How I treat… alcohol-related liver disease

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ABSTRACT

Age-standardised mortality from liver disease in the United Kingdom has risen by 400% since 1970, with three-quarters of deaths from alcohol-related liver disease (ARLD). The 2013 National Confidential Enquiry into Patient Outcome and Death report found that only 47% of the patients dying in hospital from liver disease experienced 'good' care. We discuss common complications in the care of patients with ARLD and the evidence-based best practice that can improve patient outcomes, with a focus on the initial management of patients presenting acutely to the medical take.

KEYWORDS: Alcohol, cirrhosis, decompensation, withdrawal, dependence, best practice

Introduction

Since the Gin Acts of the 18th century, alcohol has been a recognised major cause of morbidity and mortality in the United Kingdom: a fact inescapable to the practicing general physician. The extent of the problem cannot be overstated – since 1970 the age-standardised mortality from liver disease in the UK has risen by 400%, in contrast to the gradual and significant reductions in mortality from circulatory, ischaemic heart, cerebrovascular, neoplasm, respiratory, endocrine and metabolic disease. Three-quarters of these deaths are from alcohol related liver disease (ARLD).[1] Public Health England (PHE) estimates that there were 23,000 alcohol-related deaths in England in 2014[2] with most patients dying under the age of 65.[3] It is estimated that alcohol abuse costs the NHS £3.5 billion each year.[1]

Concerningly, while deaths from cirrhosis are rising in England, they are falling in most other EU countries.[1] Furthermore, the problem affects the most deprived members of our society disproportionally – PHE found the alcohol-related mortality of the most deprived lifestyle group to be 65% higher than the average.[2] In addition, the 2013 National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report found that only 47% of the patients dying in hospital from ARLD experienced 'good' care. Simple interventions such as prompt treatment of sepsis and good fluid management were, in some instances, lacking.[4]

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In response to the NCEPOD report, stakeholders including the British Association for the Study of the Liver (BASL) and the British Society of Gastroenterology (BSG) developed the Decompensated Cirrhosis Care Bundle to optimise recognition of common complications and prompt early intervention in this high-mortality condition (see supplementary material S1).[5] Our aim is to expand on this guidance and to describe what we consider to be current evidence-based best practice when treating patients with ARLD.

Alcohol

Alcohol withdrawal

Alcohol withdrawal is a common occurrence on the acute medical take, both in patients with and without liver disease. It is treated primarily with benzodiazepines. Many units routinely use fixed-dose chlordiazepoxide regimens. However, caution must be taken with patients with cirrhosis as chlordiazepoxide clearance is reduced in these patients[6] and hence chlordiazepoxide can accumulate and cause drowsiness and respiratory depression. In patients with cirrhosis and at risk of alcohol withdrawal, it is felt safer and equally efficacious to use oral lorazepam in a symptom-triggered manner as dictated by regular assessment of the patient's Clinical Institute Withdrawal Assessment Scale for Alcohol score.[7]

Alcohol dependence

An admission due to alcohol provides a unique opportunity to change a patient's clinical course by undertaking a brief intervention aimed at stopping or reducing a patient's alcohol use. A 2010 Cochrane review highlighted that alcohol consumption is reduced following a brief intervention. In addition, the reviewers note mortality was reduced at 6 months and 1 year in these patients compared to their controls.[8] We would encourage the use of a dedicated alcohol liaison service to deliver these interventions using established frameworks; for example, the Paddington Alcohol Test is used in the emergency department to identify patients misusing alcohol and to facilitate brief advice from an emergency physician or nurse, as well as the offer of an appointment with an Alcohol Liaison Nurse (ALN) for a brief intervention. A pragmatic, single-blind randomised clinical trial demonstrated that a reattendance is avoided for every two patients that accept the offer of an ALN appointment.[9]

Once a patient has been treated acutely for alcohol withdrawal, of equal importance is assisting them to maintain this withdrawal. Although not currently licensed in the UK for the treatment of

alcohol dependence, there is evidence of a significant increase (29% to 71%) in maintenance of abstinence in alcohol-dependent cirrhotics treated with baclofen 10 mg three times a day versus placebo (double-blind randomised controlled trial).[10] Acamprosate also shows a reduction in drinking and an increase of abstinence in a Cochrane meta-analysis,[11] although this is untested in liver disease. Naltrexone is also efficacious[12] but can cause hepatocellular injury. Disulfiram should be avoided as it has been linked to cases of fulminant hepatic failure.[13] Close links between the alcohol liaison service and a specialist with an interest in ARLD can help patients with alcohol dependence access suitable medication to maintain alcohol cessation.

Infection

As highlighted in the 2013 NCEPOD report, treatment of infection was often delayed.[3] Infection increases mortality significantly in patients with cirrhosis[14] and every hour that appropriate antibiotics are delayed will further increase mortality.[15] We would recommend adopting a low threshold for the instigation of broad-spectrum antibiotics in patients with decompensated cirrhosis, followed by rationalisation once a source of infection is definitively identified.

In patients who fail to respond to antibiotics, we must also consider fungal infections, seen to occur in up to 10% of critically unwell cirrhotic patients with septic shock.[15] In the presence of ascites, diagnostic paracentesis is mandatory on admission – with prompt treatment for spontaneous bacterial peritonitis with antibiotics and human albumin solution[16] should the ascitic neutrophil count be greater than 250 /mm^3. Diagnostic paracentesis should be repeated should the patient deteriorate during their admission, as part of a broader 'septic screen'.

Fluid balance

Fluid management in patients with cirrhosis is historically an area where there is heterogeneity of practice. Patients with decompensated cirrhosis are often on high doses of diuretics and are at high risk of acute kidney injury (AKI), often complicated by hyponatraemia. Treating clinicians may have concerns regarding salt balance, and about precipitating a worsening of existing ascites. However, this must be weighed against the increased mortality should AKI develop.[17]

The consensus highlighted in the Decompensated Cirrhosis Care Bundle[5] is that if there is evidence of an AKI (based on modified risk of renal dysfunction; injury to the kidney; failure of kidney function, loss of kidney function and end-stage kidney disease criteria), there is hyponatraemia (defined as serum sodium <125 mmol/L) or the patient is clinically dehydrated, then one should suspend all diuretics and nephrotoxic drugs and fluid resuscitate with 250 mL boluses of 5% albumin or 0.9% saline aiming to restore a mean arterial pressure >80 mmHg and a urine output of >0.5 mL/kg/h based on dry weight. Locally, many clinicians will use 0.9% saline in the first instance as it is readily and promptly available in an acute situation.

Frequently, one or two litres of fluid will correct the patient's losses. However, should the patient worsen or should they fail to achieve targets within the first 6 hours, escalation to a higher level of care must be considered for further resuscitation guided by central venous pressure monitoring and for consideration of inotropes.

Alcoholic hepatitis

Alcoholic hepatitis (AH) is a clinical syndrome characterised by jaundice and an acute deterioration of liver function in an actively drinking patient. AH can be diagnosed clinically in patients with recent alcohol excess and a short history of jaundice (less than 3 months), in the absence of other causes of liver failure. Characteristically the serum aspartate aminotransferase (AST): serum alanine transaminase (ALT) ratio is >2:1 although an AST >500 IU/L or an ALT >300 IU/L should prompt consideration of an alternative diagnosis.

For those with severe AH (Maddrey's Discriminant Function >32) mortality remains high – approximately 56% at 1 year in a recent trial including more than 1000 patients;[18] many of these patients have underlying cirrhosis. Liver biopsy for histological confirmation of AH is considered for patients with severe AH as these patients may be treated with corticosteroids, which are associated with an increased number of infections;[18] as such, it is desirable to limit corticosteroids only to those who may benefit.

Steroids or pentoxifylline?

Historically, patients with AH and a poor prognostic score (Maddrey's Discriminant Function >32; Glasgow Alcoholic Hepatitis Score ≥9) have been treated with corticosteroids. More recently, pentoxifylline was suggested as an alternative or additive treatment. Both were shown to reduce short term mortality in severe AH in a network meta-analysis.[19]

The Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) trial was a large multicentre, double blind, randomised trial designed to evaluate the effect of treatment with prednisolone or pentoxifylline or both compared to placebo. It was designed to settle the controversy around steroid treatment. 1053 patients were included in the final analysis. The STOPAH trial found that pentoxifylline did not improve survival in patients with AH and that prednisolone was associated with a reduction in 28-day mortality that did not reach significance. There was no improvement in mortality at 90 days or 1 year. However, in a secondary analysis adjusting for baseline determinants of prognosis, prednisolone had a significant survival benefit at 28 days. A higher rate of infection was seen in patients treated with prednisolone, but the mortality attributed to infection did not vary between those who did and did not receive steroids.[18]

A recent meta-analysis, subsequent to STOPAH, found that corticosteroids reduced risk of death at 28 days but not at 6 months.[20] Consequently, clinicians continue to use steroids in the treatment of AH in patients with a poor prognostic score. Other treatments (for example, N-acetylcysteine, obeticholic acid and interleukin-22) are currently undergoing evaluation. We would advise consulting a specialist before starting steroids in a patient with AH.

Infection

Patients with AH who show evidence of infection have a lower survival at 6 months.[21] Infection accounted for 24% of the deaths in the STOPAH trial.[18] Recently, infection has been found to be an independent risk factor for developing acute on chronic liver failure (ACLF) during the medical management of patients with AH. The presence of ACLF significantly increased mortality in this cohort.[22] We would encourage prompt treatment of suspected infection in patients with AH.

Nutrition

There has long been an awareness of the importance of good nutrition in patients with decompensated cirrhosis.[16] Numerous randomised controlled trials report that enteral and parenteral nutrition reduce mortality in AH and cirrhosis compared to no intervention. However, when looked at systematically, these trials were judged at high or unclear risk of bias.[23] Our view is that enteral nutrition (oral or nasogastric) is low risk when managed by appropriately trained professionals. Given the potential benefit of nutritional therapy in these high-risk patients, we would encourage early referral of patients with AH and cirrhosis to dietetic services.

Transplantation

Transplantation in AH has proved controversial.[24] Patients with severe AH who are failing to respond to steroids can be identified by the Lille score calculated at day seven. If a patient's Lille score is >0.45, 6-month survival is estimated at 25%, compared to 85% survival for a Lille score of <0.45.[25] Mathurin *et al* selected patients with AH failing to respond to medical therapy from seven French and Belgian centres using strict criteria (no previous AH, supportive family, no severe co-morbidities, commitment to alcohol abstinence) for early transplant and compared them to matched controls. Less than 2% of patients met their criteria. Twenty six patients were transplanted with a 6-month survival of 77.8% compared to 23.8% in the control group. Three resumed alcohol intake at 720, 740 and 1,140 days post-transplant.[26]

There is increasing international experience in, and acceptance of, early liver transplant in carefully selected patients with AH as a first presentation of ARLD.[24,26] The UK pilot programme began in 2014, aiming to recruit 20 patients. Two of the seven UK transplant centres declined to participate.[27] The pilot programme did not meet recruitment targets and was closed.

End stage ARLD

In contrast to AH, liver transplant in end-stage ARLD is widely accepted. ARLD is currently the most common indication for liver transplant, accounting for approximately 30% of transplants in the UK.[28] Abstinence from alcohol is required, traditionally for 6 months[29] and many centres send serum alcohol levels routinely during patient contacts. Urinary ethyl glucuronide is an alternative marker of alcohol consumption that is detectable for up to 5 days after alcohol ingestion.

Post-transplant, the 5-year risk-adjusted survival after liver transplant for ARLD is 84.4%. This is comparable to other indications for liver transplant.[28] Alcohol use post-transplant is independent of the indication for the liver transplant.[30] In common with other aetiologies of end stage liver disease, significant milestones in a patient's clinical course (development of hepatic encephalopathy, development of ascites, first decompensation) and a qualifying United Kingdom Model for End-Stage Liver Disease score should prompt consideration of referral to a transplant centre for patients with ARLD who have shown a commitment to alcohol abstinence.

Conclusion

Mortality from ARLD is rising in the UK. In contrast, deaths from cirrhosis are falling in other European countries. Historically, there are areas of practice that we can improve. Management decisions during the first 24 hours are critical. We believe that simple evidence-based interventions, for example adoption of the Decompensated Cirrhosis Care Bundle, can improve mortality from these common, yet deadly, conditions. ■

Supplementary material

Additional supplementary material may be found in the online version of this article at www.clinmed.rcpjournal.org:

S1 – BSG – BASL Decompensated Cirrhosis Care Bundle – First 24 Hours.[5] www.bsg.org.uk/resource/bsg-basl-decompensated-cirrhosis-care-bundle.html [Accessed 22 August 2018].

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