

# Management of chronic liver diseases and cirrhosis: current status and future directions

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Chronic liver diseases (CLD) and cirrhosis are substantial health burdens worldwide. In 2017, with an estimation of 1.5 billion cases, the age-standardized prevalence increases by 10.4% when compared with that in 2007.<sup>[1]</sup> Globally, the most common etiologies of CLD and cirrhosis are non-alcoholic fatty liver disease (NAFLD), followed by hepatitis B virus (HBV), hepatitis C virus (HCV), and alcohol liver disease (ALD) in 2017.<sup>[1]</sup> Similarly, NAFLD is a common cause of CLD and cirrhosis in China, with an estimation of 173 to 310 million cases according to recent surveys.<sup>[2]</sup> However, the majority of cirrhosis cases in China are caused by HBV currently, though the integration of hepatitis B vaccination into national immunization programs has led to dramatic reduction of HBV transmission in the past decades.<sup>[3]</sup> Despite the successful HBV vaccination plans in high endemic areas and effective anti-HBV and anti-HCV treatments, the age-standardized prevalence of CLD and cirrhosis caused by HBV and HCV kept rising at a rate of 9.0% and 10.2%, respectively, in the last decade (2007–2017). Moreover, the age-standardized prevalence of CLD and cirrhosis caused by NAFLD, leading cause of CLD and cirrhosis, increased by 23.5% within the same period.<sup>[1]</sup> Hence, optimizing the management of CLD and cirrhosis is urgently needed. Here, we discuss the contemporary and future perspectives in the management of CLD and cirrhosis.

Early diagnosis of CLD and cirrhosis is of great importance to start effective intervention and subsequently improve the prognosis. Both identification of etiology and assessment of disease severity are essential before making a treatment decision. To identify the etiology, screening tests for HBV markers, HCV markers, and metabolic panels are generally used. Collecting and analyzing information about alcohol intake and drug exposure is also necessary. Chronic drug-induced liver injury (DILI) is an emerging field of study and more prevalent than previously thought. Antibiotics are the drugs most likely to cause chronic

DILI.<sup>[4]</sup> Detecting the levels of immunoglobulin G, immunoglobulin M, and autoantibodies are pivotal to diagnose autoimmune liver diseases. Markers related to Wilson disease, hemochromatosis,  $\alpha$ 1-antitrypsin deficiency, and other rare liver diseases need to be tested when the disease is indicated. Liver biopsy for histopathological examination is optional when the routine noninvasive tests fail to determine the etiology, but become inevitable in the diagnosis of some CLD, such as autoimmune hepatitis (AIH). Regular follow-up and assessment of the disease's severity are essential to initiate treatment in time, given that CLD and cirrhosis can be asymptomatic and neglected until the occurrence of decompensation, characterized by ascites, hepatic encephalopathy, variceal bleeding, or hepato-renal syndrome. Advanced fibrosis is usually "silent" but life-threatening. For example, advanced fibrosis in patients with NAFLD dramatically increases the risk of hepatocellular carcinoma (HCC) and other complications of cirrhosis. Early diagnosis and treatment of fibrosis is the key to improve the prognosis of CLD. Liver biopsy is currently the gold standard to diagnose liver fibrosis and cirrhosis. Referral for liver biopsy should be considered if a thorough serologic and radiographic evaluation fails to confirm a diagnosis of fibrosis or cirrhosis. Given patients' preference to avoid liver biopsy and the limitations of liver biopsy, including invasiveness, associated risk of complications, costliness, and occurrence of intra- and inter-observer variability, noninvasive alternatives of liver fibrosis and cirrhosis are in high demand. Transient elastography (TE), aspartate transaminase (AST) to platelet ratio index (APRI), and Fibrosis-4 (FIB-4) are commonly used to assess liver fibrosis in clinical practice at present.

To assess the severity of CLD and cirrhosis, a liver panel, a complete blood count (CBC) with platelets, and a prothrombin time/international normalized ratio (INR) test should be performed. Common tests in liver panels include the serum enzymes such as alanine transaminase (ALT), AST, alkaline phosphatase, and  $\gamma$ -glutamyltrans-

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DOI:  
10.1097/CM9.0000000000001084

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Chinese Medical Journal 2020;133(22)

Received: 17-05-2020 Edited by: Qiang Shi

ferase; total serum bilirubin, direct serum bilirubin and indirect serum bilirubin; and serum albumin. Scoring systems involving multi-organ function such as Child-Turcotte-Pugh score and model for end-stage liver disease are used to predict the survival of cirrhosis patients. The Chinese group on the study of severe hepatitis B-acute-on-chronic liver failure score (COSSH-ACLFs) is useful to predict the evaluate the severity and short-term prognosis of patients with HBV-related acute-on-chronic liver failure (ACLF).<sup>[5]</sup> Imaging tests, including ultrasonography, computed tomography, and magnetic resonance imaging can suggest the presence of cirrhosis and provide information about complications, such as ascites, esophageal varices, and HCC.

In addition, assessment of extra-hepatic manifestations is substantially important in the management of some forms of CLD and cirrhosis, such as HCV infection. Hematologic diseases such as cryoglobulinemia and lymphoma, autoimmune disorders such as thyroiditis, renal disease, and dermatologic conditions such as lichen planus and porphyria cutanea tarda are quite uncommon in chronic HCV infection. Furthermore, evaluations of complications, including ascites, esophageal and gastric variceal bleeding, hepatic encephalopathy (HE), hepato-renal syndrome (HRS), hepatopulmonary syndrome (HPS) and others, are necessary for cirrhosis patients, which have been detailed in the guidelines.<sup>[3]</sup> It is particularly important to monitor liver malignancies through the combination of serum markers, including alpha-fetoprotein (AFP) and protein induced by vitamin K absence-II (PIVKA-II), and imaging tests in the long-term management of CLD and cirrhosis.

With regard to the treatment of CLD and cirrhosis, comprehensive measures consisting of etiological treatment and complication management should be taken immediately. Anti-inflammatory and anti-fibrosis treatments should be started when indicated. Recommendations for the treatment of cirrhosis and its complications are detailed in the guidelines.<sup>[3]</sup> In terms of etiological treatment, efficacy and effectiveness varies among CLD and cirrhosis caused by different etiologies. For the management of nonalcoholic steatohepatitis (NASH), which is the inflammatory subtype of NAFLD and is associated with disease progression, no disease-specific medication is approved so far. Hence, lifestyle modification is still the mainstay of treatment. Weight loss through dietary changes, physical exercise, and bariatric surgery when indicated, is correlated with substantial improvement in histologic outcomes, including fibrosis.<sup>[6]</sup> However, only a small portion of NASH patients can achieve and maintain the necessary degree of weight loss required for therapeutic effect, and half patients failed to achieve fibrosis regression through weight loss. NASH-specific medications are urgently needed since the prevalence of NASH keeps rising dramatically worldwide. The interim analysis of a multicenter, randomized, placebo-controlled phase 3 trial showed that obeticholic acid, an agonist of farnesoid X receptor, improved fibrosis in patients with NASH.<sup>[7]</sup> More emerging medications, such as C-C chemokine receptor types 2 and 5 inhibitor, peroxisome proliferator-activated receptor agonists, glucagon-like peptide-1 agonist, vitamin E, and some novel

drugs are being studied and potentially provide new solutions.<sup>[8]</sup>

The most gratifying progress in the area of hepatitis therapy in the last decade is the development of safe and highly effective direct-acting antivirals (DAAs). DAAs offer a sustained virologic response of greater than 95%, making chronic HCV infection curable in most patients. However, challenges remain, including high cost, limited availability, and drug-drug interactions (DDI) between DAAs and medicines used to treat comorbidities, such as human immunodeficiency virus (HIV) infection, coronary heart diseases, and hyperlipidemia. The potential risks posed by DDI should be considered when selecting DAAs regimens. On the contrary, to cure chronic HBV infection is extremely challenging. Less than 20% of patients with chronic hepatitis B (CHB) who receive currently approved anti-HBV regimens can achieve HBV surface antigen (HBsAg) loss, which is associated with functional remission and improved long-term outcome, and is considered to be a “functional cure” (also referred to as clinical or immunologic cure) for CHB. In addition, combination strategies are less cost-effective than first-line nucleos(t)ide analog monotherapy even though they might lead to higher HBsAg loss rate in some specific subgroup of CHB patients.<sup>[9]</sup> Forty-nine percent of CHB patients failed to achieve fibrosis regression after a 5-year treatment with tenofovir disoproxil fumarate, one of the first-line anti-HBV agents.<sup>[10]</sup> This failure suggests the necessity of long-term anti-HBV treatment and the urgent need of adding anti-fibrosis medication on the basis of antiviral therapy.

Recently, 2 strategies, namely curing HBV infection without killing infected cells and inducing immune control to safely eliminate HBV-infected cells were proposed by the International Coalition to Eliminate HBV (ICE-HBV) to achieve the goal of HBV cure.<sup>[11]</sup> Given the fact that persistence of viral covalently closed circular DNA (cccDNA) transcriptional template is a major barrier to curing HBV, cccDNA elimination will be the most direct and efficient strategy to cure chronic HBV infection. A better understanding of the HBV lifecycle, host immune response, and virus-immune interaction must be achieved to implement these strategies. Novel direct anti-HBV agents with superior efficacy and safety profile and immunotherapy are the predominant approaches to achieve HBV cure. On one hand, several direct anti-HBV agents that target directly the replication cycle of HBV presented promising efficacy and safety in phase 2 clinical trials. For example, nucleic acid polymers that inhibit assembly and secretion HBV subviral particles increased the rates of HBsAg loss and HBsAg seroconversion during therapy and functional cure after therapy.<sup>[12]</sup> On the other hand, better understanding of host immune response in HBV infection contribute to the development of immunotherapy of HBV. Host immune response plays an important role in HBV clearance and HBV infection control by modulating the innate and adaptive immune response. In terms of the innate immune response, pathogen recognition receptors, including Toll-like receptors, retinoic acid-inducible gene (RIG)-1-like receptors and nucleotide-binding oligomerization domain (NOD)-like receptors, natural killer cells, antigen presenting cells,

such as dendritic cells and Kupffer cells, are potential targets for HBV immunotherapy. In terms of the adaptive immune response, modulating of HBV-specific CD4+ and CD8+ T cell, regulatory T cell, HBV-specific B cell may contribute to HBV cure. However, none of the above agents has been investigated in phase 3 clinical trials.

For the treatment of chronic DILI, cessation of drugs is necessary and immunosuppressive therapy may be indicated if the injury does not resolve with drug cessation.<sup>[4]</sup> The mainstay of AIH treatment consists of prednisolone to induce remission, in combination with azathioprine, which is used to maintain it. Mycophenolate mofetil (MMF) is a standard second-line treatment for those with azathioprine-intolerance.<sup>[13]</sup> Ursodeoxycholic acid (UDCA) is the first-line therapy for primary biliary cirrhosis (PBC).

As a major consequence of the progression of CLD, portal hypertension (PHT) can lead to death or liver transplantation. In the past three decades, the prognosis of patients with PHT has improved dramatically due to the effective intervention of variceal bleeding, ascites, and other related complications. Currently, terlipressin, somatostatin, and octreotide are first-line drugs in the treatment of acute variceal bleeding in cirrhotic PHT. Administration of nonselective beta-blockers (such as carvedilol and propranolol) is the key to prevent secondary bleeding. The use of dedicated covered esophageal stents and balloon-occluded retrograde transvenous obliteration contribute to improved prognosis of PHT as well. More interestingly, along with a better understanding of pathophysiology in the progression of portal hypertension, some “new” medicines have been investigated in the management of CLD and cirrhosis. For example, accumulating evidence shows that statins have potential beneficial effects in the progression of CLD and cirrhosis, which have changed statins from previously thought risky drugs to kind of wonder drugs for patients with CLD and cirrhosis.<sup>[14]</sup>

In summary, CLD and cirrhosis are substantial health burdens. Although HBV vaccination, screening of viral infection, anti-HBV and anti-HCV treatment have significantly reduced the burden in some areas, the prevalence of CLD and cirrhosis, especially those caused by NAFLD, keeps rising globally. In the evaluation of CLD and cirrhosis, noninvasive assessment of fibrosis and cirrhosis is greatly demanded. Concerning the treatment of CLD and cirrhosis, efficacy varies among CLD and cirrhosis caused by different etiologies. In the era of DAAs, chronic HCV infection becomes curable in most patients, but HBV cure and NASH management are still challenging. DAAs targeting the HBV life cycle and immunotherapy approaches are still on the way. Treatment of NASH has been a hotspot in the field of liver research for quite a few years, but few or none specific medicines have been approved. The development of novel medications to improve the prognosis of NASH is urgently required.

### Acknowledgements

We are grateful to Dr. Ping An (Frederick National Laboratory for Cancer Research) for critically reading and editing the manuscript.

### Funding

This work was supported by a grant from the China 13th Five-Year Science and Technology Major Project on the Prevention and Treatment of Major Infectious Diseases (No. 2017ZX10202202).

### Conflicts of interest

None.

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**How to cite this article:** Xu JH, Yu YY, Xu XY. Management of chronic liver diseases and cirrhosis: current status and future directions. *Chin Med J* 2020;133:2647-2649. doi: 10.1097/CM9.0000000000001084