

# 15.24.1 Alcoholic liver disease 3142

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15.24.1 Alcoholic liver disease Ewan Forrest

**ESSENTIALS** The incidence of alcoholic liver disease (ALD) follows the trend of per capita alcohol consumption, with hepatic injury which extends from fatty liver to alcoholic hepatitis and cirrhosis. It is unclear how alcohol causes liver disease, but postulated mechanisms include (1) oxidative stress and acetaldehyde generated by the metabolism of ethanol, and (2) innate and adaptive immune responses. Factors determining the susceptibility to liver disease in heavy drinkers are believed to include a variety of host and environmental factors, with genetic factors increasingly recognized. Clinical manifestations are extremely variable, and some patients remain relatively well while others suffer the effects of severe hepatic failure. Although patients can come to light with a life-threatening complication, most often they develop symptoms which are not immediately related to the liver, such as nonspecific digestive symptoms or psychiatric complaints. The key to the early recognition of alcohol-related disease is having a high index of suspicion, with confirmation by (1) direct questioning for alcohol history and alcohol-related symptoms; (2) clinical examination for signs of chronic liver disease; (3) supportive investigations, including aspartate aminotransferase, which is less than 500 IU/litre and greater than the alanine aminotransferase level; and (4) liver biopsy, which may be required in some cases of diagnostic uncertainty and to confirm the stage of the disease, revealing alcoholic fatty liver, alcoholic hepatitis, or cirrhosis. Management is governed by the stage and severity of the liver disease, but always includes abstinence and adequate nutritional support. In selected patients with severe acute alcoholic hepatitis, corticosteroids can reduce short-term mortality. Transplantation remains the only effective treatment for advanced alcoholic cirrhosis, although this remains controversial, mainly because of concerns about post-transplant recidivism. Introduction Alcohol consumption has been a part of human society since an-

cient times. The archaeological record has found evidence of the production of fermented drinks from 7000 bce. In ancient Greece, alcohol consumption and intoxication were integral parts of male- dominated evening symposia. The Greeks believed in the medicinal properties of alcohol but were also aware of its association with liver damage. In the United Kingdom, the distillation of spirits and subsequent drunkenness became an increasing problem in the 18th century, leading to government measures to curb consumption. More recent measures taken in the 20th century such as limitation of drinking hours during the First World War and Prohibition in the United States of America (1919–1933) may not have been popular but were associated with a reduction in deaths from cirrhosis. Epidemiology The World Health Organization reports that the average annual alcohol per capita consumption worldwide is 6.2 litres of pure alcohol. In Europe, this increases to 10.9 litres, which equates to 16.8 litres 15.24 Other liver diseases

15.24.1 Alcoholic liver disease 3143 per drinker of whom 22.9% engage in heavy episodic drinking (>60 g alcohol on a single occasion at least monthly). Worldwide, 5.9% of all deaths every year result from harmful use of alcohol. Overall, 5.1% of the global burden of disease and injury is attributable to alcohol, as measured in disability-adjusted life years. There is a strong correlation between the death rate from cirrhosis and the per capita alcohol consumption. Increases in alcohol-related deaths are closely related to the affordability and availability of alcohol, with the fall in alcohol price relative to income paralleling the increase in mortality. This association is the rationale behind the campaign for control of alcohol pricing which is supported by the World Health Organization. In the United Kingdom, the death rate from liver disease has been increasing in contrast to many other Western European countries. The major cause of these liver deaths is alcoholic liver disease (ALD), and ALD is the commonest cause of alcohol related death. The peak age range for death from ALD is 50 to 59 years old, and in England one in eight hospital admissions for ALD resulted in death in 2012. Risk factors While it is clear that the risk of ALD is closely related to the amount of alcohol consumed, the exact threshold for damage is unclear. Drinking more than 60 g of alcohol per day is associated with a 60% risk of alcoholic liver injury, and the highest risk of cirrhosis occurs at more than 120 g per day. However, even drinking more than 25 g per day is associated with an overall increased risk of cirrhosis (in the United Kingdom, 1 unit of alcohol equals 8 g alcohol). The pattern of drinking is also relevant, with daily drinking and drinking outside mealtimes identified as risk factors for cirrhosis. In addition to the direct role of alcohol, individual factors also play a part in ALD development (Box 15.24.1.1). Sex is relevant, with women being more susceptible to the hepatotoxic effects of alcohol and developing ALD more quickly when compared to men drinking equal amounts of alcohol. This may be due to differences in the metabolism and volume of distribution of alcohol between men and women, but may also reflect the effect of oestrogens on oxidative stress. Genetic susceptibility also influences the development of ALD, with monozygotic twins having a higher concordance of alcohol-related cirrhosis than dizygotic twins. Extensive genetic studies have identified some polymorphisms related to alcohol metabolism and cytokine production which appear to be associated with increased risk of ALD. A variation in the prevalence of ALD between different racial groups is also noted, although it is unclear whether this is largely environmental or genetic. Obesity is a major risk factor for the development of cirrhosis among those drinking excessively. This is probably due to the overlapping pathophysiologies of both ALD and nonalcoholic fatty liver disease, with both disease processes fuelled by oxidative stress. Obesity also creates a proinflammatory and profibrogenic environment. The coexistence of chronic hepatitis C infection and alcohol misuse can rapidly accelerate liver damage and is estimated to increase the risk of cirrhosis by 30-fold.

**Pathology and pathophysiology** The term ALD encompasses a spectrum of histological features and conditions. The main histological groupings of ALD are alcoholic steatosis, with or without significant fibrosis (in up to 100% of drinkers with a daily alcohol intake of greater than 60 g/day), alcoholic steatohepatitis (in 10–35%), and established cirrhosis (in approximately 15%) (Fig. 15.24.1.1). The natural history of ALD appears to progress from a normal liver through steatosis to fibrosis and cirrhosis with some, but not all, patients also passing through a phase of clinical alcoholic hepatitis. The steatosis is macrovesicular and predominantly in perivenular hepatocytes. Although sometimes perceived as a benign manifestation of ALD, the presence of steatosis alone is a risk factor for subsequent progressive fibrosis and cirrhosis. The features of alcoholic hepatitis are a perivenular steatohepatitis, often with Mallory bodies, hepatocyte ballooning, megamitochondria, canalicular cholestasis, and a neutrophil infiltrate. The presence of an alcoholic steatohepatitis again accelerates the rate of fibrosis and risk of cirrhosis. The presence of bilirubinostasis has been recognized as an important feature of alcoholic hepatitis which may have prognostic significance. With persistent injury, progressive perivenular and perisinusoidal fibrosis develops, leading to bridging fibrosis. Over time, the fibrosis progresses with the occurrence of regenerative nodules resulting in development of a predominantly micronodular cirrhosis.

**Alcohol metabolism and the pathophysiology of ALD** The predominant mechanism of alcohol metabolism in normal circumstances is its oxidation to acetaldehyde and then to acetate, Box 15.24.1.1

**Risk factors for alcoholic liver disease** in addition to amount of alcohol ingested • Female sex • Chronic hepatitis C • Obesity • Genetic polymorphisms — Alcohol dehydrogenase and acetaldehyde dehydrogenase — TNF- $\alpha$  and IL-10 promoters — Patatin-like phospholipase domain-containing protein 3 (PNPLA3) • Daily drinking/drinking outside mealtimes

**Cirrhosis (10–15%)** **Normal Liver (0–30%)** **Steatosis (60–100%)** **Steatohepatitis (10–35%)** Fig. 15.24.1.1 Pathological patterns of alcoholic liver disease in harmful drinkers.

section 15 Gastroenterological disorders 3144 catalysed by their respective dehydrogenases (Fig. 15.24.1.2). This leads to the production of the reduced form of nicotinamide adenine dinucleotide (NADH). With excessive alcohol exposure, two other oxidative pathways become increasingly important: the microsomal ethanol oxidizing system involving the alcohol-inducible enzyme cytochrome P450 2E1, and the peroxisomal enzyme catalase. These alternative pathways lead to the production of reactive oxygen species. Nonoxidative metabolism of alcohol is relatively minor but does account for the production of fatty acid ethyl esters. Hepatic steatosis develops largely on account of the altered NADH/NAD ratio which promotes triglyceride synthesis and inhibits  $\beta$ -oxidation of fatty acids. Export of triglycerides from the liver is reduced due to alcohol-mediated downregulation of transfer proteins. Steatosis is also promoted by nonoxidative fatty acid esterification. The production of reactive oxygen species by oxidative metabolism leads to oxidative stress and lipid peroxidation (Fig. 15.24.1.3). This is augmented by further reactive oxygen species production by Kupffer cells, which are activated by low-grade portal endotoxaemia as a consequence of alcohol-induced increased intestinal permeability. The oxidative stress is amplified by the relative lack of innate antioxidants such as glutathione, which is often depleted by alcohol excess. Oxidative stress induces redox-sensitive transcription factors which lead to increased production of tumour necrosis factor- $\alpha$  (TNF $\alpha$ ) and the neutrophil activating interleukin 8 (IL-8). TNF $\alpha$  along with lipid peroxidation leads to inflammation, necrosis, mitochondrial disruption, and apoptosis. In addition, acetaldehyde may form protein adducts which can act as neoantigens, triggering immune-mediated damage. This combination of immune activation, cytokines, and oxidative stress causes alcoholic hepatitis. Fibrosis in ALD is a result of

increased collagen production by hepatic stellate cells, which are directly activated by acetaldehyde itself as well as by TNF $\alpha$ , IL-8, growth factors derived from damaged hepatocytes, and reactive oxygen species. Diagnosis A detailed clinical history documenting the type, pattern, and amount of alcohol consumed should be taken. Screening tools for alcohol use disorders such as the AUDIT questionnaire or its abbreviated forms, such as the FAST or AUDIT-C questionnaires, should be carried out, but it is important to recognize that not all patients with ALD have alcohol dependency. A diagnosis of ALD can be considered in patients with a combination of a history of alcohol excess (>30 g/day), clinical evidence of liver disease, and compatible laboratory investigations. However, as only a minority of alcohol misusers develop advanced ALD, other forms of liver disease should be excluded. A screen for chronic viral, autoimmune, and hereditary liver disease should be carried out. Up to 20% of people with alcoholic liver disease will have another coexistent liver disease such as viral hepatitis. Imaging should be performed to identify obstructive, structural, or neoplastic disease, with an abdominal ultrasound examination with Doppler of the portal and hepatic veins. Further imaging can be undertaken with either CT or MRI if other pathology is suspected. In cases of doubt, a liver biopsy can be a useful tool to exclude other causes of liver disease. However, percutaneous liver biopsy may be contraindicated in the clinical setting by the presence of ascites and/or a coagulopathy. Risks can be minimized by performing a transjugular liver biopsy, although the quality of the sample may be less satisfactory. Clinical features and investigation Many patients, even those with advanced ALD, may be asymptomatic until hepatic decompensation occurs. Presentation may vary from an incidental discovery of abnormal liver blood tests through to acute-on-chronic liver failure or decompensated cirrhosis. In ALD, serum aspartate aminotransferase (AST) is rarely more than 500 IU/litre, serum alanine aminotransferase (ALT) rarely over 300 IU/litre, and the AST:ALT ratio usually more than 1.5. The degree of elevation of the transaminase enzymes is a clue as to the presence of liver injury but not the severity of ALD. Commonly used indicators of alcohol excess such as  $\gamma$ -glutamyl transferase and mean cell volume are not specific for either alcohol abuse or ALD. Patients presenting only with abnormal liver blood tests may have simple steatosis, but may have 'silent' cirrhosis. Clues to the presence of chronic liver disease, such as stigmata of chronic liver disease (spider naevi, palmer erythema, gynaecomastia) or portal hypertension (splenomegaly, caput medusae, otherwise unexplained thrombocytopenia) should be sought. Transient elastography to assess liver stiffness can be useful to assess the stage of ALD, but the presence of ascites or acute inflammation with an alcoholic hepatitis may interfere with this assessment and render it uninterpretable. Alcoholic hepatitis Acute alcoholic hepatitis is characterized by new-onset jaundice (serum bilirubin >80  $\mu$ mol/litre)

15.24.1 Alcoholic liver disease 3145 than 500 IU/litre, serum alanine aminotransferase (ALT) rarely over 300 IU/litre, and the AST:ALT ratio usually more than 1.5. The degree of elevation of the transaminase enzymes is a clue as to the presence of liver injury but not the severity of ALD. Commonly used indicators of alcohol excess such as  $\gamma$ -glutamyl transferase and mean cell volume are not specific for either alcohol abuse or ALD. Patients presenting only with abnormal liver blood tests may have simple steatosis, but may have 'silent' cirrhosis. Clues to the presence of chronic liver disease, such as stigmata of chronic liver disease (spider naevi, palmer erythema, gynaecomastia) or portal hypertension (splenomegaly, caput medusae, otherwise unexplained thrombocytopenia) should be sought. Transient elastography to assess liver stiffness can be useful to assess the stage of ALD, but the presence of ascites or acute inflammation with an alcoholic hepatitis may interfere with this assessment and render it uninterpretable. Alcoholic hepatitis Acute alcoholic hepatitis is characterized by new-onset jaundice (serum bilirubin >80  $\mu$ mol/litre)

which has developed over the previous 3 months with a history of alcohol excess (>80 g/day males,

“ 60 g/day females) within 2 months. Alcoholic hepatitis is often, but not invariably, associated with other features such as pyrexia, a peripheral leucocytosis, hepatomegaly, or a hepatic bruit. There may be other features of decompensated liver disease such as encephalopathy and ascites. Most patients with alcoholic hepatitis will have coexistent cirrhosis. The clinical presentation of alcoholic hepatitis can be similar to sepsis and it is therefore vital that potential sources of infection are investigated with blood and urine cultures, chest radiography, and (when relevant) ascitic fluid analysis. Sepsis should be excluded or satisfactorily treated before assessment or specific treatment of alcoholic hepatitis is initiated. The need for a biopsy to diagnose alcoholic hepatitis before starting specific treatment is controversial. Histological confirmation in cases of clinical uncertainty is clearly necessary, but routine liver biopsies are probably not required where the clinical and investigational features are consistent with alcoholic hepatitis. Cirrhosis Patients may present with decompensated chronic liver disease in a less acute fashion. They may have peripheral oedema, ascites, and encephalopathy, but are not necessarily jaundiced. Precipitants of hepatic decompensation such as sepsis, gastrointestinal bleeding, electrolyte imbalance, or the development of hepatocellular carcinoma should be sought. Management Abstinence The cornerstone to the management of ALD is long-term abstinence. Brief interventions (5–20-min motivational consultations) carried out opportunistically in the hospital setting can have an effect for up to 1 year (see Chapter 26.6.1 for further discussion). As many as 50% of patients can significantly reduce or abstain from alcohol absolutely after simple advice from a physician. Ideally, alcohol dependency should be managed in concert with addiction services to ensure appropriate intervention and community follow-up. Several medical therapies are available for the treatment of alcohol abuse including disulfiram, naltrexone, nalmefene, and acamprosate. However, the evidence base for these approaches in patients with advanced ALD is sparse. There have been studies using the  $\gamma$ -aminobutyric acid type B receptor inhibitor baclofen in patients with cirrhosis, with some promising results. Patients admitted acutely with ALD are at risk of alcohol withdrawal syndrome. The oxidative metabolism of benzodiazepines may be impaired in those with advanced disease leading to an accumulation of active drug. This may precipitate or exacerbate hepatic encephalopathy. For patients with evidence of liver dysfunction, shorter-acting agents such as lorazepam should be considered. See Chapter 26.5.4 for further discussion. Nutrition Patients with ALD are typically in a hypercatabolic state with protein-energy malnutrition. This is of prognostic significance and increases the likelihood of the development of complications such as infection, encephalopathy, and ascites. Patients with alcoholic hepatitis are almost invariably malnourished to some degree. In these patients, more than 50% of

energy prior to hospital admission may have come from alcohol ingestion. Malnutrition may be self-evident on global assessment with clinical evidence of muscle wasting, but anthropometry with mid-upper arm circumference, hand grip strength and triceps skinfold thickness measurements may provide early indications of undernutrition and allow prompt nutritional support. Protein and calorie nutritional support should be provided either as dietary supplements or via enteral feeding regimens, aiming for protein consumption of up to 1.2 to 1.5 g/kg and calorie intake up to 35 to 40 kcal/kg. Thiamine replacement should be prescribed to prevent the development of Wernicke's encephalopathy, in accordance with published guidelines. Studies have not shown that combinations of antioxidants are beneficial in alcoholic hepatitis. One study has shown a long-term survival benefit in alcoholic hepatitis with a liver-specific nutritional formulation administered by nasogastric feeding tube, but tolerance of such feeding routes is often poor in patients with decompensated ALD and severe alcoholic hepatitis. Acute alcoholic hepatitis Assessment of severity A clinical diagnosis of alcoholic hepatitis encompasses a wide spectrum of disease, with severe acute alcoholic hepatitis having a 28-day mortality of up to 60%. Assessment of the severity of alcoholic hepatitis is vital not only to identify those patients with a poor prognosis, but also to target treatment effectively. The discriminant function has been used for this purpose, with a value more than 32 being associated with a poor prognosis, although it suffers from a lack

section 15 Gastroenterological disorders 3146 of specificity and overall accuracy. It relies upon the measurement of prothrombin time, which can vary significantly between different laboratories (Table 15.24.1.1). The Glasgow Alcoholic Hepatitis Score is a more accurate score, validated throughout the United Kingdom. A value of 9 or more is associated with a poor prognosis. Both the discriminant function and the Glasgow Alcoholic Hepatitis Score have been used to identify patients who will benefit from specific treatment of alcoholic hepatitis. The Model for End-Stage Liver Disease (MELD) score has been used to assess prognosis in alcoholic hepatitis, but the threshold for identifying a poor outcome remains unclear and it has yet to be shown to be able to identify patients likely to benefit from additional treatment. Steroids and other pharmacological treatments Use of corticosteroids in alcoholic hepatitis has been controversial, with concerns about the risk of precipitating sepsis with such treatment. The STOPAH trial addressed this question with the largest study of alcoholic hepatitis ever performed. Over 1000 patients with a discriminant function greater than 32 were randomized to corticosteroids (prednisolone 40 mg/day for 4 weeks), pentoxifylline (400 mg three times a day for 4 weeks), or placebo in a factorial design. Overall mortality was not significantly different between the four groups, but despite serious infections being more likely in corticosteroid-treated patients, on multivariate logistic regression corticosteroid use was associated with an improved 28-day survival, although this survival benefit was lost by 90 days. This 28-day survival advantage with corticosteroids has been observed in a subsequent meta-analysis. In STOPAH, pentoxifylline was not seen to improve survival at any time point despite a previous study suggesting benefit. Other studies have confirmed that the combination of pentoxifylline and corticosteroids offers no additional benefit to corticosteroids alone. One study has suggested that the addition of N-acetylcysteine to corticosteroids may be of use by reducing episodes of sepsis,

but confirmatory studies are required. The anti-TNF $\alpha$  drugs infliximab and etanercept have been studied in alcoholic hepatitis without evidence of improved outcome and a concerning increase in sepsis. Overall, corticosteroid is the only pharmacological treatment shown to be of any benefit in alcoholic hepatitis. It is possible to identify patients who are responding to such treatment as a fall in bilirubin after 1 week of corticosteroid treatment is associated with a survival benefit. From this observation, the Lille score has been developed to identify responders and nonresponders to corticosteroid treatment. It is possible that the measured corticosteroid benefit is limited on account of the poor specificity of the discriminant function in identifying those who might benefit from corticosteroids. The Glasgow alcoholic hepatitis score may better guide corticosteroid treatment as those patients with a score of less than 9 do not appear to benefit from it, whereas those with a score of 9 or more have improved 28- and 84-day survival with corticosteroid treatment compared with untreated controls. Survival from alcoholic hepatitis in the short-term may be modified by corticosteroid treatment, but longer-term outcome is closely related to the achievement of abstinence. Cirrhosis The complications of alcohol-related cirrhosis, such as ascites, variceal haemorrhage, and encephalopathy, should be managed in the same way as for other forms of chronic liver disease. Patients with cirrhosis should have 6-monthly liver ultrasonography and  $\alpha$ -fetoprotein for hepatocellular carcinoma screening, and screening endoscopy for oesophageal varices. There are no specific treatments available for alcoholic cirrhosis other than liver transplantation. Long-term prognosis is closely

**Table 15.24.1.1 Prognostic scores used in the assessment of alcoholic hepatitis**

**Discriminant function** Discriminant function =  $4.6 (\text{prothrombin time} - \text{control prothrombin time}) + \text{total bilirubin (mg/dl)}$  Poor prognosis  $\geq 32$

**MELD** MELD =  $3.8 \times \log(\text{bilirubin [mg/dl]}) + 11.2 \times \log(\text{INR}) + 9.6 \times \log(\text{creatinine [mg/dl]}) + 6.4$

**Glasgow Alcoholic Hepatitis Score**

| Score            | 1    | 2       | 3          |
|------------------|------|---------|------------|
| Age              | <50  | 50-64   | $\geq 65$  |
| White cell count | <15  | 15-15   | $\geq 15$  |
| Urea             | <5   | 5-5     | $\geq 5$   |
| Bilirubin        | <125 | 125-250 | $\geq 250$ |
| INR              | <1.5 | 1.5-2.0 | $\geq 2.0$ |
| Poor prognosis   | <8   | 8-10    | $\geq 11$  |

50 White cell count <15 15 Urea <5 5 Bilirubin <125 125-250 250 INR <1.5 1.5-2.0 2.0 Poor prognosis >8 Lille Score  $R = 3.19 - (0.101 \times \text{age in years}) + (0.147 \times \text{albumin day 0 in g/L}) + (0.0165 \times \text{ECBL in mM}) - (0.206 \times \text{renal insufficiency}) - (0.0065 \times \text{bilirubin day 0 in mM}) - (0.0096 \times \text{INR day 0})$  # creatinine >115 $\mu$ M Score =  $\text{EXP}(-R) / [1 + \text{EXP}(-R)]$  Poor Prognosis  $\geq 0.45$

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