

Alcoholic Liver Disease — Laboratory Evaluation and Prognosis

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Alcoholic liver disease occurs as a result of excessive alcohol consumption. Up to 20 % of heavy drinkers will develop liver cirrhosis. The amount, pattern and duration of alcohol consumption along with inflammatory changes in liver, diet, nutritional status and genetic predisposition of the patient predict the severity and prognosis of the disease. Blood test, liver function test, and liver biopsy are helpful to establish the diagnosis. General supportive measures, Prednisolone or Tumor necrosis alpha inhibitors can be used but with caution along with alcohol, abstinence is adopted to manage the case. Liver transplantation is preserved for patients with severe liver cirrhosis.



Causes of Alcoholic Liver Disease

Quantity and frequency of alcohol consumption

There is a proportional relationship between alcohol consumption and the development of **liver cirrhosis** among heavy drinkers.

Consumption of about 100 ml of alcohol per day for males and 20 ml per day for females for a period of 10 years increases the risk of hepatic cirrhosis. The risk of cirrhosis increases to 50 % for patients who consume more than 200 mg of alcohol/day for 20

years. 100 ml of alcohol according to the beverage content is about 80 mg of alcohol.

Drinking with meals is less dangerous and has 3 times less risk for liver injury than drinking without food.

Gender

Women are more susceptible to alcoholic liver disease than men. Less alcohol consumption and less duration are needed to be at risk. Women have less **intestinal mucosal alcoholic dehydrogenase enzyme** than men. The mucosal enzyme metabolizes a small amount of alcohol in the intestine, therefore less alcohol reaches the liver.

Genetic factors

Alcoholic liver disease runs in families, and monozygotic twins are more susceptible than dizygotic twins. This can be explained by a **genetic polymorphism** in some of the genes and enzymes involved in alcohol metabolism. Genetic factors also play a role in alcohol dependency.

Liver insult

The presence of **primary liver insult** will increase the risk of cirrhosis. **Viral hepatitis, hemochromatosis**, obesity and nutritional deficiency are all risk factors for susceptible liver injury with alcohol. Alcoholic dependency is a major risk for malnutrition and deficiency of vital nutrients, vitamins e.g. E, thiamine, and antioxidants needed for liver cell regeneration.

Pathophysiology of Alcoholic Liver Disease

Alcohol is readily absorbed from the **stomach** and small intestine. It is metabolized mainly in the **liver** by alcohol dehydrogenase, **cytochrome P-450 2E1**, and **microsomal oxidation**.

Alcohol dehydrogenase (ADH) oxidizes alcohol into acetaldehyde in the cytoplasm with the formation of NADH from NAD. Another oxidation in the **mitochondria** takes place by conversion of acetaldehyde into acetate by acetaldehyde dehydrogenase. NADH is also produced.

Excess NADH in the liver inhibits fat utilization for **gluconeogenesis**. This will lead to fat accumulation in the hepatocytes and development of fatty liver. **Microsomal oxidation** and **cytochrome P-450 2E1 activation** in **chronic alcoholism** will increase oxidative stress with a formation of reactive oxygen species and oxygen free radicals.

Malnutrition will subsequently lead to more **hyperlipidemia** from peripheral tissue conversion and **inhibited hepatic gluconeogenesis**. Several factors affect hepatocytes increasing the oxidative insult including more absorption of **gut bacterial toxins** after alcohol mucosal damage, **oxygen free radicals** from alcohol metabolism and reduction of protective antioxidants from malnutrition.

Acetaldehyde can also combine to and **inhibit intracellular macromolecules**, forming acetaldehyde adducts. Acetaldehyde adducts are known **immunostimulants** that attract neutrophils to attack hepatocytes.

All these factors will promote **active hepatitis** with an accumulation of neutrophils and the secretion of inflammatory cytokines e.g., **TNF-alpha** and **interleukins**.

Apoptosis of the liver cells can contribute to the inflammation and regeneration with scarring. Fibrous tissue, which is formed from myofibroblasts will lead to narrowing of the blood sinusoids and venules. **Portal hypertension** will eventually result and hepatic regenerating nodules will change the normal liver architecture.

Pathology of Alcoholic Liver Disease

Fatty liver

This condition is the earliest form of liver pathology from alcohol consumption. Grossly, the **liver appears enlarged, greasy and yellow**. Microscopically, there is **perivenular fat accumulation** inside the cells that displaces the nucleus. Fatty liver is reversible once alcohol consumption is stopped. The fat globules formed inside hepatocytes are due to high NADH content. High NADH and low NAD inhibits fatty acid oxidation and promotes synthesis and accumulation inside hepatocytes.

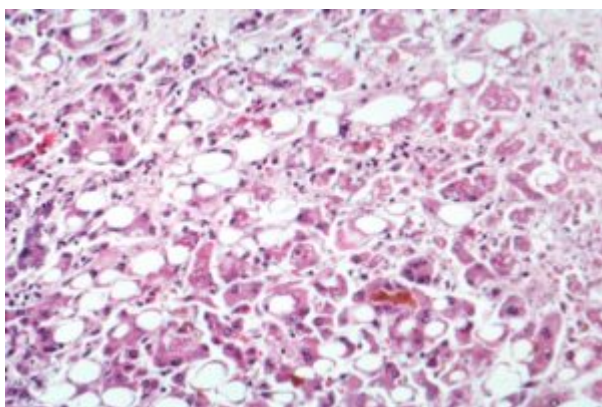


Image: "Microscopy of the liver showing evidence of alcoholic hepatitis". The original uploader was Countincr at English Wikipedia - Transferred from en.wikipedia to Commons, License: [CC BY-SA 2.5](https://creativecommons.org/licenses/by-sa/2.5/)

Alcoholic hepatitis

Liver cell death will result from inflammatory cytokines. TNF- α is produced from **Kupffer cells** due to intestinal bacterial toxins. Oxidative stress and acetaldehyde adducts will activate more cytokines and more neutrophils. **Active inflammation** of the liver will be evident with a high number of WBCs, cell degeneration, and fibrosis. Cells will appear swollen with granular cytoplasm. Mallory bodies will be seen, which are degenerated intermediate filaments. **Fibrosis** starts around blood sinusoids and spreads according to the degree of inflammation.

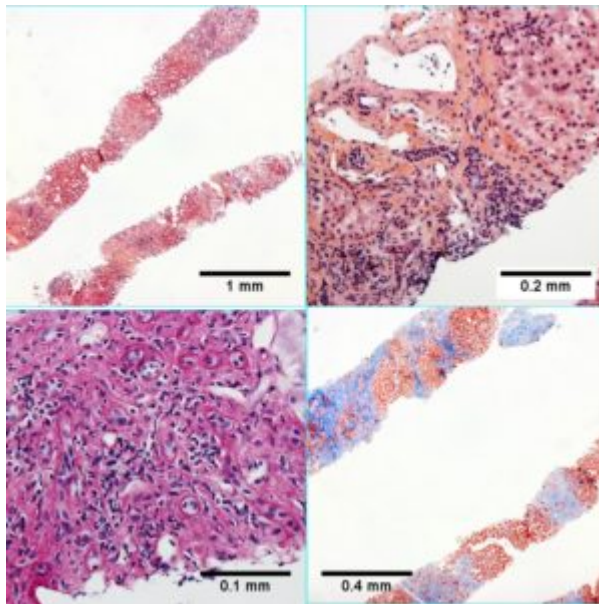


Image: "Cirrhosis in a patient with a history of alcohol abuse." by TexasPathologistMSW - Own work. License: [CC BY-SA 4.0](https://creativecommons.org/licenses/by-sa/4.0/)

Alcoholic cirrhosis

Alcoholic **steatohepatitis**, cell necrosis, and [apoptosis](#) will lead to extensive activation of fibrosis. It is an **irreversible** late stage of liver damage but alcohol abstinence can help. Macroscopically, the liver will appear shrunken in size with **regenerating micronodules**.

Microscopically, fibrosis will disrupt the normal architecture into small regenerating nodules. **Hepatitis** and fatty changes will also be seen. The fibrous tissue is secreted from stellate cells which surround hepatic [blood vessels](#).

Clinical Picture of Alcoholic Liver Disease

Fatty liver

This is asymptomatic. It is common and normal healthy people can have fatty liver a few days after heavy drinking.

Alcoholic hepatitis

Patients will present with a wide variety of symptoms according to the extent of inflammation. Early symptoms like fatigue, abdominal pain, nausea, lack of appetite and fever to late symptoms of jaundice, **ascites**, lower limb [edema](#), itching, and [encephalopathy](#).

Cirrhosis



Image: "Macroscopic image of micronodular (liver) cirrhosis caused by alcohol consumption" by Amadalvarez – Own work, License: [CC BY-SA 4.0](https://creativecommons.org/licenses/by-sa/4.0/)

Regardless of the cause, cirrhosis commonly presents with certain clinical manifestations. Patients will present with **portal hypertension** and subsequent splenomegaly, hypersplenism, portosystemic shunts, ascites, and hepatic encephalopathy.

Variceal bleeding may occur from portosystemic anastomosis at the **esophagus** or upper stomach. **Spider angiomata** from anterior abdominal wall anastomosis form. Palmer erythema, gynecomastia, testicular atrophy, and **gastric ulceration**/hyperacidity occur due to decreased hepatic function to detoxify hormones and foreign materials.

The **parotid glands** may enlarge due to protein deficiency malnutrition. **Hepatorenal syndrome** with **acute renal failure** may develop from deficient blood supply to the kidneys. Clubbing of the fingers and cyanosis will result from **hypoxemia** from arteriovenous shunting of blood in the lungs.

For evaluations of patients with liver disease, suspect alcohol as a cause of this liver disease based on the patient's history of alcohol consumption or history from family members. CAGE questions should be used if the patient is suspected to be a heavy alcohol consumer. **C** for **cut** down alcohol intake, **A** for feeling **annoyed** by criticism about alcohol intake, **G** for feeling **guilty** and **E** for the need of an **eye** opener in the morning.

Complications of Alcoholic Liver Disease

Patients may present with the clinical picture of the complications including:

- Hepatocellular carcinoma
- Bleeding tendency
- Folic acid and vitamin B deficiency
- Hypogonadism
- Dupuytren contracture of the palm
- Pancreatitis
- [Spontaneous bacterial peritonitis](#)
- [Wernicke encephalopathy](#)
- [Korsakoff psychosis](#)

Wernicke encephalopathy is due to thiamine deficiency in alcoholic patients. Wernicke encephalopathy affects the thalamus and hypothalamus. Symptoms include confusion, nystagmus, leg tremor, and ataxia. Sometimes it can progress to coma and death.

Korsakoff psychosis affects the mammillary bodies. It usually develops after Wernicke encephalopathy. Patients will present with anterograde and retrograde amnesia, confabulations to fill in the gaps in the memory and sometimes hallucinations.

Laboratory Evaluation of Alcoholic Liver Disease

Abnormal liver function tests with moderate elevation of AST, ALT, alkaline phosphatase and GGT. AST/ALT ratio is ≥ 2 due to deficiency of pyridoxine needed for ALT synthesis. Enzyme elevations do not indicate the extent of liver damage and usually do not exceed 500 unless there is another hepatic insult.

Serum bilirubin will be elevated. **Serum albumin** is usually low due to synthetic malfunction and dietary deficiency. **Prothrombin time** is prolonged. **Macrocytic anemia** will be prominent from folate deficiency. **Pancytopenia** can be a complication of hypersplenism and sometimes leukocytosis from [alcoholic hepatitis](#) and reflects the extent of liver injury.

A liver biopsy may be used to indicate the extent of liver damage, prognosis and other possible causes of liver injury. It will show the microscopic picture of active hepatitis, fibrosis and fatty changes.

Prognosis of Alcoholic Liver Disease

Prognosis is important for patients with alcoholic liver damage. Fatty liver can be completely reversible in 6 weeks of abstinence from alcohol while cirrhosis is not reversible. The prognosis is worst in patients with existing inflammation from viral hepatitis or [hemochromatosis](#). The presence of fibrosis or neutrophilic infiltration on biopsy finding is also a sign for bad prognosis.

More accurate indicators for prognostic purposes than the **Child-Pugh score** use serum creatinine, bilirubin and prothrombin time for short-term mortality risk. The formula in **Model for End-Stage Liver Disease score (MELD)** is used as follows:

$$3.8 \times \ln[\text{serum bilirubin (mg/dL)}] + 11.2 \times \ln[\text{INR}] + 9.6 \times \ln[\text{serum creatinine (mg/dL)}] + 6.4$$

A score of less than 9 has a 1.9 % mortality risk in 3 months while a score of 40 or more has more than 70 % mortality risk in 3 months.

Treatment of Alcoholic Liver Disease

The first step in treatment is **abstinence from alcohol**. All patients with alcoholic liver disease should avoid alcoholic beverages. It will always help even for patients with irreversible liver damage.

Group therapy and rehabilitation should be used for compliance.

Drugs can be used to help abstain from alcohol. **Disulfiram** can be used due to its inhibitory effects on aldehyde dehydrogenase with subsequent acetaldehyde accumulation. This has many unpleasant effects for the patients which may help avoid drinking. **Baclofen** inhibits gamma-aminobutyric acid receptors and helps with alcohol craving during the withdrawal period.

Treatment of alcohol withdrawal

Sedation with diazepam can be used to control withdrawal symptoms. It should be used with caution to avoid [hepatic encephalopathy](#). **Vitamin supplements** should be started as soon as possible. Thiamine is mandatory to avoid Wernicke encephalopathy.

Patients with **Wernicke encephalopathy** treated with low doses of thiamine have a mortality rate of about 20% and a high rate of development of **Korsakoff psychosis**. Thiamine should be administered intramuscularly for alcoholic patients, coma patients, and head injury patients at a dose of 250 mg daily for 3 days as prophylaxis. Higher doses are needed for Wernicke encephalopathy. Thiamine is utilized by the body for glucose metabolism, this is why it is mandatory to replenish the stores of thiamine in the body before starting the treatment.

Treatment of Wernicke encephalopathy

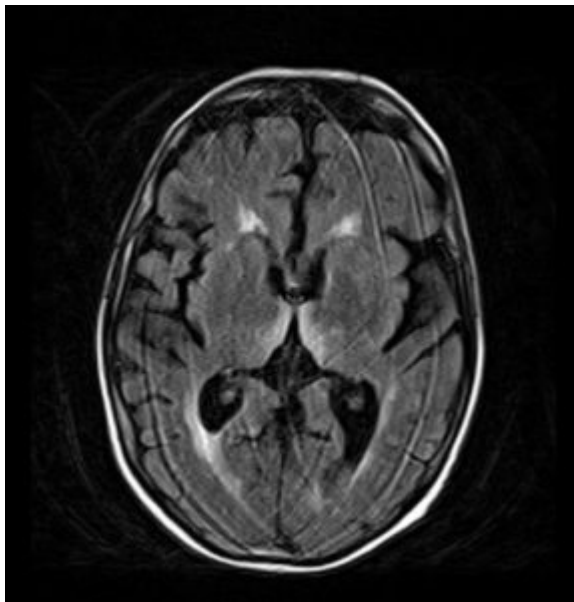


Image: "Axial MRI FLAIR image showing abnormal hyperintense signal in the mesial dorsal thalami indicative of Wernicke encephalopathy." by Jto410 - In my clinical work as a diagnostic radiologist. License: [CC BY-SA 3.0](#)

Early treatment and hospitalization are crucial to prevent memory loss. Patients should be hospitalized and admitted to the ICU if there is disturbed consciousness or coma. Once the case progresses to Korsakoff psychosis and memory loss, it is irreversible.

Treatment consists of **500 mg thiamine intramuscular three times/day for at least 2 days or until clinical improvement**. Other vitamins supplementation and nutritional support should be considered as needed.

Treatment of alcoholic hepatitis

General supportive measures for all alcoholic patients should be considered. This includes nutritional support, sedation, and management according to the presentation.

Prednisolone has been tried for patients with acute hepatitis but with caution due to **side effects**.

Antioxidants also have been tried in early cirrhosis to prevent further damage. **Tumor**

necrosis alpha inhibitors, e.g. infliximab, can be used but with caution as they increase the risk of infection and **reactivation of pulmonary tuberculosis**.

Liver transplantation remains the only definitive treatment for all patients with liver cirrhosis irrespective of the cause. For liver transplantation, patients should be free from alcohol for at least 6 months before surgery or they will lose their chance of listing for transplantation. Rehabilitation and group therapy (alcohol anonymous) is mandatory. Alcohol consumption after transplantation will lead to the same clinical consequences in the transplanted liver.

References

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