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Liver disease and frontline care

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Untreated liver disease has a devastating prognosis, but early identification can lead to a good prognosis

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Introduction

Globally, liver disease accounts for two million deaths annually. Cirrhosis accounts for one million of these, and there was a global increase of 10.4% between 2010 and 2017.[1] In South Africa, 1990-2010, cirrhotic deaths increased by 34%.[2] Hepatocellular carcinoma and complications of acute liver failure account for the same number of deaths as cirrhosis.

With regard to risk factors for liver disease, two billion people consume alcohol, of whom 75 million are diagnosed each year with alcohol-use disorder; a further two billion people are obese, of whom 400 million are diabetic; and viral hepatitis is endemic in most parts of the world, especially in southern Africa. Autoimmune liver disease and drug-related liver injuries also account for significant morbidity.

Untreated liver disease has a devastating prognosis, but early identification can lead to a good prognosis. Frontline healthcare workers are key to identifying liver problems at an early stage.

KEY MESSAGES

- Acute liver failure consequent on an overdose or viral hepatitis can be catastrophic, whereas chronic liver disease may respond to intervention
- In the cirrhotic liver, fibrous tissue deposition, active vasoconstriction and nodule formation lead to sinusoidal portal hypertension
- Decompensated cirrhosis manifests as varices, ascites and hepatic encephalopathy
- Disease progression from advanced liver disease to decompensated cirrhosis can take many years to decades
- Non-alcoholic fatty liver disease (NAFLD) is associated with the metabolic syndrome and obesity; intervention, particularly diet and lifestyle, can reverse this condition
- Alcohol-associated steatohepatitis can be aggressive and there is not much treatment available
- Liver fibrosis, with appropriate treatment for hepatitis B, can be reversed
- Drug-induced liver injury is most often associated with herbal and dietary supplements
- Essential phospholipids used for hepatic inflammation in viral, non-alcoholic and alcoholic steatohepatitis provide a substrate to promote hepatic healing.

What is driving the increase in liver disease?

The two major factors driving liver disease are increased alcohol use and non-alcoholic steatohepatitis (NASH), with NAFLD affecting 25% of adults globally. Of patients presenting with NASH, 4-25% develop cirrhosis and once this occurs, there is a 25% chance of developing decompensation or hepatocellular carcinoma (Figure 1).

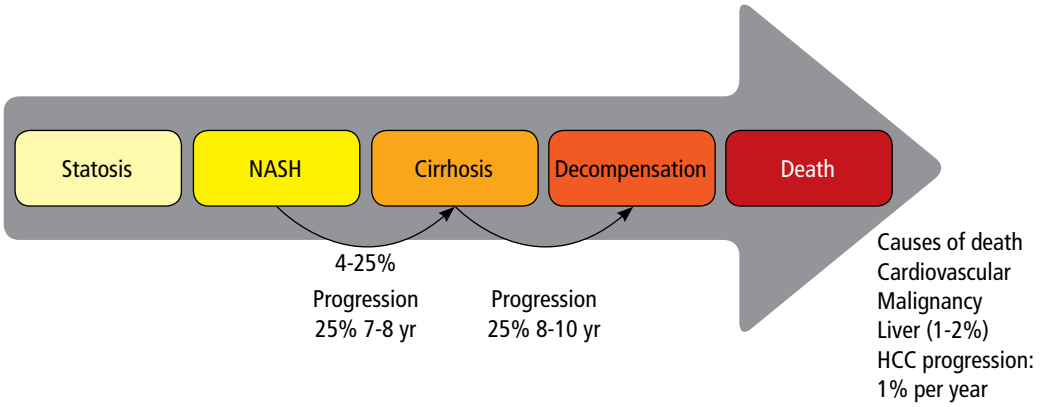

Figure 1. NASH disease progression[3]

What is liver disease?

Acute liver failure consequent on an overdose or viral hepatitis can be catastrophic, whereas chronic liver disease may respond to intervention

The term hepatitis is used to describe inflammation of the hepatocytes, caused by alcohol, fat, some viruses and some drugs. Hepatitis can be diagnosed using the blood tests alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

Bile ducts can be affected by blockage (stones, masses), inflammation and some drugs. Symptoms include right upper-quadrant pain, rapid onset of jaundice, pruritus, dark urine and pale stools. Bile duct function is tested using alkaline phosphatase (ALP) measurements.

Acute liver failure consequent on an overdose or viral hepatitis can be catastrophic, whereas chronic liver disease may respond to intervention.

Portal hypertension and decompensated cirrhosis

Increased vascular resistance is most commonly caused by cirrhosis, whereby fibrous tissue deposition, active vasoconstriction and nodule formation obstruct the sinusoids and intersinusoidal communication, leading to sinusoidal portal hypertension. Blood is redirected, but the compensatory portal systemic collaterals are unable to accommodate the required volume of blood flow and tend to bleed (Figure 2), a hallmark of decompensated cirrhosis. This can continue for a long period without being diagnosed.

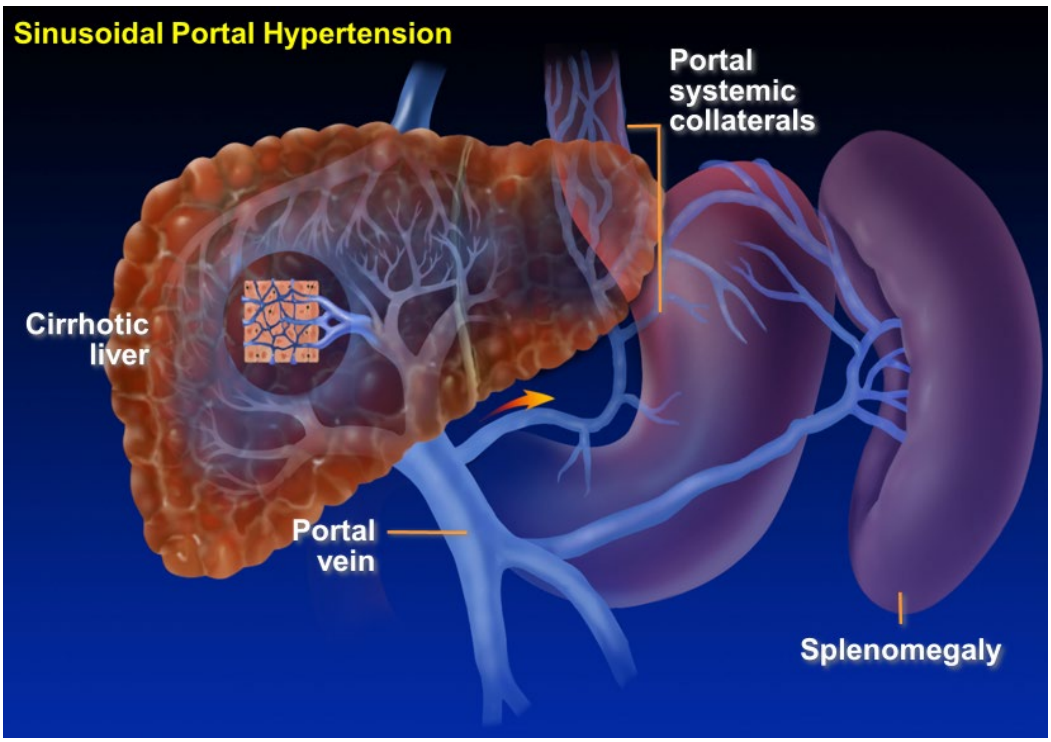

Figure 2. Sinusoidal portal hypertension

Decompensated cirrhosis may manifest as:

- **Varices**
  Because blood can't get through the liver, the body makes or finds bypass routes around it. This may result in bleeding from the gastrointestinal tract but it can occur anywhere: oesophageal varices are common as are haemorrhoidal bleeding and ectopic varices, e.g. in the duodenum.

- **Ascites**
  The heart and kidneys detect altered blood supply and compensate through the heart working harder and the kidneys retaining salt and water. Water progressively accumulates in the abdomen with fluid build-up in the peritoneal cavity.

- **Hepatic encephalopathy**
  This can be difficult to diagnose and the patient may often not be aware of it. Hepatic encephalopathy results from a build-up of toxins such as ammonia, causing brain dysfunction. Symptoms in the early stages are mild personality changes, sleep disturbances, feeling tired, stumbling and falling, confusion and difficulty performing simple tasks.

What is the time frame from advanced liver disease to decompensated cirrhosis?

Once there is a second decompensating event, two-year survival declines to 25-30%

This disease process can happen over many years or even decades (Figure 3), with quality of life steadily decreasing as risk of death increases. At some point there will be outward manifestations of liver disease such as bleeding (survival at two years is approximately 75%), fluid retention and confusion. Once there is a second decompensating event, two-year survival declines to 25-30%. When there is kidney failure associated with liver disease, survival is only weeks to months.

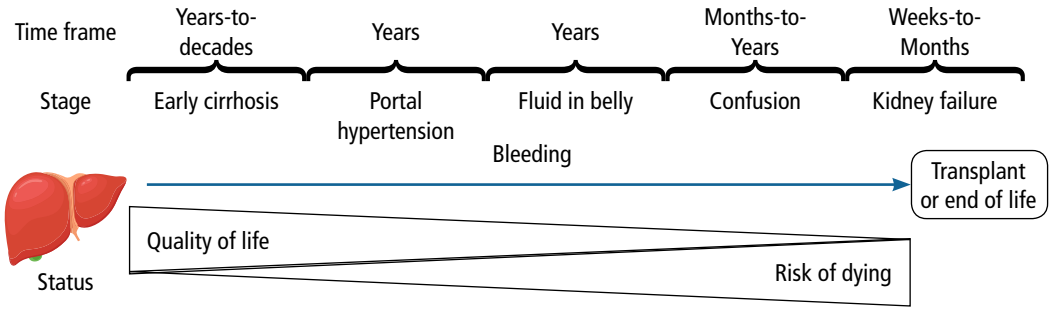

Figure 3. Progression of cirrhosis

NAFLD

This is a condition caused by energy imbalance associated with the metabolic syndrome and obesity epidemic, with fat deposited on the liver. NAFLD also occurs as a result of genetic predisposition, the presence of toxins, alcohol consumption slightly above recommended usage, certain drugs and other potential metabolic risk factors, including the constituents of the gut microbiome.

Of NAFLD patients with simple steatosis, 80-90% show no progressive liver disease and have a good prognosis; 10-20% progress to NASH, of whom 25-50% develop fibrosis. Of these, 2-5% become cirrhotic.

Of all NAFLD patients, 0-5% develop cirrhosis within 10-20 years; intervention, particularly diet and lifestyle, can reverse this condition.

What are the recommended lifestyle changes?[4]

Aim for a 7-10% weight reduction, with aerobic or resistance exercise and the Mediterranean diet (as proved by clinical trials). Try to reduce the amount of fructose consumed and increase the amount of coffee (2-3 cups per day); multiple studies show that coffee has a positive impact not only on the liver, but on general health.

Alcoholic-associated liver disease

The spectrum of pathology in alcoholic-associated liver disease shows that 90-100% of patients will present with simple steatosis, 10-35% with steatohepatitis and 50% with cirrhosis. The steatohepatitis can be aggressive, with not much treatment available to these patients once the inflammation has been initiated.

There is often confusion as to what one unit of alcohol looks like (Table 1), with standard servings often representing 1.5 units of alcohol. It is recommended that women do not regularly exceed 2-3 units of alcohol per day; for men the recommendation is to not exceed 3-4 units of alcohol per day. Ideally, there should be at least one alcohol-free day per week. Dr Bobat cautions that pregnant women, those younger than 18 years and cirrhotics should not drink alcohol at all.

Of all NAFLD patients, 0-5% develop cirrhosis within 10-20 years; intervention, particularly diet and lifestyle, can reverse this condition

Table 1. How much is one unit* of alcohol?

4.5% cider	218ml
13% wine	76ml
40% whisky	25ml
4% beer	250ml
4% alcopop	250ml
* 1 unit = 8-10g pure alcohol	

How much is too much alcohol?

- Binge drinking more than four drinks in one sitting (60g alcohol)
- If taking in more than 80g per day for five years, some form of advanced liver disease will be present
- 90% of alcohol-induced cirrhotics drink more than 160g per day for more than eight years.

Identifying the high-risk patient

Patients can often be reticent about the extent of their alcohol use; however there is a constellation of pathological changes such as rhinophyma and capillary leakage in the cheeks that may indicate chronic alcohol misuse. They may complain of intermittent diarrhoea and of right upper-quadrant pain.

Alcohol-use disorder is indicated by failure to fulfil obligations, being in hazardous situations, social or interpersonal problems from drinking, failed attempts to stop drinking, craving and giving up other activities to drink.

Useful screening tools include the CAGE questionnaire:

- Have you ever felt you should Cut down on your drinking?
- Have people Annoyed you by criticising your drinking?
- Have you ever felt bad or Guilty about your drinking?
- Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (Eye opener)?

Item responses on the CAGE questionnaire are scored 0 or 1, with a higher score an indication of alcohol problems. A total score of 2 or greater is considered clinically significant.

Viral hepatitis

Viral hepatitis B

Viral hepatitis B is endemic in South Africa, particularly in the Eastern Cape and the northern belt extending from North-West Province to Mozambique; it has a prevalence of 2.7-16% and affects 3-4 million people.[5]

Liver fibrosis, with appropriate treatment for hepatitis B, can be reversed. Tenofovir disoproxil fumarate (TDF), used over five years to adequately suppress the virus, brings about a significant reduction in fibrosis.[6]

Viral hepatitis C

Hepatitis C is now easily cured with treatment over eight weeks using a simple oral therapy that has minimal side effects.

Drug-induced liver injury

Patients can often be reticent about the extent of their alcohol use

Drug-induced liver injury is most often associated with herbal and dietary supplements and certain drugs, particularly products for sexual enhancement (sildenafil), weight loss (sibutramine) and muscle-building (anabolic steroids), among others (e.g. St John's Wort).[7] Also, new complementary and pharmaceutical drugs that may cause liver injury regularly come onto the market.

Disease of the bile ducts

Primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC) are the two most common bile duct pathologies. Both have an autoimmune basis. PBC can be well controlled with medical therapy in up to two-thirds of patients. There is no effective medical therapy for PSC yet.

Patients will present with pruritus, especially on the palms of the hands and soles of the feet, and fatigue; they will appear overtly jaundiced.

Autoimmune hepatitis

In southern Africa, there is a very aggressive phenotype for autoimmune hepatitis that occurs most commonly in young females, although it can be controlled with immunosuppressants.

Medication for existing liver disease

Drug-induced liver injury is most often associated with herbal and dietary supplements

In patients with existing liver disease, Dr Bobat cautions that particular care needs to be taken when considering the use of non-steroidal anti-inflammatory drugs (NSAIDs), benzodiazepines, diuretics and analgesic products.

NSAIDs affect the kidneys and the liver, reducing blood flow, and can result in kidney failure, the worsening of ascites and possibly gastrointestinal bleeding; all of these further decompensate the individual. Benzodiazepines are commonly prescribed in patients complaining of poor sleep; use can result in coma. Diuretics should not be used in advanced cirrhosis. For analgesia, paracetamol is still the safest option but because toxicity accumulates, it must be used at a lower dose.

Dr Bobat raises concerns about the unvaccinated liver disease patient. Effective vaccines are available against hepatitis A and B, as well as influenza and other infectious diseases that can result in decompensation.

Supplementing liver function

The general rule for patients with liver disease is 'no supplements', although there is some evidence to support certain over-the-counter products.

Bovine colostrum is rich in immunoglobulin and trophic growth factors and helps to prevent bacterial translocation from the intestine.[8] Further research is currently being conducted regarding its benefits.

Essential phospholipids used for hepatic inflammation in viral, non-alcoholic and alcoholic steatohepatitis provide a substrate to promote hepatic healing. Their use has an established record in Russia and elsewhere in Europe, with numerous studies documenting safety and efficacy.[9]

N-acetylcysteine provides glutathionine for second-order drug reactions and theoretically improves hepatic blood flow and oxygenation, thereby reducing oxidative stress within the liver.

Milk thistle is commonly used by patients; multiple trials have shown no benefit, but no harm either.

This CPD-accredited programme was written for *deNovo Medica* by
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