Understanding the Complexities of Cirrhosis

Andrew J. Muir, MD, MHS, FACP

Division of Gastroenterology, Duke University School of Medicine, Durham, North Carolina

ABSTRACT

Purpose: Cirrhosis and its related complications remain a prominent global health concern despite advances in understanding and treating the disorder. Early diagnosis and intervention strategies may reduce the impact of cirrhosis; however, it can be difficult for initial point-of-care health care providers to identify and refer patients with cirrhosis due to lack of knowledge and resources. This review examines current diagnostic strategies for cirrhosis and cirrhosis-related complications and the potential benefits of multidisciplinary care for patients with the disorder.

Methods: A PubMed search of the medical literature was conducted to identify current diagnostic methods and standards and ascertain the impact of multidisciplinary care on patients with cirrhosis.

Findings: Screening of patients at risk for cirrhosis has been recommended by several professional and governmental organizations. Unfortunately, identification of early-stage cirrhosis remains challenging despite development of novel calculations for risk (eg, aspartate transaminase-to-platelet count ratio) that use values from common, noninvasive laboratory tests to determine the extent of liver disease. Abnormal liver function test results and alterations in serum liver enzyme markers (eg, alanine and aspartate transaminases) may suggest cirrhosis in patients with chronic liver disease; however, they are not definitive. Liver biopsy is the gold standard for diagnosis and staging of cirrhosis, but its cost, invasiveness, and risk of complications have prompted the development of noninvasive tests (eg, elastography). Primary care physicians should be aware of the signs and symptoms of cirrhosis-related complications, particularly portal hypertension, and refer patients to specialists for further evaluation when warranted.

Implications: Patients at risk for cirrhosis should be screened and the underlying etiologic factor(s) of the liver disease treated or appropriately managed when possible. Primary care physicians should be aware of the signs and symptoms of cirrhosis and its related complications and adopt a low threshold for referral to a specialist when the condition is suspected. An integrated, multidisciplinary approach to care between specialists and primary care physicians may improve early detection of cirrhosis and its related complications and strengthen management strategies. (*Clin Ther.* 2015;37:1822–1836) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

Key words: chronic liver disease, cirrhosis, fibrosis, primary care, portal hypertension.

INTRODUCTION

Cirrhosis is a form of chronic liver disease (CLD) resulting from sustained liver damage from a number of causes, including viral infection, autoimmune disorders, cholestatic and metabolic disease (eg, nonalcoholic fatty liver disease [NAFLD]), or heavy alcohol use.[1,2] Progressive fibrosis (ie, scarring) of the normal liver architecture causes increased intrahepatic resistance and the development of portal hypertension, ultimately leading to diminished liver function and potentially life-threatening complications.

Cirrhosis is a major public health concern. In 2010, it was the 12th leading cause of mortality worldwide, responsible for ~1 million deaths. Among the documented deaths from cirrhosis, etiologies were found to be divided equally among hepatitis B viral infection, hepatitis C viral (HCV) infection, and alcohol misuse.[3] Consistent with worldwide statistics, in the United States in 2010, CLD/cirrhosis was the 12th leading cause of mortality, accounting for 31,903 deaths and representing a 3.3% increase in age-adjusted death since 2009.[4] More recent US data, using disease-specific definitions that include other liver-related causes of mortality (eg, hepatobiliary

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cancers, viral hepatitis, hepatorenal syndrome), suggest that this figure is substantially underestimated and that the total number of liver-related deaths exceeds 66,000, which would place total liver-related deaths in ninth place among leading causes of mortality, after nephrotic syndrome, based on the National Vital Statistics Reports of the Centers for Disease Control and Prevention.[4,5] In Europe, cirrhosis of the liver accounts for 1.8% of all deaths (170,000 deaths annually).[6,7] In the United Kingdom, mortality from liver disease continued to increase between 2001 and 2010.[8] In developed countries, the leading causes of cirrhosis are HCV infection, alcohol misuse, and NAFLD,[2,9,10] with alcohol-related cirrhosis having a worse long-term prognosis than non–alcohol-related cirrhosis.[11] Hepatitis B viral infection is the most common cause of cirrhosis in developing countries.[9]

Despite advances in understanding the pathogenesis of cirrhosis and improved treatment regimens, CLD/cirrhosis and its associated complications (eg, portal hypertension) continue to be significant global health concerns. Patients with cirrhosis, a progressive disorder, may benefit from early intervention strategies; unfortunately, difficulties in the recognition and diagnosis of early disease and cirrhosis-related complications present real challenges, especially to initial point-of-contact health care providers such as primary care physicians (PCPs) and nurses. The present review highlights current diagnostic strategies for cirrhosis and cirrhosis-related complications and discusses the importance of a multidisciplinary approach for patients with CLD/cirrhosis.

MATERIALS AND METHODS

The PubMed database was searched for English-language articles with no time limitation (up to October 1, 2014) using the following key words: "diagnosis," "cirrhosis," "portal hypertension," "variceal bleed," "ascites," "spontaneous bacterial peritonitis," "hepatic encephalopathy," "hepatorenal syndrome," "hepatocellular carcinoma," "multidisciplinary," "management," "management strategy," and "guidelines." Additional relevant publications were identified from the bibliographies of publications located through the PubMed search. Articles not related to the aforementioned topics were excluded.

RESULTS

Approximately 695 publications were identified via the PubMed search. Of these, 155 case reports were excluded. Publications that focused on accepted diagnostic techniques for cirrhosis and cirrhosis-related complications in terms of pathogenesis and articles relevant to interdisciplinary management of patients were thoroughly reviewed.

Pathogenesis and Classification of Cirrhosis

Understanding the natural history of cirrhosis can help identify patients at highest risk for life-threatening complications of CLD, as well as those for whom early intervention may help favorably alter the clinical course of the disease. Cirrhosis is a late-stage development of fibrosis of the hepatic parenchyma, a process that involves excessive accumulation of extracellular matrix proteins, including collagen (ie, scar tissue).[1] Liver fibrosis is the consequence of a repeated wound-healing response to ongoing hepatic injury (**Figure 1**).[12,13] The onset of fibrosis is usually insidious and progresses slowly, often over decades. Patients often remain asymptomatic until symptoms of cirrhosis emerge. Transition from early-stage fibrosis to cirrhosis involves multiple cell types and cellular and molecular processes, not all of which are fully understood.[14] Activation of hepatic stellate cells, which differentiate into proliferative, fibrogenic myofibroblasts, represents a pivotal event in ongoing fibrogenesis, with inflammation and angiogenesis also contributing to disease progression.[14,15] Changes in the hepatic microvasculature result in increased production of endogenous vasoconstrictors, such as endothelins, and a reduced production of vasodilators, such as nitric oxide. Cumulatively, these mechanisms contribute to increased hepatic vascular resistance and increased portal blood flow, resulting in portal hypertension and diminishing liver function.

Cirrhosis is a dynamic process that can be subclassified into distinct clinical stages.[16] In patients with diagnosed liver disease, progression to cirrhosis may occur up to 15 to 20 years after diagnosis.[17] Patients diagnosed with cirrhosis are classified as having either compensated or decompensated disease.[18,19] In compensated cirrhosis, the liver is still able to perform vital functions sufficiently, and thus few or no clinical symptoms are present or noticeable by the patient. In decompensated cirrhosis, there is sufficient organ damage such that the liver is unable to perform vital

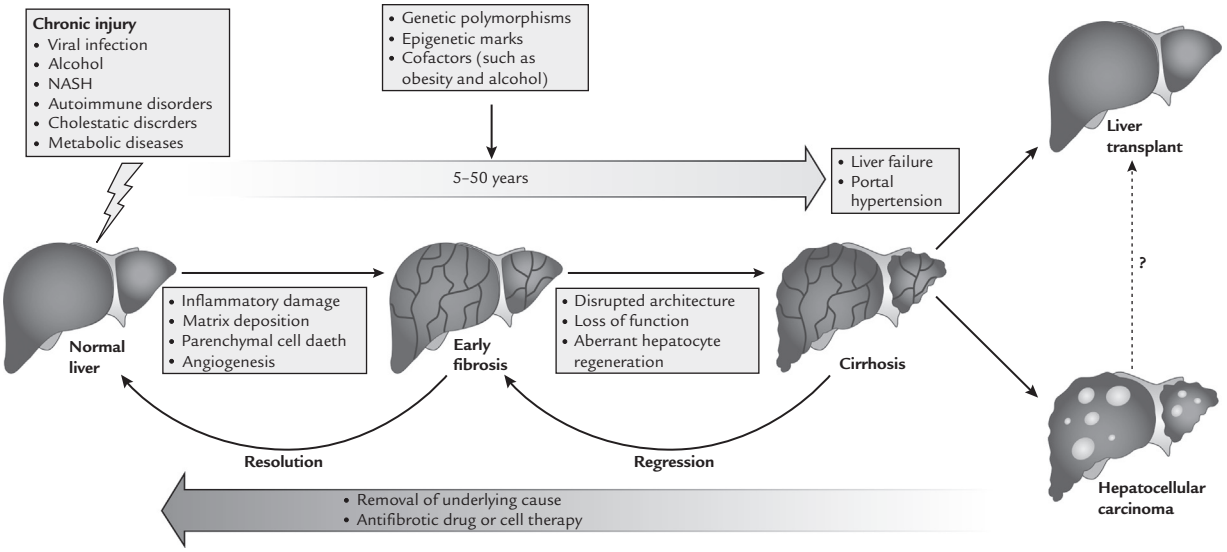

Figure 1. The natural history of chronic liver disease.[12] NASH = nonalcoholic steatohepatitis. Reprinted by permission from Macmillan Publishers Ltd: *Nat Rev Immunol*. 2014;14(3):181-194, copyright 2014.[12]

functions effectively, and functional decline progresses rapidly.[18,19]

Transition from compensated to decompensated cirrhosis is marked by the development of complications, including ascites, jaundice, and esophageal varices.[18,20] Survival associated with the 2 stages differs markedly; subjects with compensated cirrhosis have a median survival time of >12 years, whereas the median survival time for patients with decompensated disease is <2 years.[18,20,21] Rate of disease progression was the subject of a 25-year prospective inception study of 494 patients with compensated or decompensated cirrhosis.[20] Based on the 5 prognostic stages ranging from 1 (compensated cirrhosis without varices) to 5 (any second decompensating event), an exploratory analysis found that the risk of 5-year transition rate toward a different stage was 34.5%, 42%, 65%, and 78% for stages 1 through 4, respectively ($P < 0.0001$). Mortality rates paralleled the transition rate, with patients with more advanced disease (eg, bleeding) experiencing a higher mortality rate than patients with earlier stages of disease.[20] These findings seem to be consistent with other reports. In a UK study, patients with compensated cirrhosis reportedly had a nearly 5-fold increased risk of death, whereas those with decompensated cirrhosis had a nearly 10-fold increased risk, compared with the general population. Overall survival was 87% versus 75% at 1 year, and 67% versus 45% at 5 years, for patients with compensated and decompensated cirrhosis, respectively.[11] Given the difference in risk of mortality and survival rates between compensated and decompensated cirrhosis, patients and health care providers should have a clear understanding of distinctions between the 2 stages.[18,22,23]

Other tools for assessing CLD severity and prognosis have been used for decades. The extent of cirrhosis is subclassified into 4 or 5 stages with varying prognoses, each defined clinically by the presence or absence of select complications (Figure 2).[18,24–26] The Child–Pugh (or Child–Turcotte–Pugh) scoring system and the Model for End-Stage Liver Disease (MELD) score are used to help characterize patient prognosis.[16] Rather than defining a distinct stage of cirrhosis, these scoring systems help determine the degree of hepatic dysfunction.

Developed in the 1970s, the Child–Pugh (or Child–Turcotte–Pugh) scoring system was originally devised to assess mortality risk in patients with cirrhosis undergoing portosystemic shunt surgery to prevent variceal bleeding.[27] Scoring is based on bilirubin and albumin concentrations, the international normalized ratio (INR), and the presence and severity of ascites

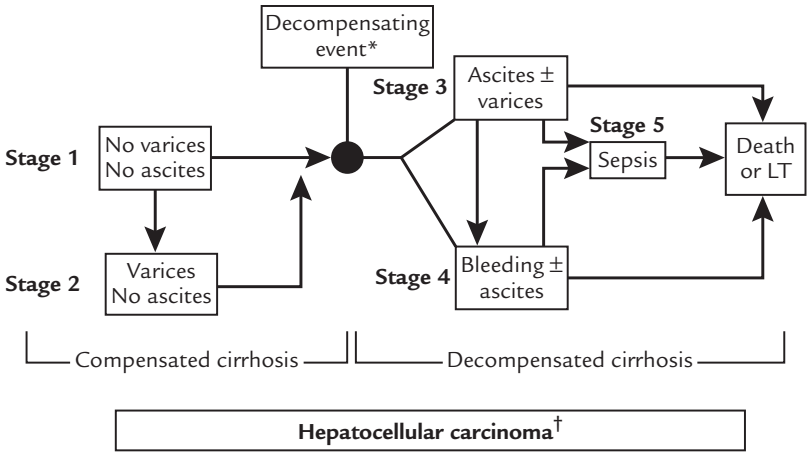

Figure 2. Stages of cirrhosis, based on presence or absence of select complications.[26] One-year mortality rates vary according to stage: compensated cirrhosis stages 1 (<1%) and 2 (~3%–4%); decompensated cirrhosis stages 3 (~20%), 4 (50%, but survival is increasing), and 5 (new proposed stage; >60%). LT = liver transplantation. *Decompensated event may be identified as ascites, hepatic encephalopathy, variceal bleeding, or jaundice.[18] †At any stage, development of hepatocellular carcinoma may accelerate the course of the disease.[18] Reprinted from *Gastroenterology*, vol. 139, no. 4, Arvaniti V, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis, pgs. 1246–1256. Copyright 2010, with permission from the AGA Institute.[26]

and hepatic encephalopathy (HE). Scores allow classification of cirrhosis as grade A, B, or C, ranked by worsening prognosis, and scores have been shown to correlate with the frequency of postoperative complications, including renal failure, HE, bleeding, infection, intractable ascites, and worsening liver failure.[28] Two older retrospective studies of patients with cirrhosis undergoing major abdominal surgery reported mortality rates of 10%, 30%, and 76% to 82% associated with cirrhosis grades A, B, and C, respectively.[29,30]

The MELD score roughly corresponds to the Child–Pugh score but excludes the subjective assessments of ascites and HE, which may lead to interobserver variability.[31,32] The MELD score is also reported on a continuous scale, in contrast to the Child–Pugh score, which assesses severity within 10 levels of difference between the least sick and sickest patients.[33] The MELD score is calculated from the natural logarithms of the serum concentrations of bilirubin and creatinine and INR, with higher scores indicative of worsening prognosis.[31,34] Although originally designed to predict mortality in patients who had undergone posttransjugular intrahepatic portosystemic shunt (TIPS), the MELD score was successfully applied to predict 3-month mortality in patients awaiting liver transplantation.[31] It is therefore valuable to prioritize liver transplant candidates by using a "sickest-first" policy, which is aimed at lowering mortality among waitlisted patients. MELD scores also provide information about prognosis, such as short-term prognosis for noncritically ill patients with cirrhosis.[34]

Diagnosis

Prevention of cirrhosis and the use of early intervention strategies once it develops are vital to maintaining patients in a symptom-free state and delaying decompensation, thus improving outcomes.[9] However, a major challenge in the diagnosis of cirrhosis is early identification of CLD. Most forms of CLD are quiescent until the disease has progressed to a later stage. Therefore, health care providers should remain vigilant and adopt a low threshold when CLD is suspected. A 2013 pilot study investigated the feasibility of screening for undiagnosed CLD in a primary care setting. Using transient elastography (a noninvasive technique for measuring liver fibrosis), asymptomatic CLD was detected in 5.7% of subjects in a randomly selected general population.[35]

Identifying the etiologic factor in CLD is important, as successful management of the underlying disease (eg, antiviral treatment for HCV) can prevent additional liver injury.[32] Indeed, the new era of antiviral therapies has been transformational with respect to achieving high cure rates (sustained virologic response [SVR]) for the underlying condition.[36–39] Early studies with interferon alfa plus ribavirin demonstrated the long-term benefit of achieving SVR in patients with compensated liver cirrhosis.[40,41] In patients with compensated hepatitis C–related cirrhosis, SVR was associated with a significant reduction in hepatocellular carcinoma (HCC)-related mortality.[40] Similarly, in patients with cirrhosis and portal hypertension, SVR was associated with fewer liver disease events than in nonresponders (6.2% vs 38.3%, respectively; $P = 0.03$).[41] By arresting or reversing hepatitis disease progression, patients may also be removed from the liver transplantation list.

Introduction of pegylated interferon marked a step forward in achieving higher overall SVR rates.[42] However, there were few options for patients with decompensated liver cirrhosis, with interferon contraindicated in this patient population.[37] Recent reviews on the topic of hepatitis C treatment cite extraordinary success rates (ie, SVR rates of 90%–100%) with interferon-free regimens containing nucleoside/nucleotide analogues (eg, sofosbuvir) alone or in combination with other direct-acting antiviral agents.[36–39] In many cases, these newer regimens are of shorter duration than interferon-based regimens, with the potential for combination therapies in the future being $\leq$8 weeks in duration.[38] Similar to the potential benefits observed with antivirologic therapies for hepatitis C, treatment of hepatitis B infection with interferon or nucleotide/nucleoside regimens has been shown to reduce the risk of HCC, improve the level of liver fibrosis, and reverse advanced fibrosis/cirrhosis in some cases.[43]

Highly effective treatments that reduce downstream liver disease events (eg, transplantation, HCC) provide a compelling rationale for identifying appropriate patients for treatment. Currently, screening for cirrhosis risk is only recommended in patients with specific etiologic risks (eg, hepatitis). In 2012, the Centers for Disease Control and Prevention recommended that all Americans born between 1945 and 1965 be tested for HCV infection.[44] Furthermore, the Centers for Medicare & Medicaid Services will now cover HCV infection screenings for high-risk subjects in this age group when ordered by the individual's Medicare-eligible PCP or practitioner, within the context of a primary care setting.[45] Screening for NAFLD, which is also an etiologic factor in the development of cirrhosis, in high-risk patients (eg, obese, diabetic) is currently debated and not yet recommended by hepatologic and gastroenterologic professional associations due to lack of knowledge related to the long-term benefit and cost-effectiveness of such screening.[46]

In the clinical setting, cirrhosis should be suspected in a patient with CLD who presents with abnormal liver function test results and abnormal serum alanine and aspartate transaminase (ALT/AST) levels, alkaline phosphatase levels, or bilirubin values.[47] It should be noted that although abnormal transaminase values are common in CLD, they may be normal in patients with cirrhosis.[32] Therefore, although most patients with CLD will present with abnormal liver test results, health care providers should consider the diagnosis of CLD if other signs or symptoms are present in patients with normal liver test results.

Unfortunately, health care providers often miss the opportunity for early detection and treatment of cirrhosis when they focus solely on abnormalities in laboratory values. Indeed, 1 study revealed that in at least 10% of patients in the primary setting who had abnormal liver function test results, there was insufficient investigation/follow-up, and referrals/diagnoses were missed.[48] A low platelet count might also be a marker of cirrhosis[47] and is generally the result of platelet sequestration in the spleen as a result of portal hypertension. Therefore, if present in a patient who has, or is at risk of, liver disease, further evaluation may be warranted. Noninvasive markers (eg, the AST-to-platelet-count ratio index [APRI], the Fibrosis-4) use routine laboratory tests in their calculations and may also be helpful in the evaluation of patients with CLD to determine if they have advanced fibrosis.[49,50] Patients with suspected cirrhosis can also be examined for evidence of so-called "CLD stigmata," such as vascular spiders, palmar erythema, and muscle wasting.[51,52] A palpable left liver lobe, hepatomegaly, and splenomegaly may also be suggestive of cirrhosis.[52]

Staging of Hepatic Fibrosis

Progressive hepatic fibrosis can lead to cirrhosis, making its early detection important. Furthermore,

fibrosis is potentially reversible in its early stages if the etiologic factor is removed.[53,54] Liver biopsy is the gold standard for the diagnosing and staging of fibrosis, providing information on the degree of fibrosis as well as other concomitant processes. Nevertheless, despite its many benefits, liver biopsy has a number of limitations, including invasiveness, cost, poor patient acceptance, and risk of complications.[55]

A number of fibrosis staging systems exist, which vary according to the underlying disease. The METAVIR system (developed by Metavir, group of pathologists in France that formed to discuss scientific problems related to hepatitis C) comprises 5 stages: F0, no fibrosis; F1, portal fibrosis without septa (minimal fibrosis); F2, portal fibrosis with few septa (moderate fibrosis or clinically significant fibrosis); F3, septal fibrosis with many septa but no cirrhosis (severe fibrosis); and F4, cirrhosis.[55] Another system, the Brunt criteria, was developed for evaluating patients with NAFLD and uses separate assessments for grade of hepatic necroinflammation and stage of fibrosis.[56] Building on the Brunt classification, the Clinical Research Network in Nonalcoholic Steatohepatitis has developed a scoring system that evaluates nonalcoholic steatohepatitis, the progressive form of NAFLD, by producing a single score (the NAFLD activity score).[56,57] The presence and extent of fibrosis can also be estimated indirectly by using biomarkers of fibrosis (eg, FibroSURE assay [Laboratory Corporation of America Holdings, Burlington, North Carolina], which has a sensitivity and specificity of 85% and 72%, respectively)[32]; however, other noninvasive assessments (eg, APRI, Fibrosis-4 scores) offer alternatives to these commercial markers and use standard laboratory tests in their calculations.[49,50]

A substantial number of noninvasive imaging and laboratory-based tests have also been developed for the diagnosis and staging of liver fibrosis, many of which have been reviewed by Gonzalez et al[58] and Kim et al.[59] Briefly, the most widely used are elastographic techniques, which measure the mechanical property (ie, stiffness) of the liver by transmitting waves into the liver parenchyma and summarizing the pattern of wave propagation.[55] One of these techniques, transient elastography (FibroScan [Echosens, Paris, France]), was approved in the United States in 2013 and is a good predictor of disease stage, providing sensitivity between 72% and 84% and specificity between 82% and 95%; however, the test is not widely available.[60,61] Acoustic radiation force impulse elastography is another noninvasive imaging technique used for fibrosis assessment, which is as efficient as transient elastography in diagnosing severe fibrosis and/or cirrhosis in patients with CLD.[62] Magnetic resonance elastography can identify patients at risk for decompensation; however, it is available only in a small number of centers.[63] Ultrasound, computed tomography, and magnetic resonance imaging are additional noninvasive imaging techniques that have been applied with varying degrees of success.

Beyond imaging modalities, there are several simple, noninvasive laboratory-based tests, including the APRI, the AST/ALT ratio, the Lok score, the Göteborg University Cirrhosis Index (GUCI), the Cirrhosis Score University of Naples score, and the fibrosis index.[64–67] The APRI is a test that was validated in patients with hepatitis C; however, similar to FibroScan, this test may not be as useful in assessing the early stages of fibrosis.[68] The Lok score uses platelet count, AST/ALT ratio, and prothrombin INR to predict histologic cirrhosis.[65] A similar test (GUCI) using 3 of the 4 inputs (AST, platelet count, prothrombin INR) that comprise the Lok score was developed by a Swedish group.[69] The Cirrhosis Score University of Naples test uses the same inputs as GUCI but with the addition of patient age.[67] Another laboratory test, the fibrosis index, was derived from measurements of platelet count and serum albumin in patients with hepatitis C. This test has shown acceptable accuracy in the assessment of liver disease progression.[70] In general, these tests have proven to be useful in assessing fibrosis/cirrhosis, but all have some limitations and may replace liver biopsy only in select patients.[58,64]

Complications of Cirrhosis

Portal Hypertension

Development of portal hypertension represents a hallmark in the clinical course of cirrhosis. It is often the earliest consequence of cirrhosis, and it underlies many of the other complications of the disorder (**Figure 3**).[71] Portal hypertension is defined as a pathologic increase in portal venous pressure; specifically, it is an increase in the hepatic venous pressure gradient (HVPG) across the liver to levels exceeding 5 mm Hg.[71] Clinically significant portal hypertension is defined as an HVPG $\geq$10 mm Hg,

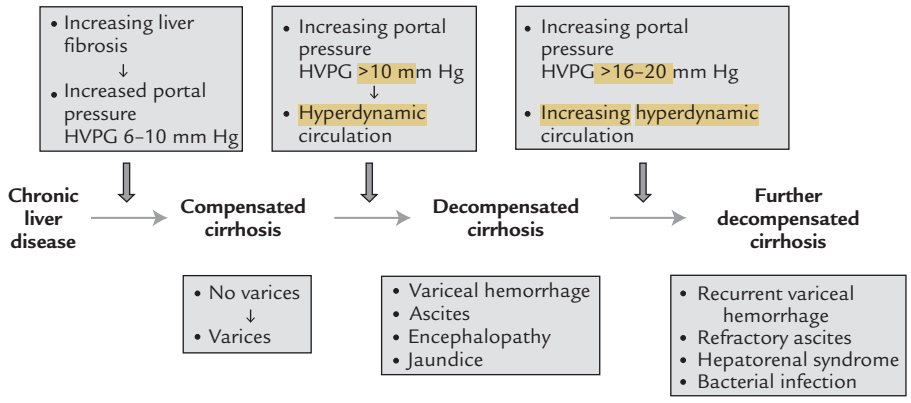

Figure 3. The role of portal pressure in the development of cirrhosis.[71] HVPG = hepatic venous pressure gradient. Reprinted with permission from Albilllos A, Garcia-Tsao G. *Dis Markers*. 2011;31(3):121-128. ©2011 Hindawi Publishing Corporation; https://creativecommons.org/licenses/by/3.0/.[71]

and an elevated HVPG is an independent predictor of the development of decompensated cirrhosis, in addition to serum albumin levels or MELD score.[72,73] Over a mean follow-up period of 4 years in patients with compensated cirrhosis, those with lower HVPG (<10 mm Hg) were found to have a 90% probability of not progressing to the decompensated stage.[72] Data suggest that a 3% increase in risk of mortality occurs with every increase in HVPG of 1 mm Hg.[74]

Management of portal hypertension remains challenging. A randomized, double-blind, placebo-controlled, multisite trial in patients with cirrhosis and portal hypertension (defined in the study as HVPG ≥6 mm Hg) but no complications, reported no benefit versus placebo from "preprimary" prophylactic treatment with a nonselective β-blocker given to prevent the development of complications.[75] At present, no specific treatments are recommended for patients at this early stage of the disease; instead, the management strategy is to treat the underlying etiologic factors of cirrhosis in an effort to reduce the hypertension.[76,77]

Variceal Bleeding

As portal pressure increases, veins in the esophagus and stomach dilate and form varices (ie, esophageal varices, gastric varices), which can hemorrhage as a result of the increased portal pressure. Esophageal varices are more common than gastric varices. Varices tend to form at portal pressures ≥10 mm Hg and occur in ~50% of patients with cirrhosis.[78] They are asymptomatic, but once ruptured, they require emergency care and, despite progress in treatment, variceal bleeds carry a ~20% mortality risk at 6 weeks.[18,76,78] Treatment of variceal hemorrhage includes infusion of vasoactive agents along with endoscopic intervention (eg, band ligation for esophageal varices, variceal obliteration for gastric varices),[79] administration of nonselective β-blockers (eg, carvedilol), placement of TIPS (particularly in subjects with recurrent variceal bleeding), and use of antibiotics (eg, quinolone, ceftriaxone) for the treatment of infection.[80,81]

Because it remains unclear whether variceal bleeding precedes infection or infection precipitates bleeding, it is appropriate to administer antibiotics as a standard practice.[82] Current guidelines recommend primary prophylaxis only for patients at high risk of bleeding, with nonselective β-blockers and band ligation considered similarly effective.[76,83] Secondary prophylaxis, with a combination of medication and endoscopic treatment (eg, β-blocker plus band ligation), is recommended as first-line therapy to prevent rebleeding.[78]

Ascites and Spontaneous Bacterial Peritonitis

Ascites (an accumulation of fluid in the peritoneal cavity) results when portal hypertension causes splanchnic vasodilation and activation of the

renin–angiotensin–aldosterone system, which culminates in sodium and water retention. The accumulation of fluid results in abdominal swelling and is associated with bloating and pain. Ascites is a marker of decompensation, and it develops in ~50% to 60% of patients within 10 years of a cirrhosis diagnosis.[21] Refractory ascites, defined as ascites that does not recede or that recurs soon after therapeutic intervention, is less common but has a predicted survival rate as low as 32% to 52% at 1 year, with prognosis worsening in the presence of hepatorenal comorbidities.[84,85] Treatment (eg, diuretics plus dietary salt restrictions) is generally not curative but may improve patient quality of life and decrease the risk of secondary complications, such as spontaneous bacterial peritonitis (SBP).[86–88] TIPS is indicated for patients with refractory ascites, although referral for transplantation is also considered.[88]

Spontaneous bacterial peritonitis is a complication of uncontrolled ascites that occurs when the body's natural bacteria enter ascitic fluid, causing infection. Typically, it is diagnosed by a polymorphonuclear cell count >250 cells/mL. Gram stain/culture can also be used to make the diagnosis, but it has a low sensitivity for detecting SBP,[89] and clinicians should not wait for results to initiate empiric therapy with broad-spectrum antibiotics in patients with signs and symptoms of infection.[86] Indeed, use of antibiotics for primary prophylaxis is recommended in some cases of advanced disease, and secondary prophylaxis (after an episode of SBP) should always be used.[86] Hospitalized patients should receive antibiotics within 6 hours and ambulatory patients within 24 hours of presentation with suspected SBP.[32]

Hepatic Encephalopathy

HE is a potentially reversible condition associated with neuropsychiatric symptoms and neuromuscular dysfunction of varying severity.[90,91] It represents a spectrum of abnormalities that range from minimal HE (subtle alteration in cognitive function determined via neuropsychometric tests) to overt HE (clinical symptoms, such as generalized motor dysfunction with alterations in consciousness). The exact pathogenesis of HE is not fully understood, although it has been hypothesized that gut-derived toxins (eg, ammonia) play a role.[92] Gut-derived substances escape hepatic clearance, due to parenchymal liver failure or portosystemic shunting, and reach the systemic circulation where they can exert toxic effects on the brain. A number of factors, including infection and electrolyte disturbances, can elicit an overt HE episode and should be treated to gain control of the episode.[93] However, the presentation of HE demonstrates progression to decompensated cirrhosis and the need for long-term treatment and monitoring to prevent recurrence.[94] The first goal of treatment for HE is to identify and cure the underlying condition that has precipitated HE (eg, infection). In addition to addressing the underlying causes, nonabsorbable disaccharides and minimally absorbed antibiotics are commonly administered for the treatment of overt HE.[91] Lactulose, a nonabsorbable disaccharide, is recommended as a first-line treatment option for patients with an overt HE episode and to prevent its recurrence.[93] However, lactulose is poorly tolerated, and thus there is a risk for nonadherence.[95] Rifaximin is a nonsystemic antibiotic that is well tolerated and efficacious as an add-on therapy to lactulose for the prevention of HE recurrence.[91,93]

Hepatorenal Syndrome

Renal function is affected in patients with advanced cirrhosis and, as such, it is an integral component of the MELD score (estimated by using serum creatinine levels). Hepatorenal syndrome is caused by progressive systemic arterial vasodilation, particularly in the splanchnic bed, resulting in reduced arterial blood volume and activation of sodium-retentive mechanisms and intrarenal arterial vasoconstriction. Hepatorenal syndrome is a potentially reversible complication of cirrhosis that is associated with a rapid deterioration of kidney function in the absence of intrinsic kidney disease but often with poor prognosis and high mortality.[91] It can be categorized as type 1 (rapid decline in renal function with a mortality rate of 50% at <1 month) or type 2 (steady decline in renal function with a mortality rate of 50% at 4 to 6 months).[96] Due to the role of arterial vasodilation in the pathogenesis of hepatorenal syndrome, vasoconstrictors are administered, but despite their use, patient prognosis remains poor.[91,97,98]

Hepatocellular Carcinoma

Accounting for >90% of all cancers of the liver, HCC is the leading cause of death in patients with cirrhosis, and in >80% of cases, its management is complicated by the underlying cirrhosis.[6,99,100] The age-adjusted incidence rates of HCC tripled in the United States from 1975 to 2005 (mostly as a

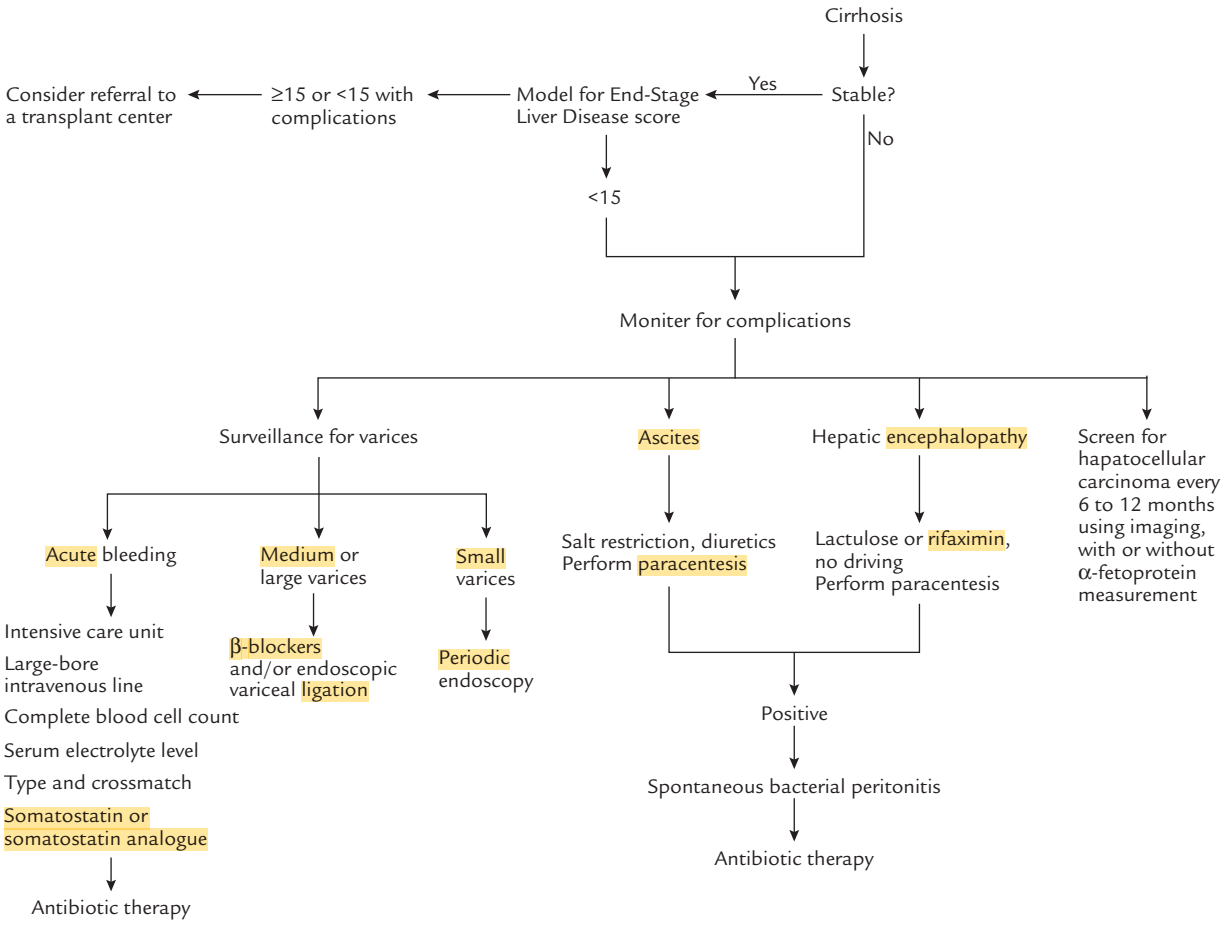

Figure 4. Algorithm for the management of complications of cirrhosis.[32] In patients with advanced disease (not shown in the figure), the use of intravenous antibiotics in conjunction with intravenous albumin has been shown to reduce the incidence of renal impairment and mortality compared with antibiotics alone.[104] Adapted with permission from Starr SP, et al. *Am Fam Physician*. 2011;84:1353-1359.[32]

consequence of HCV-related cirrhosis).[101] Data indicate that portal hypertension is an independent predictor of HCC development, with HVPG >10 mm Hg associated with a 6-fold increase in HCC risk.[72] Current guidelines recommend that patients at risk for HCC undergo ultrasound-based surveillance at 6-month intervals (α-fetoprotein determination is no longer recommended).[99,102]

Multimodal Management of Cirrhosis

Management guidelines for cirrhosis and its complications are based on a large body of high-quality evidence from numerous randomized controlled trials and meta-analyses (Figure 4).[32,52,103,104] CLD is a challenging condition to manage and is characterized by frequent, prolonged, and costly hospital readmissions. In 1 study, 69% of patients (N = 402) had ≥1 readmission, with 14% readmitted within 1 week and 37% within 1 month.[105] In the context of relatively high rates of hospitalization, it is not surprising that patient care varies among health care providers, with appropriate coordination of care between PCPs and specialists generally regarded as limited and with room for improvement.[103] As in the management of any chronic disease state, an opportunity exists to reduce the number of patients who are hospitalized or readmitted for cirrhosis-related complications. In a cohort of the aforementioned study of patients with decompensated cirrhosis, 22% of 165 readmissions within 30 days of discharge were considered preventable.[105]

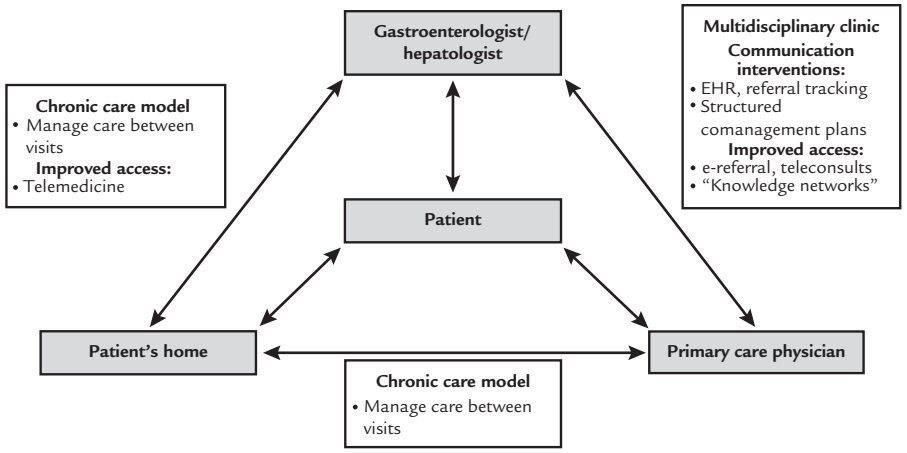

Figure 5. Improving the management of cirrhosis: a conceptual model.[103] EHR = electronic health record. Reprinted from *Clin Gastroenterol Hepatol,* vol. 11, no. 3: Mellinger JL, Volk ML, Multidisciplinary management of patients with cirrhosis: a need for care coordination, pg. 217-223. Copyright 2013, with permission from the AGA Institute.[103]

Studies have shown that the optimal management strategy for improving outcomes in patients with cirrhosis is achieved when a multidisciplinary, integrated approach between specialists and PCPs is adopted.[52,103,106,107] To improve the quality and efficiency of care in patients with cirrhosis and move toward a unified and multidisciplinary approach, a number of improvements to the current models of care are needed (**Figure 5**).[103] Proposed strategies include active management between visits/telemedicine (ie, chronic care model); coordination between medical specialties (eg, colocation within a single clinic); and improvement in communication and delineation of responsibilities (and time taken) between specialists and generalists (eg, electronic health records, e-referrals).[103] The focus of the chronic care model is to keep patients actively engaged between clinic visits, whether using home visits, telephone calls, and/or mailings. Of these techniques, home-based interventions seemed to provide the greatest benefit in a study of heart failure patients.[108] In addition to keeping patients actively engaged in the management of cirrhosis, multidisciplinary care should include a gastroenterologist/hepatologist, PCP, and other potential specialists (eg, radiologist, endocrinologist, infectious disease specialist, psychiatrist). Importantly, coordinating communication between practitioners is a vital strategy to help ensure quality and efficiency of care.[103]

Looking more specifically at roles and responsibilities, PCPs can play a key role in the identification of patients at risk for or symptomatic of CLD, and in the collaborative management and prevention of cirrhosis-related complications. Because PCPs are the first medical contact for the majority of patients, they must be able to recognize potential diagnoses as early as possible and manage patients appropriately by using treatments that are supported by guidelines and high-quality evidence.[52,103,107] The only definitive cure for cirrhosis is liver transplantation. The severity of the liver disease, assessed by using MELD or Child–Pugh scores and the development of complications, determines when a patient should be referred for liver transplantation.[109,110] Health care providers, including PCPs, should be educated to facilitate timely referral, and they must be able to recognize essential turning points at which a patient may become eligible for a transplantation referral.[109,110]

Chronic disease management programs have met with success in other chronic disease areas, including heart disease and diabetes. A pilot study applying such a model to patients with chronic liver failure did not seem to reduce hospital admission rates or disease severity or to improve patient quality of life. However, some benefits were observed (eg, significant increases in outpatient attendance), and the authors concluded that larger trials with longer follow-up periods were warranted.[111,112] A 2013 study has shown the benefits

of an integrated management approach to CLD care. The "care management check-up" model of specialized caregiving reported significant reductions in mortality and hospital readmissions in outpatients allocated to the integrated management scheme versus standard outpatients. Global health care costs were also reduced as a result of a more rational use of hospital services. Clearly, the application of such models to CLD management warrants further investigation.

CONCLUSIONS AND FUTURE DIRECTIONS

A key component in the management of patients with cirrhosis is the treatment and prevention of associated complications.[16,113] In addition to treating the underlying disease leading to cirrhosis, early intervention and ongoing surveillance for cirrhosis-related complications are critical to outcomes and patients' quality of life. A major challenge in the diagnosis of cirrhosis is recognizing underlying liver disease, particularly in its earlier stages. Health care providers should be vigilant and adopt a low diagnosis threshold when CLD is suspected. Patients at risk for developing cirrhosis should be screened, and the etiologic factor(s) identified and treated or eliminated whenever possible. The management of patients with cirrhosis should move toward a multidisciplinary, integrated approach between specialists and PCPs.

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CONFLICTS OF INTEREST

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Address correspondence to: Andrew J. Muir, MD, MHS, FACP, Division of Gastroenterology, Duke University School of Medicine, DUMC Box 3913, Durham, NC 27710. E-mail: andrew.muir@duke.edu