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Alcoholic liver disease: A review

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Abstract
Alcoholic Liver Disease (ALD) is the most advanced form of liver disease that's related to drinking alcohol. The disease is part of a progression. Alcoholic liver disease comprises a clinical-histologic spectrum including fatty liver, alcoholic hepatitis, and cirrhosis with its complications. The diagnosis of ALD can generally be made based on clinical and laboratory features alone in patients with a history of significant alcohol consumption after other etiologies for chronic liver disease have been ruled out. Therapies for treatment of ALD aim at achieving complete alcohol abstinence with use of pharmacological therapy and behavioral therapy with motivational interviewing. Many pharmacological agents have been used for treatment of ALD including disulfiram, acamprosate, gabapentin, naltrexone, topiramate, sertraline, & baclofen. Life style changes help to delay or stop progression of the disease, reduce the severity of symptoms and help to prevent the complications.

Keywords: Alcoholic liver disease, cirrhosis, baclofen, fatty liver

Introduction
Alcoholic Liver Disease (ALD) is a leading cause of cirrhosis, liver cancer, & acute and chronic liver failure leading to significant morbidity and mortality [1]. ALD is one of the main causes of chronic liver disease worldwide and accounts for up to 48 % of cirrhosis-associated deaths in the United States. 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 Hepato Cellular Carcinoma (HCC) [2]. Excessive alcohol consumption is a risk factor for a multitude of adverse health consequences and is indeed one of the leading causes of preventable morbidity and mortality worldwide with a significant burden attributable to ALD [3]. The liver is the primary site of ethanol metabolism, thus sustaining the greatest degree of tissue injury by heavy drinking **[4]**. A strong determinant for alcohol-related organ damage in many–but not all–patients is the alcohol dependence syndrome, a common behavioral disorder characterized by tolerance to the psychotropic effects of alcohol consumption, a preoccupation with alcohol and persistent drinking despite its harmful consequences. Chronic and episodes of binge alcohol abuse also contribute to the development of various somatic and psychiatric disorders and injuries, as well as to several diseases which are predominantly or entirely attributable to alcohol, such as alcohol-induced pancreatitis and the fetal alcohol syndrome. Furthermore, alcohol is also a contributory factor to other, diseases and injuries. Important disease conditions affected by alcohol consumption are cancers of the oropharynx, esophagus, liver, colon, rectum and the female breast; cardiovascular diseases; neuropsychiatric disorders (epilepsy, depressive disorders) [1].

Alcohol-Associated Somatic and Mental Diseases [1]
- Acute intoxication (apnea, aspiration of gastric content
- Alcoholic liver disease
- Alcoholic pancreatitis
- Cancer of the upper digestive tract (oral cavity, pharynx, hypo pharynx, pharynx, esophagus)
- Motility disorders (esophagus, gastro esophageal reflux, gastric emptying, and diarrhea)
- Mucosal damage (including hemorrhagic gastritis)
- Lactose intolerance
- Colorectal cancer

Metabolic disorders
- Hypoglycemia
- Hyperlipoproteinemia
- Hyperuricemia (including gout)
- Porphyria
- Hyperferritinemia

Fetal alcohol syndrome
Cardiovascular diseases
- Cardiomyopathy
- Arrhythmia (including atrial fibrillation)
- Arterial hypertension

Neurological and psychiatric disorders
- Peripheral neuropathy
- Dementia
- Cerebellar atrophy with dyskinesia
- Depression (including suicide)

Trauma
- Bone fractures
- Subdural hematoma

Breast cancer
Infections
- Endocarditis
- Viral hepatitis
- Sepsis
- Tuberculosis

Skin disease
- Psoriasis
- Teleangiectasias
- Spider angiomas
- Rhinophyma
- Palmar erythema

Etiology

As only about 10–20 % of individuals with chronic heavy alcohol use develop advanced liver disease and cirrhosis, other disease modifiers and cofactors, such as behavioral, environmental, and genetic factors, possibly have a role. There is a clear dose relationship between the amount of alcohol intake and the likelihood of developing ALD; yet, extensive individual variability exists [2]. Female are at risk for ALD at a lower daily intake of alcohol, probably due to higher body fat component and lower gastric alcohol dehydrogenase activity [5]. Obesity is one of most important environmental risk factor determining the risk of cirrhosis in heavy drinkers [6].

The coexistence of chronic hepatitis B or HCV infection leads to an acceleration of liver injury, with more frequent and faster development of cirrhosis and its complications including Hepato Cellular Carcinoma (HCC) [2]. Iron accumulation, which is a common finding in advanced ALD, has also been associated with hepatic fibrosis in ALD and increased mortality in alcoholic cirrhosis [7]. Cigarette smoking is common among alcoholic patients. It exacerbates the effects of alcohol in inducing severe ALD and favors development of HCC among patients with alcoholic cirrhosis [2].

Genetic factors influence the susceptibility for advanced ALD. Monozygotic twins have a higher concordance rate for alcohol-related cirrhosis than dizygotic twins [2]. Genetic factors may influence susceptibility to alcohol consumption or predisposition to development of ALD among those with AUD. Genes influencing the susceptibility for alcoholism include modifiers of neurotransmission such as γ-amino butyric acid and modifiers of alcohol metabolism such as alcoholic dehydrogenase and acetaldehyde dehydrogenase enzymes. The polymorphisms in these genes may be involved in an individual's susceptibility to alcoholism, with wide allelic variation between different ethnic groups, but their role in the progression of ALD remains controversial. The second group of genes modifies the natural history of ALD through different mechanisms. Small candidate gene studies initially suggested a role for polymorphisms in genes encoding inflammatory mediators, endotoxin response and oxidative stress. However, larger studies including a recent genome-wide association study revealed that patatinlike phospholipase domain containing protein 3, may be the main genetic determinant of risk for and severity of ALD [8, 9].

Pathophysiology
Hepatic Alcohol Metabolism

Beverage alcohol (i.e., ethanol) is chiefly metabolized in the main parenchymal cells of the liver (i.e., hepatocytes) that make up about 70 percent of the liver mass. These cells express the highest levels of the major ethanol-oxidizing enzymes, alcohol dehydrogenase (ADH), which is located in the cytosol, and cytochrome P450 2E1 (CYP2E1), which resides in the smooth endoplasmic reticulum (ER). Hepatocytes also express very high levels of catalase, an enzyme that inhibits peroxisomes. Catalase normally carries out the detoxification of hydrogen peroxide (H_2O_2) to water and oxygen. However, when ethanol is present, catalase has an accessory role in ethanol metabolism by using H_2O_2 to oxidize ethanol to acetaldehyde. Ethanol oxidation by catalase is a relatively minor pathway in the liver, but has a larger ethanol-oxidizing function in the brain [10].

Alcohol, a polar molecular substance, is soluble in both water and lipid. After being consumed, it is absorbed into the blood circulation through the gastrointestinal tract. Generally, more than 95% of absorbed alcohol is metabolized by the liver, and a small amount is directly excreted through the lungs, urine, and sweat [11]. As shown in previous studies, there are three main metabolic systems which participate in the oxidative metabolism of alcohol into acetaldehyde. First is the hepatocyte cytoplasmic Alcohol Dehydrogenase (ADH) system, which oxidizes ethanol into acetaldehyde using Nicotinamide Adenine Dinucleotide (NAD+) as a co-factor. ADH1, amongst the other isoenzymes of ADH, plays a main role in ethanol metabolism in the liver. Acetaldehyde, which is produced by ADH, is further oxidized to acetate by Acetaldehyde Dehydrogenase (ALDH) [11].

The second main metabolic system of alcohol is cytochrome P450 2E1 (CYP2E1) enzymes that convert chemical molecules into polar metabolites prior to excretion. CYP2E1 is considered to be the main component of this system. Under normal physiological conditions, CYP2E1 catalyzes the oxidization of a small amount of ethanol, such as 10 %, into acetaldehyde. However, it is increased in chronic alcohol abuse conditions due to the induction of the expression of CYP2E1. The third metabolic system is the catalase endoplasmic reticulum (CAT) system, which is considered as the other main metabolic system that relies on NADPH for oxidative metabolism. This heme-containing catalase enzyme usually catalyzes the H_2O_2 removal but also is capable of

catalyzing the oxidation of alcohol to acetaldehyde [12, 13].
When the concentration of ethanol in blood and tissue fluid is low, it is mainly metabolized by the ADH pathway. However, when the concentration of ethanol is higher than10 mol/L, the other two enzyme systems also begin to participate in ethanol metabolism [13].

The spectrum of ALD
ALD comprises a broad spectrum of liver disorders ranging from simple alcoholic fatty liver/steatosis to severe lesion of liver injuries including steatohepatitis, fibrosis/cirrhosis, and Hepatocellular carcinoma. These stages are classified based on the histology of the liver of patients [14]. Frequently, the pathologic processes are overlapped instead of being distinct disorder entities [15].

Risk factors
Several factors have been identified at individual and society levels to affect the pattern or extent of alcohol consumption and the risk to develop many liver diseases.

Alcohol Consumption: The main epidemiological risk factor for ALD is excessive alcohol consumption. There is a great regional variability in alcohol consumption due to socioeconomic, cultural and religious factors with the highest levels in Europe and USA and the lowest ones in South-East Asia and Eastern Mediterranean countries. Thus, alcohol-related diseases occur more frequently in the developed world. Several large prospective cohort studies have shown that in individuals with high alcohol consumption (40 g/day for women and 60 g/day for men) there is a dose-dependent increase in cirrhosis risk. A population study demonstrated that subjects with a daily intake greater than 30 g of alcohol had an enhanced risk of developing alcoholic liver injury and cirrhosis. Subjects who consumed more than 120 g/day of alcohol have increased risk of cirrhosis although the length of time during which an individual has regularly drunk impacts the risk of cirrhosis more than the amount of alcohol consumed. Moreover, it has been described that daily drinking compared to episodic or binge drinking is associated with higher risk of cirrhosis. In addition, consumption of alcohol with food is less harmful than drinking on an empty stomach and wine has less serious consequences on ALD development than beer, although this could be explained by the fact that beer drinkers consume more caloric diets [4].

Age: It is not completely clear how age modifies ALD progression. It is, however, a predictor for ALD, because older adults (i.e., ages 65 and up) are more vulnerable to and show greater degrees of ethanol-induced impairments than younger people [16].

Gender: Gender also plays an important role in alcohol susceptibility. Men consume significantly more alcohol than women and consequently have nine times more alcohol-related liver disease. However, for a given levels of drinking, women are more vulnerable to alcohol-related liver damage than men. This appears to be related to higher blood alcohol concentrations in women than in men with the same amount of alcohol ingested and to the effects of estrogen on alcohol-related liver injury [4]. Moreover, chronic alcohol abuse induces a pro-inflammatory response in adipose tissue possibly in a sex dependent manner with a greater inflammation that influence liver damage in female mice exposed to chronic-binge ethanol [17]. Several studies demonstrated that even Non Alcoholic Fatty Liver Disease (NAFLD) is more prevalent in males than in women. Conversely, in NAFLD patients, estrogens seem to have a protective effect. Indeed, estrogen deficiency and ovarian senescence due to old age may increase the susceptibility to NAFLD [18].

Ethnicity: There is a huge inter-ethnic variability in the predisposition towards ALD. Indeed, ethnicity represents one of the major factors which affect the development and outcome of ALD and there are several inter-ethnic differences in alcohol-related cirrhosis risk [19]. American Indians and Native Alaskans have a significantly greater mortality from chronic ALD compared to White people [20].

Obesity: Among environmental risk factors, obesity is the widest recognized. It has been described that overweight or obese women in the UK who consume low to moderate amounts of alcohol had growing risk of liver cirrhosis compared to women with a BMI between 22.5 and 25. Obesity leads to steatohepatitis affecting hepatic insulin sensitivity and the lipid solubility of ethanol influences adipose tissue production of hormones and cytokines. Meanwhile, alcoholic fatty liver induces peripheral insulin resistance, thus promoting obesity. It has been demonstrated that in patients with alcoholic liver disease, a previous history of excess weight was an independent risk factor for the pathogenesis of steatosis, fibrosis and cirrhosis .Bellentani and colleagues found that alcohol and obesity are both associated with hepatic steatosis, whose prevalence is higher (94.5 %) in obese drinkers [4].

Epidemiology
Alcohol-use disorder (AUD) is one of the main causes of preventable disease and liver disease-associated mortality in the United States and worldwide. A recent report from the World Health Organization indicates that 3.3 million deaths (6 % of all global deaths) are attributable to alcohol use, and that alcohol abuse is a risk factor in about 50 % of cases of cirrhosis [21]. Approximately 1 in 12 adults have AUD defined as consumption of >3 drinks per day in males and >2 drinks per day in female, or binge drinking (defined by the National Institute of Alcoholism and Alcohol Abuse as >5 drinks in males and >4 drinks in female, consumed over 2 h period). In the United States, one drink is defined as a beverage containing about 14 g of alcohol, which is present in 12 ounces of beer (5 % weight/volume) or 5 ounces of wine (8–10 % weight/volume), or 1.5 ounces of hard liquor (40–45 % weight/volume) [22].
Economic costs due to AUD (249 billion USD per year) are increasing. An estimated 88,000 people (~62,000 men and 26,000 women) die from alcohol-related causes annually, making alcohol the fourth leading preventable cause of death in the United States [23].
The association between alcohol and liver-related mortality is strongly supported by data showing a linear relationship between the standard liver death rate and overall alcohol consumption in many countries [24, 25]. Importantly, drinking patterns such as heavy episodic drinking vs. heavy daily use and the type of alcohol consumed may not independently predict the alcohol-attributable fraction of cirrhosis [26].

Clinical features of ALD [3]

Table 1: Typical clinical features of Alcoholic Liver Disease

Spectrum of ALD	Clinical Features
Alcoholic Alcoholic fatty liver hepatitis	Asymptomatic
	Jaundice
	Anorexia
	Fever
	+/-Right Upper Quadrant(RUQ)/epigastric pain
	+/- Abdominal distention due to ascites
	+/- Proximal muscle weakness
	+/- Confusion due to Hepatic Encephalopathy
Compensated cirrhosis	Asymptomatic
	Anorexia
	Weight loss
	Weakness
	Fatigue
	Muscle cramps
De-compensated cirrhosis	Amenorrhea or irregular menses
	Impotence, infertility, loss of sexual drive
	Jaundice
	Pruritus
	Gastrointestinal bleeding
	Weight gain
	Abdominal distention due to ascites
	Lower extremity edema
	Easy bruising
	Sleep disturbances
	Confusion

Diagnosis for (ALD)

General diagnostic approach for Alcoholic Liver Disease

- The diagnosis of ALD can generally be made based on clinical and laboratory features alone in patients with a history of significant alcohol consumption after other etiologies for chronic liver disease have been ruled out.
- However, the diagnosis of ALD can be clinically challenging as there is no single laboratory or imaging study that can confirm the diagnosis.
- Furthermore, patients may be completely asymptomatic, have no clinical signs of early ALD or early cirrhosis and may have normal liver enzymes.
- In addition, patients may have co-existing risk factors for non-alcoholic fatty liver disease such as obesity and diabetes and some may not be entirely forthcoming as to their degree of alcohol consumption.
- In general, ALD should be suspected in patients with a significant history of alcohol use who present with abnormal serum transaminases, particularly if the level of aspartate aminotransferase (AST) is greater than that of alanine aminotransferase (ALT), hepatomegaly, clinical signs of chronic liver disease, radiographic evidence of hepatic steatosis or fibrosis/cirrhosis, or who have had a liver biopsy showing macro vesicular steatosis or cirrhosis.
- Patients with ALD may or may not have elevated serum aminotransferase levels. The absolute level of liver enzyme elevation does not correlate well with the severity of ALD; however, the pattern of elevation in transaminases is helpful in making a diagnosis of liver injury due to alcohol as AST is typically two to three times greater than ALT in alcoholic liver injury.
- They will also typically have an elevated serum gamma-glutamyltranspeptidase (GGT). However, it is important to rule out other etiologies for the patient's liver disease before making a definitive diagnosis of ALD, including chronic viral hepatitis, autoimmune hepatitis, hemochromatosis and drug related hepatotoxicity.
- In some cases, when the diagnosis is unclear, a liver biopsy may be warranted [3].

Table 2: Physical Findings of Alcoholic Liver Disease [27]

Spectrum of ALD	Physical Examination Findings
Fatty liver Alcoholic Hepatitis	Normal examination
	+/- Hepatomegaly
	Jaundice
	Tender hepatomegaly
	+/- Ascites
	+/- Hepatic bruit
	Proximal muscle wasting
	Decreased grip strength
	+/- Hepatic encephalopathy
	(confusion, asterixis, hippus)
Cirrhosis	Spider angiomata (face, trunk, upper extremities)
	Parotid gland enlargement
	+/- Fetor hepaticus

	Gynecomastia
	+/- Hepatomegaly
	Firm liver edge with nodular contour
	+/- Splenomegaly
	Caput medusa (abdominal wall collaterals)
	Cruveilhier-Baumgarten murmur
	Testicular atrophy
	Palmar erythema
	Digital clubbing
De-compensated Cirrhosis	Muehrcke nails (paired horizontal white bands)
	Terry nails (large white proximal nail bed)
	Hypertrophic osteoarthropathy
	Dupuytren's contracture
	Cirrhotic physical finding plus:
	Jaundice
	Ascites
	Peripheral edema
	Hepatic encephalopathy
	(confusion, asterixis, hippus)

Laboratory Tests

- Laboratory tests such as mean corpuscular volume of red blood cells, γ-glutamyltransferase (GGT) and aspartate aminotransferase (AST), IgA, can indicate early ALD while a decrease of albumin, increased international normalized ratio (INR), elevated bilirubin level and/or a low platelet count are signs of advanced ALD.
- Many heavy drinkers also reveal elevated levels of triglycerides and uric acid, the latter often associated with gout attacks [28].
- Alcohol-specific markers include carbohydrate deficient transferrin and ethyl-glucuronide; however, sensitivity of the former is limited as many drinkers remain undetected due to normal levels [29].
- Clinically, GGT is the most frequently used marker to detect previous alcohol consumption, however, it lacks specificity and can also rise due to other etiologies. In patients with ALD, the AST/alanine aminotransferase (ALT) ratio typically is >1, and may be >2 in patients with AH. However, it can also be found in patients with advanced cirrhosis regardless of the etiology [1].
- Imaging techniques can also be used to assess the severity of ALD. Ultrasonography, magnetic resonance imaging (MRI), and computed tomography are useful to detect steatosis, advanced fibrosis/ cirrhosis as well as signs of portal hypertension [30].
- Moreover, they are useful for the screening and assessment of complications such as ascites and portal vein thrombosis. Among those methods, ultrasound is the most widely used due to its low cost. MRI and MR spectroscopy are reliable tools for quantifying steatosis but their use is limited by high cost [31].
- Transient elastography offers a software update to quantify liver fat termed Controlled Attenuation Parameter (CAP function) as a significantly cheaper alternative [32].
- Liver biopsy is not clearly indicated in patients with early stages of ALD or when established cirrhosis is revealed by clinical, analytical and imaging data.
- The liver biopsy can be done percutaneously in most patients but requires a transjugular approach in patients with a low platelet count and/or a prolonged prothrombin time. The precise indications of liver biopsy are not well established in routine practice. However, it is suggested in patients with aggressive forms of ALD such as AH requiring specific therapies (e.g., corticosteroids and/or pentoxifylline) and in patients with other cofactors suspected of contributing to liver disease.
- In the setting of clinical trials, the assessment of liver histology by performing a liver biopsy is recommended. The typical findings in patients with ALD include steatosis, hepatocellular damage (ballooning and/or Mallory-Denk bodies), an inflammatory infiltrate basically composed of PMN cells that predominates in the lobules, and a variable degree of fibrosis and lobular distortion that may progress to cirrhosis [33].

Management of ALD

Therapies for treatment of AUD aim at achieving complete alcohol abstinence with use of pharmacological therapy and behavioral therapy with motivational interviewing. Patients actively drinking are at a high risk of severe AWS during inpatient alcohol detoxification. Obstacles to completing addiction therapies include the following: lack of specialized care, refusal by the patient, lack of insurance coverage, patient too sick to attend therapy sessions, and transportation. Recognizing these obstacles will help the clinician to address these with the patient as basis of providing optimal management [2].

Pharmacological Therapies

Many pharmacological agents have been used for treatment of ALD including disulfiram, acamprosate, gabapentin, naltrexone, topiramate, sertraline, & baclofen. Of these, only baclofen, a γ-amino butyric acid-B receptor agonist has been found to be safe in patients with ALD and cirrhosis. Its efficacy is shown with increase in abstinence rates [34]

Baclofen can be started in a dose of 5 mg three times a day and the dose can be increased at a 3–5 days interval based on patient tolerance to a maximum dose of 15 mg three times a day. Considering its excellent safety profile, even among patients with advanced liver disease and AH, patients on baclofen therapy can be monitored by hepatologists or addiction specialists [34].

Corticosteroids have been used to improve the nutritional status of AH patients. The anti-thyroid Drug propylthiouracil also has been evaluated for the treatment of acute AH. Since ALD is associated with elevated levels of oxidative stress, antioxidants such as vitamin E and silymarin have been investigated and evaluated for the treatment of AH patients in

previous studies. Unfortunately, the survival time of patients did not increase. However, another study, which evaluated the potential benefits of the combination of N-acetylcysteine and corticosteroids, showed an increase in patient survival [11]. Losartan is considered a treatment to prevent the development of hepatic fibrosis and progression and regression of fibrosis stage. Prednisolone, a steroid medication, is used to inhibit the inflammation of hepatocytes [35].

Non Pharmacological Therapies

The other major approach to induce or to maintain alcohol abstinence in patients with ALD is behavioral interventions such as motivational enhancement therapy, cognitive behavioral therapy, motivational interviewing, supportive therapy, and psycho education [36]. Motivational interviewing, the most commonly used intervention, is a technique that aims to be both non-judgmental and non-confrontational. It attempts to increase a patient's awareness of the potential problems caused, consequences experienced, and risks faced because of excessive alcohol use. Essential components of a motivational approach are an empathic attitude and a collaborative approach that respects the patients' autonomy [37].

Psychological interventions can be difficult in patients with hepatic encephalopathy, cognitive impairment, or poor performance status. Moreover, patients with end-stage liver disease have frequent hospitalizations that preclude attendance at psychosocial interventions. No psychosocial intervention has been consistently shown to be successful in maintaining abstinence in patients with ALD. Rather, an integrated therapy with cognitive behavioral therapy and medical care appear to reduce recidivism. There is a clear need for clinical trials combining psychosocial and pharmacological interventions in ALD patients with AUD [2].

Management of Alcohol Withdrawal

Alcohol Withdrawal Syndrome (AWS) is a common condition affecting alcohol-dependent patients who abruptly discontinue or markedly decrease alcohol consumption. Light or moderate AWS usually develops within 6–24 h after the last drink and symptoms may include nausea/vomiting, hypertension, tachycardia, tremors, hyperreflexia, irritability, anxiety, and headache. These symptoms may progress to more severe forms of AWS, characterized by delirium tremens, generalized seizures, coma, and even cardiac arrest and death. Older patients are at greater risk for delirium tremens [38].

Patients with moderate or severe alcohol withdrawal should be closely monitored in an intensive care unit (ICU), where vital signs, volume status, and neurological function are monitored on a regular basis. Severity scores for AWS such as the Clinical Institute Withdrawal Assessment for Alcohol score are useful in the management of patients, although they have not been validated in patients with severe ALD and a symptom-triggered approach is preferred.

Benzodiazepines are the most commonly used drugs to treat AWS. Long-acting benzodiazepines (e.g., diazepam and chlordi-azepoxide) predominantly protect against seizures and delirium; short and intermediate-acting benzodiazepines (e.g., lorazepam and oxazepam) are safer for patients with poor liver function. Patients with AWS and concomitant hepatic encephalopathy should be treated for both the conditions. Of note, high-dose benzodiazepines may precipitate and worsen hepatic encephalopathy; thus, careful monitoring and titration is critical for optimal outcomes. Given the side effects of benzodiazepines in patients with advanced liver disease and the potential for abuse in an addictive population, other drugs such as baclofen, clonidine, gabapentin, and topiramate have been proposed to treat AWS in patients with ALD including alcoholic cirrhosis. However, the efficacy and safety of these substances in patients with AH is unknown and therefore prospective studies are required. A promising approach is to use baclofen to prevent and treat moderate AWS first, and continue the medication to prevent alcohol relapse [38].

Liver Transplantation

Liver transplantation is the main choice for patients with advanced-stages of ALD. Liver transplantation has a better prognosis for patients with severe alcoholic hepatitis, who are not sensitive to drug treatments [11]. A physiologically functioning liver can be provided to patients with ALD by liver transplantation. Even though it increases the survival and quality of patient's life, it does not eliminate the underlying alcoholism. Therefore, it may have a potential for relapse [39].

Lifestyle modifications for ALD [40, 41, 42]

Life style changes help to delay or stop progression of the disease, reduce the severity of symptoms and help to prevent the complications.

1. Avoid drinking alcohol
2. Eat a balanced diet.
3. An appropriate diet can help liver tissues to regenerate and can reduce the severity of symptoms in more advanced disease.
4. To reduce the chances of infection, avoid raw seafood and dishes that contain raw seafood, such as sushi. Raw fish can be contaminated with hepatitis A, as well as other viruses, bacteria, and parasites, which could further stress liver function. Raw oysters can be especially dangerous.
5. In the early stages of recovery, take more calories and protein. Adequate amounts of amino acids from proteins and other nutrients are necessary to regenerate liver tissue. Take more vitamin and mineral supplements. This can help to correct deficiencies that may have developed from cirrhosis. Supplements and supplemental nutritional beverages also may help support tissue growth and repair.
6. Avoid taking excessive amounts of vitamins A and D, and avoid foods that have been supplemented with iron.
7. In some cases, a salt-restricted diet may be necessary, Salt contributes to fluid retention. Restricting salt can help alleviate fluid-related swelling in the abdomen and legs.
8. If the disease is advanced, maintain protein-restricted diet, decreasing the amount of protein helps to reduce the production of nitrogen-containing wastes, like ammonia. In a severely damaged liver, detoxification of ammonia is impaired, which can lead to high blood levels of ammonia. These, in turn, can produce mental changes, known as encephalopathy, which eventually may lead to coma and death.
9. Do not take any medications, including over-the-counter drugs and herbal remedies, without doctor's approval. The liver is responsible for metabolizing drugs, when the liver is damaged because of cirrhosis, drug metabolism may be altered. Dangerously high levels of medications can remain in the blood and interfere with drugs which are administered to treat cirrhosis. Always get the

doctor's approval before taking any medication.
10. Even drugs that seem relatively harmless, such as acetaminophen (Tylenol) can be harmful in some circumstances. The same is true of all nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen.
11. Vaccinations will help to reduce the likelihood of becoming infected and also help to reduce the severity of disease.
12. Gravity helps to pull fluid down into the feet and legs, lifting up the feet will reduce the swelling and relieve pain in swollen legs and feet.

References

1. Felix Stickel, Christian Datz, Jochen Hampe, Ramon Bataller. Pathophysiology and Management of Alcoholic Liver Disease: Update 2016 Gut and Liver. 2017; 11(2):173-188.
2. Ashwani Singal K, MDMS FACG, Ramon Bataller, MD FACG, Joseph Ahn, MD MS FACG. [(GRADE Methodologist)], Patrick Kamath S, MD Vijay H Shah, MD FACG ACG. Clinical Guideline: Alcoholic Liver Disease Am J Gastroenterol. 2018; 113(2):175-194. DOI:10.1038/ajg.2017.469.
3. Cara Torruellas, Samuel W French. Valentina Medici Diagnosis of alcoholic liver disease World J Gastroenterol September. 2014; 20(33):11684-11699.
4. Marica Meroni, Miriam Longo, Raffaela Rametta. Paola Dongiovanni Genetic and Epigenetic Modifiers of Alcoholic Liver Disease Received: 17 October 2018; Accepted: 28 November 2018; Published: 3 December, 2018.
5. Frezza M, di Padova C, Pozzato G *et al*. High blood alcohol levels in women. The role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. N Engl J Med. 1990; 322:95-9.
6. Hart CL, Morrison DS, Batty GD *et al*. Effect of body mass index and alcohol consumption on liver disease: analysis of data from two prospective cohort studies. BMJ. 2010; 340:c1240.
7. Nahon P, Nuraldeen R, Rufat P *et al*. In alcoholic cirrhosis, low-serum hepcidin levels associate with poor long-term survival. Liver Int. 2016; 36:185-8.
8. Salameh H, Raff E, Erwin A *et al*. pnpla gene polymorphism is associated with predisposition to and severity of alcoholic liver disease. Am J Gastroenterol. 2015; 110:846-56.
9. Ali M, Yopp A, Gopal P *et al*. A variant in PNPLA Associated with fibrosis progression but not hepatocellular carcinoma in patients with hepatitis C virus infection. Clin Gastroenterol Hepatol. 2016; 14:295-300.
10. Natalia Osna A, Terrence Donohue M Jr., Kusum Kharbanda K. Alcoholic Liver Disease: Pathogenesis and Current Management.
11. Ling-Zu Kong Y, Nisansala Chandimali Y, Ying-Hao Han Y, Dong-Ho Lee, Ji-Su Kim *et al*. Pathogenesis, Early Diagnosis, and Therapeutic Management of Alcoholic Liver Disease Received: 9 April. 2019; Accepted: 31 May 2019; Published: 2 June, 2019.
12. Cederbaum AI. Alcohol metabolism. Clin. Liver Dis. 2012; 16:667-685.
13. Ceni E, Mello T, Galli A. Pathogenesis of alcoholic liver disease: Role of oxidative metabolism. World J Gastroenterol. 2014; 20:17756-17772.
14. Teschke R. Alcoholic steatohepatitis (ASH) and alcoholic hepatitis (AH): Cascade of events, clinical aspects, and pharmacotherapy options. Expert Opin. Pharm. 2018; 19:779-793.
15. Chacko KR, Reinus J. Spectrum of Alcoholic Liver Disease. Clin. Liver Dis. 2016; 20:419-427.
16. Masson S, Emmerson I, Henderson E *et al*. Clinical but not histological factors predict long-term prognosis in patients with histologically advanced non-decompensated alcoholic liver disease. Liver International. 2014; 34(2):235-242.
17. Fulham MA, Mandrekar P. Sexual dimorphism in alcohol induced adipose inflammation relates to liver injury. PLoS ONE. 2016; 11:e0164225.
18. Ballestri S, Nascimbeni F, Baldelli E, Marrazzo A, Romagnoli D, Lonardo A. NAFLD as a Sexual Dimorphic Disease: Role of Gender and Reproductive Status in the Development and Progression of Nonalcoholic Fatty Liver Disease and Inherent Cardiovascular Risk. Adv. Ther. 2017; 34:1291-1326.
19. Levy RE, Catana AM, Durbin-Johnson B, Halsted CH, Medici V. Ethnic differences in presentation and severity of alcoholic liver disease. Alcohol. Clin. Exp. Res. 2015; 39:566-574.
20. Landen M, Roeber J, Naimi T, Nielsen L, Sewell M. Alcohol-attributablemortality among American Indians and Alaska Natives in the United States, 1999-2009. Am. J Public Health. 2014; 104:S343-S349.
21. Yoon YH, Chen CM. Surveillance Report #105. Liver cirrhosis mortality in the United States: national, state, and regional trends, 2000-2013, 2016, cited 19 April, 2017.
22. Alcohol Facts and Statistics In: Alcoholism NIoAAa, editor, 2017.
23. Yoon YH CC. Liver cirrhosis mortality in the United States: National, State, and Regional trends, 2000-2013. In: Alcoholism NIoAAa, editor, 2016.
24. Stein E, Cruz-Lemini M, Altamirano J *et al*. Heavy daily alcohol intake at the population level predicts the weight of alcohol in cirrhosis burden worldwide. J Hepatol. 2016; 65:998-1005.
25. Sheron N. Alcohol and liver disease in Europe-simple measures have the potential to prevent tens of thousands of premature deaths. J Hepatol. 2016; 64:957-67.
26. Askgaard G, Gronbaek M, Kjaer MS *et al*. Alcohol drinking pattern and risk of alcoholic liver cirrhosis: a prospective cohort study. J Hepatol. 2015; 62:1061-7.
27. Klatsky AL, Chartier D, Udaltsova N, Gronningen S, Brar S, Friedman GD *et al*. Alcohol drinking and risk of hospitalization for heart failure with and without associated coronary artery disease. Am J Cardiol. 2015; 96:346-351.
28. Tu HP, Tung YC, Tsai WC, Lin GT, Ko YC, Lee SS. Alcoholrelated diseases and alcohol dependence syndrome is associated with increased gout risk: a nationwide population based cohort study. Joint Bone Spine. Epub, 2016.
29. Lowe JM, McDonell MG, Leickly E *et al*. Determining ethyl glucuronide cutoffs when detecting self-reported alcohol use in addiction treatment patients. Alcohol Clin Exp Res. 2015; 39:905-910.
30. Penny SM. Alcoholic liver disease. Radiol Technol. 2013; 84:577-592.

31. D'Assignies G, Fontés G, Kauffmann C *et al*. Early detection of liver steatosis by magnetic resonance imaging in rats infused with glucose and intralipid solutions and correlation to insulin levels. Metabolism. 2013; 62:1850-1857.
32. De Lédinghen V, Vergniol J, Capdepont M *et al*. Controlled attenuation parameter (CAP) for the diagnosis of steatosis: A prospective study of 5323 examinations. J Hepatol. 2014; 60:1026 1031.
33. Philippe Mathurin, Ramon Bataller. Trends in the management and burden of alcoholic liver disease J Hepatol. 2015; 62(1 Suppl):S38-S46. DOI: 10.1016/j.jhep.2015.03.006.
34. Jonas DE, Amick HR, Feltner C *et al*. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: A systematic review and metaanalysis. JAMA. 2014; 311:1889-900.
35. Salama ZA, Sadek A, Abdelhady AM, Darweesh SK, Morsy SA, Esmat G. Losartan may inhibit the progression of liver fibrosis in chronic HCV patients. Hepatobiliary Surg. Nutr. 2016; 5:249-255.
36. Leggio L, Lee MR. Treatment ofalcohol use disorder in patients with alcoholic liver disease. Am J Med. 2017; 130:124-34.
37. Foxcroft DR, Coombes L, Wood S *et al*. Motivational interviewing for alcohol misuse in young adults. Cochrane Database Syst Rev, 2014, CD007025.
38. Garcia-Tsao G, Abraldes JG, Berzigotti A *et al*. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology. 2017; 65:310-35.
39. Marroni CA, Fleck AM, Fernandes SA Jr., Galant LH, Mucenic M, de Mattos Meine MH, Mariante-Neto G *et al*. Liver transplantation and alcoholic liver disease: History, controversies, and considerations. World J Gastroenterol. 2018; 24:2785-2805.
40. Cirrhosis. American Liver Foundation at: http://www.liver foundation.org/about thrliver/info/cirrhosis. Updated December 6, 2016. Accessed March 28, 2017.
41. Cirrhosis. National Institute of Diabetes and Digestive and Kidney Diseases website. Available at: https: //www.niddk.nih.Gov/ health- information / liver-disease/ cirrhosis. Updated April 2014. Accessed March 28, 2018.
42. Cirrhosis of the liver EBSCO Dynamed plus website. Available at: http://www.dynamed.Com/ topics/ dmp~AN~T114078/ cirrhosis-of-the-liver. Updated January 12, 2017. Accessed March 28, 2017.