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# Understanding the Complexities of Cirrhosis

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## 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;▮:▮▮▮–▮▮▮) © 2015 Elsevier HS Journals, Inc. All rights reserved.

**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