

Alcohol Induced Fatty Liver: A Tragic Inception of Wrong Turn

AK Mohiuddin*

Assistant Professor, Department of Pharmacy, World University of Bangladesh, Bangladesh

***Corresponding Author:** AK Mohiuddin, Assistant Professor, Department of Pharmacy, World University of Bangladesh, Bangladesh. **Email:** trymohi@gmail.com

Abstract: Alcohol is a noteworthy reason for liver cirrhosis in the Western world and records for most of instances of liver cirrhosis found in region general emergency clinics in the UK. Alcoholic liver disease is a term that incorporates the liver appearances of alcohol overconsumption, including fatty liver, alcoholic hepatitis, and constant hepatitis with liver fibrosis or cirrhosis. As per the American Liver Foundation (ALF), somewhere in the range of 10 and 20 percent of substantial consumers will develop cirrhosis. The disease is a piece of a progression. It might begin with fatty liver disease, at that point advancement to alcoholic hepatitis, and after that to alcoholic cirrhosis. Be that as it may, it's conceivable an individual can develop alcoholic liver cirrhosis while never having alcoholic hepatitis. Symptoms of alcoholic liver cirrhosis regularly develop when an individual is between the ages of 30 and 40. All things considered, it takes around one hour for the body to utilize (separate) one standard beverage as characterized by U.S. rules (for example 12 ounces of 4.5% brew, 5 ounces of 11% wine, or 1.5 ounces of 35% alcohol). Utilization of 60–80g every day (14g is viewed as one standard beverage in the US, i.e., 1.5 fl oz hard alcohol, 5 fl oz wine, 12 fl oz lager; drinking a six-pack of brew day by day would be amidst the range) for a long time or more in men, or 20g/day for ladies fundamentally builds the danger of hepatitis and fibrosis by 7% to 47%. Of all endless substantial consumers, just 15–20% develop hepatitis or cirrhosis, which can happen correspondingly or in progression. The purpose for is accepted to be the liver has gigantic ability to recover and notwithstanding when 75% of hepatocytes are dead, it keeps on working as should be expected. As indicated by NIAAA (1993), somewhere in the range of 10% and 35% of substantial consumers develop alcoholic hepatitis. While development of hepatitis isn't specifically identified with the portion of alcohol, a few people appear to be more prone to this response than others. This is called alcoholic steato-necrosis (Steatosis) and the inflammation seems to incline to liver fibrosis.

Keywords: Alcohol use, abuse and dependence; alcoholic liver disease; inflammation; Steatohepatitis; ALD

Abbreviations: Fatty liver disease (FLD); Non-alcoholic fatty liver disease (NAFLD); Non-alcoholic steatohepatitis (NASH); American Liver Foundation (ALF); National Institute on Alcohol Abuse and Alcoholism (NIAAA); Alcoholic hepatitis (AH); Alcoholic Steatohepatitis (ASH); Hepatocellular Carcinoma (HCC); Alcoholic Steatohepatitis (ASH); Alcohol Use Disorder (AUD); Disability-Adjusted Life-Years (DALYs); Alcoholic liver disease (ALD); Alcoholic hepatitis (AH); Reactive Oxygen Species (ROS); Tumor Necrosis Factor Alpha (TNF alpha); Interleukin-8 (IL-8); Platelet-Derived Growth Factor (PDGF); lipopolysaccharides (LPS); MER tyrosine kinase (MERTK); Human Leucocyte Antigen-D Related (HLA-DR); Cytochrome P450 2E1 (CYP2E1); Early growth response-1 (Egr-1); Hepatitis C virus (HCV); Bone Marrow-Derived Cells (BMDCs); Hepatic Stellate Cell (HSC)

1. BACKGROUND

The liver, the largest internal organ (second largest whenever thought about the entire) in the body, is essential in keeping the body working legitimately. In cirrhosis of the liver, scar tissue replaces ordinary, sound tissue, hindering the stream of blood through the organ and keeping it from functioning as it should. At the point when complications can't be controlled or when the liver turns out to be so harmed from scarring that

it totally quits working, a liver transplant is essential. Around 80 to 90% of patients endure liver transplantation. About 90% of extremely chubby patients show histological abnormalities of the liver. 33% of patients have fatty change including over half of hepatocytes. In spite of the fact that alcohol, drugs, diabetes, poor nourishment, and weight-lesening medical procedure add to dynamic liver harm, yet dismal heftiness alone may prompt serious disease

demonstrating every one of the highlights of alcoholic hepatitis and may finish in cirrhosis and liver failure. Fatty liver disease (FLD) depicts a scope of conditions brought about by an accumulation of fat in the liver. Most basic causes are corpulence (about 20% of individuals considered fat have fatty liver disease), high blood cholesterol and triglycerides, type 2 diabetes mellitus, overwhelming alcohol utilize and less normal causes are underactive thyroid, certain meds, polycystic ovary syndrome and complications late in pregnancy. NASH is an endless disease in which amassed fat in liver cells causes liver inflammation. It ordinarily happens in individuals who are overweight and diabetic, with high blood cholesterol and triglyceride levels. Since FLD does not for the most part cause agony, queasiness or fatty sustenance intolerance, numerous individuals don't understand they have it until a normal blood test recommends a liver issue. It can advance to advanced fibrosis, cirrhosis, hepatocellular carcinoma and liver-related morbidity and mortality. Be that as it may, liver biopsy might be proposed yet this is seldom essential. The biopsy enables liver cells to be inspected under a magnifying instrument so as to survey the level of fat accumulation, inflammation and all the more critically, scarring of the liver. Alcoholic liver cirrhosis is the most exceptional type of liver disease that is identified with drinking alcohol.

2. INTRODUCTION

There are 3 sorts of liver disease identified with alcohol utilization: fatty liver, alcoholic hepatitis, or cirrhosis. Fatty liver disease happens after intense alcohol ingestion and is commonly reversible with restraint. Fatty liver isn't accepted to incline a patient to any constant type of liver disease if restraint or balance is kept up. Alcoholic hepatitis is an intense type of alcohol-incited liver damage that happens with the utilization of a huge amount of alcohol over a prolonged period. Alcoholic hepatitis can run in seriousness from asymptomatic unsettling of biochemistries to liver failure and passing. Cirrhosis includes substitution of the typical hepatic parenchyma with broad thick bands of fibrous tissue and regenerative knobs, which results in the clinical indications of entry

hypertension and liver failure. Harm to the liver is preventable, and on the off chance that it is recognized sufficiently early, issues like fatty liver are reversible. Be that as it may, individuals who struggle with alcohol misuse are more averse to look for medical treatment and will experience serious difficulties halting urgent practices around alcohol, so they may endure continuous harm to their liver, prompting liver failure, on the off chance that they don't get help. The most well-known symptoms and indications of alcohol-incited liver disease are amplified liver, fever, sickness, heaving, jaundice (yellowing of the skin and eyes), expanded white platelet include, arachnid like veins in the skin (spider naevi), entry hypertension, developed spleen, ascites (liquid development in the stomach pit), kidney failure, disarray and so forth. The liver has extraordinary helpful power and is regularly ready to fix a portion of the harm brought about by alcohol. The scarring from cirrhosis isn't reversible, and when liver tissue misfortune is sufficiently serious to cause liver failure, a large portion of the harm might be irreversible. Now and again, liver transplant might be considered. General measures in patients hospitalized with ALD incorporate inpatient the board of liver disease complications, the executives of alcohol withdrawal syndrome, reconnaissance for contaminations and early successful anti-toxin treatment, healthful supplementation, and treatment of the hidden alcohol-use issue. Liver transplantation, a complete treatment choice in patients with cutting edge alcoholic cirrhosis, may likewise be considered in chosen patients with AH cases, who don't react to medical treatment. There is a clinical neglected need to develop progressively viable and more secure therapies for patients with ALD. Alcohol is also a frequent co-factor in patients with other type of liver disease such as hepatitis C virus (HCV) infection where it accelerates hepatic fibrosis. Owing to various susceptibility factors, individuals with long-term heavy alcohol use remain at risk for advanced liver disease with alcoholic steatohepatitis (ASH), cirrhosis, and hepatocellular carcinoma (HCC). Most patients with ALD present for medical care after they have developed jaundice or complications of cirrhosis.

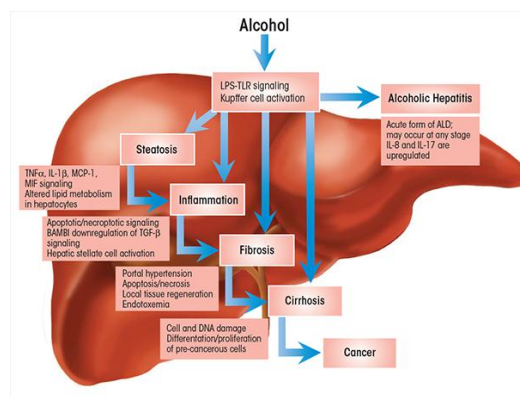


Figure 1. The damaging effects of alcohol and its metabolism on cells trigger additional immune responses. Steatosis and inflammation in hepatocytes represent the early stages of ALD; continued alcohol-induced inflammation leads to apoptosis/necroptosis in hepatocytes. Downregulation of BMP and activin membrane-bound inhibitor (BAMBI) and increased transforming growth factor β ($TGF-\beta$) signaling activate hepatic stellate cells, which differentiate into myofibroblasts causing fibrosis. About 10 to 20 percent of patients with ALD (about 70 percent of patients with alcoholic hepatitis) progress to cirrhosis. Differentiation and proliferation of precancerous liver cells present in cirrhosis lead to cancer in about 10 percent of cirrhosis patients. Acute alcohol-induced inflammation (i.e., alcoholic hepatitis), characterized by high levels of pro-inflammatory cytokines (e.g., interleukin [IL]-17 and IL-8), may occur at any stage of ALD and, in severe cases, may cause death in about 50 percent of patients [1].



Figure 2. Illustration of “standard drinks” in order of increasing ethanol content among currently available alcoholic beverages. According to the National Institute on Alcohol Abuse and Alcoholism, the amount of beverage containing approximately 14 g of pure ethanol is defined as a standard drink. The percent of pure alcohol, expressed as alcohol by volume (alc/vol), varies by beverage. Thus, 12 ounces (360 mL) of beer at 6 percent alc/vol, 5 ounces (150 mL) of wine at 12 percent alc/vol, or 1.5 ounces (45 mL) of distilled spirits at 40 percent alc/vol each are equivalent to a standard drink. Although the standard-drink amounts are helpful for following health guidelines, they may not reflect customary serving sizes. In addition, although the alcohol concentrations listed are typical, there is considerable variability in actual alcohol content within each type of beverage [2].

3. EPIDEMIOLOGY OF ALCOHOL CONSUMPTION AND RELATED LIVER DISEASES

Harmful use of alcohol is related to over 200 diseases [31]. Alcohol consumption accounts for 3.8% of global mortality and 4.6% of DALYs lost due to premature death [27]. The WHO estimates 16% of drinkers worldwide engage in heavy episodic drinking and 7.5% have at least one heavy drinking episode per month [21]. The risk of alcohol dependence increases based on genetic and psychosocial factors [11].

Worldwide data from 2016 indicate that alcohol is the seventh leading risk factor in terms of disability-adjusted life years, an increase of more than 25% from 1990 to 2016 [10]. Approximately 7% of the adults in the United States meets the criteria for alcohol abuse/dependence. In Italy, more than one third of hospitalized patients presented a clinical history characterized by excessive alcohol consumption (more than 60 g of alcohol per day) [18]. AUD was reported in 29.2% population in a community survey in India [19]. AUDs have consistently been identified as a public health

concern over the past 20 years, during which time per capita consumption of alcohol has increased by 55% [20]. In 2015, there were 8758 avoidable deaths in the UK that were directly caused by alcohol. Moreover, 2.5 million people who regularly drink alcohol report exceeding weekly alcohol thresholds in a single drinking occasion [23]. Alcohol is second only to tobacco as a cause of drug-related death and hospitalization, responsible for 5.1% of the total burden of disease and injury in Australia in 2011. Each week, on average, more than 100 Australians die and more than 3000 are hospitalized as a result of excessive alcohol consumption [25]. Every year, approximately 2.5 million people die from alcohol worldwide, with 320,000 deaths among 15-29 aged people [15]. Harmful use of alcohol results in approximately 3.3 million deaths annually (5.9% of all deaths) and alcohol-attributable deaths are the highest for middle-aged people [26]. Cirrhosis is currently the 11th most common cause of death globally and liver cancer is the 16th leading cause of death; combined, they account for 3.5% of all deaths worldwide. Alcohol is a known cause of liver cirrhosis, with its incidence increasing in relation to the total amount of alcohol consumed [13]. About 2 billion people consume alcohol worldwide and upwards of 75 million are diagnosed with alcohol-use disorders and are at risk of alcohol-associated liver disease [12]. Although 80%–90% of heavy drinkers show evidence of fatty livers, only 30%–35% develop alcoholic hepatitis and 5%–15% develop alcoholic liver cirrhosis [17]. The five-year survival of patients with alcoholic cirrhosis and nonalcoholic cirrhosis are 36% and 14%, respectively [40]. ALD has been estimated to account for nearly 50% of all deaths from cirrhosis [41]. About 20% to 40% of those who drink alcohol in heavy amounts and have fatty liver eventually develop liver inflammation, which is known as ASH [14]. The one-month survival for severe alcoholic hepatitis is low with mortality rates high as 30%-50% [16]. Nowadays, in Europe, alcohol excessive consumption accounts for 40–50% of all liver cancer cases [18]. A study confirmed a 45% increase in the incidence of cirrhosis in the UK during the last decade [42]. Between 2012 and 2013 in the UK, alcohol was responsible for over 330 000 hospital admissions, as estimated from attributable fractions, with 21% of these were due to cancer [24]. Alcoholism accounts for about one-third of all cases of pancreatitis. The risk of pancreatitis in patients with alcohol dependence is approximately 4-fold higher than that in the

general population, and it increases according to dose [27]. According to WHO, the prevalence of alcohol consumption among the Indonesian population was about 7.1% [39]. Alcoholic hepatitis (AH) presents with rapid onset or worsening of jaundice, and in severe cases may transition to acute on chronic liver failure when the risk for mortality, depending on the number of extra-hepatic organ failures, may be as high as 20-50% at 1 month [9]. Steatosis, which is present in more than 90% of heavy drinkers, is asymptomatic and reversible with abstinence [35,36]. HCC annually occurs in 2–3% of both alcoholic and nonalcoholic-related cirrhosis and only half of the patients are eligible for therapeutic treatments (liver transplantation, resection, and percutaneous ablation) [37].

4. ECONOMICAL BURDEN OF ALCOHOL INDUCED LIVER DISEASES

Both alcohol addiction and alcohol induced diseases, both have separate issues of economic burden. The financial burden of alcohol-related harm is estimated to annually cost UK society between 1.3 and 2.7% gross GDP [23]. Approximately 64,000,000 people in the US report binge drinking at least once in a single month of 2018 [32]. Sacks et al. (2015) estimate the cost of binge drinking at \$190 billion per year in the United States; approximately 40 percent of that cost, \$80 billion, accrues to the U.S. Government [33]. Among the people studied in US, nearly 300,000 had cirrhosis in 2015, with 36 percent of these cases attributed to alcohol use [38]. Impact of alcohol on cancer have been increased from 4% to about 25% of the diseases burden worldwide [39]. The estimated costs attributable to alcohol range from 1.3 to 3.3% of the gross domestic product in high and middle-income countries [22]. The estimated present value of current and future economic cost of the alcohol-related conditions for Sri Lanka in 2015 was USD 885.86 million, 1.07% of the GDP of that year [30]. The ALD is responsible for 15% of all deaths on an average in the last 3 years in Bhutan [34]. With recent changes in the economies and increases in average incomes in developing regions of the world, there has been a rapid rise in per capita alcohol consumption in countries such as China and India. In fact, alcohol consumption is increasing faster in China than other parts of the world. The per capita consumption of alcohol in India has increased by 55% over the past decade [41]. The burden of liver diseases in North America and Europe is mainly attributable to alcohol whereas in Africa and Asia viral hepatitis is the dominant force. In

2010, cirrhosis accounted for more than 493,300 deaths (156,900 female and 336,400 male deaths) and for more than 14.5 million DALYs (disability-adjusted life year) (around 4.1 million DALYs for women and 10.4 million DALYs for men) [42]. It has been reported that alcoholic patients with HCV infection have a 30 fold increased risk of getting cirrhosis [64].

5. PATHOPHYSIOLOGY OF ALCOHOLIC LIVER DISEASE

Patients with alcoholic liver disease are at increased risk for malnutrition, occurring in 20%-90% of cases [5], [27]. Alcoholic hepatitis is a unique type of alcohol-associated liver disease characterized by acute liver inflammation caused by prolonged heavy alcohol use [6]. Optimal treatment requires a multidisciplinary team approach and a working alliance between patients and providers [8]. Alcohol is a leading cause of cirrhosis and its subsequent complications, including portal hypertension, ascites, spontaneous bacterial peritonitis, variceal bleeding, hepatic encephalopathy, and hepatorenal syndrome. If they decompensate without receiving a liver transplant, one-third of patients with alcoholic cirrhosis who abstain from alcohol and two-thirds of those who continue to drink will die within 5 years [28]. Recent research has elucidated several key mechanisms that potentiate ethanol's damage to the liver parenchyma, such as generation of free radicals, activation of Kupffer cells, and alterations to the human bacterial and fungal microbiome. Genetic studies have suggested the role of PNPLA3 and TM6SF2 gene mutations in the progression of alcoholic liver disease [7]. Cost of liver cancer-related to alcohol consumption was USD 93,253 in Indonesia [39].

Liver transplantation is the second most common solid organ transplantation, yet less than 10% of global transplantation needs are met at current rates [12]. The classical clinical syndrome of alcoholic steatohepatitis (ASH) consists of jaundice, varying degrees of hepatic failure, abdominal distress, fever, and leukocytosis, although patients with the histological features of the entity may be asymptomatic and anicteric. Factors that affect the development of liver injury include the dose, duration, and type of alcohol consumption, drinking patterns, sex, age, ethnicity, as well as associated risk factors such as obesity, iron overload, concomitant infections, and genetics [43]. Alcohol undergoes an oxidative metabolic pathway in the hepatocytes, leading to a reduced ratio of the nicotinamide adenine dinucleotide (NAD) to NADH. This promotes lipogenesis by inhibiting oxidation of triglyceride and fatty acids [14]. Another known mechanism of alcohol-induced liver injury is the translocation of endotoxins in the form of lipopolysaccharides (LPS), from the intestines into the hepatocytes. In the hepatic Kupffer cells, the LPS binds to CD 14 and toll-like receptor 4 to release a barrage of reactive oxygen species (ROS) [44]. The ROS activates the release of cytokines such as tumor necrosis factor alpha (TNF alpha), interleukin-8, monocyte chemotactic protein 1 (MCP-1) and platelet-derived growth factor (PDGF), all of which leads to accumulation of neutrophils, macrophages and systemic clinical features of alcohol injury [45,46]. Animals and humans exposed to alcohol chronically exhibit overgrowth of opportunistic pathogenic and depletion of beneficial intestinal bacteria. *Lactobacillus*, *Clostridium butyricum* and *Bacteroides* decreased in diabetic liver injury mice [81].

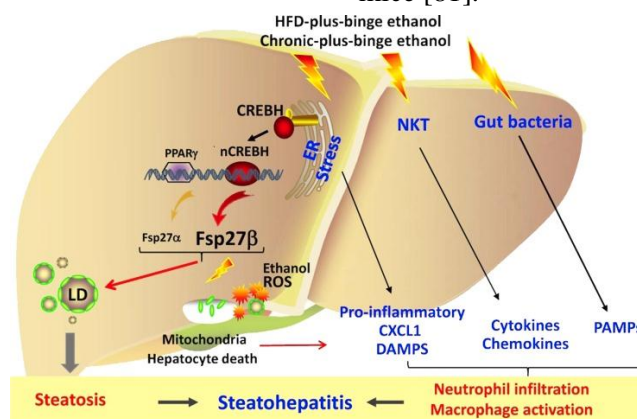


Figure3. Multiple mechanisms underlying alcoholic steatohepatitis. Chronic-plus-binge or HFD-plus-binge ethanol consumption induces ER stress, followed by activation of the cyclic AMP-responsive element-binding protein H (CREBH) and nuclear translocation of nCREBH, and subsequent upregulation of the predominant form of FSP27β. FSP27 interacts with lipid droplet (LD) membrane proteins and subsequently promotes LD formation and steatosis. In addition, ethanol promotes FSP27 translocation into the mitochondria and subsequent

mitochondrial injury and hepatocyte death. Ethanol also induces ER stress and subsequently produces proinflammatory mediators and danger-associated molecular patterns (DAMPs). Ethanol feeding activates natural killer T (NKT) cells to release proinflammatory mediators. Ethanol alters gut bacteria and elevates pathogen-associated molecular patterns (PAMPs). All of these factors lead to hepatic neutrophil infiltration and liver inflammation [3].

The liver is the primary site of ethanol metabolism, as hepatocytes express the major ethanol metabolizing enzymes, alcohol dehydrogenase (ADH), and cytochrome P450 2E1 (CYP2E1) at higher levels than any other tissue [47]. Alcohol consumption activates T cells with production of cytokines and chemokines including upregulation of NF-κB-mediated inflammatory genes. Alcohol inhibits the NK cells, which have anti-HCV and antifibrotic effects [48,49]. Among patients with advanced liver disease and severe AH, monocytes fail to respond with production of TNF-α, which has been shown to be due to reduced human leucocyte antigen-D related (HLA-DR) and increased MER tyrosine kinase (MERTK) expression on cell surface [50]. The main function of neutrophils recruited into the liver is to remove dead cells as a basis for regeneration, but neutrophils may also be involved in mediating hepatic inflammation and cell injury. Neutrophil recruitment and activation

are associated with increased proinflammatory cytokines such as IL-8 and TNF-α with decreased levels of anti-inflammatory cytokines such as IL-10 [51,52]. Mitochondrial dysfunction in AALD can be caused by numerous factors following alcohol exposure, including inflammation from gut-derived bacterial endotoxin, hepatic inflammation and apoptosis releasing damage-associated molecular patterns, activation of Kupffer cells with nitric oxide synthase induction and nitrative stress, and mitochondrial-mediated metabolism of alcohol via the CYP2E1 pathway of alcohol resulting in tissue hypoxia and enhanced oxidative stress [9], [53]. A third transcription factor is the early growth response-1 (Egr-1), which is strongly induced prior to the onset of steatosis. The activities of all these factors are governed by that of the principal regulatory enzyme, AMP kinase. Important humoral factors, including adiponectin, and tumor necrosis factor-α (TNF-α), also regulate alcohol-induced steatosis [47], [54,55].

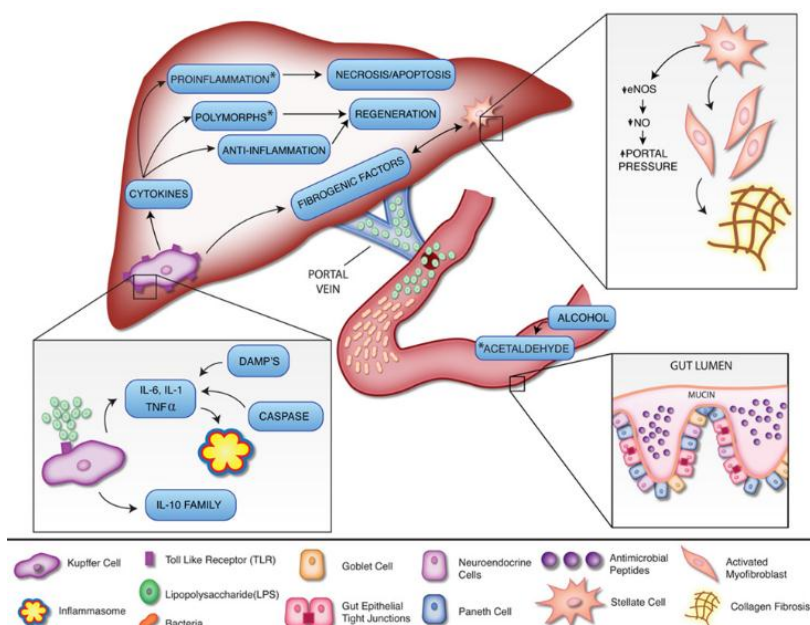


Figure 4. Alcohol's direct effects on activity and viability of parenchymal liver cells (i.e., hepatocytes) and on immune-cell signaling to hepatocytes. Excessive alcohol consumption increases the permeability of the gastrointestinal (GI) tract, exposing hepatocytes to bacterial endotoxin (i.e., lipopolysaccharide [LPS]). LPS is bound by LPS-binding protein (LBP), enabling engagement with Toll-like receptor 4 (TLR4) and activation of pro-inflammatory signaling pathways. TLR4 signaling activates expression of nuclear factor κB (NF-κB), which, along with reactive oxygen species (ROS) generated in mitochondria (as a result of exposure to the toxic alcohol-breakdown product acetaldehyde) and Kupffer cells, activates transcription of pro-inflammatory cytokines (i.e., IL-8). Tumor necrosis factor α (TNFα) produced by activated Kupffer cells stimulates sterol regulatory element-binding protein 1c (SREBP-1c), which triggers expression of genes in lipid synthesis, in turn initiating the development of abnormal fat deposition (i.e., steatosis). The combined action of lipid synthesis and upregulated expression of pro-inflammatory cytokines may spur programmed cell death (i.e., apoptosis) and necrosis, resulting in alcohol-induced loss of hepatocytes from tissues [4].

6. TREATMENT OPTIONS FOR ALCOHOL INDUCED FLD

For the last 50 years, abstinence has remained the primary therapy for ALD treatment. However, serious symptoms develop with the abrupt

cessation of alcohol. Treating the alcohol withdrawal syndrome is thus extremely important and requires administration of fluid, calories, vitamins and minerals. The key concepts are summarized in Table 1.

Table 1. Key concepts and statements on the management of alcoholic liver disease [9]

Disease spectrum of alcoholic liver disease
1. Liver function tests and ultrasound examination should be performed among patients with harmful alcohol use and/or alcohol use disorders (AUD)
2. Liver biopsy is not routinely recommended for diagnosis of alcoholic fatty liver disease. However, liver biopsy and non-invasive tools of fibrosis may be considered for diagnosis of steatohepatitis and/or liver fibrosis
Diagnosis of alcoholic use disorder
3. The Alcohol Use Disorders Inventory Test (AUDIT) is a validated tool for identifying patients with alcohol use and dependence
Management of alcoholic liver disease
Management of alcohol use disorder
4. Alcohol consumption is a major determinant of disease progression and long-term outcome of patients with alcoholic liver disease (ALD). Complete abstinence from alcohol consumption is the cornerstone in the management of every spectrum of ALD
5. Medical treatment of ALD should be ideally performed by multidisciplinary teams including addiction specialists
Management of alcohol withdrawal
6. Alcohol withdrawal syndrome (AWS) should be stratified and managed as per Clinical Institute Withdrawal Assessment for Alcohol protocol
7. In patients with severe AWS and ALD, benzodiazepines are the treatment of choice
Alcoholic hepatitis
Diagnosis of alcoholic hepatitis
8. Clinical diagnosis of alcoholic hepatitis (AH) is determined in a patient with rapid development or worsening of jaundice and liver-related complications, with serum total bilirubin >3 mg/dL; ALT and AST elevated >1.5 times the upper limit of normal but <400 U/L with the AST/ALT ratio >1.5; documentation of heavy alcohol use until 8 weeks prior to onset of symptoms; and exclusion of other liver diseases
9. In patients with suspected AH, a trans-jugular liver biopsy is recommended when the clinical diagnosis is confounded by another liver disease etiology or there is uncertainty on alcohol consumption history
10. Patients with severe AH should preferably be hospitalized for management
Treatment of alcoholic hepatitis
11. Severe AH is identified by Maddrey's discriminant function score >32 or MELD score >20
12. Systemic inflammatory response syndrome (SIRS) at admission predisposes to acute kidney injury and multi-organ failure, which are associated with a poor prognosis. Physicians should take appropriate measures to prevent renal injury, such as avoidance of nephrotoxic drugs, judicious use of diuretics, and low threshold for expanding circulating blood volume with albumin or saline infusions
13. Infections are common in AH patients and comprehensive infectious screen is recommended as part of routine work-up of these patients. The development of bacterial infections during hospitalization is associated with poor prognosis
14. Response to treatment with corticosteroids should be determined at 7 days using the Lille score. Treatment should be discontinued among non-responders to therapy, defined as those with a Lille score >0.45
15. Patients non-responsive to corticosteroids, ineligible for early LT, and with multiple organ failures, may be considered for palliative therapy
Liver transplantation in alcoholic liver disease
Liver transplantation for alcoholic cirrhosis
16. Physicians should consider LT while formulating a management plan for patients with end-stage ALD
17. The decision on LT evaluation should not be based solely on minimum 6 months of alcohol abstinence, and other criteria should be taken into consideration
18. Patients too sick to complete rehabilitation therapy may be considered for transplantation via exception pathway dependent on individual center policy and the patient's profile. These patients can complete rehabilitation therapy after transplantation
19. Transplant recipients should be screened at each visit for use of alcohol and other substances especially tobacco and cannabis. Among recidivists, alcohol use should be quantified to identify harmful use
20. Immunosuppression should be optimized to use lowest possible dose needed to prevent graft rejection. Use of sirolimus or everolimus may be considered over other immunosuppression drugs

Abstinence: One month of alcohol abstinence results in decreased gamma-glutamyl transferase levels, which return to baseline levels after resumption of alcohol consumption [56]. Pancreatic dysfunction is also rare among abstinent patients [57]. Abstinence can resolve alcoholic fatty liver disease and can improve the survival rate of cirrhotic or decompensated liver failure patients. Thus, motivating the patients to abstain from alcohol and follow the proper treatment regime are major steps. If the patient has simple fatty liver, then cessation will allow the liver to heal and return to normal. If a patient has alcohol-induced fibrosis or cirrhosis and abstains from alcohol, damage to the liver will stop and the liver will get better, although liver scar tissue will remain [58]. The beneficial effects of stopping alcohol start immediately, but probably are not achieved in the full sense for several weeks or longer. Currently, there are no treatments for fatty liver, alcoholic fibrosis, or alcoholic cirrhosis other than abstinence from alcohol. Psychological support by an addiction specialist or can also help in maintaining sobriety. Effective treatment of ALD to reduce

alcohol consumption or to achieve complete alcohol abstinence must be based on a multidisciplinary approach which should include public health intervention, addiction behavior and alcohol-induced organ injury management [56].

Alcohol withdrawal syndrome: Symptoms of alcohol withdrawal syndrome may develop within 6–24 hours after the abrupt discontinuation or decrease of alcohol consumption. Symptoms can vary from autonomic hyperactivity and agitation to delirium tremens [61]. Long acting benzodiazepines like chlordiazepoxide or diazepam are administered for prevention of seizures while intermediate acting benzodiazepines like lorazepam are recommended in withdrawal patients who are elderly or have had recent head trauma or liver or respiratory failure. Alcohol withdrawal is highly dangerous and if done incorrectly, may result in seizures, heart attack and death [60]. An IV dose of 500 mg (three times daily for two consecutive days) is recommended, followed by 500 mg of IV or IM thiamine for five more days if a response to the therapy is seen [61].

Exhibit1. Signs and symptoms of alcohol withdrawal syndrome, divided per stage [60]

Stage	Time of onset after last drink	Signs and symptoms
I – Minor Withdrawal Symptoms	6–12 h	Tremors, diaphoresis, nausea/vomiting, hypertension, tachycardia, hyperthermia, tachypnea
II – Alcoholic Hallucinosi	12–24 h	Dysperceptions: Visual (zoopsy), auditory (voices) and tactile (paresthesia)
III – Alcohol Withdrawal seizures	24–48 h	Generalized tonic-clonic seizures (with short or no postictal period)
IV – Delirium Tremens	48–72 h	delirium, psychosis, hallucinations, hyperthermia, malignant hypertension, seizures and coma

Nutritional support: The American College of Gastroenterology and the American Association for the Study of Liver Diseases guidelines recommend 1.2 to 1.5 g/kg per d of protein intake and 35 to 40 kcal/kg per d of body weight for energy intake in patients with ALD [62]. Malnutrition is present in 20-90% of patients with liver disease and sarcopenia in nearly 70% of these patients. Micronutrient deficiencies occur in patients with ALD because the major proportion of calories derived from alcohol lack minerals and vitamins. Specific emphasis is necessary for zinc, vitamin D, thiamine, folate, cyanocobalamin, and selenium. Oral supplementation may not be effective due to poor intake and compliance due to anorexia,

dysguesia, impaired absorption, and continued hypermetabolic states [63].

Anti-TNF Therapy: Alcohol abuse promotes the migration of bone marrow-derived cells (BMDCs) to the liver and then reprograms TNF- α expression from BMDCs and HSC-derived TNF- α overproduction [67]. TNFi therapy is widely used to treat immune-mediated diseases like rheumatoid arthritis and inflammatory bowel disease. FLD can be a side effect of TNFi therapy, and that methotrexate exposure and PNPLA3 gene mutations might be risk factors [65]. Anti-TNF (tumor necrosis factor) agents like Infliximab and Etanercept have been used with no proven survival benefits. Anti-TNF agents may even increase the incidence of

infections and death [14]. A large randomized controlled trial comparing prednisolone alone with a combination of prednisolone and infliximab had to be stopped before completion because of an increase in infection rate in the prednisolone and infliximab combination group [66]. However, two larger randomized controlled trials evaluating anti-TNF- α therapy failed to demonstrate benefit and even suggested harm. Therefore, use of anti-TNF- α therapy in AH to date remains investigational [68].

Pentoxifylline (PTX): The body of evidence for corticosteroids has been greater than pentoxifylline, although there are higher risks of complications. Pentoxifylline has been considered an alternative treatment for patients with severe alcoholic hepatitis, largely due to its good safety profile along with the lack of other alternative medications to corticosteroids. Pentoxifylline, a methylxanthine, mitigates production of tumor necrosis factor alpha which plays a role in the pathogenesis of AH. Frequent side effects include vomiting, diarrhea and headache leading to drug discontinuation [79]. There has been an increasing trend for physicians to treat alcoholic hepatitis with pentoxifylline given its good safety profile and concern with prescribing long-term glucocorticoids in patients with alcohol abuse and dependence [69]. The reported pharmacologic effects of PTX include an increase in red blood cell deformability. PTX, at a dose of 400 mg 3 times daily, is FDA-approved for treatment of claudication. PTX has multiple effects on the cytokine/chemokine pathway that are potentially beneficial. Further studies are needed to establish the primary pathway by which PTX exerts its beneficial effects in alcoholic hepatitis [70].

Corticosteroids: Despite mixed outcomes, corticosteroids are overall beneficial for survival of these patients. Unfortunately, 40% of patients are unresponsive to corticosteroid with virtually no other treatment options [71]. The treatment of severe forms of alcoholic hepatitis (AH) remains a challenge, especially for non-responders to corticosteroids who only have a 25% survival probability at 6 months [73].

Liver transplantation (LT): Alcoholic liver disease remains the second most common indication for LT, accounting for approximately 40% of all primary transplants in Europe and

about 25% in the US [80]. LT is the treatment of choice for patients with liver failure in end-stage liver disease, and it is their only chance of survival [27]. Severe alcoholic hepatitis patients nonresponsive to steroids have a 3 months mortality rate of 70% and with HRS the mortality rate is $\geq 90\%$ unless the patients get liver transplantation [74]. Alcohol consumption can complicate a patient's health after LT, as it increases the risk of liver fibrosis, mainly in women, even if alcohol consumption is < 12 g/d [75]. Alcohol relapse after LT is not uncommon and is reported to occur in 10% to 60% of recipients of LT for ALD [76]. Before transplantation, chronic poor prognosis hepatopathy can lead to painful consequences, affecting the whole family unit. In addition, daily family life undergoes sudden changes; parents, siblings, spouses and relatives are suddenly uprooted from their domestic ordinary activities and thrown into a strenuous routine of medical appointments, examinations and other medical procedures, which create an atmosphere of uneasiness, uncertainty and instability [77]. Patients who have received liver transplantation show a high incidence of de novo cancer, lymphoproliferative disorder and skin cancer. Also, liver transplantation due to ALD is associated with a high rate of cardiovascular complications [78]. Daswani et.al. expressed problems with liver transplantation for patients with AH are complex. Starting with, regardless of whether a patient with self-incurred illness merits the accessible liver graft which is a rare asset. Second, recidivism and relapse are real worries in these patients. Third, the way that liquor abuse is multisystem infection which blocks great outcome from surgery alongside the danger of poor consistence in these patients. Fourth and the most far from being obviously true is the correct determination of patients who ought to be transplanted: the ones who are probably going to pass on without a liver transplant and the individuals who are probably not going to come back to drinking. About 25% of the steroid invalid responders will in the long run recuperate with medical management and whenever transplanted at beginning time would prompt wastage of valuable liver grafts. The public perceptions of utilization of organs for patients with liquor addiction confound the issue further [79].



Figure 5. Liver Transplant in University of Chicago Medicine [72]. Most donated livers come from people who have died. Less commonly, liver transplants involve a living donor, often a friend, family member, or stranger whose tissue matches, and who donates a segment of their liver. Though liver transplants carry a risk of significant complications, the procedure has a high success rate. When looking for a matching donor liver, doctors consider several factors, including: severity of a person's liver failure, their blood type, a person's overall health, a person's body size location, as some U.S. states have bigger populations, donor bases, and donor centers than others, availability of matching livers in the national waiting list system.

7. INDIVIDUAL AND SOCIAL SUFFERINGS WITH ALCOHOL

Heavy alcohol use is associated with a broad range of problematic outcomes, including elevated risk of all-cause mortality, suicide, accidents, and risk of diseases including heart disease, liver disease, and specific cancers [84]. For patients with ALD, alcohol causes severe social disruption. There is a huge financial burden in both family and the state. Alcoholic liver disease is a major source of alcohol-related morbidity and mortality. While risky drinking in adolescence has been found to be rooted in childhood, evidence is scarce regarding where early alcohol-related knowledge originates. When frequently surrounded by alcohol-consuming adults, children may get the impression that alcohol consumption is a common human behavior, which may put them at risk for early alcohol initiation and risky drinking later in life [82]. A parent with a SUD is 3 times more likely to physically or sexually abuse their child. The sequelae of this is that these children are more than 50% more likely to be arrested as juveniles, and 40% more likely to commit a violent crime [83]. Alcohol use may be heaviest during the divorce transition, especially with advancing age, when both stress and the loss of marital resources are most severe [85]. Several studies demonstrate that drinking increases the likelihood of risky sexual behavior, with an association between alcohol consumption and multiple and casual partners, and less consistent condom use. Alcohol consumption has also been linked to negative sexual outcomes, including sexual assault [86]. Alcohol abuse is associated with multiple negative workplace outcomes, including absenteeism, accidents, turnover, and other sources of productivity losses. Specific job-related influences associated with problem drinking, including job stressors and participation in work-based drinking networks,

may pose a particular problem for young adults as they try to fit in their workplace [87]. In both men and women, daily alcohol intake was significantly higher in short-duration sleepers having a high disinhibition eating behavior trait.

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