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Comprehensive Review of Alcoholic Liver Disease



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ABSTRACT

Alcohol-related toxicity is the third most common cause of morbidity and the fifth most common cause of disease burden worldwide. Alcoholic liver disease (ALD) is a term that encompasses the liver manifestation of alcohol overconsumption, including fatty liver, alcoholic hepatitis, and chronic hepatitis with liver fibrosis or cirrhosis. Alcohol remains the second most common cause of liver cirrhosis after hepatitis C virus infection in the United States, contributing to approximately 20% to 25% cases of liver cirrhosis. The various factor responsible for the liver disease, duration and amount of drinking alcohol is the most important factor. These epidemiological studies show a minimum intake of 30g/day of alcohol in women and 50g/day in men consumed over at least 5 years to cause these diseases. Estimates of the amount of alcohol consumed may not be accurate since it is based on interviewing the patient/family members. The liver and, to the lesser extent, the gastrointestinal tract, are the main sites of alcohol metabolism. Within the liver, there are two main pathways of alcohol metabolism: *alcohol dehydrogenase* and cytochrome P-450 (CYP) 2E1. *Alcohol dehydrogenase* is a hepatocyte cytosolic enzyme that converts alcohol to acetaldehyde. Acetaldehyde subsequently is metabolized to acetate via the mitochondria enzyme *acetaldehyde dehydrogenase*. CYP 2E1 also converts alcohol to acetaldehyde.



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INTRODUCTION

Alcohol-related toxicity is the third most common cause of morbidity [1] and the fifth most common cause of disease burden worldwide [2]. Alcoholic liver disease (ALD) is a term that encompasses the liver manifestation of alcohol overconsumption, including fatty liver, alcoholic hepatitis, and chronic hepatitis with liver fibrosis or cirrhosis.

It is the major cause of liver disease in western countries. Although steatosis will develop in any individual who consumes a large number of alcoholic beverages over a long period, this process is transient and reversible [3]. There are no effective antifibrotic treatments. Patients who progressed to cirrhosis have a poor prognosis and liver transplantation is often indicated. Increase mortality in patients with liver cirrhosis is most often attributed to direct complications resulting from a loss of liver function, variceal hemorrhage as a sequel of portal hypertension and the development of hepatocellular carcinoma. A significant percentage of patients also succumb to bacterial infections with an infection-attributed mortality of 30%-50% [4-6]. Bacterial translocation not only causes severe infection in patients with cirrhosis, it may also cause progression of early alcoholic liver injury and fibrosis. Plasma levels of lipopolysaccharide (LSP) or endotoxin, a major component of the gram-negative bacterial outer membrane, increases with the severity of liver dysfunction in patients with cirrhosis, and are significantly higher in patients with chronic hepatitis than in healthy subject [7].

Endotoxin is significantly higher in patients with alcoholic cirrhosis than patients with non-alcoholic cirrhosis are [8] and the mechanism behind in alcoholic liver disease is not completely understood. Total 80% of alcohol passes through the liver to be detoxified. Chronic consumption of alcohol results in the secretion of pro-inflammatory cytokines (TNF-alpha, interleukin-6 and interleukin-8, oxidative stress, lipid peroxidation, and apoptosis and eventually fibrosis of liver cells. This occurs in only a few individuals is still unclear. Additionally, the liver has the tremendous capacity to regenerate and even 75% of hepatocytes are dead, it continues to function as normal [9].

Types of Alcoholic Liver Disease

There are three types of alcohol-related liver disease. They are alcoholic fatty liver disease, alcoholic hepatitis, and alcoholic cirrhosis.

1. Alcoholic fatty liver disease

The alcoholic fatty liver disease is the accumulation of fat in the liver caused by excessive consumption of alcohol. In fact, fatty liver may occur after as little as three days of excessive alcohol ingestion. A person can have fatty liver but not exhibit signs or symptoms of liver disease other than fatigue, although other symptoms like nausea and vomiting may occur. Many people who consume a large amount of alcohol on a regular basis have fatty liver. Blood test results will usually show elevations in blood levels of AST &/or ALT, however, a liver biopsy is the only way to diagnose fatty liver. The alcoholic fatty liver is generally a benign condition, which is reversible by eliminating consumption of alcohol.

2. Alcoholic hepatitis

Alcoholic hepatitis is liver inflammation caused by excessive alcohol consumption symptoms can be non-existent in some people and severe in others. In the case of non-existent symptoms, alcoholic hepatitis may be discovered during a routine blood test. Some people experience mild symptoms such as loss of appetite, nausea and abdominal discomfort while others experience more severe symptoms such as vomiting, severe pain in the right upper abdomen and fever. A liver biopsy that determines alcoholic hepatitis indicates that a person is a high risk of developing cirrhosis. However, as is the case with alcoholic fatty liver disease, alcoholic hepatitis is very reversible if the person immediately and completely abstains from drinking alcohol.

3. Alcoholic cirrhosis

Alcoholic cirrhosis is scarring of the liver caused by excessive alcohol consumption-hard, dead, scar tissue replaces soft healthy tissue. In the United States, alcohol is the number one cause of cirrhosis. Symptoms of cirrhosis may include fatigue, bleeding easily, easy bruising, fluid accumulation in the abdomen (ascites), nausea swelling in the legs (edema) and weight loss. A liver biopsy may be necessary to establish the existence of cirrhosis if it is not clinically apparent. All people with cirrhosis are at risk of developing liver cancer. In general, people with alcoholic cirrhosis have about a 15 percent overall lifetime risk of developing liver cancer [10-13]. Although alcoholic cirrhosis is irreversible and can lead to end-stage liver disease if not treated.

Etiology

Quantity and duration of alcohol intake are the most important risk factors involved in the development of alcoholic liver disease[14] shown in Table No. 01.

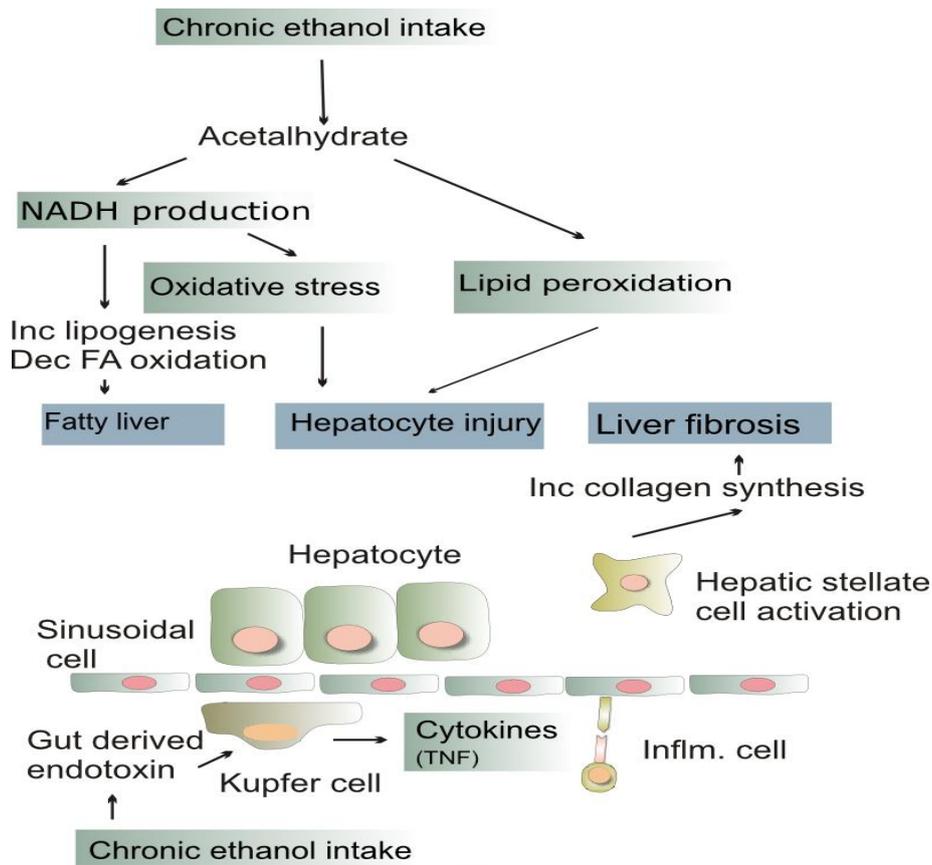
Table No. 01: Risk Factors for Alcoholic Liver Disease

Risk Factor	Comment
Quantity	In men 40-80g/d of ethanol produces fatty liver; 160g/d for 10-20 years causes hepatitis or cirrhosis. Only 15% of alcoholics develop ALD.
Gender	Women exhibit increased susceptibility to ALD at amounts >20g/d; two drinks per day probably safe.
Hepatitis C	HCV infection concurrent with ALD is associated with younger age for severity, more advanced histology, decreased survivals.
Genetics	Gene polymorphisms may include alcohol dehydrogenase, CYP 4502E1.
Malnutrition	Alcohol injury does not require malnutrition, but obesity and fatty liver from the effect of carbohydrate on the transcriptional control of lipid synthesis and transport may be factors, the patient should receive vigorous attention to nutritional support.

The common etiologic denominator in ALD is chronic heavy alcohol ingestion. A threshold amount for alcohol ingestion is about 40 to 80g/day in men and 20 to 40g/day in women for 10-12 years to cause alcoholic hepatitis or cirrhosis, although no set amount of alcohol consumption reliably predicts the development of ALD [15]. The risk of ALD is 2 to 3 times higher in patients with obesity than in patients with a normal BMI [16]. The progression of fibrosis in patients with ALD is faster in those who smoke [17].

Pathophysiology

The liver and, to the lesser extent, the gastrointestinal tract, are the main sites of alcohol metabolism. Within the liver, there are 2 main pathways of alcohol metabolism: alcohol dehydrogenase and cytochrome P-450 (CYP) 2E1. Alcohol dehydrogenase is a hepatocyte cytosolic enzyme that converts alcohol to acetaldehyde. Acetaldehyde subsequently is metabolized to acetate via the mitochondria enzyme *acetaldehyde dehydrogenase*. YP 2E1 also converts alcohol to acetaldehyde [18].



Flowchart 01: Pathogenesis of alcohol-induced liver injury

These liver damages occur through severe interrelated pathways. The main pathways are *alcohol dehydrogenase* and acetaldehyde cause the reduction of nicotinamide adenine dinucleotide (NAD) to NADH. This NADH is the reduced form of NAD. The altered ratio of NAD/NADH promotes fatty liver through the inhibition of gluconeogenesis and fatty acid oxidation. CYP 2E1, which is up regulated in chronic alcohol use, generate free radicals through the oxidation of nicotinamide adenine dinucleotide phosphate to NADP [18]. Chronic alcohol exposure also activates hepatic macrophages, which then produce tumor necrosis factor-alpha [19]. TNF-alpha induces mitochondria to increase the production of reactive oxygen species. This oxidative stress promotes hepatocytes necrosis and apoptosis, which is exaggerated in the alcoholic who is deficient in antioxidants such as glutathione and vitamin E. Free radicals initiate lipid peroxidation, which causes inflammation and fibrosis. Inflammation is also incited by acetaldehyde that, when bound covalently to cellular proteins, forms adducts that are antigenic [18].

Epidemiology

Alcohol remains the second most common cause of liver cirrhosis after hepatitis C virus infection in the United States, contributing to approximately 20% to 25% cases of liver cirrhosis. The various factor responsible for the liver disease, duration and amount of drinking alcohol is the most important factor. These epidemiological studies show a minimum intake of 30g/day of alcohol in women and 50g/day in men consumed over at least 5 years to cause these diseases. Estimates of the amount of alcohol consumed may not be accurate since it is based on interviewing the patient/family members [20]. Commonly used alcohol beverages with alcohol content shown in Table No. 02.

Table No. 02: Alcohol content of some common beverages

Drink	Amount (OZ)	Absolute alcohol (g)
Beer	12	12
Wine	5	12
Liquor (80 proof)	1.5	12

The highest amount of alcohol per adult was reported in Europe, especially Russia and surrounding countries and the least was in the mostly Islamic region of the eastern Mediterranean and in the less developed region of southeast Asia, predominantly India [21]. A Canadian study confirmed that per capita alcohol consumption is closely related to mortality rates from alcoholic cirrhosis in both men and women [22]. In another analysis of European countries, the relationship between increases in liver disease and increase in per capita alcohol intake was shown for both men and women [23]. Population-based surveys indicate that 68% of adult American drink at least one alcoholic beverage per month. Drinking alcohol is a harmful impact on daily functioning and social life and death [24].

Symptoms

There may be no symptoms, or symptoms may come on slowly, depending on how well the liver is working. Symptoms tend to be worse after a period of heavy drinking.

Early symptoms include-

- Fatigue and loss of energy

- Poor appetite and weight loss
- Nausea or belly pain
- Small, red spider-like blood vessels on the skin.

As liver function worsens, symptoms may include-

- A fluid build-up of the legs (edema) and in the abdomen (ascites)
- Yellow color in the skin, mucous membranes, or eyes (jaundice)
- Redness on the palms of the hands
- In men, impotence, shrinking of the testicles, and breast swelling
- Easy bruising and abnormal bleeding
- Confusion or problems thinking
- Pale or clay-coloured stools [25]



Symptoms of alcoholic liver cirrhosis: -

The symptoms are typically developed when a person is between the ages of 30 to 40. Your body will be able to compensate for your liver's limited function in the early stages of the disease. As the disease progresses, symptoms will become more noticeable. The symptoms of alcoholic liver cirrhosis are similar to other alcohol-related liver disorder symptoms include:

- Jaundice
- Portal hypertension, which increases blood pressure in the vein that travels through the liver
- Skin itching (Pruritus) [26].

Diagnosis

In the early stages, patients with ALD exhibits subtle and often no abnormal physical findings. It is usually not until the development of advanced liver disease that stigmata of chronic liver disease become apparent.

Early ALD is usually discovered during routine health examinations when liver enzyme levels are found to be elevated. These usually reflect alcoholic hepatic steatosis. Macrovascular and micro-vascular steatosis with inflammation are seen in liver biopsy specimens. Continuation of alcohol use results in a higher risk of progression of liver disease and cirrhosis.

In patients with acute alcoholic hepatitis, clinical manifestations include fever, jaundice, hepatomegaly, and possible hepatic decompensation with hepatic encephalopathy, variceal bleeding, and ascites accumulation. Tender hepatomegaly may be present but abdominal pain is unusual. Occasionally, the patient may be asymptomatic [27].

Laboratory Findings

In people with alcoholic hepatitis, the serum *aspartate aminotransferase* (AST) will exceed that of alanine aminotransferase (ALT), but both will be below 300 international units per milliliter (IU/ml). When the ratio of AST to ALT is greater than 2, the most likely diagnosis is ALD. In some studies, more than 80% of patient attain this ratio.

Elevated blood levels of the liver enzyme *gamma-glutamyl transferase* (GGT) indicate heavy alcohol use and liver injury. This test has greater ability to correctly test positive (i.e., sensitivity) but less ability to correctly test negative (i.e., specificity) than AST or ALT tests. Of the three enzymes, GGT is the best indicator of excessive alcohol consumption, but because GGT is present in many organs and because some drugs raise GGT levels, high GGT levels are not necessarily an indicator of alcohol abuse.

Chronic alcohol consumption also may be associated with abnormally high triglyceride levels (i.e., hypertriglyceridemia), high blood levels of uric acid (i.e., hyperuricemia) and low amounts of potassium (i.e., hypokalemia) and magnesium as well as an elevated index of red blood cell size (i.e., mean corpuscular erythrocyte volume).

Hyperuricemia and hypertriglyceridemia after normalizing with abstinence and hypokalemia normalize with adequate potassium replacement. Elevated MCV often is found in people who ingest more than 50 grams of alcohol per day with the sensitivity of 27 to 52 and specificity of 85 to 90%. The blood protein is known as carbohydrate-deficient transferrin frequently is used to detect current or recent alcohol abuse, especially consumption in excess of 60 grams per day but there are no ideal tests to identify continuing alcohol intake [28, 29].

Other laboratory findings include red blood cell macrocytosis (mean corpuscular volume >100) and elevations of serum *gamma-glutamyl transferase*, *alkaline phosphatase*, and bilirubin levels.

Folate level is reduced in alcoholic patients due to decreased intestinal absorption, increased bone marrow requirement for folate in the presence of alcohol and increased urinary loss. The magnitude of leukocytosis mitochondria, hepatocyte necrosis, and neutrophil infiltration at the perivenular area. Mallory bodies, which are also present in other liver disease are condensations of cytokeratin components in the hepatocyte cytoplasm and do not contribute to liver injury.

Up to 70% of patients with moderate to severe alcoholic hepatitis already have cirrhosis identifiable on biopsy examination at the time of diagnosis [30].

Treatment

Life Style Modifications

- Drink less alcohol.
- Eat a healthy diet that is low in salt.
- Get vaccinated for diseases such as influenza, hepatitis A and hepatitis B and pneumococcal pneumonia.
- Talk to your doctor about all medicines you take, including herbs and supplements and over-the-counter medicines. [31]
- Smoking cessation and weight loss because smoking is an independent risk factor for advancement of hepatic fibrosis, which can lead to more severe ALD and may link to the development. [32]
- Obesity, which can also cause fatty liver, non-alcoholic steatohepatitis, and cirrhosis, may be an independent risk factor for the progression of ALD. [33]

Pharmacological Treatment

ALD is preventable and reversible by timely treatment. However, ALD is often asymptomatic in the early stages and can only be identified by laboratory findings. Screening

and treatment for alcohol –use disorder is the first approach for treating ALD. [34] ALD treatment varies depending on the stages of disease [34, 35]. Abstinence is the most important therapeutic intervention for the patient with ALD.

Various treatment such as abstinence, nutritional therapy, pharmacological therapy, psychotherapy, and surgery is currently available of ALD [35]. In particular, in patients with severe alcoholic hepatitis, steroids or pentoxifylline can be used according to recommendations of the guidelines. In patients with cirrhosis, portal hypertension and complications such as bleeding, encephalopathy, or ascites, should be treated according to the treatment guidelines [36, 37].

Abstinence

Immediately abstinence is the most important treatment option for patients with ALD [38]. Continued drinking is associated with the eventual development of cirrhosis in approximately 20% of individuals [39]. Abstinence has been shown to improve the outcome and histological features of hepatic injury, to reduce portal pressure and decrease progression to cirrhosis and to improve survival at all stages in patients with ALD [40]. Alcoholic steatosis can be reversed after abstinence for several weeks [41]. With respect to pharmacological treatment, some medications such as baclofen, Acamprosate, and naltrexone have been used to encourage abstinence in patients with alcohol use disorder [42, 43]. Few data are available regarding the use of pharmacological agents in the treatment of ALD, because agents such as naltrexone or Acamprosate undergo extensive liver metabolism; thus, drug-related liver damage is possible [44]. Baclofen is a GABA receptor agonist that is used as an anti-spasticity medication to treat neurological disorder [45]. Some reports have recently suggested that baclofen may be available for the treatment of alcohol dependence. Acamprosate reduces withdrawal and cravings for alcohol in the meta-analysis, Acamprosate had a significant beneficial effect on enhancing abstinence in recently detoxified, alcohol-dependent patients [46].

Nutritional Therapy

In two large veterans, administration studies the 6-month mortality rate in severe alcoholic hepatitis correlated in a dose-response fashion with voluntary dietary intake. Despite this, two third of the patients failed to consume the recommended caloric intake of 2,500 kcal/day. Therefore, there should be hesitation in placing a nasogastric feeding tube if the patient

cannot voluntarily ingest at least 2,500 kcal/day, even when oesophageal varices are present. Glucocorticoid therapy can increase voluntary dietary intake but providing adequate calories through enteral feeding provides the same 1-month survival benefit with significantly lower mortality at 1 year [47-50]. Symptom based and supportive approach is necessary to achieve appropriate nutritional therapy in patients with ALD [51].

Nutrition goals include providing adequate calories protein, and nutrients to support hepatocyte regeneration within the existing metabolic alteration of liver disease [52]. Depending on the status of ALD, 1.2-1.5g/kg per day of protein and 35-40kcal/kg per day should be supplied in treatment [53].

Vitamin A, thiamine, vitamin B12, folic acid, pyridoxine, vitamin D, magnesium, selenium, and zinc may be administered to patients with ALD along with nutritional therapy [54].

Corticosteroids

Prednisolone 40 mg/d for 28 days followed by tapering over 2-4 weeks for the treatment of severe alcoholic hepatitis. Typically, in patients with severe alcoholic hepatitis, mortality rate within 28 days was 30%-50%. To estimate the prognosis for corticosteroids treatment, early changes in bilirubin levels and the Lille model were introduced [55, 56]. For early changes in bilirubin level was defined by the lowering of bilirubin level at 7 days after that on the first day of the treatment [56].

The mechanism of this drug is used to reduce inflammation and calm down an overactive immune system. It has predominant glucocorticoid and low mineral corticoid activity, which means it, affects the immune response and inflammation rather than electrolytes and water. Prednisolone mimics the effect of cortisol a hormone released by the adrenal glands that control metabolism and stress [57].

Pentoxifylline

In patients with severe alcoholic hepatitis, in whom glucocorticoids cannot be used, pentoxifylline is an effective alternative that has been shown to have short-term mortality (30 days) benefit and to reduce the incidence of the hepatorenal syndrome [58]. Renal failure as a cause of death in patients treated cirrhosis is remarkably low in the patients treated with pentoxifylline (10% compared with 70%) [58]. Pentoxifylline has lower short-term (2

months) mortality and incidence of hepatorenal syndrome, compared with glucocorticoids in patients with severe alcoholic hepatitis [59]. In a large (n=1103) multicentre, double-blind randomized trial investigating whether prednisolone and pentoxifylline are effective in alcoholic hepatitis, pentoxifylline did not improve survival. Prednisolone was associated with a reduction in short-term mortality without any effect on immediate and long-term mortality [60].

Combination Therapy and Comparative Efficacy

Glucocorticoids and pentoxifylline combination therapy have similar mortality but a lower incidence of hepatorenal syndrome as the cause of death compared to glucocorticoids alone [61]. Comparative efficacy of pharmacological agents and investigators have shown that in severe alcoholic hepatitis, glucocorticoid monotherapy or combination therapies and pentoxifylline reduce short-term mortality without any decrease in medium-term mortality [62]. The treatment of ALD is given in the Table No. 03.

Table No. 03: Treatment for ALD

ALD	TARGET	METHOD	CHARACTERISTICS
Abstinence	Stop Drinking	Baclofen, Acamprosate, Naltrexone & Psychotherapy	The rate of pharmacologic agents in maintaining abstinence is unclear.
Nutritional Support	Correct Malnutrition	1.2-1.5g/kg per day of protein and 35-40 kcal/kg per day	Vitamin A, thiamine, folic acid, pyridoxine, vitamin D, magnesium, selenium, and zinc may be administered.
Corticosteroids	Decrease Inflammation	Prednisolone 40mg/d for 28day followed by tapering over 2-4weeks	Increase in the serum bilirubin and Lille score >0.45 after 1 week of therapy are associated with worse outcome.
Pentoxifylline	Ablate Cytokines	400mg 3 times/ d for 28 days	Protective effect against hepatorenal syndrome.

Liver Transplantation

Survival after liver transplant for alcoholic cirrhosis is similar or even better than for other end-stage liver disease. Because of the limited availability of liver transplants, using this option in the management of ALD has become highly emotive because the disease is self-inflicted. Most centers demand that patients be abstinent for six months before transplantation. Many candidates are deemed unsuitable because of socioeconomic reasons, psychiatric problems, or coexistent alcoholic damage to other organs such as cardiomyopathy. A major worry after transplantation [63].

CONCLUSION

In alcoholic liver disease, alcohol abstinence and nutritional support are of paramount importance as none of the pharmacological agents increase intermediate and long-term mortality. Alcoholic liver disease with sepsis and multi-organ dysfunction has the dismal prognosis, so alcohol abuse should be diagnosed early. HCC surveillance should be done as in other causes of cirrhosis. Glucocorticoids and pentoxifylline either alone or in combination, along with other newer agents, can reduce short-term mortality but the long-term benefit is uncertain. Liver transplantation can substantially improve the survival in selected patients with alcoholic cirrhosis and severe alcoholic hepatitis that are resistant to all forms of therapy.

Clinicians should screen all patients for harmful patterns of alcohol use. All patients with the alcohol-related liver disease should abstain from alcohol. For those with severe disease (i.e., MDF>32 and/or hepatic encephalopathy), and no contraindications to their use, steroids should be considered. Liver transplantation remains an option for select patients with end-stage liver disease due to alcohol.

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