Alcohol and the liver

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Abstract

Hospital admissions because of alcohol-related liver disease (ArLD) are increasing. The amount of alcohol consumed and pattern of drinking are linked to increased risk of ArLD. However, other factors such as obesity, co-existent liver disease – particularly hepatitis C, gender, nutritional status and genetic factors also play a role. The spectrum of ArLD ranges from steatosis to alcoholic hepatitis to established cirrhosis, and the alcohol-related injury involves multiple mechanisms. Chronic, excessive alcohol consumption can cause cirrhosis in the absence of alcohol dependency syndrome or indicators of alcohol abuse. Presentation is variable, and recognition requires the clinician to be aware of the significance of a history of alcohol excess, clinical stigmata of liver disease and compatible laboratory investigations. Not all people who drink excess alcohol have alcohol as the cause of their liver disease, and other aetiologies must be excluded. The key to management is long-term abstinence, and interventions should be delivered in conjunction with addiction services. Nutritional issues should also be addressed. Acute alcoholic hepatitis has a high mortality, and patients with the highest risk can benefit from short-term corticosteroids. Cirrhotic patients require hepatoma surveillance and variceal screening; liver transplant should be considered in selected cases.

Keywords Alcohol; alcoholic hepatitis; alcoholic liver disease; cirrhosis

Key points

- Long-term abstinence from alcohol is the cornerstone of management of alcohol-related liver disease (ArLD)
- Patients with advanced ArLD can be asymptomatic
- Alcoholic hepatitis can be diagnosed clinically based on the onset of jaundice and compatible laboratory values
- Corticosteroids should be given for acute alcoholic hepatitis based on estimated mortality and initial response to treatment
- Surveillance for the complications of chronic liver disease should be established for those with alcohol-related cirrhosis

Epidemiology[1]

Alcohol-related hospital admissions have risen by up to 17% in parts of the UK over the last 10 years, with an increase in alcohol-specific deaths; patients aged 50–69 years are particularly vulnerable. The major cause of death is alcoholic-related liver disease (ArLD), which now directly accounts for over one-third of liver deaths in England. This is particularly alarming as liver disease is the fifth most common cause of death nationally, with death rates increasing year on year. In 2012, 1 in every 8 hospital admissions for ARLD in England resulted in death.

The population incidence of cirrhosis increases with the total amount of alcohol consumed, and this has been shown to correlate closely with affordability of alcohol. The current estimated cost of a hospital admission for a single episode of decompensated ArLD is approximately £3400.

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Risk factors

The relationship between alcohol consumption and development of liver damage and cirrhosis is complex. There is a clear link between the amount of alcohol intake and drinking patterns in the development of ArLD. People who drink daily and consume alcohol without meals are at higher risk of developing cirrhosis.

Other undisputed risk factors for ArLD include obesity and co-infection with hepatitis C virus. Several studies have shown obesity to be the single most important risk factor determining the risk of cirrhosis in heavy drinkers, with visceral fat accumulation affecting individual susceptibility to liver fibrosis in alcoholic patients. Coexistent hepatitis C infection increases the risk of cirrhosis 30-fold in those who take alcohol to excess.

Gender and genetics play a part as well. Women are more susceptible to the hepatotoxic effects of alcohol and develop ArLD more quickly than men who consume equivalent amounts. The reason is poorly understood but could be a combination of metabolic, hormonal and psychosocial factors. Twin studies have revealed the importance of genetic susceptibility to ArLD, with monozygotic twins having higher concordance for alcohol-related cirrhosis than dizygotic twins. Such studies suggest that genetic factors could represent up to 50% of an individual's susceptibility to ArLD, although the search for specific polymorphisms is still continuing. So far, only two candidate gene polymorphisms (*TNFα*-238A, *PNPLA3* rs738409 G) have sufficient data to consider them highly suspicious as genetic risk factors for ArLD.

Pathophysiology

Multiple mechanisms have been implicated in alcohol-associated hepatocyte damage. Progressive fibrosis and inflammation are central to the development of chronic ArLD.

Cytochrome P450 2E1 (CYP2E1), which is induced by chronic alcohol consumption, metabolizes ethanol to acetaldehyde. This highly toxic molecule leads to the production of reactive oxygen species (ROS) and lipid peroxidation. In addition, acetaldehyde

can form protein adducts that can act as neo-antigens, triggering immune-mediated damage (Figure 1). Alcohol also increases intestinal permeability, leading to endotoxaemia. This in turn activates Kupffer cells in the liver to release tumour necrosis factor-α (TNF-α), which results in the further production of ROS. These multiple 'hits' on the liver lead to hepatocyte necrosis, but perhaps more significantly to apoptosis.

Pathology

The spectrum of ArLD encompasses alcoholic steatosis, with or without significant fibrosis (in up to 100% of drinkers with a daily alcohol intake >60 g/day), alcoholic steatohepatitis (in 10–35%) and established cirrhosis (in approximately 15%) (Figure 2). The natural history of ArLD appears to progress through steatosis to steatohepatitis to fibrosis and cirrhosis, with some, but probably not all, patients also passing through a phase of clinical alcoholic hepatitis. Steatosis is the earliest finding in ArLD and is reversible on cessation of alcohol intake. It is predominantly evident in perivenular hepatocytes and can be microvesicular or macrovesicular, the latter being more prevalent. The features of steatohepatitis are perivenular changes, often with Mallory bodies, hepatocyte ballooning, megamitochondria, canalicular cholestasis and a neutrophil infiltrate. Regenerative nodules and perivenular fibrosis develop with repeated episodes of injury, leading to micronodular cirrhosis.

Diagnosis[2]

The history should document the type, pattern and amount of alcohol consumed. Useful screening tools for harmful alcohol use include the Alcohol Use Disorders Identification Test (AUDIT) or its abbreviated forms, the Fast Alcohol Screening Test (FAST) and AUDIT for Consumption (AUDIT-C). However, it is important to recognize that not all patients with ArLD have alcohol dependency and that not all alcohol misusers develop significant liver disease. ArLD should be suspected in patients with a combination of a history of alcohol excess, clinical evidence of liver disease and compatible laboratory investigations.

A screen to exclude other forms of liver disease such as viral, autoimmune and hereditary liver disease should be carried out as up to 20% of people with ArLD have a coexistent liver disease such as viral hepatitis. An ultrasound scan of the abdomen should be performed to identify obstructive, structural or neoplastic disease, with Doppler scanning of the portal and hepatic veins to assess flow patterns. Further imaging can be undertaken with computed tomography or magnetic resonance imaging if other pathology is suspected. Where uncertainty remains, a liver biopsy can be useful to exclude other causes of liver disease. However, in certain clinical settings, percutaneous liver biopsy can be contraindicated by the presence of ascites and/or coagulopathy. In these circumstances, liver biopsy can be performed via a transjugular route.

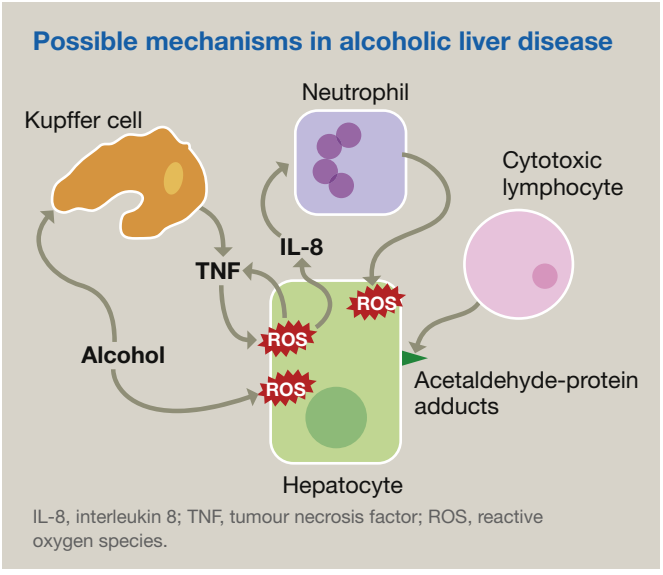

Figure 1

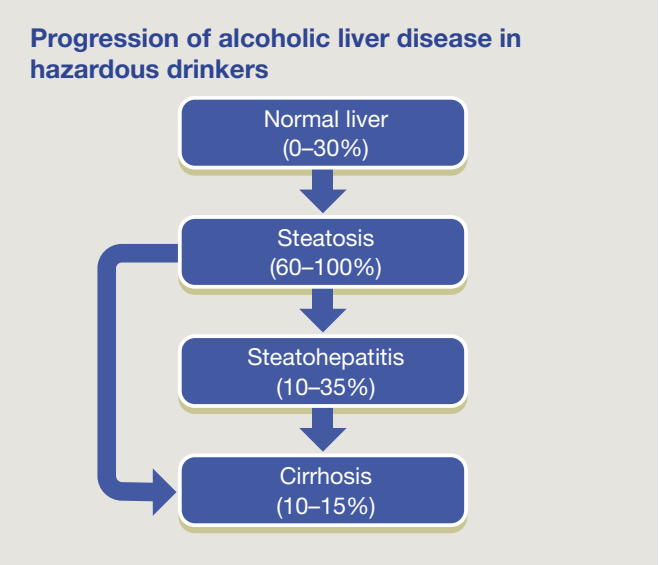

Figure 2

Screening[3]

Non-invasive tests to estimate the severity of liver fibrosis have been applied to ArLD for screening high-risk populations. The role of simple composite scores such as the Fibrosis 4 (FIB-4) score is unclear as aspartate aminotransferase (AST) is preferentially elevated in ArLD, leading to an overestimation of liver fibrosis. Elastography is probably the most effective screening tool; however, it can overestimate liver fibrosis if the patient is actively drinking or there is active liver inflammation (AST>100U/litre), and it is not readily accessible for many patients at present.

Presentation

Presentation varies from an incidental discovery of abnormal liver blood tests to acute-on-chronic liver failure or decompensated cirrhosis. In ArLD, aminotransferase levels are generally <300 IU/litre, but an AST to alanine aminotransferase ratio >1.5 is highly suggestive of alcohol-related liver injury. Patients presenting only with abnormal liver blood tests may have simple

steatosis, but clues to the presence of 'silent' advanced chronic liver disease should be sought. These include stigmata of chronic liver disease (spider naevi, palmar erythema, gynaecomastia) or signs of portal hypertension (caput medusae, otherwise unexplained thrombocytopenia).

Other laboratory abnormalities, such as raised γ-glutamyl transpeptidase, red cell macrocytosis, electrolyte disturbances, high serum uric acid levels and prolonged prothrombin time, can also reflect underlying ArLD but do not necessarily correlate with severity of disease.

Acute alcoholic hepatitis is characterized by a new onset of jaundice (serum bilirubin >80 micromol/litre developing within 8 weeks) in the context of recent alcohol excess (within 8 weeks), often associated with other features such as pyrexia, peripheral leucocytosis, hepatomegaly or a hepatic bruit. Most of these patients have coexistent cirrhosis, and other features of decompensated liver disease, such as encephalopathy and ascites, can be present.

Alternatively, patients can present with decompensated chronic liver disease in a more insidious fashion. There can be peripheral oedema, ascites and encephalopathy but not necessarily jaundice. Evidence of precipitants of hepatic decompensation, such as sepsis, gastrointestinal bleeding, electrolyte imbalance, portal vein thrombosis or development of hepatocellular carcinoma, should always be sought.

Treatment

Abstinence

The cornerstone of management in ArLD is long-term abstinence, and this benefits patients at any stage of the disease. Brief interventions (5–20-minute consultations) carried out opportunistically in the hospital setting can have an effect for up to 1 year. Alcohol dependency should ideally be managed in concert with addiction services to ensure appropriate intervention and community follow-up. Patients admitted acutely with ArLD are at risk of alcohol withdrawal syndrome (AWS), which should be managed using symptom-triggered severity scores. As advanced liver disease impairs the metabolism of benzodiazepines, shorter acting agents such as lorazepam should be considered for the management of AWS.

Pharmacological treatment for alcohol dependency can be considered, but a reliance on drug therapy for alcohol use disorders is not advised: a multidisciplinary team approach is imperative to manage complex psychosocial factors. There has been little study of pharmacotherapy in ArLD, and some licensed agents are contraindicated in liver disease. Acamprosate is relatively safe, and baclofen has shown some promise in ArLD.

Nutrition

Patients with ARLD are typically in a hypercatabolic state with protein–energy malnutrition. This is of prognostic significance and increases the likelihood of complications such as infection, encephalopathy and ascites. Protein and calorie nutritional support should be provided, either as dietary supplements or via enteral feeding regimens, aiming for a daily protein intake of up to 1.2–1.5 g/kg, and daily calorie intake of up to 35–40 kcal/kg. Thiamine replacement should be prescribed to prevent the development of Wernicke's encephalopathy. Other vitamin B and micronutrient deficiencies, particularly folate, pyridoxine, riboflavin and zinc, are also common in ArLD and should be checked, with supplementation if necessary, if there is evidence of malnutrition.

Acute alcoholic hepatitis[4,5]

Severe acute alcoholic hepatitis has a 28-day mortality of up to 60%. Patients present with a recent onset of significant jaundice and typically have a history of prolonged heavy daily alcohol use. The diagnosis still encompasses a spectrum of disease severity, and prognostic assessment is vital not only to identify individuals with a poor prognosis, but also to target treatment effectively.

The discriminant function (DF) and Model for End-stage Liver Disease (MELD) have been used for this purpose, with scores of >32 and >21, respectively, associated with a poor prognosis (Table 1). However, the DF suffers from a lack of specificity and overall accuracy, and relies on measurement of prothrombin time, which can vary significantly between different laboratories. Similar issues can affect the MELD. The Glasgow Alcoholic Hepatitis Score (GAHS) has been validated throughout the UK, a score of ≥9 being associated with a poor prognosis. Both the DF and the GAHS have been used to identify patients who will benefit from corticosteroid treatment, and these score are recommended in the European Association for the Study of the Liver guidelines.

The management of alcoholic hepatitis includes alcohol abstinence, and surveillance for and prompt treatment of

Prognostic scores used in the assessment of alcoholic hepatitis

- **DF** = 4.6(PT − control PT) + total bilirubin [mg/dl]

Poor prognosis if score ≥32

- **MELD** = 3.8 log bilirubin [mg/dl] + 11.2*log INR + 9.6*log creatinine [mg/dl] + 6.4

Poor prognosis if score ≥21

- **GAHS**

	1	2	3
Age (years)	<50	>50	
White cell count (x10^9/litre	<15	>15	
Urea (mmol/litre)	<5	>5	
Bilirubin (micromol/litre)	<125	125–250	>250
INR	<1.5	1.5–2.0	>2.0

Poor prognosis if score ≥9

- **Lille score** = EXP (−R)/[1 + EXP (−R)]

Where R = 3.19 − (0.101 age in years) + (0.147 albumin day 0 in g/litre) + 0.0165 evolution in bilirubin concentration in micromol/litre) − (0.206 renal insufficiency) − (0.0065 bilirubin day 0 in micromol/litre) − (0.0096 INR)

renal insufficiency = 1 (if creatinine is >115 micromol/litre) or 0 (if creatinine is ≤115 micromol/litre)

Scores >0.45 predict a 6-month survival of 25%.
Scores <0.45 predict a 6-month survival of 85%.
INR, international normalized ratio; PT, prothrombin time.
EXP, exponential function.

Table 1

infection and acute kidney injury. Adequate nutrition must be maintained as low daily calorie intake in these patients is associated with a higher mortality. The use of corticosteroids in alcoholic hepatitis has been controversial. The UK-based STeroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) trial assessed both prednisolone and pentoxifylline. Pentoxifylline did not affect outcome at any time point, but on multivariate analysis prednisolone use was associated with an improved 28-day survival, although this benefit was lost by 90 days. Serious infections were more likely in corticosteroid-treated patients, so effective treatment of infection before corticosteroids is necessary. The addition of acetylcysteine to corticosteroids can be of benefit by reducing episodes of sepsis, but confirmatory studies are required before this can be routinely recommended.

Patients with more severe disease i.e. GAHS ≥ 9, may benefit from corticosteroids, whereas those with a GAHS <9 show no significant improvement with corticosteroids even if the DF is >32. The response to treatment with corticosteroids and any associated survival benefit is assessed by a fall in bilirubin concentration. The Lille Model helps to risk-stratify patients on day 7 of corticosteroid treatment and identify responders to treatment with a score <0.45. These responders show benefit from corticosteroids beyond 30 days, but survival beyond 90 days is significantly affected by other factors, predominantly continued alcohol use.

Cirrhosis

The complications of alcohol-related cirrhosis, such as ascites, variceal bleeding, coagulopathy, renal impairment and encephalopathy, should be managed in the same way as for other forms of chronic liver disease. Patients with cirrhosis should have a screening endoscopy for oesophageal varices, and in individuals suitable for further intervention in the event of a tumour being detected, a 6 monthly ultrasonography and α-fetoprotein measurement should be performed as part of hepatocellular carcinoma surveillance. The long-term prognosis is closely related to the stage of disease, as assessed by standard chronic liver disease scores such as the United Kingdom Model for End-Stage Liver Disease (UKELD), MELD or Child–Pugh scores, and subsequent alcohol use.

Liver transplantation

Liver transplantation should be considered for individuals whose clinical condition remains poor despite sustained abstinence. Post-transplant survival for alcoholic cirrhosis is similar to, and in some cases even better than for, other causes of end-stage liver disease. There is no strict requirement for a set period of abstinence before considering liver transplantation in the UK, but many patients improve clinically up to 6 months after stopping drinking, which might render referral for transplant unnecessary. Rigorous psychiatric evaluation is included in the transplant assessment and aims to identify risk factors for relapse. Early liver transplant for alcoholic hepatitis has been suggested for those who do not respond to corticosteroids, but concerns remain about the suitability of such intervention and whether the Lille score is specific enough to identify individuals with little chance of survival. However, there is increasing evidence that these patients have similar outcomes and rates of recidivism to those transplanted for alcohol-related cirrhosis. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 45-year-old man presented as an inpatient with a 3-hour history of tremulousness, anxiety and agitation. He had been admitted with a right shoulder dislocation after a fall at home. He had a history of alcohol-related cirrhosis. He was drinking two bottles of wine a day and his last drink had been 12 hours previously.

On clinical examination, he was disruptive and slightly jaundiced, with a heart rate of 105 beats/minute.

Investigations

- Blood glucose 6.5 mmol/litre (3.0–6.0)

What is the best management for this patient's symptoms?

A. An urgent abdominal ultrasound scan
B. Lactulose 20 ml 8-hourly by mouth
C. Diazepam 20 mg 6-hourly by mouth
D. Lorazepam 1–2 mg by mouth in a symptom-triggered fashion
E. Prednisolone 20 mg once by mouth

Question 2

A 54-year-old man presented with a 2-week history of increasing confusion and becoming yellow. He had been consuming a bottle of vodka daily until 10 days before admission. His diet had been poor for 4 weeks.

On clinical examination, he was unkempt and jaundiced, with bitemporal muscle wasting, a distended abdomen with shifting dullness and lower extremity pitting oedema.

Investigations

- Haemoglobin 113 g/litre (130–180)
- White cell count 16 $\times$ 10^9/litre (4.0–10.0)
- Platelets 239 $\times 10^9$/litre (150–400)
- Sodium 120 mmol/litre (137–144)
- Urea 2.4 mmol/litre (2.5–7.0)
- Creatinine 44 micromol/litre (60–110)
- Total bilirubin 220 micromol/litre (1–22)
- Alanine aminotransferase 74 U/litre (5–35)
- Aspartate aminotransferase 248 U/litre (1–31)
- Alkaline phosphatase 156 U/litre (45–105)
- Albumin 24 g/litre (37–49)
- Prothrombin time ratio 2.2 (<1.4)
- C-reactive protein 25 mg/litre (<10)
- Doppler ultrasonography of the abdomen showed an enlarged, brightly echogenic liver with moderate ascites
- An infection screen was negative

Which of the following is the next most appropriate treatment option?

A. Start on broad-spectrum antibiotics and give intravenous albumin on days 1 and 3
B. Start on therapeutic low-molecular-weight heparin (LMWH) for 3 months
C. Commence prednisolone 40 mg orally once daily
D. Give pentoxifylline 400 mg orally once daily
E. Start on spironolactone 100 mg orally once daily

Question 3

A 58-year-old man presented for review with abnormal liver blood tests. He had a 20-year history of daily consumption of alcohol, drinking ‘a few shots’ of whisky a day along with additional glasses of gin and tonic over the weekend.

Which of the following features would be most suggestive of underlying fibrotic liver disease?

A. High mean cell volume
B. Low platelet counts
C. High aspartate aminotransferase to alanine aminotransferase ratio
D. Bright liver on an ultrasound scan
E. High liver stiffness measurement on elastography