention

This step aims at preventing the appearance of cirrhosis

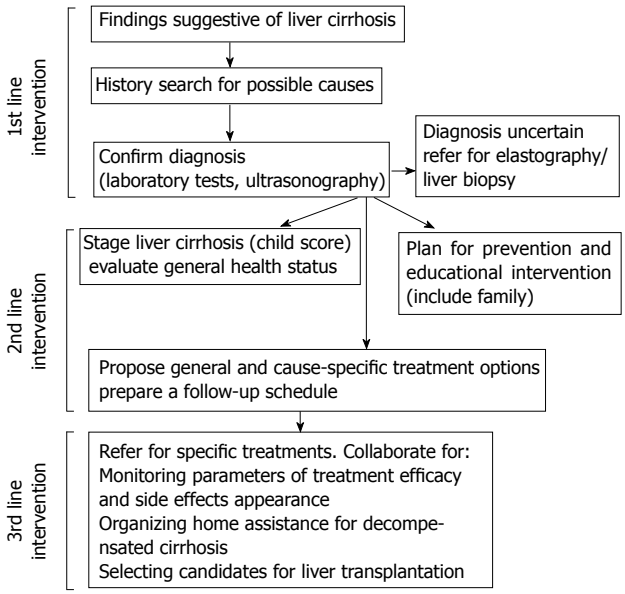

Figure 1 Algorithm for the management of patients with (or with suspected) liver cirrhosis in General Practice.

in patients with chronic liver disease and includes etiologic treatment for viral hepatitis, alcohol abstinence, phlebotomy in hemochromatosis, weight loss and improving insulin resistance in NASH patients[1]. Early detection of HCC by six-monthly ultrasonography and blood alpha-fetoprotein measurement may allow successful liver transplantation or mini-invasive treatments (LEVEL Ⅰ).

Prevention of infections

Vaccine immunization against hepatitis A and B, pneumococcus and influenza is important in preventing general status deterioration. SBP recurrence can be reduced by antibiotic prophylaxis (once-daily 400 mg norfloxacin or once-weekly 750 mg of ciprofloxacin)[55].

THE ROLE OF PCPs FOR OPTIMIZING CARE

The incidence of liver cirrhosis is expected to increase in the near future. Beside B and C viral infection and alcoholic cirrhosis, nonalcoholic liver steatosis (non-alcoholic fatty liver disease, NAFLD) is considered the hepatic manifestation of a new epidemic: the metabolic syndrome. This frequent condition is a cluster of risk factors for coronary heart disease and type 2 diabetes mellitus that includes visceral obesity, elevated blood pressure, insulin resistance, and dyslipidemia[56,57]. The onset of NAFLD represents a bridging condition between cardiovascular risk and potentially evolutive forms of liver diseases, namely steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma[58,59]. The PCPs are therefore asked to play a key role in programs involving prevention, treatment, surveillance, and home care of populations at risk (Figure 1)[4,60]. Referral of patients to specialists at least once is a good practice, since integrated management between PCPs and specialists is indeed associated with better outcomes[61]. Active cooperation is required for etiologic treatments, screening for complications and approaches to liver failure. However, appropriate timing for referral varies on an individual basis according to liver function and general health status, and this should include patient age, level of test abnormality, need for prognosis, and therapeutic decision. The need for a multidisciplinary approach should be considered, which includes feedback from dietitians, psychologists, and physical activity supervisors[62]. This integrated approach optimizes therapy adhesion, but necessitates the regular updating of health personnel[60].

Table 5 Features of home assistance in patients with liver cirrhosis

Advantages
Decreased number of hospitalization and re-admissions
Decreased costs of treatments
Assist the patient within his familiar comfort
Criteria of eligibility
Identification of a clinical status allowing home stay
Identification of priority criteria
Presence of a valid family support or of an active aid system
Selection criteria
Use the Karnofsky Performance Status[1] for patients with decompensated liver cirrhosis and limited self-sufficiency (set to < 50%)

[1]The Karnofsky Performance Scale Index allows patients to be classified as to their functional impairment. This scale is often used in the primary care setting to assess the prognosis in individual patients and to decide a treatment; the lower the score, the worse the survival.

PCPs can manage cirrhotic patients by checking therapy effectiveness and side effects. With the exclusion of major digestive bleeding, even severely decompensated patients or those in an irreversible coma or advanced HCC can be home managed (with the assistance of specialists and specialized nurses). Hepatic encephalopathy can be treated with lactulose (oral or rectal enema) and the minimally absorbed rifaximin, by controlling electrolytes, and treating infections. Ascites can be controlled with diuretics, albumin infusion or paracentesis. Albumin boosts the efficacy of diuretics, and reduces the number of hospital admissions[35]. Home care of cirrhotic patients should be encouraged since it allows a saving of up to two/third of the normal cost (Table 5) (LEVEL Ⅱ-Ⅲ).

CONCLUSION

Liver cirrhosis has an increasing prevalence worldwide, which matches the increasing diffusion of viral hepatitis infection, and metabolic steatohepatitis and fibrosis. Managing cirrhotic patients at home is challenging but cost-effective, although this policy requires active collaboration between PCPs and specialists, as well as nurses and paramedical staff. A set of conclusive key messages for practice are reported in Table 6.

Table 6 Key messages for best management of cirrhotic patients

	Statement	Evidence level
1	A compensated liver cirrhosis is suspected with abnormal liver function tests, low platelets count, and prolonged prothrombin time[63]	Ⅲ
2	Ultrasonography is a reliable, non-invasive, fast, and cost-effective test working as a first-line tool for diagnosing liver cirrhosis[64]	Ⅱ-Ⅲ
3	Child-Pugh and MELD scores assess the prognosis of liver cirrhosis[19,20]	Ⅰ
4	First-line treatment of patients with cirrhotic ascites includes diuretics and sodium restriction. Anti-aldosterone drugs are given with loop diuretics to increase diuretic response or when renal perfusion is impaired. Dietary salt intake should be restricted to approximately 88 mmol/day (2000 mg/d). Marked salt restriction can expose the risk of hyponatremia[32,37]	Ⅰ
5	Removal of less than 5 liters of fluid does not appear to have a hemodynamic consequence. For larger paracentesis, albumin (6 to 8 g/L of fluid removed) can be administered. Albumin is indicated in patients with PBS to prevent renal failure, and in patients with hepatorenal syndrome. Albumin can be also used to treat refractory ascites. Its infusion at home is safe and cost-effective[37,65]	Ⅱ
6	β-blockers (e.g. propranolol or nadolol) are recommended for prophylaxis of variceal bleeding at a dosage titrated to a 25 percent reduction in pulse rate[66]	Ⅰ
7	Liver transplantation is the only definitive care for patients with major complications (ascites, bleeding, HCC) and/or MELD above 13[1]	Ⅰ
8	Osteoporosis is an important systemic complication of end-stage liver cirrhosis. Management includes vitamin D and bisphosphonates[53]	Ⅱ
9	Malnutrition is a negative and independent predictor of survival in patients with liver cirrhosis[67]	Ⅱ
10	An integrated assistance of patients with liver cirrhosis has a better outcome than the management by generalists/specialists alone[61]	Ⅱ

LEVEL Ⅰ: At least one properly conducted RCT, systematic review, or meta-analysis; LEVEL Ⅱ: Other comparison trials, non-randomized, cohort, case-control, or epidemiologic studies, and preferably more than one study; LEVEL Ⅲ: Expert opinion or consensus statements (see text for details); MELD: Model for end-stage liver disease.

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