In the UK it is estimated that 24% of adult men and 13% of adult women drink alcohol in a hazardous or harmful way. Alcohol consumption is a major risk factor for liver disease, but evidence on the precise relationship between the amount of alcohol a person drinks and the incidence of liver disease is unclear.

Liver disease related to alcohol consumption fits into one of three stages — fatty liver (steatosis), alcoholic hepatitis or cirrhosis. However, the liver damage caused by alcohol is not uniform and these stages overlap. At least 80% of heavy drinkers develop fatty liver, 10–35% develop alcoholic hepatitis and about 10% will develop cirrhosis.

Excessive alcohol consumption, even for just a few days, can result in a fatty liver, in which the affected hepatocytes contain a large triglyceride occlusion. Fatty liver is generally reversible with abstinence from alcohol consumption. It is important to note that fatty liver is not specific to alcohol ingestion and can also be associated with obesity, insulin resistance, hyperlipidemia, malnutrition and some medicines. Therefore a detailed and accurate patient history is required to attribute the cause to alcohol.

Alcoholic hepatitis is an acute form of alcohol-induced liver injury that occurs with the consumption of a large quantity of alcohol over a prolonged period.

Cirrhosis is the most severe form of alcoholic liver injury. It involves the replacement of the normal hepatic structure with extensive thick bands of fibrotic tissue and regenerative nodules (see accompanying article, p140).

Risk factors

The risk of alcoholic liver disease is influenced by many factors, including genetics and the environment. In general the risk of liver disease increases with the quantity of alcohol intake and the duration of misuse.

Pathophysiology

The liver is the main site of alcohol metabolism, which occurs via two main pathways. One pathway involves the enzyme alcohol dehydrogenase — alcohol is converted to acetaldehyde, which is subsequently metabolised to acetate by the mitochondrial enzyme acetaldehyde dehydrogenase. The second pathway involves cytochrome P450 2E1, which also converts alcohol to acetaldehyde.

Liver damage from alcohol occurs through several mechanisms. Alcohol dehydrogenase and acetaldehyde dehydrogenase cause the reduction of NAD (nicotinamide adenine dinucleotide) to NADH. The altered ratio of NAD to NADH promotes fatty liver through inhibition of gluconeogenesis and fatty acid oxidation. In addition, CYP 2E1, which is unregulated in chronic alcohol use, generates free radicals through the oxidation of NADPH to NADP (nicotinamide adenine dinucleotide phosphate).

Chronic alcohol exposure also activates hepatic macrophages, which then produce tumour necrosis factor alpha (TNF-α). TNF-α induces mitochondria to increase the production of reactive oxygen species. This oxidative stress promotes hepatocyte necrosis and apoptosis which is exaggerated in alcoholics (who are deficient in antioxidants such as glutathione and vitamin E). Free radicals initiate lipid peroxidation, which causes inflammation and fibrosis.

MEN ARE ADVISED TO DRINK NO MORE THAN 21 UNITS OF ALCOHOL, AND WOMEN NO MORE THAN 14 UNITS, PER WEEK

SUMMARY

Liver disease related to alcohol consumption fits into one of three stages — fatty liver (steatosis), alcoholic hepatitis or cirrhosis. Many factors can influence its development, including genetics and the environment. In general the risk of liver disease increases with the quantity of alcohol consumed and the duration of misuse.

Abstinence is the cornerstone of treatment for alcoholic liver disease, and treatment with thiamine can help to prevent Wernicke’s encephalopathy. Patients with alcoholic hepatitis may benefit from treatment with corticosteroids or pentoxifylline, although the best treatment approach is subject to debate. Complications of cirrhosis are treated as for patients with non-alcoholic liver disease.
Signs and symptoms
Alcohol can cause significant liver damage without producing any symptoms or signs of liver disease. Therefore, many people are diagnosed with alcoholic liver disease when they have routine liver function tests as part of a routine medical check-up.

Patients with fatty liver are typically asymptomatic or present with non-specific symptoms (e.g., nausea) that do not suggest acute liver disease.

Alcoholic hepatitis can vary in severity and therefore the symptoms also vary. Symptoms can be non-specific and mild, including anorexia, weight loss, abdominal pain and distension and nausea and vomiting. Physical findings can include hepatomegaly, jaundice, ascites, fever and encephalopathy.

Established alcoholic cirrhosis presents in a similar way to that of non-alcoholic cirrhosis. Decompensation can occur without a preceding history of fatty liver or alcoholic hepatitis. The symptoms and signs of alcoholic cirrhosis are not different from those associated with cirrhosis from other causes (see accompanying article, p140).

Diagnosis
The overall clinical diagnosis of alcoholic liver disease relies on a detailed, accurate patient history. It is important to note that patients tend to under-report alcohol consumption and discussions with family members and close friends might provide a more accurate estimation of intake. The level of alcohol consumption, combined with physical findings and laboratory values, helps guide diagnosis.

A common laboratory marker in detecting excessive alcohol consumption is a raised gamma glutamyl transferase (GGT). Generally, serum transaminases (AST and ALT) are not greatly raised; values greater than five times the upper limit of the normal reference range should lead to consideration of other diagnoses such as viral or autoimmune hepatitis. Hyperbilirubinaemia reflects the severity of the hepatitis and is highly pronounced in alcoholic hepatitis. Prolongation of the prothrombin time and hypoalbuminaemia reflect poor hepatocyte function.

A liver ultrasound can help to diagnose fatty liver and hepatitis and a liver biopsy is necessary to confirm the extent of liver injury. As well as confirming diagnosis the liver biopsy is also useful for ruling out other causes of liver disease. Histology findings following a biopsy typically include inflammation and necrosis.

A variety of scoring systems have been used to assess the severity of alcoholic hepatitis and guide treatment. “Maddrey’s discriminant function” (DF) is a scoring system that is calculated using the prothrombin time and bilirubin level. This scoring system correlates well with mortality (e.g., a score >32 denotes severe disease and is associated with a two-month mortality of 50%). Other scoring systems have been used, such as the “Glasgow alcoholic hepatitis score” (GAHS) and the “Model of end-stage liver disease” (MELD) score (see p144 of accompanying article), but DF is the one most widely used in UK practice.

The diagnosis of alcoholic cirrhosis relies on the presence of signs and symptoms of end-stage liver disease in a patient with a history of significant alcohol intake. When a patient has advanced cirrhosis and is showing signs of decompensation, he or she may require a liver transplant.

Treatment
Treatment of alcoholic liver disease is based on the stage of the disease. Complications of cirrhosis such as encephalopathy and portal hypertension are treated as for patients with non-alcoholic liver disease (for further details see the accompanying article, p145).

Some of those who consume alcohol in quantities outside healthy limits will develop an acute withdrawal syndrome when they abruptly stop or reduce their alcohol consumption. Alcohol withdrawal can be characterised by tremor, weakness, sweating, hyperreflexia, gastrointestinal symptoms, hallucinations and seizures. Patients in acute alcohol withdrawal, or those who are assessed to be at high risk of developing alcohol withdrawal, will require medical management. Several drugs can be used to treat symptoms of alcohol withdrawal. The most widely used are benzodiazepines (e.g., chlordiazepoxide) and most centres have protocols in place for their use in this indication.

Abstinence is the cornerstone of treatment for alcoholic liver disease. Some patients may not be able to achieve complete and durable alcohol abstinence without assistance and therefore referral to specialist services is required. Counselling may be required along with the addition of anti-addiction drugs (e.g., acamprosate).

Because most patients with alcoholic liver disease have some degree of malnutrition, it is important for the pharmacy team to liaise with dietitians, who can assess the degree of malnutrition and guide nutritional supplementation.

Wernicke’s encephalopathy
Vitamin B deficiency is common in alcoholic liver disease, in particular deficiency of thiamine, folate, pyridoxine and riboflavin. Therefore, these patients are at risk of developing Wernicke’s encephalopathy — a condition caused by thiamine deficiency. The common signs of Wernicke’s encephalopathy include confusion, ataxia and varying levels of impaired consciousness; these symptoms are difficult to differentiate from drunkenness, so the complication may go unrecognised.

Wernicke’s encephalopathy is reversible if treated promptly and, as such, is now common practice to treat patients who have, or are suspected to have, the condition with intravenous and oral thiamine. The National Institute for Health and Clinical Excellence has issued specific recommendations on the prevention and treatment of Wernicke’s encephalopathy. These are summarised in Box 1 (p151).

Alcoholic hepatitis
For patients with alcoholic hepatitis, abstinence is essential to prevent further progression and to reduce the risk of developing cirrhosis. The need to consider therapy is less urgent in patients with alcoholic hepatitis who have a low risk of complications (DF score <32), those without hepatic encephalopathy and those with a low MELD score. For those with more severe disease, the following treatments should be considered.

Corticosteroids
The rationale behind the use of corticosteroids for the treatment of alcoholic liver disease is linked to the possible role of the immune system in
Box 1: Treatment with thiamine

Offer thiamine to people at high risk of developing, or with suspected, Wernicke’s encephalopathy. Thiamine should be given in doses towards the upper end of the range quoted in the British National Formulary and as described below.

Prophylactic oral thiamine

Prophylactic oral thiamine should be offered to harmful or dependent drinkers if they:

- Are malnourished or at risk of malnourishment
- Have decompensated liver disease
- Are in acute withdrawal
- Are to undergo planned medically assisted alcohol withdrawal (before and during)

Prophylactic parenteral thiamine

Offer prophylactic parenteral thiamine followed by oral thiamine to harmful or dependent drinkers who attend an emergency department or are admitted to hospital if they:

- Are malnourished or at risk of malnourishment
- Have decompensated liver disease

In addition, parenteral thiamine should be offered to people with suspected Wernicke’s encephalopathy. A high level of suspicion for the possibility of Wernicke’s encephalopathy should be maintained, particularly if the person is intoxicated. Parenteral thiamine should be given for a minimum of five days unless Wernicke’s encephalopathy is excluded. Oral thiamine should follow parenteral therapy.

In initiating and perpetuating hepatic damage. However, the use of corticosteroids to treat alcoholic hepatitis remains controversial. Corticosteroids have been studied in several randomised trials and meta-analyses, none of which reached a consensus regarding their efficacy in the treatment of alcoholic hepatitis. Most of the trials were small and therefore had only limited statistical power to detect even moderate treatment effects.

The most recent meta-analysis did not show a statistically significant effect of corticosteroids on mortality among all patients treated, although it did show an effect of corticosteroids in the sub-group of patients with hepatic encephalopathy or a DF score >32.

A reanalysis of the combined individual data from three studies in which corticosteroids were administered to patients for 28 days indicated that the one-month survival rate for patients with severe alcoholic hepatitis (DF score >32) who were treated with corticosteroids was 85%, compared with 65% for those who received placebo.

The most common corticosteroid therapy for alcoholic hepatitis is prednisolone at a dose of 40mg daily for 28 days. Indications for treatment include DF score >32 (or a MELD score >21). Contraindications for corticosteroid treatment include sepsis, gastrointestinal bleeding and renal failure.

A fall in bilirubin at day 7 of corticosteroid treatment is highly predictive of survival. For patients whose bilirubin rises or remains static after seven days of therapy, corticosteroids should be stopped.

Pentoxifylline

Pentoxifylline is a phosphodiesterase inhibitor used in the treatment of intermittent claudication. It also inhibits TNF-α by modulating the transcription of the TNF-α gene. A randomised placebo-controlled trial showed that pentoxifylline reduced short-term mortality among patients with alcoholic hepatitis.

The study involved 101 patients with a DF score ≥32. Patients received either pentoxifylline 400mg three times a day or placebo for 28 days. None of the patients in this trial received corticosteroids. Of the 49 patients who received pentoxifylline, 25% died during the initial hospital admission, compared with 46% of the 52 patients who received placebo. Hepatorenal syndrome was the cause of death in six of 12 cases (50%) in the treated group and 22 of 24 cases (92%) in the placebo group. Thus the benefit of pentoxifylline in treating acute alcoholic hepatitis appears to be related to prevention of hepatorenal syndrome.

The use of pentoxifylline may be of benefit for patients with severe disease (DF score >32) especially if there are contraindications to corticosteroid therapy.

A large UK study — “Steroids or pentoxifylline for alcoholic hepatitis” (STOPAH) — is now under way. The results of this trial are eagerly awaited and will further inform the debate regarding the best treatment for patients with alcoholic hepatitis.

Other treatments

Other treatments that have been investigated in the treatment of alcoholic hepatitis include infliximab, antioxidants and insulin plus glucagon, but there is little evidence to support their use in practice.

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References


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