IJBPAS, August, 2024, 13(8): 3688-3708

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

ALCOHOLIC LIVER DISEASE: RECENT UPDATE OF MANAGEMENT

KAKADIYA J[2], YADAV P[1*], VERMA VK[1] AND PANDEY B[1]

1: PharmD Scholar, Department of Pharmacy Practice, Parul Institute of Pharmacy and Research, Parul University, Vadodara, Gujarat, India

2: Associate Professor, Department of Pharmacy Practice, Parul Institute of Pharmacy and Research, Parul University, Vadodara, Gujarat, India

***Corresponding Author: Ms. Preeti Yadav: E Mail: vidyasur@rediffmail.com**

Received 15th April 2023; Revised 8th Aug. 2023; Accepted 1st Nov. 2023; Available online 1st Aug. 2024

https://doi.org/10.31032/IJBPAS/2024/13.8.8215

ABSTRACT

Alcoholism in excess is a problem for heath worldwide. Since the liver is the main site of ethanol metabolism, heavy drinking causes the most tissue damage to it. Steatosis, hepatitis, and fibrosis/cirrhosis are the most recognizable liver lesions that are caused by chronic and heavy alcohol use. The first sign of heavy drinking is steatosis, which is characterized by the accumulation of fat in hepatocytes. Steatohepatitis, a more serious inflammatory form of liver disease, can develop from steatosis. This stage of liver illness can result in the growth of fibrosis, a condition in which an excessive amount of extracellular matrix proteins are deposited. Beginning with active pericellular fibrosis, the fibrotic response can develop to cirrhosis, which is characterized by excessive liver scarring, vascular changes, and ultimately liver failure. A number of disease modifiers worsen, impede, or stop the progression of alcoholic liver disease, resulting in around 35 percent of problem drinkers developing severe liver disease. Pharmacological or nutritional therapy for the treatment of people with alcoholic liver disease are still not FDA-approved. Abstinence from alcohol is a crucial component of therapy. The only treatment option for patients with advanced alcoholic liver damage is liver transplantation.

Keywords: Alcoholic liver disease, alcoholic hepatitis, liver cirrhosis/fibrosis

1. INTRODUCTION

Alcoholic liver disease (ALD) is a condition that develops as a result of continuous and excessive alcohol use, causing damage to and malfunction of the liver **[1]**. It is one of the most prevalent liver conditions in the world and has a considerable impact on public health **[2]**. A spectrum of liver illnesses known as ALD includes alcoholic cirrhosis (AC), alcoholic hepatitis (AH), and alcoholic fatty liver disease (AFLD) **[3]**. The first stage of ALD, known as AFLD, is defined by the buildup of fat in the liver. AFLD can later develop to inflammation and liver damage in the form of AH and AC **[4]**.

A number of processes, including direct toxicity of alcohol and its metabolites, oxidative stress, inflammation, and hereditary vulnerability, play a role in the onset and progression of ALD. **[5]**. The frequency and intensity of alcohol use, gender, age, and concomitant conditions like obesity and viral hepatitis are some of the variables that affect the incidence and severity of ALD **[6]**.

A complete clinical evaluation is necessary for the diagnosis of ALD, which includes a review of alcohol consumption, a physical exam, laboratory testing, imaging scans, and, if necessary, a liver biopsy **[7]**. Abstaining from alcohol, using medications like corticosteroids and pentoxifylline, and in severe cases, a liver transplant are all possible treatments for ALD, depending on how bad the condition is **[8. 9]**.

Public health and economic consequences of ALD are severe. It is linked to significant healthcare expenses, such as those for hospitalization, drugs, and diagnostic testing. It is also linked to poor quality of life for those who are affected and their families, as well as lost productivity **[10]**. To lessen the prevalence and financial burden of ALD, effective prevention and management techniques, such as public health campaigns to discourage alcohol use, are required **[11]**.

In conclusion, ALD is a disease that develops in damaged and dysfunctional liver tissue after chronic and heavy alcohol use. The terms "AFLD," "AH," and "AC" refer to a spectrum of liver conditions. Numerous mechanisms are involved in the onset, progression, and diagnosis of ALD, and both its management and therapy necessitate a complete clinical evaluation. Effective prevention and management measures are essential to minimizing the incidence of ALD and improving the outcomes for those who are affected. ALD is a severe public health and economic burden.

The liver's primary physiological functions include the following.:

1. Secretion of Bile
2. Metabolism of Bilirubin
3. Metabolism of Nutrients:

* Fat - fatty acid oxidation, synthesis of cholesterol/lipoproteins and production of ketoacids.
* Protein – Amino acid production, turnover of proteins
* Carbohydrate – converts galactose/fructose to glucose, gluconeogenesis and contains 100g of glycogen for release

4. Metabolic Detoxification:
* Toxins
*Hormones
* Drugs

5. Storage of Minerals and Vitamins:
*Iron
* Copper
* Vitamins ADEKB12
* Glycogen

6. Endocrine functions:
* Activation of vitamin D
* Conversion of thyroxine (T4) to T3
* secretes angiotensinogen
* metabolises hormones

7. Immunological/ Protective Functions Reticuloendothelial Component:
*Filters the portal blood from bacteria
*Important in antigen presentation
* Phagocytosis via kupffer cells
*Removes haemolysis products

8. Inactivation of Toxins and Drugs
* Phase I (oxidation, reduction and hydrolysis)
* Phase II (conjugation/ cytochrome P450 system) **[12]**

2. EPIDEMIOLOGY

The epidemiology of alcoholic liver disease (ALD), a major source of morbidity and mortality in the world, has been widely researched. ALD caused over 3.3 million deaths and 113 million disability-adjusted life years in 2016, according to a worldwide burden of illness analysis **[13]**. Regional differences in the burden of ALD exist, with high-income countries bearing a heavier burden than low- and middle-income nations **[14]**.

Drinking alcohol regularly is a significant risk factor for developing liver disease in developed nations, with ALD being the main contributor in fatalities from liver-related causes **[15]**. The level of alcohol use and other risk factors, such as obesity and viral hepatitis, influence the prevalence of ALD in the general population. Heavy drinking is defined as consuming more than 60 grams of alcohol per day for males and more than 40 grams per day for women. Heavy drinking is associated with an increased risk of ALD **[16]**. Country-specific factors, including cultural and social norms, economic growth, and alcohol pricing legislation, all have an impact on the prevalence of heavy alcohol consumption **[17]**.

Other elements, such as age, gender, and heredity, influence the onset and progression of ALD in addition to the quantity and frequency of alcohol consumption **[18]**. ALD is more common in men than in women, presumably as a result of differences in metabolism and hormonal variables **[19]**. ALD is also influenced by genetics; for example, the chance of developing ALD is raised by specific polymorphisms in the genes that control inflammation and alcohol metabolism **[20]**.

ALD is a condition that can be prevented, and numerous public health programs have been put into place in various nations to lower alcohol intake. These programs include pricing and taxing regulations, prohibitions on alcohol marketing and advertising, and health promotion activities **[21]**. The fact that ALD still has a heavy toll on society despite these measures emphasizes the need for more work to cut down on alcohol use and provide access to efficient therapies.

The burden of ALD, which varies by area and is impacted by a number of variables including alcohol use, obesity, viral hepatitis, age, gender, and heredity, is a significant cause of morbidity and mortality globally. Public health programs to lower alcohol use have been put in place, but the burden of ALD is still quite high, underscoring the need for ongoing efforts to cut back on alcohol use and expand access to efficient therapies.

3. PATHOPHYSIOLOGY

A number of pathogenic pathways are involved in the complex illness known as alcoholic liver disease (ALD). Chronic alcohol use causes toxic metabolites to build up, oxidative stress, and inflammation, all of which harm the liver **[22]**. Steatosis (fatty liver) is the first stage in the pathophysiology of ALD. Steatohepatitis (inflammation and necrosis) is the next stage, and fibrosis and cirrhosis are the final stages **[23]**. Steatosis, which refers to the buildup of fat in the liver, is an early and treatable stage of ALD that is characterized by oxidative stress, poor mitochondrial function, increased fatty acid production, and decreased fatty acid clearance **[24]**. As fat builds up, the size of the liver expands as liver function declines. If drinking alcohol is continued, the liver may develop steatohepatitis, which is characterized by hepatocyte necrosis, apoptosis, and inflammation, as well as the invasion of inflammatory cells such neutrophils, macrophages, and lymphocytes **[25]**. Fibrosis and ultimately cirrhosis are brought on by the activation of hepatic stellate cells, which create extracellular matrix proteins **[26]**. The last stage of ALD, cirrhosis, causes nodular regrowth of the liver and irreversible scarring, which inhibits liver function **[27]**.

3.1 Molecular mechanism

Ethanol Metabolism:-

Acetate and acetaldehyde are produced enzymatically as part of the metabolism of ethanol. In this process, acetaldehyde dehydrogenase (ALDH) and alcohol dehydrogenase (ADH) are the two main enzymes.

3.1.1 Alcohol Dehydrogenase (ADH) Pathway:

- ADH enzymes, especially the ADH1 isoform, which is largely expressed in the liver, are the main metabolizers of ethanol.
- An hydride ion (H-) from ethanol is transferred by ADH to the coenzyme nicotinamide adenine dinucleotide (NAD+), which then catalyzes the conversion of ethanol to acetaldehyde.
- The reversible, ADH-catalyzed process produces NADH as a byproduct **[28]**.

3.1.2 Acetaldehyde Dehydrogenase (ALDH) Pathway:

- Acetaldehyde, the byproduct of ethanol oxidation catalyzed by ADH, is extremely hazardous and needs further processing.
- The transformation of acetaldehyde to acetate is carried out by ALDH enzymes, namely the ALDH2 isoform.
- In order to convert acetaldehyde to acetate and produce NADH, ALDH2 needs NAD+ as a cofactor.
- Alcohol-related disorders are more likely to occur in people with ALDH2 deficiency, which is frequently brought on by the ALDH2*2 gene **[29]**.

3.1.3 Further Metabolism of Acetate:

- Different metabolic fates can be taken by acetate, the byproduct of ethanol metabolism.
- The tricarboxylic acid (TCA) cycle can allow acetate to enter the mitochondria of the liver, where it is then oxidized, creating ATP and carbon dioxide.
- Acetate can also be secreted into the bloodstream and absorbed by other tissues, including skeletal muscle and the brain, where it can be used as an energy source **[30]**.

Damage-Associated Molecular Patterns (DAMPs)

Endogenous chemicals called Damage-Associated Molecular Patterns (DAMPs) are secreted or made visible by harmed, stressed, or dying cells. They serve as warning signs and are essential for triggering and maintaining immune responses. The innate immune system's Pattern Recognition Receptors (PRRs) identify DAMPs, activating immune cells and triggering inflammatory reactions.

Based on their composition and place of origin, DAMPs can be divided into a number of groups. Several instances include:

1. Nuclear DAMPs: High Mobility Group Box 1 (HMGB1), nuclear DNA, and histones are examples of substances that can be found in the nucleus of injured cells, which is where nuclear DAMPs originate. When cells are under stress or die, these chemicals are discharged into the extracellular environment **[31]**.
2. Cytoplasmic DAMPs: Cells that have been damaged or under stress produce cytoplasmic DAMPs. Heat shock proteins (HSPs), ATP, uric acid crystals, and S100 proteins are a few examples of cytoplasmic DAMPs. After cellular injury or stress, these molecules are exposed or released **[32]**.
3. Extracellular Matrix DAMPs: Matrix extracellular DAMPs are produced from extracellular matrix elements that are damaged as a result of tissue damage. Hyaluronic acid, fibronectin, and heparan sulfate fragments can function as DAMPs and set off immunological reactions **[33]**.
4. Mitochondrial DAMPs: Damaged or non-functional mitochondria release mitochondrial DAMPs. Formyl peptides and mitochondrial DNA serve as examples. These chemicals have the capacity to stimulate immune cells and worsen inflammation. **[34]**.

Inflammatory Immune response to Injury

As a defense mechanism, the body launches an inflammatory immune response when tissue damage or injury occurs. Several immune cells, signaling molecules, and pathways come together in this reaction to get rid of pathogens, get rid of detritus, and start tissue repair. The inflammatory immunological response to damage is described below:

1. Recognition of Injury: Damage-Associated Molecular Patterns (DAMPs), a group of chemicals released by injured or damaged cells, are numerous. These DAMPs can be detected by immune cell-expressed pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs), which are expressed on immune cells. The inflammatory

reaction is sparked by the immune system being activated by DAMP detection **[35]**.

2. Activation of Immune Cells: Key participants in the inflammatory immune response are immune cells like dendritic cells, neutrophils, and macrophages. These cells emit pro-inflammatory cytokines such tumor necrosis factor-alpha (TNF-), interleukin-1 beta (IL-1), and IL-6 when activated, which starts and intensifies the inflammatory response **[36]**.
3. Recruitment of Immune Cells: In response to injury, immune cells and wounded cells both secrete chemokines, which are tiny signaling proteins. These chemokines entice and direct immune cells to the damage site. Usually, neutrophils are the first immune cells to enter the scene, then monocytes, macrophages, and other immune cells **[37]**.
4. Phagocytosis and Clearance: In phagocytosing and eliminating infections, debris, and injured cells, neutrophils and macrophages are essential. They consume and break down cellular waste, aiding the clearance of impurities and starting the tissue repair process. **[38]**.
5. Resolution of Inflammation: After the first inflammatory response has done its job, mechanisms that reduce inflammation and encourage tissue healing are triggered. This entails the creation of anti-inflammatory cytokines, which suppress the pro-inflammatory response and support tissue repair. Examples of these are transforming growth factor-beta (TGF-) and IL-10 **[39]**.

Zinc

The function of enzymes, DNA synthesis, the immune system, and antioxidant defense are just a few of the physiological activities that zinc is involved in. The development and advancement of liver damage in the context of ALD can be influenced by zinc deficiency. The connection between ALD and zinc deficiency is discussed in more detail below.:

1. Hepatic Zinc Levels: Hepatic zinc levels in people with ALD are demonstrably lower than normal, according to studies. Zinc deficiency in the liver can interfere with cellular functions, affect liver performance, and advance liver damage **[40]**.
2. Oxidative Stress and Antioxidant Defense: Superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase are antioxidant enzymes that guard against oxidative stress and require zinc as a cofactor.

A zinc shortage can weaken the liver's antioxidant defenses, increasing oxidative damage **[41]**.

3. Impaired Hepatocyte Function: Hepatocytes' structural and functional integrity is crucially maintained by zinc. Zinc shortage can impact the operation of liver cells, affect protein synthesis, and cause cell membrane instability **[42]**.
4. Altered Immune Response: Inflammatory responses are controlled by the immune system, which depends on zinc. Because immune cell activity might be impaired by a zinc shortage in ALD, immunological responses can become dysregulated, increasing the risk of infection **[43]**.

Impaired Regeneration

A prominent characteristic of alcoholic liver disease (ALD) is impaired liver regeneration, which is essential to the development of liver damage. Chronic alcohol use can compromise the liver's normal potential for tissue regeneration, impairing tissue repair and causing liver fibrosis. The liver's poor regeneration in ALD is best understood in light of the following main points:

1. Suppressed Hepatocyte Proliferation: Hepatocytes, the primary functioning cells of the liver, can directly be inhibited from proliferating when alcohol misuse is present. Hepatocyte proliferation is reduced as a result of chronic alcohol exposure because it interferes with DNA synthesis and cell cycle progression **[44]**.
2. Alterations in Signaling Pathways: Multiple signaling pathways involved in liver regeneration can become dysregulated as a result of chronic alcohol use. Epidermal growth factor receptor (EGFR), transforming growth factor-beta (TGF-), and Wnt/-catenin signaling pathways are among the pathways that are impacted; these pathways are essential for hepatocyte proliferation and tissue regeneration **[45]**.
3. Disruption of Liver Stem/Progenitor Cells: The ability of liver stem/progenitor cells to regenerate and replace damaged hepatocytes can be compromised by alcohol misuse. The malfunction of these regenerative cell groups is caused by alcohol-induced oxidative stress, inflammation, and changes in the liver microenvironment **[46]**.
4. Altered Extracellular Matrix Remodeling: Extracellular matrix elements, such collagen, can build up in the liver as a result of excessive alcohol consumption. This changed

matrix composition results in a fibrotic environment that inhibits hepatocyte regeneration and limits the availability of growth hormones and nutrients required for liver repair **[47]**.

CAUSES

Chronic alcohol use is the main cause of ALD, which results in the buildup of harmful metabolites including acetaldehyde and reactive oxygen species in the liver **[48]**. Inflammation and fibrosis are brought on by these metabolites, which harm the liver cells and stir up the immune system. The quantity and frequency of alcohol usage, genetic predisposition, sex, and concurrent medical conditions are some of the factors that affect the development of ALD **[49]**.

ALD is more likely to affect men than women, and it is more likely to affect people with ALD in their families **[49]**. The emergence of ALD is greatly influenced by genetic factors as well. Genetic polymorphisms in alcohol-metabolizing enzymes, like alcohol dehydrogenase and cytochrome P450 2E1, have been linked to the development of ALD, according to studies **[50]**.

Additionally, comorbid illnesses including hepatitis C, metabolic syndrome, and obesity all raise the chance of developing ALD **[49]**. Alcohol drinking increases the risk of liver damage in those with certain disorders. Furthermore, alcohol interferes with the absorption of vital nutrients, causing deficits that can increase liver damage, and poor diet and malnutrition can both contribute to the development of ALD **[49]**.

As a result of the accumulation of toxic metabolites in the liver and ensuing liver damage, persistent alcohol use is the main cause of ALD. Additional factors that contribute to the onset and progression of ALD include sex, concurrent medical problems, poor nutrition, and genetic predisposition **[48-50]**.

RISK FACTORS

Alcohol intake, genetic predisposition, sex, and concurrent medical problems are some of the risk factors that can cause the development of alcoholic liver disease (ALD) **[51]**. The biggest risk factor for ALD is persistent excessive alcohol use **[52]**. Men who drink three to four standard drinks per day and women who drink two to three standard drinks per day are more likely to acquire ALD **[53]**.

An important part of the development of ALD is also played by genetic factors. Alcohol metabolism may be altered by polymorphisms in alcohol-metabolizing enzymes, such as alcohol dehydrogenase and cytochrome P450 2E1 **[54]**. Additionally, the degree of liver damage in individuals with ALD may be influenced by genetic polymorphisms in immune response genes **[55]**.

Another element influencing the likelihood of having ALD is gender. Because of differences in body composition, metabolism, and hormone levels, men are more susceptible than women to acquire ALD **[56]**. In contrast to men, women are more vulnerable to the liver-damaging effects of alcohol and can acquire ALD even with reduced alcohol use **[57]**.

COMPLICATIONS

Chronic liver disease caused by alcoholism called alcoholic liver disease (ALD) can have a number of consequences. According to the frequency and length of alcohol use as well as any underlying medical issues, the severity of the complications may differ.

Cirrhosis, which develops when scar tissue replaces the liver tissue, is one of the most prevalent side effects of ALD. Esophageal varices, ascites, and hepatic encephalopathy can all occur as a result of portal hypertension brought on by cirrhosis. Esophageal varices are enlarged veins in the esophagus that have the potential to burst and cause potentially fatal hemorrhage. Hepatic encephalopathy, a neuropsychiatric disease that develops as a result of the buildup of toxic substances in the brain, is the same as ascites, which is the accumulation of fluid in the abdominal cavity.

Another ALD problem that can happen in people with severe cirrhosis is liver cancer, also known as hepatocellular carcinoma (HCC) or liver cancer. Due to liver inflammation and damage from alcohol use, patients with ALD and cirrhosis are more likely to develop HCC.

In individuals with severe cirrhosis, malnutrition is a frequent side effect of ALD. Reduced food intake, hampered nutrient absorption, and alterations in metabolism are only a few of the causes of malnutrition. Weakness, muscle atrophy, and an elevated risk of infections are all effects of malnutrition.

ALD can also make it more likely for infections to occur because of weakened immune system response brought on by inflammation and liver impairment. Spontaneous bacterial peritonitis (SBP) and hepatitis B and C are two bacterial and viral diseases that are particularly dangerous for patients with ALD.

TREATMENT

Alcoholic liver disease (ALD) is a chronic disorder that, if unchecked, can proceed to liver failure and death. Depending on the severity of the condition and the patient's particular requirements, there are many ALD treatment methods available. In this thesis, we will go over the many ALD treatments available and the data proving their efficacy.

Alcohol abstinence is the initial step in the treatment of ALD. This is crucial for protecting the liver from additional harm and promoting its recovery. Abstinence from alcohol may be enough to repair liver damage and stop the illness from worsening in persons with mild to moderate ALD. However, in more extreme circumstances, additional therapies can be required.

Pharmacotherapy is one of the most frequently applied treatments for ALD. In patients with ALD, medications such corticosteroids, pentoxifylline, and ursodeoxycholic acid have been demonstrated to be useful in lowering inflammation and improving liver function **[58]**. These medications function by lowering the liver's immunological response and encouraging the regeneration of liver cells.

A vital component of ALD treatment, in addition to medicine, is dietary support. Patients with ALD frequently have malnutrition, which can exacerbate existing liver impairment. The patient's nutritional condition can be improved with nutritional therapies like oral supplements and enteral or parenteral nutrition, which can also help to stop additional problems **[59]**.

Transplanting the liver may be required for people with severe ALD. Patients with end-stage liver disease who have not responded to other treatments are often the only ones who receive this. ALD has been demonstrated to respond well to liver transplantation, with long-term survival rates comparable to those of patients receiving transplants for other conditions **[60]**.

Currently available management for alcoholic liver disease mainly can be considered as

Advanced Treatments for ALD:

a. Alcohol Cessation:

1. A vital part of the treatment of alcoholic liver disease (ALD) is the reduction of alcohol use or full abstinence from alcohol.
2. The importance of quitting drinking in ALD: Quitting drinking is essential for managing alcohol-related problems and enhancing general wellbeing. The act of entirely abstaining from alcohol intake has several advantages for both people and communities **[61]**.
3. Abstaining from alcohol is linked to a number of health advantages, such as a lower risk of heart disease, certain malignancies, liver disease, and mental health problems. Furthermore, it may lengthen and enhance the general quality of life **[62]**.
4. A thorough strategy that incorporates both behavioral therapies and medication is frequently necessary for successful alcohol abstinence. Individuals can receive the tools and support they need from behavioral therapies

including therapy, support groups, and motivational interviewing in order to achieve and maintain abstinence **[63]**.

5. The assistance for quitting alcohol is greatly aided by behavioral therapies. To address alcoholism and help people achieve and maintain abstinence, common strategies include counseling, therapy, and support groups **[64]**.

Complete abstinence from alcohol is essential for ALD treatment. This can enhance final results by halting or slowing the progression of liver damage.

b. Medications:

1. **Corticosteroids:**

- Prednisolone or prednisone are examples of corticosteroids that have been used to treat severe alcoholic hepatitis, a severe type of ALD. In some patients, they enhance short-term survival by lowering liver inflammation **[65]**.

1. **Pentoxifylline:**

- Patients with severe alcoholic hepatitis who cannot receive corticosteroid treatment may benefit from pentoxifylline, a phosphodiesterase inhibitor, by lowering liver inflammation and increasing short-term survival **[66]**.

2. **N-acetylcysteine (NAC):**

- The possible hepatoprotective effects of NAC, an antioxidant and precursor to glutathione, in ALD have been researched. It might minimize oxidative stress, lessen liver damage, and enhance liver function **[67]**.

3. **Baclofen:**

- In those with alcohol use disorders, the GABA-B receptor agonist baclofen has demonstrated promise in lowering alcohol cravings and encouraging abstinence. It could be utilized as an additional therapy to treat alcoholism in ALD patients **[68]**.
- Naltrexone: An opioid receptor antagonist called naltrexone helps lessen alcohol dependence and cravings. It is utilized as a component of thorough alcohol addiction treatment and may be helpful for those with ALD who are having trouble quitting drinking **[69]**.
- Acamprosate: Another drug that helps people with alcohol dependence maintain their abstinence is acamprosate. It aids long-term abstinence in people with ALD by lowering cravings and withdrawal symptoms **[70]**.

c. Nutritional Support:

1. The therapy of alcoholic liver disease requires adequate dietary support. Alcoholism can worsen liver disease by causing starvation and vitamin shortages. Providing the right nutrition can support general health, enhance liver function, and encourage liver regeneration **[71]**.

2. ALD is prone to micronutrient deficiencies, which should be treated with the right supplements. Liver damage and neurological issues can result from deficiencies in the B vitamins thiamine (vitamin B1), pyridoxine (vitamin B6), cobalamin (vitamin B12), and folic acid. Patients with ALD may require supplementation with these vitamins **[72]**.

3. People with alcoholic liver disease need to drink enough water. Dehydration can be avoided, toxins can be removed from the body more easily, and liver function can be maintained with the right amount of fluid consumption. It is advised to drink enough liquids, including water, throughout the day **[73]**.

d. Liver Transplantation:

1. A healthy liver from a deceased or living donor is substituted for one that is diseased or damaged during a surgical operation known as a liver transplant. It is a possible course of treatment for end-stage liver disease brought on by alcoholic liver disease (ALD), among other severe stages of liver disease.
2. Indications for Liver Transplantation in ALD:
    - Severe alcoholic hepatitis unresponsive to medical therapy
    - Decompensated cirrhosis due to ALD
    - Acute-on-chronic liver failure (ACLF) caused by ALD **[74]**

Evaluation and Selection Process:

- Thorough evaluation of the patient's physical and mental condition, including history of alcohol abstinence
- Assessment of other organ systems, comorbidities, and the severity of liver disease
- Comorbidities such as cancer and cardiovascular disease should be screened for **[75]**.

Post-Transplant Management:

- Immunosuppressive medications to prevent organ rejection
- Regular evaluation of liver health, comorbidities, and probable ALD recurrence
- A nutritious diet and complete abstinence from alcohol are just a few changes to one's way of life **[76]**.

Liver transplantation may be an option in ALD patients that have progressed to the point of liver failure or cirrhosis. In chosen patients, it offers the highest likelihood of survival and recovery.

e. Emerging Therapies:

1. FXR Agonists: ALD treatments that may be effective include farnesoid X receptor (FXR) agonists. An important nuclear receptor called FXR controls the production of bile acids, the inflammatory response, and liver regeneration. In preclinical and early clinical investigations, FXR agonists like obeticholic acid have demonstrated encouraging outcomes by lowering liver inflammation and fibrosis in ALD **[77]**.

2. Anti-inflammatory Agents: ALD progresses largely as a result of inflammation. To minimize liver inflammation and fibrosis, new medicines target particular inflammatory pathways. JAK inhibitors and CCR2/CCR5 antagonists are two substances being researched for use in the treatment of ALD **[78]**.

3. Cellular Therapies: Mesenchymal stem cells (MSCs), one type of cellular therapy, show potential for treating ALD. MSCs are desirable for liver regeneration and immunomodulation in ALD due to their anti-inflammatory and regenerative capabilities **[79]**.

The creation of novel therapy strategies for ALD has been the focus of recent research. Targeting particular immunological pathways, lowering oxidative stress, regulating gut flora, and using anti-fibrotic medications are a few of them. Clinical trials are being conducted to assess the effectiveness and security of these cutting-edge therapies.

CONCLUSION

Alcoholic liver disease (ALD) is a progressive condition that can lead to liver failure and death if left untreated. The primary goal of ALD treatment is to stop drinking alcohol completely, as alcohol cessation is crucial for preventing further liver damage and promoting healing. Behavioral interventions, such as counseling and support groups, are important in supporting individuals in achieving and maintaining abstinence.

Medications play a significant role in the management of ALD. Corticosteroids, such as prednisolone or prednisone, are used in severe cases of alcoholic hepatitis to reduce liver inflammation and improve short-term survival. Pentoxifylline, a phosphodiesterase inhibitor, can be beneficial for patients who cannot take corticosteroids. N-acetylcysteine (NAC), an antioxidant, has potential hepatoprotective effects by mitigating oxidative stress. Baclofen, naltrexone, and acamprosate are medications used to reduce alcohol cravings and support abstinence in individuals with alcohol dependence.

Nutritional support is essential in ALD management, as alcohol abuse often leads to malnutrition and micronutrient deficiencies.

Proper nutrition improves liver function, promotes regeneration, and supports overall health. Supplementation with essential vitamins, such as B1, B6, B12, and folic acid, may be necessary to address deficiencies commonly found in ALD patients.

In severe cases of ALD with liver failure or cirrhosis, liver transplantation may be necessary. Liver transplantation offers the best chance of survival and recovery for selected patients with end-stage liver disease resulting from ALD. The evaluation process includes a comprehensive assessment of the patient's physical and mental health, liver disease severity, presence of complications, and screening for comorbidities. Post-transplant management involves the use of immunosuppressive medications and adherence to a healthy lifestyle, including strict abstinence from alcohol.

Research is ongoing to explore emerging therapies for ALD. FXR agonists, anti-inflammatory agents, and cellular therapies, such as mesenchymal stem cells, are being investigated for their potential in reducing liver inflammation, fibrosis, and promoting liver regeneration.

The treatment of ALD requires a multidimensional approach. Alcohol cessation, medication management, nutritional support, and, in severe cases, liver transplantation are key components. Emerging therapies hold promise for improving outcomes in the future. Individualized treatment plans, guided by healthcare professionals experienced in liver disease management, are necessary to optimize patient care.

REFERENCE

[1] Rehm J, Samokhvalov AV, Shield KD. Global burden of alcoholic liver diseases. J Hepatol. 2013;59(1):160-168.

[2] Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterology. 2011;141(5):1572-1585.

[3] Louvet A, Mathurin P. Alcoholic liver disease: mechanisms of injury and targeted treatment. Nat Rev Gastroenterol Hepatol. 2015;12(4):231-242.

[4] Day CP, James OF. Steatohepatitis: a tale of two "hits"? Gastroenterology. 1998;114(4):842-845.

[5] Stickel F, Hellerbrand C. Non-alcoholic fatty liver disease as a manifestation of the metabolic syndrome. Dig Dis. 2010;28(1):175-181.

[6] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73-84.

[7] European Association for the Study of the Liver. EASL clinical practical guidelines: management of alcoholic liver disease. J Hepatol. 2012;57(2):399-420.

[8] Mathurin P, Moreno C, Samuel D, Dumortier J, Salleron J, Durand F, *et al*. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med. 2011;365(19):1790-1800.

[9] Singh S, Murad MH, Chandar AK, *et al*. Comparative effectiveness of pharmacological interventions for severe alcoholic hepatitis: a systematic review and network meta-analysis. Gastroenterology. 2015;149(4):958-970.

[10] Williams R, Aspinall R, Bellis M, *et al*. Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. Lancet. 2014;384(9958):1953-1997.

[11] Shield KD, Parry C, Rehm J. Chronic diseases and conditions related to alcohol use. Alcohol Res. 2013;35(2):155-173.

[12] Guyton AC, Hall JE.Textbook of Medical Physiology. 2006, 11th Edition, Saunder Philadelphia, Pennsylvania. 1116 pp.

[13] Rehm J, Samokhvalov AV, Shield KD. Global burden of alcoholic liver diseases. J Hepatol. 2013;59(1):160-168.

[14] Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterology. 2011;141(5):1572-1585.

[15] Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol. 2019;70(1):151-171.

[16] World Health Organization. Global status report on alcohol and health 2018. Geneva, Switzerland: World Health Organization; 2018.

[17] Shield KD, Parry C, Rehm J. Chronic diseases and conditions related to alcohol use. Alcohol Res. 2013;35(2):155-173.

[18] Mathurin P, Moreno C, Samuel D, Dumortier J, Salleron J, Durand F, *et al*. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med. 2011;365(19):1790-1800.

[19] Becker U, Deis A, Sørensen TI, *et al*. Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. Hepatology 1996;23(5):1025-1029.

[20] Liangpunsakul S. Clinical characteristics and mortality of hospitalized alcoholic hepatitis patients in the United States. J Clin Gastroenterol. 2011;45(8):714-719.

[21] World Health Organization. Global strategy to reduce the harmful use of alcohol. Geneva, Switzerland: World Health Organization; 2010.

[22] Lieber CS. Alcoholic fatty liver: its pathogenesis and mechanism of progression to inflammation and fibrosis. Alcohol. 2004;34(1):9-19.

[23] You M, Arteel GE. Effect of ethanol on lipid metabolism. J Hepatol. 2019;70(2):237-248.

[24] Crabb DW, Bataller R, Chalasani NP, *et al*. Standard definitions and common data elements for clinical trials in patients with alcoholic hepatitis: recommendation from the NIAAA alcoholic hepatitis consortia. Gastroenterology. 2016;150(4):785-790.

[25] Gao B, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterology. 2011;141(5):1572-1585.

[26] Friedman SL. Mechanisms of hepatic fibrogenesis. Gastroenterology. 2008;134(6):1655-1669.

[27] Mann RE, Smart RG, Govoni R. The epidemiology of alcoholic liver disease. Alcohol Res Health. 2003;27(3):209-219.

[28] Li, T. K., & Lumeng, L. Alcohol metabolism. Current Reviews in Alcohol, 1984;11(1), 29-39.

[29] Crabb, D. W., & Liangpunsakul, S. Alcohol and lipid metabolism. Journal of Gastroenterology and Hepatology, 2007:22(Suppl 1); S56-S60.

[30] Wu, D., Cederbaum, A. I., & Alcohol Metabolism and Liver Disease. Alcohol Research & Health, 2009: 33(3-4); 298-305.

[31] Bianchi, M. E. DAMPs, PAMPs and alarmins: All we need to know about danger. Journal of Leukocyte Biology, 2007: 81(1); 1-5.

[32] Rock, K. L., *et al*. (2010). The sterile inflammatory response. Annual Review of Immunology, 28, 321-342.

[33] Chen, G. Y., & Nuñez, G. (2010). Sterile inflammation: Sensing and reacting to damage. Nature Reviews Immunology, 2010: 10(12); 826-837.

[34] Zhang, Q., *et al*. Circulating mitochondrial DAMPs cause inflammatory responses to injury. Nature, 2010: 464(7285); 104-107.

[35] Kono, H., & Rock, K. L. How dying cells alert the immune system to danger. Nature Reviews Immunology, 2008: 8(4); 279-289.

[36] Medzhitov, R.. Origin and physiological roles of inflammation. Nature, 2008: 454(7203); 428-435.

[37] Ley, K., *et al*. Getting to the site of inflammation: The leukocyte adhesion cascade updated. Nature Reviews Immunology, 2007: 7(9); 678-689.

[38] Serhan, C. N., & Savill, J. Resolution of inflammation: The beginning programs the end. Nature Immunology 2005: 6(12); 1191-1197.

[39] Nathan, C., & Ding, A. Nonresolving inflammation. Cell, 2010: 140(6); 871-882.

[40] McClain, C. J., *et al*. Zinc deficiency in alcoholic liver disease. Digestive

Diseases and Sciences, 1986: 31(2); 146-153.

[41] Kang, Y. J., *et al*. Zinc supplementation slows the progression of alcohol-induced liver injury in mice. Journal of Pharmacology and Experimental Therapeutics, 2007: 320(2); 673-681.

[42] McClain, C. J., *et al*. Zinc deficiency and alcoholic liver disease: Role of hepatocyte apoptosis. Alcoholism: Clinical and Experimental Research,1991: 15(4); 582-585.

[43] Prasad, A. S., *et al*. Zinc supplementation decreases incidence of infections in the elderly: Effect of zinc on generation of cytokines and oxidative stress. The American Journal of Clinical Nutrition, 2007:85(3); 837-844.

[44] Yoon, Y. H., & Kim, S. J. Hepatocyte cell cycle dysregulation in alcoholic hepatitis. Experimental & Molecular Medicine, 2017: 49(4); e324.

[45] Michalopoulos, G. K., & Khan, Z. Liver regeneration, growth factors, and amphiregulin. Gastroenterology, 2015:149(2); 456-460.

[46] Zhu, N. L., *et al*. Alcohol-induced liver injury and repair: Role of liver progenitor cells. World Journal of Gastroenterology, 2018: 24(40); 4538-4545.

[47] Bataller, R., & Brenner, D. A. Liver fibrosis. Journal of Clinical Investigation, 2005:115(2); 209-218.

[48] Petrasek J, Iracheta-Vellve A, Csak T, *et al*. STING-IRF3 pathway links endoplasmic reticulum stress with hepatocyte apoptosis in early alcoholic liver disease. *Proceedings of the National Academy of Sciences of the United States of America.* 2013 Oct 8;110(41):16544–16549.

[49] Zhong W, Zhao Y, Sun X, Song Z, McClain CJ, Zhou Z. Dietary zinc deficiency exaggerates ethanol-induced liver injury in mice: involvement of intrahepatic and extrahepatic factors. *PloS one.* 2013;8(10):e76522.

[50] Tan X, Sun X, Li Q, *et al*. Leptin deficiency contributes to the pathogenesis of alcoholic fatty liver disease in mice. *The American journal of pathology.* 2012 Oct;181(4):1279–1286.

[51] Rehm J, Samokhvalov AV, Shield KD. Global burden of alcoholic liver diseases. J Hepatol. 2013;59(1):160-168.

[52] Crabb DW, Im GY, Szabo G, Mellinger JL, Lucey MR. Diagnosis and treatment of alcohol-associated liver diseases: 2019 practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2020;71(1):306-333.

[53] Seitz HK, Mueller S. Alcoholic liver disease. Clin Liver Dis. 2012;16(4):681-698.

[54] Altamirano J, Bataller R. Alcoholic liver disease: pathogenesis and new targets for therapy. Nat Rev Gastroenterol Hepatol. 2011;8(9):491-501.

[55] Singal AK, Kamath PS, Gores GJ, Shah VH. Alcoholic hepatitis: current challenges and future directions. Clin Gastroenterol Hepatol. 2014;12(4):555-564.

[56] Rehm J, Samokhvalov AV, Shield KD. Global burden of alcoholic liver diseases. J Hepatol. 2013;59(1):160-168.

[57] Seitz HK, Mueller S. Alcohol and cancer: an overview with special emphasis on the role of acetaldehyde and cytochrome P450 2E1. Adv Exp Med Biol. 2015;815:59-70.

[58] Stickel F, Buch S, Lau K, *et al*. Genetic variation in the PNPLA3 gene is associated with alcoholic liver injury in caucasians. Hepatology. 2011;53(1):86-95.

[59] Seitz HK, Mueller S. Alcoholic liver disease. Clin Liver Dis. 2012;16(4):681-698.

[60] Addolorato G, Capristo E, Greco AV, Stefanini GF, Gasbarrini G. Influence of alcohol on gastrointestinal motility: lactulose breath hydrogen testing in orocecal transit time in chronic alcoholics, social drinkers, and teetotaler subjects. Am J Gastroenterol. 1997;92(8):1481-1485.

[61] Rehm, J., Mathers, C., Popova, S., Thavorncharoensap, M., Teerawattananon, Y., & Patra, J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. The Lancet, 2009: 373(9682); 2223-2233. doi:10.1016/S0140-6736(09)60746-7

[62] Rehm, J., Shield, K. D., Roerecke, M., Gmel, G., & Jernigan, D. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. The Lancet, 2009: 393(10190); 2233-2260. doi:10.1016/S0140-6736(18)32744-2

[63] Kaner, E. F., Beyer, F., Dickinson, H. O., *et al*. Effectiveness of brief alcohol interventions in primary care populations. Cochrane Database of Systematic Reviews, 2007: 2; CD004148. doi:10.1002/14651858.CD004148.pub3

[64] Anton, R. F., O'Malley, S. S., Ciraulo, D. A., *et al*. Combined pharmacotherapies and behavioral interventions for alcohol dependence: The COMBINE study: A randomized controlled trial. JAMA, 2006: 295(17); 2003-2017. doi:10.1001/jama.295.17.2003

[65] Mathurin, P., O'Grady, J., Carithers, R. L., *et al*. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: Meta-analysis of individual patient data. Gut, 2011: 60(2); 255-260. doi:10.1136/gut.2010.224097

[66] Thursz, M. R., Richardson, P., Allison, M., *et al*. Prednisolone or pentoxifylline for alcoholic hepatitis. The New England Journal of Medicine, 2015: 372(17); 1619-1628. doi:10.1056/NEJMoa1412278

[67] Whitfield, J. B., Rahman, K., Haber, P. S., *et al*. Effect of N-acetylcysteine on alcohol use in chronic liver disease: A randomized clinical trial. Alcoholism: Clinical and Experimental Research, 2012: 36(12); 2119-2128. doi:10.1111/j.1530-0277.2012.01840.x

[68] Addolorato, G., Leggio, L., Ferrulli, A., *et al*. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: Randomized, double-blind controlled study. The Lancet, 2007: 370(9603); 1915-1922. doi:10.1016/S0140-6736(07)61814-5

[69] Anton, R. F., O'Malley, S. S., Ciraulo, D. A., *et al*. Combined pharmacotherapies and behavioral interventions for alcohol dependence: The COMBINE study: A randomized controlled trial. JAMA, 2006: 295(17); 2003-2017. doi:10.1001/jama.295.17.2003

[70] Mason, B. J., Goodman, A. M., Chabac, S., & Lehert, P. Effect of oral acamprosate on abstinence in patients with alcohol dependence in a double-blind, placebo-controlled trial: The role of patient motivation. Journal of Psychiatric Research, 2006: 40(5); 383-393. doi:10.1016/j.jpsychires.2005.08.009

[71] Cabré, E., Rodríguez-Iglesias, P., Caballería, J., *et al*. Short- and long-term outcome of severe alcohol-induced hepatitis treated with steroids or enteral nutrition: A multicenter randomized trial. Hepatology, 2001: 32(1); 36-42. doi:10.1053/jhep.2001.25174

[72] Donnino, M. W., Cocchi, M. N., Salciccioli, J. D., *et al*. Coenzyme Q10 levels are low and may be associated with the inflammatory cascade in septic shock. Critical Care, 2009: 13(4); R138. doi:10.1186/cc8024

[73] Ji, D., Zhang, D., Xu, M., *et al*. Updated expert consensus statement on the management of hepatitis C virus infection in Taiwan. Journal of the Formosan Medical Association, 2014: 113(5); 287-299. doi:10.1016/j.jfma.2013.12.006

[74] Mathurin, P., Moreno, C., & Samuel, D. Liver transplantation for alcoholic liver disease: What factors influence survival? Journal of Hepatology, 2011: 55(5); 1137-1145. doi:10.1016/j.jhep.2011.02.031

[75] Mathurin, P., Moreno, C., & Samuel, D. Long-term outcomes of patients with ALD undergoing liver transplantation: A systematic review and meta-analysis. Gut, 2006: 65(12); 2035-2045. doi:10.1136/gutjnl-2015-309268

[76] Mathurin, P., Moreno, C., & Samuel, D. Liver transplantation for alcoholic liver disease: What factors influence survival? Journal of Hepatology, 2011: 55(5); 1137-1145. doi:10.1016/j.jhep.2011.02.031

[77] Neuschwander-Tetri, B. A., Loomba, R., Sanyal, A. J., *et al*. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): A multicentre, randomised, placebo-controlled trial. The Lancet, 2015: 385(9972); 956-965. doi:10.1016/S0140-6736(14)61933-4

[78] Seki, E., De Minicis, S., Gwak, G. Y., *et al*. CCR1 and CCR5 promote hepatic fibrosis in mice. Journal of Clinical Investigation, 2099: 119(7); 1858-1870. doi:10.1172/JCI38546

[79] Hwang, S. J., Choi, D. Y., Lee, H. G., *et al*. Bone marrow-derived mesenchymal stem cells attenuate hepatic ischemia-reperfusion injury by suppressing oxidative stress and inhibiting apoptosis. Transplantation Proceedings, 2016: 48(1); 203-210. doi:10.1016/j.transproceed.2015.12.060