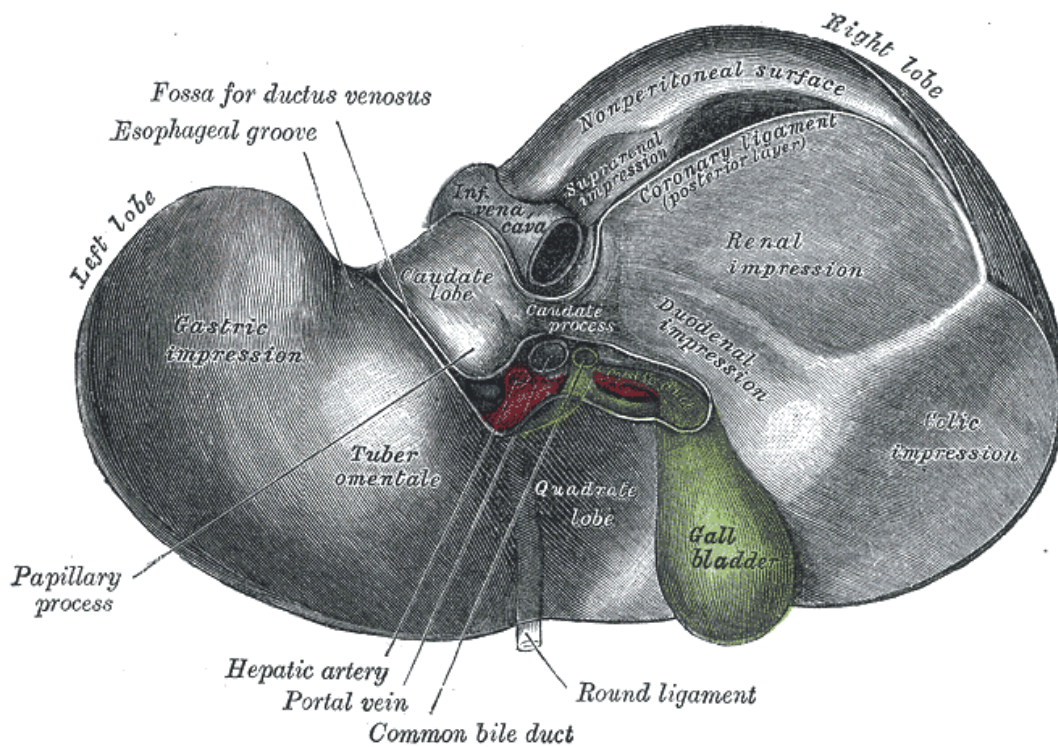


Acute Liver Failure (ALF) — Causes and Treatment

[See online here](#)

Acute (or fulminant) liver failure results from severe liver damage brought about by a number of different causes. It is characterized by rapidly developing dysfunction in the hepatocytes. Patients may or may not have a history of liver disease. Because ALF is a fatal condition, a rapid and accurate diagnosis is crucial. This can be done clinically by using key observations in history and through a physical examination. The timely use of supplemental tools to reinforce the diagnosis should also be instigated.



Etiology

The causes of acute [liver](#) failure vary from country to country. In France, Japan, and India, for example, a key cause of ALF is the **hepatitis B virus (HBV)**. However, a number of other causes are common across countries.

Acetaminophen toxicity

Because it is a readily available over-the-counter medication for mild pain and fever, many people tend to overuse **acetaminophen**. This drug has many different preparations, including tablets, syrups, suspensions, suppositories, and intravenous

solutions.

The mechanism of damage by acetaminophen starts when excessive amounts of the drug overwhelm the physiological conjugation processes in the liver and “spill over” to another means of drug metabolism by the liver. Instead of being harmlessly metabolized and bound to glucuronates and sulfates, however, excessive acetaminophen compounds enter **cytochrome P450 protein-mediated metabolic reactions** in the liver. This results in the formation of **N-acetyl-p-benzoquinoneimine (NAPQI)**. Under normal circumstances, a reducing agent such as **glutathione** neutralizes the metabolites, rendering them inactive.

Excessive amounts of NAPQI, such as occurs after an overdose of acetaminophen, overwhelm the internal stores for glutathione, leading to the destruction of hepatocytes by NAPQI. This results in **centrilobular necrosis** and **hepatocellular injury**.

Idiosyncratic drug toxicity

Unusual drug reactions are also implicated in the development of ALF, although they are not as common a cause as acetaminophen toxicity. **Antibiotics, pain relievers,** and **anti-seizure** medication can sometimes have unpredictable reactions, resulting in **metabolic idiosyncrasy**. Specific medications under this category include **isoniazid propylthiouracil, phenytoin,** and **valproic acid**. Women are more commonly affected by these reactions than men.

Some **herbal preparations** are also known to cause ALF. These include **kava kava, green tea, black cohosh, weight-loss supplements,** and **ephedra**. These compounds' contribution to the number of cases of ALF is important to note, as the distribution of these products is not strictly regulated in many countries.

The diagnosis of ALF caused by idiosyncratic reactions from certain medications and herbal sources can be challenging, as it is often difficult to accurately pinpoint a certain laboratory marker to use as a basis for diagnosis. The primary management for these unusual hepatic reactions is therefore simply the **discontinuation of suspected medications**.

Viral infections

The most common viruses associated with AFL are **hepatitis A (HAV) and HBV**. These viruses are more prevalent in developing countries.

Because it is both highly preventable and curable, HAV infection rarely results in viral liver failure and, when it does, the prognosis is usually positive. The availability of vaccines worldwide against HAV also has contributed to the declining prevalence of ALF from this virus.

Hepatitis B is a more common cause of viral ALF. However, like HAV, HBV rarely results in liver failure. Some studies have found that **certain components of the virus**, such as the **precore or core promoters**, are responsible for a predisposition to liver failure.

Other hepatitis-associated viruses that can cause acute liver failure include:

- **HDV**—requires that an existing infection with HBV is present
- **HEV**—one of the most common viral causes of acute liver failure in India; pregnant women are especially predisposed
- **HCV**—rarely causes ALF

| | HBsAg | IgM anti-core | HBeAg | HBeAb | HBV DNA | Comment |
|-----------------------|----------|---------------|----------|----------|------------------|--|
| Acute infection | Variable | Positive | Variable | Variable | Usually negative | Hyperactive immune response |
| Seroconversion | Positive | Negative | Negative | Positive | Negative | Immune-mediated |
| Replication surge | Positive | Negative | Variable | Variable | High | Spontaneous or after immunosuppression |
| Delta super-infection | Positive | Negative | Variable | Variable | Low | New positive serology for delta virus |

Hepatitis B-associated liver failure. Table adapted from Textbook of Clinical Gastroenterology and Hepatology, 2nd ed. by Hawkey CJ, Bosch J, Richter JE, Tsao GG and Chan FKL

Other non-hepatotropic viruses that can result in ALF include:

- Epstein-Barr virus (EBV)
- Cytomegalovirus (CMV)
- [Varicella-zoster virus](#)
- [Herpes simplex virus \(HSV\)](#)

Miscellaneous causes

In some cases, fulminant liver disease can result from **pregnancy**, particularly during the **3rd trimester**. This is thought to happen because of an **inborn deficiency** in an enzyme involved in fatty acid oxidation in the liver. Sometimes, liver failure during pregnancy can also be attributed to accompanying **preeclampsia**.

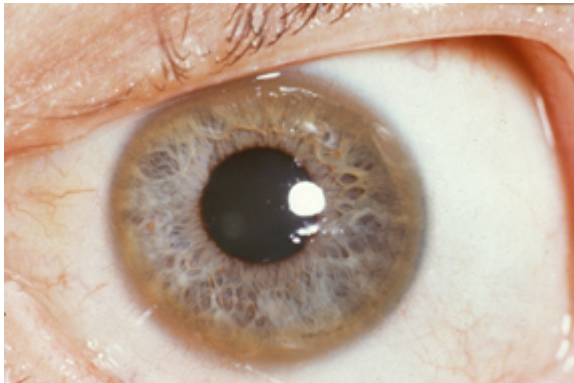


Image: "Kayser-Fleischer ring: copper deposition in Descemet's membrane of the cornea. These rings can be either dark brown, golden, or reddish-green, are 1-3 mm wide, and appear at the corneal limbus. With rare exceptions, they are diagnostic of inherited hepatolenticular degeneration—Wilson's disease."
by Herbert L. Fred, MD, Hendrik A. van Dijk - <http://cnx.org/content/m15007/latest/>, License: [CC BY 3.0](#)

Another disorder that sometimes contributes to the development of ALF is **Wilson's disease**. This is an **autosomal recessive disorder** that manifests with **excessive copper stores in the liver** as a result of impaired biliary excretion of the element.

Patients who present with this disorder are usually in their 20s or 30s, have **prominent hemolysis**, a **low serum alkaline phosphatase level**, an **elevated serum aspartate aminotransferase to alanine aminotransferase ratio (AST-to-ALT ratio)**, the presence of **excessive copper in the urine**, and **Kayser-Fleischer rings**.

Indeterminate acute liver failure

In some cases, [acute liver failure](#) is preceded by signs and symptoms of viral infections.

However, during testing, patients may appear **seronegative to HAV, HBV, and other hepatitis viruses**. They may also be **free from metabolites of idiosyncratically reacting medications**. These cases are usually described as indeterminate ALF.

Clinical Features

Generally speaking, the manifestation of ALF results from the **cessation of function of the hepatocytes**, such as in the **production of amino acids**, the **metabolism of nutrients and medications**, and the **neutralization of radicals** in the body.

Initially, patients with ALF present with **nonspecific signs and symptoms** such as **nausea, vomiting, fatigue, and jaundice**. More liver-specific manifestations such as **bilirubin excretion, clotting factor deficiency, and impaired glucose synthesis** follow soon after.

Hepatic encephalopathy

Historically, practitioners believed that hepatic encephalopathy was the result of the shunting of toxins and radicals to the bloodstream and into the central nervous system. However, recent studies have suggested that hepatic encephalopathy is caused by **cerebral edema** and **increased intracranial pressure**. Other contributory factors that could lead to **nervous system** disturbances in ALF include:

- Hypoglycemia
- Sepsis
- Fever
- Hypoxemia
- Hypotension

All of these factors can result from impairment of the liver's functions. Staging for **hepatic encephalopathy** is the same as staging for liver cirrhosis.

Coagulopathy and bleeding

In ALF, clotting and bleeding problems coexist as a result of the **impairment of the clotting factor synthesis and degradation functions** of the liver. Laboratory findings for patients with ALF may show results that are indicative of the following:

- Fibrinolysis
- Hypofibrinogenemia
- Dysfibrinogenemia
- Disseminated intravascular coagulopathy

Infection

There are 3 mechanisms by which patients with fulminant liver failure are predisposed to infections:

1. Damage to the hepatic macrophages or **Kupffer cells** in the liver results in the entry of microorganisms from the **portal venous system** to the systemic circulation.
2. There is a decrease in the production of acute-phase reactants in the liver, which sometimes results in impaired neutrophil action.
3. Breaks in the physical barriers, such as in diagnostic testing and invasive therapeutic measures, create a pathway for infection.

The presence of infection among AFL patients accounts for a significant percentage of the **rejection cases for liver transplantation** and **deaths after transplantation**. Infections also tend to worsen preexisting liver failure-related manifestations such as hepatic encephalopathy and coagulation problems.

Multiple organ failure syndrome

Multiple organ failure syndrome from AFL can occur by means of 2 mechanisms:

1. Polymerized actin from damaged hepatocytes and platelet activation irritate and damage the endothelium of **blood vessels**.
2. Many vasoactive substances that are normally present in the bloodstream are retained in the circulation because of an impaired excretory mechanism in the liver.

This syndrome can manifest as **peripheral dilation of blood vessels with hypotension, pulmonary edema, renal failure**, and **disseminated intravascular coagulopathy**.

Diagnosis

Since there are varying etiologies for different cases of AFL, it is important to uncover clues as to the cause of the patient's **history and physical examination**. Although histologic examination of the damaged liver tissue does not make a significant contribution to the diagnosis of ALF, it can help rule out certain causes.

| Etiology | Investigation | Comment |
|------------------------------|--------------------------|---|
| Hepatitis A | IgM anti-HAV | 95% positive initially; 100% on repeat testing |
| Hepatitis B and D | Full profile | See the previous table for interpretation |
| Hepatitis E | Anti-HEV | IgM antibody test |
| Seronegative hepatitis | All tests | Diagnosis of exclusion |
| Acetaminophen | Drug levels in the blood | May be negative on 3rd or subsequent days after an overdose |
| Idiosyncratic drug reactions | Eosinophil count | Most diagnoses based on temporal relationship |

Diagnosis for the different causative agents for liver failure. Table adapted from Textbook of Clinical Gastroenterology and Hepatology, 2nd ed. by Hawkey CJ, Bosch J, Richter JE, Tsao GG and Chan FKL

Treatment

Initially, the management of a patient with ALF involves the **identification of the causative agent**, as the management of each cause varies significantly. In most hospital protocols, ALF is treated in the **intensive care unit** due to its **unpredictable development**.

Encephalopathy

When associated with liver failure, encephalopathy tends to be **very progressive**. Medications such as sedatives are avoided unless intubation is required. Reversible conditions such as **infections, hypoglycemia**, and **hypoxemia** should be addressed immediately.

Airway management should be provided as needed. **Intracranial pressure** should be

monitored and controlled accordingly in order to prevent further complications.

Coagulopathy and bleeding

Patients with ALF should have a **nasogastric tube** inserted to monitor for **gastrointestinal bleeding** and **gastric pH fluctuations**. Medications such as **H2-receptor antagonists** and **proton pump inhibitors** are provided in order to decrease the risk of gastrointestinal bleeding. **Vitamin K** is also administered subcutaneously to address a deficiency in vitamin K-dependent clotting factors. A **blood coagulation panel** should also be measured regularly to monitor the progress of the treatment.

Infection

Monitoring of the **cultures from blood, urine, and ascitic fluid** should be done daily, as the assessment for infections among ALF patients is difficult due to the presence of relatively nonspecific manifestations (**e.g., hypotension, leukocytosis, and acidosis**). **Antibiotics** can help delay the development of infections in patients. However, not all practitioners agree that this is helpful, due to the fact that it can **aggravate idiosyncratic reactions**. The most commonly prescribed empirical regimen is a **combination of intravenous vancomycin and a 3rd-generation cephalosporin or fluoroquinolone**.

Multiple organ failure syndrome

The primary treatment goal for patients manifesting with this syndrome is to **normalize the arterial pressure** and to **ensure proper tissue oxygenation**. This can be done by regularly **monitoring blood pressure, adequate volume replacement, and careful use of vasopressors**.

Prognosis

| Acetaminophen toxicity | Non-acetaminophen causes |
|--|---|
| Arterial pH < 7.3 | PT > 100 sec (INR > 7.7) |
| OR | OR |
| All 3 of the following: <ul style="list-style-type: none">• PT > 100 sec (INR > 7.7)• Creatinine > 3.4 mg/dL• Encephalopathy grade 3 or 4 | Any 3 of the following: <ul style="list-style-type: none">• Drug or non-viral hepatitis• Jaundice > 7 d prior to HE• Age < 10 years or > 40 years• PT > 50 sec (INR > 3.85)• Bilirubin > 17.4 mg/dL |

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