WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL RESEARCH

Review Article

Coden USA: WJPPCL

2026
Volume: 03
Issue: 07
Page: 125-145

ALCOHOLIC LIVER DISEASE: A COMPREHENSIVE REVIEW OF PATHOGENESIS, DIAGNOSIS, AND CURRENT THERAPEUTIC APPROACHES

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Received: 20 May 2026 **Revised: 08 June 2026** **Accepted: 28 June 2026**

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DOI: https://doi.org/10.5281/zenodo.21106403,

ABSTRACT

Alcoholic liver disease (ALD) is a major cause of chronic liver disease and liver-related mortality worldwide. It represents a spectrum of hepatic disorders ranging from simple steatosis and alcoholic steatohepatitis to fibrosis, cirrhosis, hepatocellular carcinoma, and hepatic encephalopathy. Chronic excessive alcohol consumption is the principal risk factor for ALD, although genetic susceptibility, nutritional status, immune dysregulation, oxidative stress, and environmental factors also contribute significantly to disease progression. Ethanol metabolism through alcohol dehydrogenase, cytochrome P450 2E1, and catalase generates acetaldehyde and reactive oxygen species, leading to hepatocellular injury, inflammation, and fibrosis. Early stages of ALD are often asymptomatic, making timely diagnosis challenging. Diagnosis is based on a combination of clinical history, laboratory investigations, non-invasive imaging techniques such as ultrasonography and transient elastography, serum biomarkers, and liver biopsy when indicated. Complete alcohol abstinence remains the cornerstone of treatment and is the most effective intervention for preventing disease progression. Current management strategies include nutritional support, pharmacological therapy for alcohol use disorder, corticosteroids for selected patients with severe alcoholic hepatitis, and liver transplantation for end-stage liver disease. Recent advances in understanding the molecular mechanisms of ALD have led to the investigation of novel therapeutic approaches targeting oxidative stress, inflammation, fibrosis, liver regeneration,

and the gut–liver axis. Although these emerging therapies show considerable promise, further clinical studies are required to establish their efficacy and long-term safety. This review summarizes the epidemiology, pathogenesis, clinical spectrum, diagnosis, current management strategies, and emerging therapeutic approaches for alcoholic liver disease, highlighting recent advances and future directions aimed at improving patient outcomes.

KEYWORDS: Alcoholic liver disease, Alcoholic hepatitis, Hepatic steatosis, Liver fibrosis, Cirrhosis, Hepatocellular carcinoma, Oxidative stress, Alcohol abstinence, Liver transplantation.

INTRODUCTION

Alcoholic liver disease (ALD) is one of the leading causes of chronic liver disease and liver-related mortality worldwide. It develops as a consequence of prolonged excessive alcohol consumption and encompasses a spectrum of hepatic disorders, ranging from simple steatosis (fatty liver) to alcoholic steatohepatitis (ASH), progressive fibrosis, cirrhosis, and ultimately hepatocellular carcinoma (HCC). Although hepatic steatosis is reversible with alcohol abstinence, continued alcohol intake promotes persistent inflammation and hepatocellular injury, leading to irreversible liver damage.[1]

Globally, alcohol consumption remains a major public health concern. According to the World Health Organization, more than 2 billion people consume alcohol, with approximately 57% of the world's population drinking alcohol at some point in their lives. Harmful alcohol use is responsible for nearly 2.3 million deaths annually, accounting for a substantial proportion of liver-related morbidity and mortality. Men generally consume more alcohol than women and therefore have a higher risk of developing ALD, although women are more susceptible to alcohol-induced liver injury at lower levels of consumption.[2]

The risk of ALD is strongly associated with both the quantity and duration of alcohol intake. Chronic consumption of more than 40g of pure alcohol per day significantly increases the likelihood of developing liver injury. The pathological progression of ALD typically begins with alcoholic fatty liver, advances to alcoholic steatohepatitis, and subsequently progresses to fibrosis and cirrhosis. In advanced stages, cirrhosis markedly increases the risk of hepatocellular carcinoma and liver failure.[3]

Alcoholic liver disease represents a significant healthcare burden in both developed and developing countries. Liver cirrhosis remains one of the leading causes of liver-related deaths, and excessive alcohol consumption is a major preventable risk factor. Epidemiological studies, beginning with the pioneering work of Pearl in 1926, demonstrated that heavy alcohol consumption is associated with significantly higher mortality rates, particularly from liver cirrhosis and other chronic liver diseases.[4]

Management of ALD requires a multidisciplinary approach that includes complete alcohol abstinence, treatment of alcohol use disorder, nutritional support, pharmacological therapy for alcoholic hepatitis, and liver transplantation for selected patients with end-stage liver disease. Clinical practice guidelines published by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) provide evidence-based recommendations for the diagnosis, management, and prevention of ALD.[5,6]

This review summarizes the epidemiology, risk factors, pathogenesis, clinical manifestations, diagnosis, current therapeutic strategies, and recent advances in the management of alcoholic liver disease.

Alcohol Metabolism:

Alcohol is rapidly absorbed from the gastrointestinal tract, with approximately 20–30% absorbed through the stomach and 70–80% through the small intestine. After absorption, ethanol is distributed throughout body fluids and is metabolized primarily in the liver, where nearly 90–98% of ingested alcohol undergoes metabolism, while the remaining 2–10% is excreted unchanged through breath, urine, and sweat.

Ethanol metabolism occurs through both oxidative and non-oxidative pathways. The oxidative pathway is the principal route and involves three major enzyme systems: alcohol dehydrogenase (ADH), the microsomal ethanol-oxidizing system (MEOS) mediated by cytochrome P450 2E1 (CYP2E1), and catalase.[7]

Oxidative Pathway:

The major pathway of ethanol metabolism is catalyzed by alcohol dehydrogenase (ADH), a cytosolic enzyme predominantly expressed in hepatocytes. Human ADHs are encoded by seven genes located on chromosome 4 and are classified into five enzyme classes. Among these, Class I ADH enzymes (ADH1A, ADH1B, and ADH1C) are responsible for

metabolizing most ingested ethanol to acetaldehyde, a highly reactive and toxic intermediate. During this reaction, nicotinamide adenine dinucleotide (NAD^+) is reduced to NADH, resulting in an increased hepatic NADH/NAD^+ ratio. This altered redox state disrupts normal cellular metabolism, promotes lipid accumulation, inhibits fatty acid oxidation, and enhances susceptibility to oxidative stress and liver injury.[8]

The metabolic pathway can be summarized as follows:
Ethanol → Acetaldehyde → Acetate → CO_2 + H_2O

Acetaldehyde is subsequently oxidized by aldehyde dehydrogenase (ALDH) to acetate, which is further converted into carbon dioxide and water through the tricarboxylic acid (TCA) cycle.

Microsomal Ethanol-Oxidizing System (MEOS):

During chronic alcohol consumption, the activity of the MEOS, particularly CYP2E1, is markedly induced. CYP2E1 becomes increasingly important at higher blood ethanol concentrations and converts ethanol to acetaldehyde. Unlike ADH, CYP2E1 metabolism generates excessive reactive oxygen species (ROS), including superoxide anions, hydroxyl radicals, and hydroxyethyl radicals. These reactive molecules initiate lipid peroxidation, mitochondrial dysfunction, protein oxidation, and DNA damage, thereby contributing significantly to hepatocellular injury and the progression of alcoholic liver disease. Furthermore, CYP2E1 is expressed in extrahepatic tissues such as the brain, where ADH activity is relatively low, allowing ethanol metabolism to occur outside the liver.[9]

Catalase Pathway:

Catalase is a heme-containing enzyme located mainly in the peroxisomes of hepatocytes. Under physiological conditions, catalase decomposes hydrogen peroxide (H_2O_2) into water and oxygen. In the presence of ethanol, catalase can also oxidize ethanol to acetaldehyde using hydrogen peroxide as an electron acceptor. Although this pathway contributes only a minor proportion of total ethanol metabolism in humans, it may play a more significant role in tissues with limited ADH activity, such as the brain.[10]

Non-Oxidative Pathway:

A small fraction of ethanol is metabolized through non-oxidative pathways, which involve conjugation reactions rather than oxidation. These pathways produce metabolites including

ethyl glucuronide (EtG), ethyl sulfate (EtS), phosphatidylethanol (PEth), and fatty acid ethyl esters (FAEEs). Although these metabolites account for only a small percentage of total ethanol metabolism, they persist in biological fluids longer than ethanol itself and serve as valuable biomarkers of recent or chronic alcohol consumption in clinical and forensic investigations.

Spectrum of Alcoholic Liver Disease:

Alcoholic Steatosis (Fatty Liver):

Alcoholic steatosis is the earliest and most common manifestation of alcoholic liver disease (ALD). It develops in nearly all individuals who consume more than 40g of alcohol daily over a prolonged period. Steatosis is characterized by the abnormal accumulation of triglycerides, diglycerides, monoglycerides, and free fatty acids within hepatocytes in the form of lipid droplets. Under normal physiological conditions, the liver contains less than 5% lipid; hepatic fat accumulation exceeding this level is considered pathological and is referred to as fatty liver.[11,12]

Grossly, the liver is enlarged, soft, yellow, and greasy in appearance. Histologically, steatosis is classified into microvesicular and macrovesicular forms, with lesions predominantly affecting zone 3 (centrilobular or perivenular region) of the hepatic lobule.[13]

Microvesicular steatosis is characterized by numerous small lipid droplets surrounding a centrally located nucleus, whereas macrovesicular steatosis, the predominant pattern in ALD, consists of a single large lipid droplet that displaces the nucleus to the cell periphery.[14]

Although alcoholic steatosis is generally asymptomatic and completely reversible following alcohol abstinence, persistent alcohol consumption promotes progression to alcoholic steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. Furthermore, fatty liver increases hepatic susceptibility to toxic injury from drugs and chemicals such as carbon tetrachloride because chronic alcohol exposure induces CYP2E1, enhancing the generation of toxic metabolites and oxidative stress.[15-19]

Alcoholic Steatohepatitis (ASH):

Alcoholic steatohepatitis (ASH) represents the intermediate stage between simple steatosis and advanced liver injury. It is characterized by hepatic steatosis accompanied by hepatocellular inflammation, ballooning degeneration, and varying degrees of fibrosis. Unlike

simple steatosis, ASH carries a substantially greater risk of progression to cirrhosis and liver failure.

Patients with ASH are frequently asymptomatic or present with mild, nonspecific symptoms. The cornerstone of treatment is complete alcohol abstinence, together with nutritional support and appropriate medical management. Early intervention may halt disease progression and improve liver function.[20]

Alcoholic Hepatitis (AH):

Alcoholic hepatitis is an acute inflammatory syndrome occurring in individuals with prolonged excessive alcohol consumption. Approximately 10–35% of heavy drinkers develop alcoholic hepatitis during their lifetime.[22] The condition is characterized by hepatocyte injury, inflammatory cell infiltration, and varying degrees of hepatic necrosis.

The pathogenesis involves activation of inflammatory pathways mediated by cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8). Chronic alcohol consumption increases intestinal permeability, allowing bacterial endotoxins to enter the portal circulation. These endotoxins activate hepatic Kupffer cells, leading to excessive cytokine release. TNF-α subsequently activates caspase-dependent apoptotic pathways, resulting in hepatocyte death and progressive liver injury.[23]

Clinically, alcoholic hepatitis presents with jaundice, fever, hepatomegaly, right upper quadrant pain, anorexia, weight loss, ascites, hepatic encephalopathy, and varying degrees of hepatic and renal dysfunction. Severe alcoholic hepatitis is associated with high short-term mortality and requires prompt medical management.

Alcoholic Cirrhosis

Alcoholic cirrhosis represents the end stage of chronic alcoholic liver disease and is characterized by diffuse fibrosis, regenerative nodules, distortion of hepatic architecture, and progressive loss of liver function. Approximately 10–20% of chronic heavy drinkers eventually develop cirrhosis.

Persistent exposure to acetaldehyde stimulates hepatic stellate cells, leading to excessive collagen synthesis and extracellular matrix deposition. Simultaneously, reactive oxygen species generated by CYP2E1 and NADPH oxidase cause lipid peroxidation, protein

oxidation, mitochondrial dysfunction, and hepatocyte membrane damage, thereby accelerating fibrosis.[24]

Several factors influence the development of alcoholic cirrhosis, including the duration and quantity of alcohol intake, nutritional status, obesity, viral hepatitis, and genetic susceptibility. Women are particularly vulnerable to alcohol-induced liver injury, developing cirrhosis after lower cumulative alcohol exposure than men. Increased Kupffer cell activity and differences in alcohol metabolism are believed to contribute to this enhanced susceptibility.[25-28]

Alcoholic Hepatocellular Carcinoma (HCC):

Patients with alcoholic cirrhosis have a significantly increased risk of developing hepatocellular carcinoma (HCC). Chronic inflammation, oxidative stress, acetaldehyde-mediated DNA damage, and continuous hepatocyte regeneration contribute to hepatic carcinogenesis. Reactive oxygen species and acetaldehyde induce genetic mutations, chromosomal instability, and impaired DNA repair mechanisms, promoting malignant transformation.[29]

Clinical manifestations include fatigue, anorexia, unintended weight loss, abdominal discomfort, hepatomegaly, and worsening liver function. Surveillance with abdominal ultrasonography every six months, with or without serum alpha-fetoprotein (AFP) estimation, is recommended for patients with alcoholic cirrhosis to facilitate early detection.

Treatment depends on tumor stage and liver function. Curative options include surgical resection, liver transplantation, radiofrequency ablation, microwave ablation, and percutaneous ethanol injection, whereas advanced disease is managed with systemic therapies or palliative treatment.[30]

Hepatic Encephalopathy:

Hepatic encephalopathy (HE) is a potentially reversible neuropsychiatric disorder resulting from severe liver dysfunction or portosystemic shunting. Impaired hepatic detoxification leads to the accumulation of neurotoxins, particularly ammonia, which cross the blood-brain barrier and disrupt normal neuronal function.[31]

Clinical manifestations range from subtle cognitive impairment and personality changes to confusion, disorientation, asterixis (flapping tremor), seizures, and coma. Early-stage HE commonly presents with memory impairment, irritability, reduced attention, and sleep–wake

cycle disturbances, whereas advanced stages are characterized by severe neurological dysfunction and cerebral edema. Electroencephalography (EEG) typically demonstrates generalized slowing of alpha-wave activity.[32,33]

Hepatic encephalopathy is clinically classified into four stages:

- Stage I: Mild confusion, irritability, impaired concentration, and reversal of the sleep–wake cycle.
- Stage II: Lethargy, disorientation, personality changes, and asterixis.
- Stage III: Marked confusion, incoherent speech, somnolence, and inability to perform mental tasks.
- Stage IV: Deep coma, with severe cerebral edema and a high risk of death if untreated.

Early diagnosis and prompt management are essential to prevent irreversible neurological damage and improve survival in patients with advanced alcoholic liver disease.

Signs and Symptoms of Alcoholic Liver Disease

The clinical manifestations of alcoholic liver disease (ALD) vary according to the stage and severity of liver injury. Early-stage disease, particularly alcoholic steatosis, is often asymptomatic and is frequently detected incidentally during routine laboratory investigations or imaging studies. As liver injury progresses to alcoholic hepatitis, fibrosis, and cirrhosis, patients develop increasingly severe clinical features.

Patients with alcoholic steatosis are generally asymptomatic, although some may complain of fatigue, malaise, right upper quadrant discomfort, or mild hepatomegaly. These symptoms are usually reversible with sustained alcohol abstinence.

Alcoholic hepatitis presents with acute inflammation of the liver and is characterized by jaundice, fever, anorexia, nausea, vomiting, weight loss, fatigue, tender hepatomegaly, and right upper quadrant abdominal pain. In severe cases, patients may develop ascites, coagulopathy, hepatic encephalopathy, renal dysfunction, and multiorgan failure, resulting in a high risk of mortality.

As the disease progresses to alcoholic cirrhosis, patients develop manifestations of chronic liver failure and portal hypertension. Common clinical findings include hepatomegaly or a shrunken nodular liver, splenomegaly, ascites, peripheral edema, jaundice, muscle wasting, spider angiomas, palmar erythema, gynecomastia, testicular atrophy, caput medusae, and easy

bruising due to impaired coagulation. Advanced cirrhosis may also present with esophageal variceal bleeding, spontaneous bacterial peritonitis, hepatorenal syndrome, and hepatic encephalopathy.

Patients with hepatocellular carcinoma (HCC) arising from alcoholic cirrhosis may present with persistent abdominal pain, progressive weight loss, anorexia, fatigue, worsening jaundice, abdominal mass, or sudden hepatic decompensation. Since early HCC is often asymptomatic, regular surveillance with abdominal ultrasonography, with or without serum alpha-fetoprotein (AFP), is recommended in patients with cirrhosis.[3,4]

The severity of clinical manifestations generally correlates with the extent of hepatic injury. Early recognition of these signs and symptoms, together with prompt alcohol abstinence and appropriate medical management, is essential to prevent disease progression and improve long-term clinical outcomes.

Diagnosis:

Alcoholic liver disease (ALD) is diagnosed through a combination of clinical history, physical examination, laboratory investigations, imaging techniques, and, when necessary, liver biopsy. Since no single diagnostic test is specific for ALD, diagnosis primarily depends on documenting excessive alcohol consumption together with clinical and biochemical evidence of liver injury while excluding other causes of chronic liver disease. Early stages of ALD, particularly alcoholic steatosis, are often asymptomatic, making timely identification challenging.[34]

Individuals presenting with elevated liver enzymes, clinical features of hepatitis, or signs of chronic liver disease should be carefully evaluated for alcohol use disorder (AUD). However, obtaining an accurate alcohol consumption history may be difficult because patients frequently underreport their alcohol intake. Therefore, laboratory markers and imaging studies play an important role in supporting the diagnosis.[35]

Routine laboratory findings in ALD typically demonstrate an aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio greater than 2:1, elevated gamma-glutamyl transferase (GGT), increased mean corpuscular volume (MCV), and elevated serum immunoglobulin A (IgA) levels. These findings are suggestive but not diagnostic of ALD. In selected patients, liver biopsy may be required to confirm the diagnosis or exclude other liver

diseases. Histopathological features commonly include macrovesicular steatosis, hepatocyte ballooning, neutrophilic infiltration, Mallory-Denk bodies, and varying degrees of fibrosis.[36-38]

Early diagnosis is essential because alcohol abstinence can halt disease progression and even reverse steatosis and mild alcoholic hepatitis. Regular screening of high-risk individuals facilitates timely intervention and improves clinical outcomes.

Non-Invasive Diagnostic Tools:

Ultrasonography:

Abdominal ultrasonography is the first-line imaging modality for evaluating ALD because it is non-invasive, inexpensive, widely available, and easy to perform. It is particularly useful for detecting hepatic steatosis, with a reported sensitivity of 60–94% and specificity of 88–95%. However, its diagnostic accuracy decreases in patients with mild steatosis or obesity.[39,40]

Magnetic Resonance Imaging (MRI):

Magnetic resonance imaging (MRI), including MRI-proton density fat fraction (MRI-PDFF) techniques, provides accurate and reproducible quantification of hepatic fat content. MRI is more sensitive than ultrasonography for detecting mild steatosis but is limited by higher cost and reduced availability.[41]

Controlled Attenuation Parameter (CAP):

Controlled attenuation parameter (CAP), measured during transient elastography, is a novel ultrasound-based technique used to quantify hepatic steatosis. CAP offers a rapid, non-invasive assessment of liver fat and has demonstrated good diagnostic accuracy for grading steatosis in patients with chronic liver disease.[42]

Transient Elastography:

Transient elastography (FibroScan®) has become an established non-invasive method for assessing liver stiffness, allowing early detection of hepatic fibrosis and cirrhosis. Liver stiffness measurements correlate well with the severity of fibrosis and are increasingly used for routine screening and follow-up of patients with ALD.[43]

Blood Tests and Biomarkers:

Several biochemical markers are available to assess chronic alcohol consumption and alcohol-induced liver injury. These biomarkers are broadly classified as indirect and direct markers.

Indirect Biomarkers:

Indirect biomarkers reflect physiological changes associated with chronic alcohol intake and include Gamma-glutamyl transferase (GGT), Mean corpuscular volume (MCV), Carbohydrate-deficient transferrin (CDT), 5-Hydroxytryptophol (5-HTOL)

Among these, carbohydrate-deficient transferrin (CDT) is considered one of the most specific laboratory markers for identifying sustained heavy alcohol consumption over several weeks. However, combining CDT with GGT improves diagnostic sensitivity.[44]

Direct Biomarkers:

Direct biomarkers are metabolites formed during ethanol metabolism and provide objective evidence of recent alcohol intake. These include Ethyl glucuronide (EtG), Ethyl sulfate (EtS), Phosphatidylethanol (PEth), Fatty acid ethyl esters (FAEEs).

These biomarkers are highly useful for monitoring alcohol abstinence, detecting relapse, and supporting the diagnosis of alcohol use disorder because they remain detectable for longer periods than ethanol itself.[45]

Liver Biopsy:

Although liver biopsy is not routinely required, it remains the gold standard when the diagnosis is uncertain or when coexisting liver diseases are suspected. Histological examination provides valuable information regarding the degree of steatosis, inflammation, hepatocyte ballooning, Mallory-Denk bodies, fibrosis, and cirrhosis, thereby assisting in disease staging and prognosis.[45]

Management:

The primary goal in the management of alcoholic liver disease (ALD) is complete and sustained abstinence from alcohol, which remains the most effective intervention at every stage of the disease. Alcohol cessation slows disease progression, improves liver function, reduces complications, and enhances long-term survival. In patients with early-stage ALD,

abstinence may completely reverse hepatic steatosis, while in advanced disease it reduces the risk of hepatic decompensation and mortality.

Successful management of ALD requires a multidisciplinary approach involving hepatologists, addiction specialists, psychiatrists, nutritionists, and social support services. Management includes treatment of alcohol use disorder (AUD), nutritional rehabilitation, pharmacotherapy, psychosocial counselling, and regular follow-up to prevent relapse.[46]

Patients with alcohol dependence who abruptly discontinue alcohol intake are at risk of developing alcohol withdrawal syndrome (AWS), which usually begins within 6–24 hours after the last drink. Clinical manifestations range from tremors, anxiety, insomnia, sweating, tachycardia, and hypertension to severe complications such as seizures, delirium tremens, coma, and death. Benzodiazepines remain the first-line treatment for AWS because they effectively reduce withdrawal symptoms and prevent seizures. Adjunctive agents such as β-blockers or α_2-adrenergic agonists may be used to control autonomic hyperactivity in selected patients.[47]

Nutritional assessment and correction of protein-calorie malnutrition, vitamin deficiencies (particularly thiamine, folic acid, and vitamin D), and electrolyte abnormalities are essential components of ALD management. Regular physical activity and lifestyle modification further improve overall health and support long-term abstinence.[48]

At the population level, public health measures such as increased alcohol taxation, restriction of alcohol availability, increasing the legal drinking age, and limiting alcohol advertising have proven effective in reducing harmful alcohol consumption and the burden of ALD.[49]

Current Therapies and Future Approaches:

Continued alcohol consumption remains the most important predictor of disease progression; therefore, maintaining lifelong abstinence is the cornerstone of treatment. Patients with advanced ALD who continue drinking are generally not considered suitable candidates for liver transplantation. Long-term recovery often requires structured rehabilitation programs, behavioural therapy, and strong family support.[50]

Pharmacological Treatment for Alcohol Use Disorder:

Several medications are available to reduce alcohol craving and prevent relapse:

- Disulfiram, an irreversible inhibitor of aldehyde dehydrogenase, produces unpleasant reactions following alcohol consumption. However, because of its potential hepatotoxicity, it is not recommended in patients with alcoholic liver disease.
- Acamprosate reduces alcohol craving and helps maintain abstinence. Since it is primarily excreted by the kidneys, it is generally considered safer than hepatically metabolized medications in patients with liver disease.
- Naltrexone, an opioid receptor antagonist, decreases alcohol craving and relapse rates, although its clinical efficacy is modest. Because of possible hepatotoxicity, liver function should be monitored during therapy.[51]
- Baclofen, a GABA-B receptor agonist, has shown promising results in promoting abstinence and is considered relatively safe in patients with advanced liver disease. It is increasingly used when other anti-craving medications are contraindicated.

Currently, no approved antifibrotic therapy is available to prevent or reverse hepatic fibrosis in ALD. Disease progression is monitored using liver biopsy or non-invasive methods such as transient elastography and serum fibrosis biomarkers.[52,53]

Specific Treatment of Alcoholic Hepatitis:

1. Corticosteroids:

Corticosteroids remain the standard pharmacological treatment for severe alcoholic hepatitis in patients without contraindications. They suppress hepatic inflammation by reducing pro-inflammatory cytokine production while enhancing anti-inflammatory responses. Clinical trials have demonstrated that prednisolone improves short-term (28-day) survival in selected patients with severe alcoholic hepatitis.[54,55]

2. Antioxidant Therapy:

Oxidative stress plays a central role in the pathogenesis of alcoholic liver injury, making antioxidant therapy an attractive therapeutic strategy.

N-acetylcysteine (NAC) replenishes intracellular glutathione stores, reduces oxidative stress, and improves mitochondrial function. Although NAC alone has limited survival benefit, its combination with prednisolone has been shown to improve one-month survival and reduce

the incidence of hepatorenal syndrome and severe infections compared with corticosteroid therapy alone.[56-58]

Metadoxine enhances glutathione metabolism, accelerates ethanol clearance, and inhibits hepatic steatosis. Clinical studies suggest that combining metadoxine with corticosteroids improves both short-term and long-term survival while promoting sustained alcohol abstinence.[59-61]

3. Liver Regeneration Therapy:

Impaired liver regeneration contributes significantly to the poor prognosis of severe alcoholic hepatitis. Novel regenerative therapies are currently under investigation and include Granulocyte colony-stimulating factor (G-CSF), Interleukin-22 (IL-22), Mesenchymal stem cell (MSC) therapy, Induced pluripotent stem cell (iPSC)-based therapy

Although these approaches have shown encouraging preliminary results, current evidence remains insufficient for routine clinical use, and further large-scale clinical trials are required.[62,63]

4. Anti-inflammatory and Anti-apoptotic Therapies:

Alcoholic hepatitis is characterized by excessive activation of inflammatory pathways involving cytokines such as TNF-α, IL-1β, and IL-6.

Pentoxifylline (PTX), a non-selective phosphodiesterase inhibitor that suppresses TNF-α production, was previously used in severe alcoholic hepatitis. However, recent clinical trials failed to demonstrate significant survival benefits, and current international guidelines no longer recommend its routine use.[64,65]

Several novel immunomodulatory therapies, including IL-1β antagonists, IL-22 agonists, and C-C chemokine receptor antagonists, are currently being investigated as potential treatments for alcoholic hepatitis.[66,67]

5. Liver Transplantation:

Liver transplantation remains the definitive treatment for patients with end-stage alcoholic liver disease or severe alcoholic hepatitis who fail to respond to medical therapy. Studies have demonstrated that early liver transplantation significantly improves six-month survival

in carefully selected patients with severe alcoholic hepatitis who are non-responsive to corticosteroid therapy.[68-70]

Advances in patient selection and post-transplant care have resulted in survival outcomes comparable to those of liver transplantation performed for other chronic liver diseases. Nevertheless, transplantation is limited by donor organ shortage, surgical complexity, high cost, immunological complications, and ethical concerns regarding alcohol relapse. Careful psychosocial assessment and commitment to long-term abstinence remain essential criteria for transplantation eligibility.[71]

Future Perspectives:

Recent advances in understanding the molecular mechanisms underlying alcoholic liver disease have led to the development of several emerging therapeutic strategies. These include antifibrotic agents, gut microbiota-targeted therapies, cytokine modulators, stem cell therapy, regenerative medicine, and precision medicine approaches based on genetic and molecular profiling. Although many of these therapies remain investigational, they offer promising opportunities to improve outcomes in patients with advanced alcoholic liver disease. Future large-scale randomized clinical trials are needed to establish their long-term efficacy and safety.

CONCLUSION

Alcoholic liver disease (ALD) remains a major global health challenge and a leading cause of chronic liver disease, liver-related morbidity, and mortality. It encompasses a broad spectrum of pathological conditions ranging from reversible hepatic steatosis to alcoholic hepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma. The progression of ALD is driven by complex interactions among excessive alcohol consumption, oxidative stress, acetaldehyde toxicity, immune dysregulation, genetic susceptibility, and environmental factors, resulting in progressive hepatic injury and fibrosis.

Early diagnosis and sustained alcohol abstinence remain the cornerstone of ALD management and are the most effective strategies for preventing disease progression and improving long-term survival. Comprehensive patient care should include nutritional support, management of alcohol use disorder, pharmacological therapy for selected patients, and timely intervention for complications of advanced liver disease. Although corticosteroids and

liver transplantation provide benefit in carefully selected patients with severe alcoholic hepatitis or end-stage liver disease, effective disease-modifying therapies remain limited.

Recent advances in the understanding of ALD pathogenesis have identified several promising therapeutic targets, including oxidative stress, inflammatory cytokines, fibrogenic pathways, gut–liver axis modulation, and regenerative medicine. Emerging approaches such as antifibrotic agents, immunomodulatory therapies, stem cell therapy, and precision medicine hold considerable potential for improving clinical outcomes. However, further large-scale clinical trials are required to establish their long-term efficacy and safety.

In conclusion, reducing the global burden of ALD requires an integrated approach that combines effective public health policies, early diagnosis, comprehensive clinical management, and continued research into novel therapeutic strategies. Advances in personalized medicine and targeted therapies are expected to improve prognosis, reduce liver-related complications, and enhance the quality of life of patients with alcoholic liver disease.

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