



## Scholars Research Library

Der Pharmacia Lettre, 2009, 1 (2) 83-92  
(<http://scholarsresearchlibrary.com/archive.html>)



ISSN 0975-5071

### Emerging trends of drug used in treatment of liver cirrhosis

Debjit Bhowmik, Margret Chandira\*, Chiranjib, Shrideshwar sukhla, B.Jayakar

*Vinayaka Mission College of Pharmacy, Salem, Tamilnadu, India*

---

#### Abstract

Cirrhosis is a condition in which the liver slowly deteriorates and malfunctions due to chronic injury. Scar tissue replaces healthy liver tissue, partially blocking the flow of blood through the liver. A healthy liver is able to regenerate most of its own cells when they become damaged. With end-stage cirrhosis, the liver can no longer effectively replace damaged cells. A healthy liver is necessary for survival. Cirrhosis is the twelfth leading cause of death by disease, accounting for 27,000 deaths each year. The condition affects men slightly more often than women. Heavy alcohol consumption and chronic hepatitis C have been the most common causes of cirrhosis. Obesity is becoming a common cause of cirrhosis, either as the sole cause or in combination with alcohol, hepatitis C, or both. Usually years of chronic injury are required to cause cirrhosis. The goals of treatment are to slow the progression of scar tissue in the liver and prevent or treat the complications of the disease. Hospitalization may be necessary for cirrhosis with complications. Treatment for cirrhosis also addresses specific complications. For edema and ascites, the doctor will recommend diuretics—medications that remove fluid from the body. Large amounts of ascitic fluid may be removed from the abdomen and checked for bacterial peritonitis. Oral antibiotics may be prescribed to prevent infection. Severe infection with ascites will require intravenous (IV) antibiotics. may prescribe a beta-blocker or nitrate for portal hypertension. Beta-blockers can lower the pressure in the varices and reduce the risk of bleeding. Gastrointestinal bleeding requires an immediate upper endoscopy to look for esophageal varices. The doctor may perform a band-ligation using a special device to compress the varices and stop the bleeding. People who have had varices in the past may need to take medicine to prevent future episodes.

---

#### Introduction

An abnormal liver condition characterized by irreversible scarring of the liver. Alcohol and viral hepatitis B and C are among the many causes of cirrhosis. Cirrhosis can cause yellowing of the skin (jaundice), itching, and fatigue. Diagnosis of cirrhosis can be suggested by physical

examination and blood tests, and can be confirmed by liver biopsy in some patients. Complications of cirrhosis include mental confusion, coma, fluid accumulation (ascites), internal bleeding, and kidney failure. Treatment of cirrhosis is designed to limit any further damage to the liver as well as complications. Liver transplantation is becoming an important option for patients with advanced cirrhosis. In the United States, heavy alcohol consumption and chronic hepatitis C have been the most common causes of cirrhosis. Other causes of cirrhosis include hepatitis B, hepatitis D, and autoimmune hepatitis; diseases that damage or destroy bile ducts, inherited diseases, and nonalcoholic fatty liver disease; and drugs, toxins, and infections. Many people with cirrhosis have no symptoms in the early stages of the disease. As the disease progresses, symptoms may include weakness, fatigue, loss of appetite, nausea, vomiting, weight loss, abdominal pain and bloating, itching, and spider like blood vessels on the skin. As liver function deteriorates, one or more complications may develop. In some people, complications may be the first signs of the disease. The goals of treatment are to stop the progression of scar tissue in the liver and prevent or treat complications. Treatment for cirrhosis includes avoidance of alcohol and other drugs, nutrition therapy, and other therapies that treat specific complications or causes of the disease. Hospitalization may be necessary for cirrhosis with complications. A liver transplant is considered when complications of cirrhosis cannot be controlled by treatment. Progress in the management and prevention of cirrhosis continues. Research is ongoing to determine the mechanism of scar formation in the liver and how this process of scarring can be interrupted or even reversed. Newer and better treatments for viral liver disease are being developed to prevent the progression to cirrhosis. Prevention of viral hepatitis by vaccination, which is available for hepatitis B, is being developed for hepatitis C. Treatments for the complications of cirrhosis are being developed or revised and tested continually. Finally, research is being directed at identifying new proteins in the blood that can detect liver cancer early or predict which patients will develop liver cancer. Liver transplantation is highly effective for the treatment of end-stage cirrhosis. Transplantation is usually needed when complications such as encephalopathy, ascites or bleeding varices are uncontrollable or when biochemical function is severely depressed. In patients with primary biliary cirrhosis, a rising bilirubin indicates a poor prognosis and such patients should be considered for transplantation as the serum bilirubin concentration begins to rise. Active drug or alcohol abuse are contraindications to liver transplantation. However, alcoholics who have abstained from drinking for an extended period of time (usually more than six months), and have participated in rehabilitation programs and support groups such as Alcoholics Anonymous, can be considered as candidates and will often have a good prognosis. Liver cancer is usually a contraindication to transplantation, except in experimental protocols. Liver transplantation is usually not performed in patients more than 70 years old.

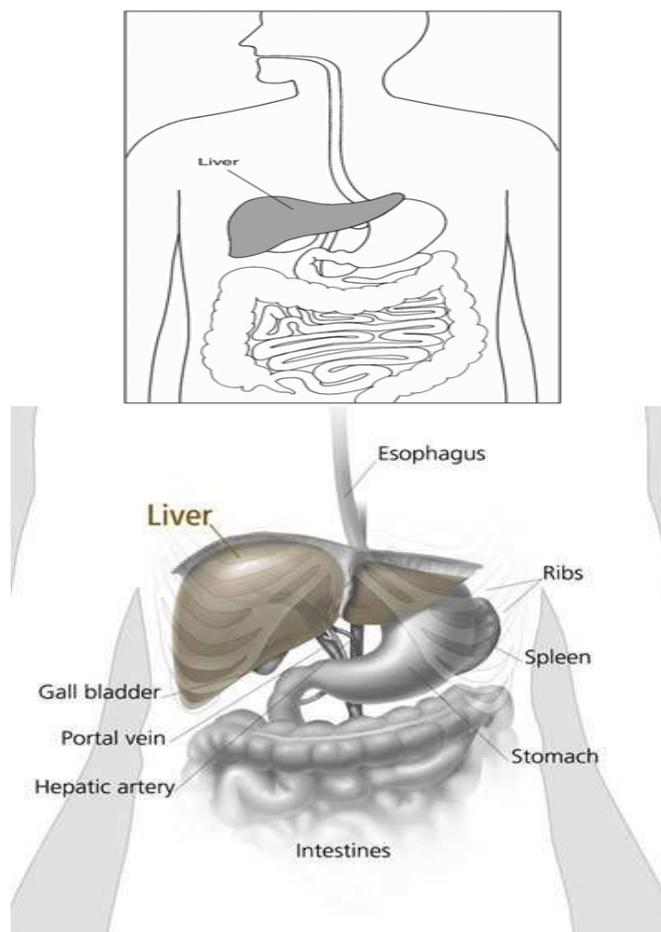
### ***Cirrhosis of the liver***

The liver weighs about 3 pounds and is the largest solid organ in the body. It performs many important functions, such as:

- 1) Manufacturing blood proteins that aid in clotting, oxygen transport, and immune system function.
- 2) Storing excess nutrients and returning some of the nutrients to the bloodstream.
- 3) Manufacturing bile, a substance needed to help digest food.
- 4) Helping the body store sugar (glucose) in the form of glycogen.
- 5) Ridding the body of harmful substances in the bloodstream, including drugs and alcohol.

## 6) Breaking down saturated fat and producing cholesterol.

The liver, the largest organ in the body, is essential in keeping the body functioning properly. It removes or neutralizes poisons from the blood, produces immune agents to control infection, and removes germs and bacteria from the blood. It makes proteins that regulate blood clotting and produces bile to help absorb fats and fat-soluble vitamins. You cannot live without a functioning liver. Cirrhosis is a complication of many liver diseases that is characterized by abnormal structure and function of the liver. The diseases that lead to cirrhosis do so because they injure and kill liver cells, and the inflammation and repair that is associated with the dying liver cells causes scar tissue to form. The liver cells that do not die multiply in an attempt to replace the cells that have died. This results in clusters of newly-formed liver cells (regenerative nodules) within the scar tissue. There are many causes of cirrhosis; they include chemicals (such as alcohol, fat, and certain medications), viruses, toxic metals (such as iron and copper that accumulate in the liver as a result of genetic diseases), and autoimmune liver disease in which the body's immune system attacks the liver.



**Figure-The liver and digestive system.**

*Symptoms of cirrhosis of the liver*

The condition manifests in the form of signs and symptoms that occur as a direct result of cirrhosis or from the complications associated. The signs and symptoms include:

- 1) Vascular lesions due to increased estradiol.
- 2) Speckled mottling of the palm due to the resultant alteration of sex hormone metabolism.
- 3) Paired, separated bands visible on the nails due to low albumin production.
- 4) White nail plate with distal red due to hypoalbuminemia.
- 5) Painful proliferative periostitis of long bones.
- 6) Thickening of palmar fascia, accompanied by flexion deformities due to collagen deposition and fibroblastic proliferation.
- 7) Proliferation of glandular breast tissue in males due to increased estradiol.
- 8) Impotence, loss of sexual drive and testicular atrophy due to suppression of pituitary function.
- 9) Enlarged or shrunken liver size.
- 10) Increase in spleen size due to portal hypertension.
- 11) Fluid retention within the peritoneal cavity.
- 12) Shunting of blood from the portal venous system into the umbilical vein.
- 13) Venous hum in epigastric region.
- 14) Musty breath odor due to dimethyl sulfide increase.
- 15) Development of jaundice due to increased bilirubin.
- 16) Weakness and fatigue.
- 17) Anorexia and subsequent weight loss.

#### ***Causes of cirrhosis of the liver***

Cirrhosis has many causes. In the chronic alcoholism and hepatitis C are the most common causes.

- 1) *Alcoholic liver disease*- To many people, cirrhosis of the liver is synonymous with chronic alcoholism, but in fact, alcoholism is only one of the causes. Alcoholic cirrhosis usually develops after more than a decade of heavy drinking. The amount of alcohol that can injure the liver varies greatly from person to person. In women, as few as two to three drinks per day have been linked with cirrhosis and in men, as few as three to four drinks per day. Alcohol seems to injure the liver by blocking the normal metabolism of protein, fats, and carbohydrates.
- 2) *Chronic hepatitis C*- The hepatitis C virus ranks with alcohol as the major cause of chronic liver disease and cirrhosis in the United States. Infection with this virus causes inflammation of and low grade damage to the liver that over several decades can lead to cirrhosis.
- 3) *Chronic hepatitis B and D*-The hepatitis B virus is probably the most common cause of cirrhosis worldwide, but in the United States and Western world it is less common. Hepatitis B, like hepatitis C, causes liver inflammation and injury that over several decades can lead to cirrhosis. The hepatitis D virus is another virus that infects the liver, but only in people who already have hepatitis B.
- 4) *Autoimmune hepatitis*- This type of hepatitis is caused by a problem with the immune system.

- 5) *Inherited diseases*- Alpha-1 antitrypsin deficiency, hemochromatosis, Wilson's disease, galactosemia, and glycogen storage diseases are among the inherited diseases that interfere with the way the liver produces, processes, and stores enzymes, proteins, metals, and other substances the body needs to function properly.
- 6) *Nonalcoholic steatohepatitis (NASH)*- In NASH, fat builds up in the liver and eventually causes scar tissue. This type of hepatitis appears to be associated with diabetes, protein malnutrition, obesity, coronary artery disease, and corticosteroid treatment.
- 7) *Blocked bile ducts*- When the ducts that carry bile out of the liver are blocked, bile backs up and damages liver tissue. In babies, blocked bile ducts are most commonly caused by biliary atresia, a disease in which the bile ducts are absent or injured. In adults, the most common cause is primary biliary cirrhosis, a disease in which the ducts become inflamed, blocked, and scarred. Secondary biliary cirrhosis can happen after gallbladder surgery, if the ducts are inadvertently tied off or injured.
- 8) *Drugs, toxins, and infections*- Severe reactions to prescription drugs, prolonged exposure to environmental toxins, the parasitic infection schistosomiasis, and repeated bouts of heart.

### ***Complications of cirrhosis of liver***

As liver function deteriorates, one or more complications may develop. In some people, complications may be the first signs of the disease.

- 1) *Edema and ascites*- When liver damage progresses to an advanced stage, fluid collects in the legs, called edema, and in the abdomen, called ascites. Ascites can lead to bacterial peritonitis, a serious infection.
- 2) *Bruising and bleeding*-When the liver slows or stops producing the proteins needed for blood clotting, a person will bruise or bleed easily.
- 3) *Portal hypertension*. Normally, blood from the intestines and spleen is carried to the liver through the portal vein. But cirrhosis slows the normal flow of blood, which increases the pressure in the portal vein. This condition is called portal hypertension.
- 4) *Esophageal varices and gastropathy*- When portal hypertension occurs, it may cause enlarged blood vessels in the esophagus, called varices, or in the stomach, called gastropathy, or both. Enlarged blood vessels are more likely to burst due to thin walls and increased pressure. If they burst, serious bleeding can occur in the esophagus or upper stomach, requiring immediate medical attention.
- 5) *Splenomegaly*- When portal hypertension occurs, the spleen frequently enlarges and holds white blood cells and platelets, reducing the numbers of these cells in the blood. A low platelet count may be the first evidence that a person has developed cirrhosis.
- 6) *Jaundice*-Jaundice occurs when the diseased liver does not remove enough bilirubin from the blood, causing yellowing of the skin and whites of the eyes and darkening of the urine. Bilirubin is the pigment that gives bile its reddish-yellow color.
- 7) *Gallstones*-If cirrhosis prevents bile from flowing freely to and from the gallbladder, the bile hardens as gallstones.

- 8) *Sensitivity to medications*-Cirrhosis slows the liver's ability to filter medications from the blood. When this occurs, medications act longer than expected and build up in the body. This causes a person to be more sensitive to medications and their side effects.
- 9) *Hepatic encephalopathy*- A failing liver cannot remove toxins from the blood, and they eventually accumulate in the brain. The buildup of toxins in the brain—called hepatic encephalopathy—can decrease mental function and cause coma. Signs of decreased mental function include confusion, personality changes, memory loss, trouble concentrating, and a change in sleep habits.
- 10) *Insulin resistance and type 2 diabetes*- Cirrhosis causes resistance to insulin—a hormone produced by the pancreas that enables the body to use glucose as energy. With insulin resistance, the body's muscle, fat, and liver cells do not use insulin properly. The pancreas tries to keep up with the demand for insulin by producing more, but excess glucose builds up in the bloodstream causing type 2 diabetes.
- 11) *Liver cancer*-Hepatocellular carcinoma is a type of liver cancer that can occur in people with cirrhosis. Hepatocellular carcinoma has a high mortality rate, but several treatment options are available.
- 12) *Other problems*- Cirrhosis can cause immune system dysfunction, leading to the risk of infection. Cirrhosis can also cause kidney and lung failure, known as hepatorenal and hepatopulmonary syndromes.

### ***Diagnosis of liver cirrhosis***

- 1) The diagnosis of cirrhosis is usually based on the presence of a risk factor for cirrhosis, such as alcohol use or obesity, and is confirmed by physical examination, blood tests, and imaging. The doctor will ask about the person's medical history and symptoms and perform a thorough physical examination to observe for clinical signs of the disease. For example, on abdominal examination, the liver may feel hard or enlarged with signs of ascites. The doctor will order blood tests that may be helpful in evaluating the liver and increasing the suspicion of cirrhosis.
- 2) To view the liver for signs of enlargement, reduced blood flow, or ascites, the doctor may order a computerized tomography (CT) scan, ultrasound, magnetic resonance imaging (MRI), or liver scan. The doctor may look at the liver directly by inserting a laparoscope into the abdomen. A laparoscope is an instrument with a camera that relays pictures to a computer screen.
- 3) A liver biopsy can confirm the diagnosis of cirrhosis but is not always necessary. A biopsy is usually done if the result might have an impact on treatment. The biopsy is performed with a needle inserted between the ribs or into a vein in the neck. Precautions are taken to minimize discomfort. A tiny sample of liver tissue is examined with a microscope for scarring or other signs of cirrhosis. Sometimes a cause of liver damage other than cirrhosis is found during biopsy.

### ***Drug used treatment of liver cirrhosis***

#### ***Edema and ascites***

Retention of salt and water can lead to swelling of the ankles and legs (edema) or abdomen (ascites) in patients with cirrhosis. Doctors often advise patients with cirrhosis to restrict dietary salt (sodium) and fluid to decrease edema and ascites. The amount of salt in the diet usually is restricted to 2 grams per day and fluid to 1.2 liters per day. In most patients with cirrhosis,

however, salt and fluid restriction is not enough, and diuretics have to be added. Diuretics are medications that work in the kidneys to promote the elimination of salt and water into the urine. A combination of the diuretics spironolactone (Aldactone) and furosemide can reduce or eliminate the edema and ascites in most patients. During treatment with diuretics, it is important to monitor the function of the kidneys by measuring blood levels of blood urea nitrogen (BUN) and creatinine to determine if too much diuretic is being used. Too much diuretic can lead to kidney dysfunction that is reflected in elevations of the BUN and creatinine levels in the blood. Sometimes, when the diuretics do not work (in which case the ascites is said to be refractory), a long needle or catheter is used to draw out the ascitic fluid directly from the abdomen, a procedure called abdominal paracentesis. It is common to withdraw large amounts (liters) of fluid from the abdomen when the ascites is causing painful abdominal distension and/or difficulty breathing because it limits the movements of the diaphragms.

### ***Bleeding from varices***

If large varices develop in the esophagus or upper stomach, patients with cirrhosis are at risk for serious bleeding due to rupture of these varices. Once varices have bled, they tend to rebleed and the probability that a patient will die from each bleeding episode is high (30%-35%). Therefore, treatment is necessary to prevent the first (initial) bleeding episode as well as rebleeding. Treatments include medications and procedures to decrease the pressure in the portal vein and procedures to destroy the varices. Propranolol (Inderal), a beta blocker, is effective in lowering pressure in the portal vein and is used to prevent initial bleeding and rebleeding from varices in patients with cirrhosis. Another class of oral medications that lowers portal pressure is the nitrates, for example, isosorbide dinitrate (Isordil). Nitrates often are added to propranolol if propranolol alone does not adequately lower portal pressure or prevent bleeding. Octreotide (Sandostatin) also decreases portal vein pressure and has been used to treat variceal bleeding.

### ***Treatment of liver cirrhosis***

*During upper endoscopy (EGD)*- either sclerotherapy or band ligation can be performed to obliterate varices and stop active bleeding and prevent rebleeding. Sclerotherapy involves infusing small doses of sclerosing solutions into the varices. The sclerosing solutions cause inflammation and then scarring of the varices, obliterating them in the process. Band ligation involves applying rubber bands around the varices to obliterate them. (Band ligation of the varices is analogous to rubber banding of hemorrhoids.) Complications of sclerotherapy include esophageal ulcers, bleeding from the esophageal ulcers, esophageal perforation, esophageal stricture (narrowing due to scarring that can cause dysphagia), mediastinitis (inflammation in the chest that can cause chest pain), pericarditis (inflammation around the heart that can cause chest pain), and peritonitis (infection in the abdominal cavity). Studies have shown that band ligation may be slightly more effective with fewer complications than sclerotherapy.

*Transjugular intrahepatic portosystemic shunt (TIPS)*-is a non-surgical procedure to decrease the pressure in the portal vein. TIPS is performed by a radiologist who inserts a stent (tube) through a neck vein, down the inferior vena cava and into the hepatic vein within the liver. The stent then is placed so that one end is in the high pressure portal vein and the other end is in the low pressure hepatic vein. This tube shunts blood around the liver and by so doing lowers the pressure in the portal vein and varices and prevents bleeding from the varices. TIPS is particularly useful in patients who fail to respond to beta blockers, variceal sclerotherapy, or

banding. (TIPS also is useful in treating patients with ascites that do not respond to salt and fluid restriction and diuretics.) TIPS can be used in patients with cirrhosis to prevent variceal bleeding while the patients are waiting for liver transplantation. The most common side effect of TIPS is hepatic encephalopathy. Another major problem with TIPS is the development of narrowing and occlusion of the stent, causing recurrence of portal hypertension and variceal bleeding and ascites. The estimated frequency of stent occlusion ranges from 30%-50% in 12 months. Fortunately, there are methods to open occluded stents. Other complications of TIPS include bleeding due to inadvertent puncture of the liver capsule or a bile duct, infection, heart failure, and liver failure.

*A surgical operation to create a shunt (passage)-*from the high-pressure portal vein to veins with lower pressure can lower blood flow and pressure in the portal vein and prevent varices from bleeding. One such surgical procedure is called distal splenorenal shunt (DSRS). It is appropriate to consider such a surgical shunt for patients with portal hypertension who have early cirrhosis. (The risks of major shunt surgery in these patients is less than in patients with advanced cirrhosis.) During DSRS, the surgeon detaches the splenic vein from the portal vein, and attaches it to the renal vein. Blood then is shunted from the spleen around the liver, lowering the pressure in the portal vein and varices and preventing bleeding from the varices.

*Hepatic encephalopathy-*Patients with an abnormal sleep cycle, impaired thinking, odd behavior, or other signs of hepatic encephalopathy usually should be treated with a low protein diet and oral lactulose. Dietary protein is restricted because it is a source of the toxic compounds that cause hepatic encephalopathy. Lactulose, which is a liquid, traps the toxic compounds in the colon. Consequently, they cannot be absorbed into the blood stream and cause encephalopathy. To be sure that adequate lactulose is present in the colon at all times, the patient should adjust the dose to produce 2-3 semiformal bowel movements a day. (Lactulose is a laxative, and the adequacy of treatment can be judged by loosening or increasing frequency of stools.) If symptoms of encephalopathy persist, oral antibiotics such as neomycin or metronidazole (Flagyl), can be added to the treatment regimen. Antibiotics work by blocking the production of the toxic compounds by the bacteria in the colon.

*Hypersplenism-*The filtration of blood by an enlarged spleen usually results in only mild reductions of red blood cells (anemia), white blood cells (leukopenia) and platelets (thrombocytopenia) that do not require treatment. Severe anemia, however, may require blood transfusions or treatment with erythropoietin or epoetin alfa (Epogen, Procrit), hormones that stimulate the production of red blood cells. If the numbers of white blood cells are severely reduced, another hormone called granulocyte-colony stimulating factor is available to increase the numbers of white blood cells. An example of one such factor is filgrastim (Neupogen). No approved medication is available yet to increase the number of platelets. As a necessary precaution, patients with low platelets should not use aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDS) since these drugs can hinder the function of platelets. If a low number of platelets is associated with significant bleeding, transfusions of platelets usually should be given. Surgical removal of the spleen (called splenectomy) should be avoided, if possible, because of the risk of excessive bleeding during the operation and the risk of anesthesia in advanced liver disease.

*Spontaneous bacterial peritonitis (SBP)*--Patients suspected of having spontaneous bacterial peritonitis usually will undergo paracentesis. Fluid that is removed is examined for white blood cells and cultured for bacteria. Culturing involves inoculating a sample of the ascites into a bottle of nutrient-rich fluid that encourages the growth of bacteria, thus facilitating the identification of even small numbers of bacteria. Blood and urine samples often are obtained as well for culturing because many patients with spontaneous bacterial peritonitis also will have infection in their blood and urine. In fact, many doctors believe that infection may have begun in the blood and the urine and spread to the ascitic fluid to cause spontaneous bacterial peritonitis. Most patients with spontaneous bacterial peritonitis are hospitalized and treated with intravenous antibiotics such as ampicillin, gentamycin, and one of the newer generation cephalosporin.

*Prevention and early detection of liver cancer* -Several types of liver disease that cause cirrhosis are associated with a particularly high incidence of liver cancer, for example, hepatitis B and C, and it would be useful to screen for liver cancer since early surgical treatment or transplantation of the liver can cure the patient of cancer. The difficulty is that the methods available for screening are only partially effective, identifying at best only 50% of patients at a curable stage of their cancer. Despite the partial effectiveness of screening, most patients with cirrhosis, particularly hepatitis B and C, are screened yearly or every six months with ultrasound examination of the liver and measurements of cancer-produced proteins in the blood, e.g. alpha fetoprotein.

*Liver transplantation* -Cirrhosis is irreversible. Many patients' liver function will gradually worsen despite treatment and complications of cirrhosis will increase and become difficult to treat. Therefore, when cirrhosis is far advanced, liver transplantation often is the only option for treatment. Recent advances in surgical transplantation and medications to prevent infection and rejection of the transplanted liver have greatly improved survival after transplantation. On average, more than 80% of patients who receive transplants are alive after five years. Not everyone with cirrhosis is a candidate for transplantation. Furthermore, there is a shortage of livers to transplant, and there usually is a long (months to years) wait before a liver for transplanting becomes available. Therefore, measures to retard the progression of liver disease and treat and prevent complications of cirrhosis are vitally important.

## Conclusion

Cirrhosis is a complication of liver disease which involves loss of liver cells and irreversible scarring of the liver. Alcohol and viral hepatitis B and C are common causes of cirrhosis, although there are many other causes. Cirrhosis can cause weakness, loss of appetite, easy bruising, yellowing of the skin (jaundice), itching, and fatigue. Diagnosis of cirrhosis can be suggested by the history, physical examination and blood tests, and can be confirmed by liver biopsy. Complications of cirrhosis include edema and ascites, spontaneous bacterial peritonitis, bleeding from varices, hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome, hypersplenism, and liver cancer. Treatment of cirrhosis is designed to prevent further damage to the liver, treat complications of cirrhosis, and preventing or detecting liver cancer early. Transplantation of the liver is becoming an important option for treating patients with advanced cirrhosis. Don't abuse alcohol. If you do drink alcohol, limit how much you drink and how often. Remember it's not only the heavy drinker who gets cirrhosis. If you drink more than 2

drinks a day, you are increasing your risk. A drink is a 5 oz glass of wine, a 12-oz can of beer, or a 1 1/2 oz portion of hard liquor. Be careful around synthetic chemicals, such as cleaning products and pesticides. If you come into contact with chemicals often, wear protective clothing and a facemask. Get vaccinated against hepatitis B. Eat a well-balanced, low-fat diet and take vitamins.

## Reference

- [1] [http://www.cdc.gov/nchs/data/nvsr/nvsr55/nvsr55\\_19.pdf](http://www.cdc.gov/nchs/data/nvsr/nvsr55/nvsr55_19.pdf)
- [2] Giallourakis CC, Rosenberg PM, Friedman LS (2002). *Clin Liver Dis* 6 (4): 947–67.
- [3] Heathcote EJ (2003). *Clin Liver Dis* 7 (4): 735–40.
- [4] Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R (1973). *Br J Surg*, 60 (8): 646–9.
- [5] <http://gut.bmj.com/cgi/content/abstract/44/2/264>.
- [6] Iredale JP (2003). *BMJ* 327 (7407): 143–7.
- [7] Ginés P, Arroyo V, Quintero E, et al. (1987). *Gastroenterology* 93 (2): 234–41.
- [8] Cosby RL, Yee B, Schrier RW (1989), *Mineral and electrolyte metabolism* 15 (5): 261.
- [9] Anderson RN, Smith BL (2003). "Deaths: leading causes for 2001". *National vital statistics reports: from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System* 52 (9): 1–85.
- [10] Sørensen HT, Thulstrup AM, Mellekjar L, et al. (2003). " *Journal of clinical epidemiology* 56 (1): 88–93.