Guidelines of prevention and treatment for alcoholic liver disease

(2018, China)

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1. INTRODUCTION
Alcoholic liver disease (ALD), induced by long-term heavy alcohol consumption, encompasses a progressive clinical–histological spectrum of liver injuries from simple fatty liver to alcoholic hepatitis, hepatic fibrosis and cirrhosis. Excessive alcohol consumption may lead to extensive hepatocellular necrosis, and in severe cases to liver failure. ALD is one of the most common liver diseases in China, posing a heavy burden to public health. The guidelines, as an update from the 2010 version, provide a more standardized and up-to-date approach to the prevention and treatment of ALD, with reference to the latest researches and consensuses both at home and abroad. The guidelines were developed by the National Workshop on Fatty Liver and Alcoholic Liver Disease, Chinese Society of Hepatology, Chinese Medical Association, in conjunction with the Fatty Liver Disease Expert Committee, Chinese Medical Doctor Association. In the guidelines, quality of evidence (A, B and C) and strength of each recommendation (1 and 2) are rated according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Table 1).

Table 1. Evidence quality and grades of strength of recommendation of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system

<table>
<thead>
<tr>
<th>Grade</th>
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<tr>
<td>Evidence</td>
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<tr>
<td>High quality</td>
<td>A</td>
<td>Further research is less likely to change the confidence in the estimated effect.</td>
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<td>Moderate quality</td>
<td>B</td>
<td>Further research is likely to have an important impact on the confidence in the estimated effect.</td>
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<tr>
<td>Low quality</td>
<td>C</td>
<td>Further research is most likely to have an important impact on the confidence in the estimated effect and may change the estimated effect.</td>
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<td>Recommendation</td>
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<td>Strong</td>
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<td>The final recommendation is based on the quality of evidence, patient's prognosis and treatment costs.</td>
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<tr>
<td>Weak</td>
<td>2</td>
<td>The final recommendation is based on evidence with mixed values, uncertainties and higher costs.</td>
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The guidelines, rather than mandatory standards, are intended to assist clinicians in making appropriate decisions on the diagnosis and treatment of ALD patients. Clinical management should be tailored for each specific individual, in consideration of optimal clinical evidence, medical resources currently available, exact conditions and requirements of each patient, as well as personal knowledge and experience of the decision-maker. As research work on ALD is progressing rapidly, the current guidelines anticipate renewal and further improvement.

2. EPIDEMIOLOGY OF ALD
Despite a lack of nationwide epidemiological data about ALD, endemic investigations have shown an escalating trend in the proportion of drinkers and the prevalence of ALD in China. An epidemiological investigation conducted in North China showed that from the early 1980s to the early 1990s, the proportion of heavy drinkers in
general population had risen from 0.21% to 14.3%. At the beginning of this century, the number was 26.98% in Northeast China, and in some areas, as high as 42.76%. In South, Central and West China, the proportion of drinkers ranged from 30.9% to 43.4%. Some heavy drinkers or binge drinkers may be confronted with alcohol-related health problems, among which ALD is the most common ethanol-induced organ injury. Early in this century, epidemiological investigations carried out in some provinces claimed the prevalence of ALD in China as 0.5–8.55% people in their 40s showed the highest number of up to over 10%. The percentage of ALD patients in those who are hospitalized due to liver diseases keeps rising, from 2.4% in 2000 to 4.3% in 2004; alcohol abuse accounted for up to 24% of cirrhotic cases in 2003, which had risen from 10.8% in 1999. ALD has become one of the most popular chronic liver diseases in China.

3. RISK FACTORS OF ALD

Risk factors that have been considered to be relevant to alcoholic liver injury and ALD include dose, pattern and duration of alcohol consumption, variety of alcoholic beverages, gender, ethnicity, obesity, hepatitis virus infection, genetic variability, and nutritional conditions.

A threshold effect of alcohol-induced liver injury has been noted, based on epidemiological data, that the risk of liver injury is significantly increased when the dose or duration of alcohol consumption reaches a certain point. Yet, individual difference could be observed in the dose–effect relationship between alcohol consumption and liver injury. Alcoholic beverages vary; different alcoholic beverages do harm to the liver on different degrees. Drinking pattern also plays a role in alcohol-related liver injury; drinking on an empty stomach is more prone to cause liver injury than drinking with meals. Compared to episodic or binge drinking, drinking daily is more likely to cause severe alcoholic liver injury. Compared with men, women tend to be more susceptible ethanol-induced liver injury. Moreover, a smaller dose or a shorter drinking duration could give rise to more severe forms of ALD, alcoholic hepatitis and cirrhosis in females. Blood alcohol concentration turns out to be significantly different in men and women after alcohol intake at the same dose. Ethnicity, genetic variability, individual difference are also important risk factors. The difference between Chinese Han population and Western population in allele frequency and genotype distribution of ALD-predisposing genes, such as alcohol dehydrogenase (ADH) 2, ADH3 and acetaldehyde dehydrogenase (ALDH) 2, may partly accounts for the lower ALD incidence in heavy drinkers in China than that in Western countries. Besides, not all drinkers will develop ALD, which suggests that individual difference does exist in the susceptibility of ALD.

The degree of malnutrition correlates closely with ALD mortality. Vitamin A deficiency or a lower serum level of vitamin E can aggravate liver injury. A diet rich in polyunsaturated fatty acid accelerates the progress of ALD while saturated fatty
acid plays a protective role.\textsuperscript{31} Obesity or overweight also leads to a higher risk of ALD progression.\textsuperscript{15}

Hepatitis virus infection exerts a synergistic effect on alcohol-induced liver injury,\textsuperscript{32} drinking based on hepatitis virus infection and hepatitis B virus (HBV) or hepatitis C virus (HCV) infection based on ALD could both accelerate the development and progression of liver diseases.

4. CLINICAL DIAGNOSTIC CRITERIA OF ALD
   (i) A history of long-term alcohol consumption is required, which is generally over 5 years, amounting to ethanol consumption of $\geq 40$ g/day for men and $\geq 20$ g/day for women; or an evidence of binge drinking within 2 weeks, amounting to ethanol consumption of $> 80$ g/day.\textsuperscript{33} Factors such as gender and hereditary susceptibility should be considered. Ethanol consumption (g) = alcohol consumption (mL) $\times$ ethanol content (%) $\times$ 0.8. Such scales as the Alcohol Use Disorders Inventory Test (AUDIT), the Michigan Alcoholism Screening Test (MAST), the CAGE, can be used to screen for alcohol abuse and dependence.\textsuperscript{34,35}

   (ii) Symptoms and signs are non-specific and variable, from asymptomatic to possible complaints include right upper abdominal pain, inappetence, fatigue, weight loss and jaundice. As the disease progresses, neuropsychical symptoms, spider angiomia and palmar erythema, etc., can be observed.\textsuperscript{33}

   (iii) Laboratory abnormalities in ALD may include elevated serum levels of aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyltransferase (GGT), total bilirubin (TBIL), prothrombin time (PT), mean corpuscular volume (MCV), and carbohydrate deficient transferrin (CDT). The ratio of AST/ALT $> 2$, as well as elevated GGT and MCV levels are deemed as markers of ALD.\textsuperscript{33,36–38} CDT test, although quite specific, has not been routinely applied in clinical practice. Significant decrease in these indices could be observed after the discontinuation of alcohol consumption, usually back to normal level within 4 weeks (though GGT presented a slower decreasing curve),\textsuperscript{39,40} which may be helpful in the diagnosis of ALD.

   (iv) Typical manifestations can be observed in liver B-type ultrasonography, X-ray computed tomography (CT), magnetic resonance imaging (MRI) or transient elastography (TE) examination (see the section of imaging diagnosis).\textsuperscript{41–50}

   (v) Absence of current infection of hepatotropic viruses, drug or toxin-induced liver injury, autoimmune diseases, etc.\textsuperscript{33}

Recommendation 1: Since there is no specific clinical diagnostic method for ALD, possessing a history of long-term alcohol consumption is essential for identifying alcohol as the cause of liver disease. Patients who meet the criteria i, iii and iv can be diagnosed as ALD to the exclusion of liver diseases resulting from other causes; those who meet the criteria i, iii and iv with evidence of current hepatitis virus infection can be diagnosed as ALD with viral hepatitis. (A1)

Those who meet the clinical diagnostic criteria can be classified as follows.
(vi) Mild ALD: results of liver biochemical, imaging and histopathological tests are basically normal or slightly abnormal.

(vii) Alcoholic fatty liver: imaging results are consistent with the diagnostic criteria of fatty liver, with or without slight abnormality of serum ALT, AST or GGT levels.

(viii) Alcoholic hepatitis: it is a clinical syndrome induced by extensive hepatocellular necrosis within a short period of time, mainly manifested as elevated levels of serum ALT, AST or GGT, with or without elevated TBIL level, possibly accompanied by fever or elevated neutrophil level in peripheral blood. Severe alcoholic hepatitis can be diagnosed when a ALD patient presents signs of liver failure, such as jaundice, coagulation disturbance, hepatic encephalopathy, acute renal failure, upper gastrointestinal bleeding, usually accompanied by endotoxemia.

(ix) Alcoholic hepatic fibrosis: no characteristic changes in clinical symptoms, signs, ultrasonography or CT findings. Without liver biopsy, diagnosis should be made through a comprehensive evaluation of drinking history, TE or MRI examination, laboratory tests of serum markers indicating fibrosis (hyaluronic acid, type III collagen, type IV collagen, laminin), GGT, AST/ALT, AST/platelet (PLT) ratio, cholesterol, apolipoprotein A1, TBIL, a2-macroglobulin, ferritin, homeostatic model assessment for insulin resistance (HOMA-IR), and so on.

(x) Alcoholic cirrhosis: clinical manifestations of cirrhosis can be seen along with its typical changes in serum biochemical markers, TE and other imaging examinations.

5. IMAGING DIAGNOSIS OF ALD

5.1. Ultrasonography
Diffuse fatty liver can be diagnosed when at least two of the following three abdominal ultrasonographic manifestations are present: (i) diffuse enhancement of near field echo in the hepatic region, which is stronger than that in the renal region; (ii) gradual attenuation of far field echo; (iii) unclear display of intrahepatic lacuna structure. However, only when fatty infiltration exceeds 30% can hepatic steatosis be determined by ultrasonography. Other limitations of ultrasonography include its equipment or operator-dependency and inability to distinguish steatohepatitis from simple fatty liver.

5.2. TE examination
Liver stiffness and steatosis can be measured at the same time. Controlled attenuation parameter (CAP), a highly sensitive, non-invasive method for the assessment of steatosis based on TE, is able to detect steatosis as mild as 5%. CAP also features its high specificity and stability. Furthermore, its diagnostic thresholds for hepatic steatosis at different grades are free from disturbance of any other causes of chronic liver diseases. For advanced ALD, thresholds of liver stiffness measurement (LSM) for fibrosis and cirrhosis are 12.96 kPa and 22.7 kPa, respectively. TE monitoring is of prognostic value as well.

5.3. CT
Diffusely decreased liver density with the ratio of liver/spleen CT value of \( \leq 1 \) is adopted as the diagnostic standard: mild fatty liver, liver/spleen CT value ratio \( >1.0 \) but \( >0.7 \); moderate fatty liver, liver/spleen CT value \( \leq 0.7 \) but \( >0.5 \); severe fatty liver,
liver/spleen CT value ≤0.5.

5.4. MRI
Magnetic resonance spectroscopy (MRS), dual gradient-echo in-phase and out-of-phase hepatic MRI are useful tools to quantitatively assess hepatic steatosis in ALD. The threshold of magnetic resonance elastography (MRE) for the diagnosis of hepatic fibrosis is 2.93 kPa, with a sensitivity of 98% and a specificity of 99%. MRE can make a complete assessment of lesions in liver parenchyma that is unaffected by obesity or ascites. The area under the receiver operating characteristic curve (AUROC) of MRE for the staging of hepatic fibrosis (F2–F4) approximates 1. Shortcomings should also be noted. Other causes that can result in increased hepatic stiffness, such as inflammation, steatosis, congestion, cholestasis and portal hypertension, may disturb fibrosis assessment by MRE. Besides, the high cost as well as the special demand on equipment makes MRE less utilized than TE.55,56

**Recommendation 2:** Ultrasonography is currently the most commonly used technique for the diagnosis of ALD, and can be adopted as the first choice in virtue of its non-radioactive, non-invasive nature and low cost. However, ultrasonography cannot sensitively identify fatty infiltration below 30%. Other limitations include equipment or operator-dependency and inability to distinguish between simple fatty liver and steatohepatitis. CT can make an overall assessment of liver and distinguish liver cancer from local adipose deposition, yet CT examination is radioactive and can hardly assess fibrosis. MRI, especially 1H magnetic resonance mass spectrometry, is able to non-invasively, quantitatively assess liver fat content, though the high cost and equipment-dependency confines its wide use. (A1)

**Recommendation 3:** As hepatic fibrosis is the most important factor that determines the outcome of the disease, it is of vital significance to identify and quantify fibrosis in order to make definite diagnosis, conduct follow-up visit and evaluate prognosis. On limited resources, AST/PLT ratio is recommended as preliminary non-invasive evaluation of hepatic fibrosis; on occasions when equipment and other economic conditions are available, TE or FibroTest is recommended as the preferred examination. (A1)

**Recommendation 4:** TE provides a rapid, simple, safe and widely adoptable way for hepatic fibrosis assessment in ALD patients. However, hardly can it make accurate determination regarding patients with ascites or morbid obesity. Its demand on operating experience also hinders it from further promotion of application. In order to correctly interpret TE, the following factors should be considered: interquartile range (IQR)/median (<30%), serum transaminase level (<5 × upper limit of normal [ULN]), body mass index (BMI) >30 kg/m², usage of XL probe when skin–liver capsule distance >25 mm, absence of extrahepatic cholestasis, no evidence of right heart failure or liver congestion due to other causes, and exclusion of long-term excessive alcohol consumption. (A1)

6. HISTOPATHOLOGICAL DIAGNOSIS OF ALD
Major pathological changes of ALD are macro-vesicular hepatocyte fatty
degeneration or a mixed type of macro-vesicular dominant with coexistent micro-vesicular fatty degeneration. According to whether the diseased hepatic tissue develops inflammation and fibrosis, ALD can be stratified into simple fatty liver, alcoholic hepatitis, hepatic fibrosis and cirrhosis. A pathological diagnosis report of ALD should cover such parameters as the severity of hepatic steatosis (F0–F3) and inflammation (G0–G4) as well as the staging of hepatic fibrosis (S0–S4).

6.1. Simple fatty liver
Simple fatty liver can be stratified into three grades according to the proportion of hepatocytes with fatty degeneration in the hepatic tissue specimen (F0–F3): F0, presence of fatty degeneration in <5% of the hepatocytes; F1, presence of fatty degeneration in ≥5% but <33% of the hepatocytes; F2, presence of fatty degeneration in ≥33% but <66% of the hepatocytes; F3, presence of fatty degeneration in ≥66% of the hepatocytes.

6.2. Alcoholic hepatitis and fibrosis
Severity of fatty degeneration in alcoholic hepatitis can also be stratified into three grades (F0–F3), in accordance with that of simple fatty liver. In light of the severity of inflammation, alcoholic hepatitis can be divided into four grades (G0–G4): G0, no inflammation; G1, presence of a few balloon-shaped hepatocytes in acinar zone 3, with sporadic isolated spotty acinar necrosis and peri-central vein inflammation; G2, presence of apparent balloon-shaped hepatocytes in acinar zone 3, increased spotty acinar necrosis, Mallory bodies and mild-to-moderate inflammation in portal area; G3, extensive balloon-shaped hepatocytes in acinar zone 3, obvious spotty acinar necrosis, presence of Mallory bodies and apoptotic bodies, moderate inflammation in portal or peri-portal area or both; G4, confluent necrosis or bridging necrosis, or both.

According to the scope and pattern of fibrosis, hepatic fibrosis can be divided into four grades (S0–S4): S0, no fibrosis; S1, focal or extensive peri-sinusoidal or peri-cellular fibrosis in acinar zone 3 and peri-central fibrosis; S2, fibrosis extending to portal area, peri-central sclerosing hyaline necrosis, focal or extensive asterism-shaped fibrosis in portal area; S3, extensive acinar fibrosis, focal or extensive bridging fibrosis; S4, cirrhosis.

**Recommendation 5:** A pathological diagnosis report of ALD should cover the severity of hepatic steatosis (F0–F3) and inflammation (G0–G4) as well as the staging of hepatic fibrosis (S0–S4). (C1)

6.3. Alcoholic cirrhosis
Hepatic lobular structure is completely destroyed, replaced by false lobules and extensive fibrosis, which is defined as micronodular cirrhosis. Cirrhosis is described as active or inactive based on the presence or absence of interface hepatitis at fibrous septa.

7. MANAGEMENT OF ALD

7.1. Evaluation methods
Many methods have been proposed and validated to evaluate the severity and prognosis of ALD, including Child–Pugh classification, Maddrey’s discriminant function (MDF), model for end-stage liver disease (MELD), Glasgow alcoholic
hepatitis score (GAHS), age, bilirubin, international normalized ratio and creatinine score (ABIC), Lille scoring system and TE. The MDF is calculated as 4.6 × increase in PT (s) + TbIL (mg/dL), in which a score of over 32 suggests a high risk of 30-day mortality. MELD score >18, GAHS >8, ABIC >9 can all be deemed as predictors of poor prognosis. As for patients with severe alcoholic hepatitis, after a 7-day corticosteroid therapy, efficacy of treatment can be evaluated by the Lille scoring system, in which a score of >0.45 indicates steroid resistance.

7.2. Treatment

Therapeutic principles of ALD include discontinuation of alcohol consumption, nutrition supplementation, alleviation of the severity of ALD, treatment of existing secondary malnutrition and symptom-oriented treatment of alcoholic cirrhosis as well as its complications.64–66

(i) Abstinence from alcohol

The cornerstone measurement is to ensure a thorough, immediate abstinence from alcohol,67 which can help improve prognosis, histologically ameliorate liver injury, reduce portal pressure, retard the progression of fibrosis and improve survival rates of ALD patients at all stages. Those who have difficulty in quitting drinking proactively could receive an oral baclofen therapy. Alcohol addicts should pay attention to prevention and management of alcohol withdrawal syndrome, which can be treated with tranquilizers.

(ii) Nutrition supplementation

Nutrition support is essential for ALD patients. A high-protein, low-fat diet on the basis of abstinence is recommended; supplementation of vitamin B, vitamin C, vitamin K and folic acid should be noted as well.68–70 The gap in protein intake should be filled in patients with alcoholic cirrhosis. Patients with severe alcoholic hepatitis are encouraged to take an extra meal at night (about 700 kcal/day) to prevent muscle atrophy and increase skeletal muscle capacity. B-group vitamin supplementation should be conducted in time for those presenting obvious symptoms of Wernickel’s encephalopathy.

(iii) Pharmacological treatment

Corticosteroids can improve 28-day survival rates in patients with severe alcoholic hepatitis,71 but fail to make significant improvement in 90-day or half-year survival rates.72 Metadoxine can accelerate clearance of alcohol from the blood and thereby help relieve alcohol poisoning, addiction and behavioral abnormalities,73–75 thus improving survival76,77.

S-adenosyl-L-methionine can improve clinical symptoms and serum biochemical indices of ALD patients.78–80 Polyene phosphatidylcholine can prevent against histological aggravation of ALD.81,82 Glycyrrhizic acid products, silymarin and reduced glutathione, which play their anti-oxidative, anti-inflammatory, and hepatocyte membrane or organelle protective roles on different degrees, can improve liver biochemical indices according to some clinical trials.81,83–85 Bicyclol therapy can also ameliorate alcoholic liver injury.86,87 In particular, in order to avoid further burden on the liver and adverse reactions resulting from drug interactions,
co-administration of multiple anti-inflammatory and liver protective drugs is not recommended.

As ALD patients often present pathological changes of liver fibrosis, treatment against fibrosis should be taken seriously. Up to now, some Chinese traditional herbal medications have been available to treat hepatic fibrosis. Large-sample-sized, randomized, double-blind, placebo-controlled clinical trials should be performed in the future in accordance with evidence-based principles or histological examinations to evaluate objectively the efficacy and safety of these drugs.

Management of ALD-related complications (e.g. esophagogastric variceal bleeding, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatocellular carcinoma) should be actively conducted.\(^\text{67}\)

Liver transplantation should be considered in patients with severe alcoholic cirrhosis, which in the early stage can improve survival. Abstinence from alcohol for 3–6 months is required before transplantation as well as absence of severe alcohol-induced injury of other organs.\(^\text{88,89}\)

**Recommendation 6:** Abstinence from alcohol is the cornerstone of ALD management. Nutrition supplementation is of vital importance. Treatment should be tailored for each patient to decide whether and which kind of pharmacological intervention should be adopted. (A1)

**Recommendation 7:** Hepatic inflammation and fibrosis may continue to exist after abstinence. Pharmacological intervention should be adopted if there is evidence of hepatic inflammation and fibrosis grading \(\geq F2\). Though some anti-inflammatory, liver protective drugs have been validated to be effective in animal models, strict large-sample-sized clinical trials remain anticipated. There is yet no pharmacological recommendation of definite curative effects for alcoholic hepatitis. (B1)

**Recommendation 8:** Active prevention and treatment of ALD-related complications is recommended. For end-stage liver disease, liver transplantation may be considered after abstinence from alcohol for 3–6 months. (B1)

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**REFERENCES**

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