Mistakes in alcoholic liver disease and how to avoid them

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Alcohol consumption is the most prevalent aetiology for liver cirrhosis in Europe and the third leading risk factor for overall mortality. In fact, alcoholic liver cirrhosis accounts for almost half a million deaths a year worldwide, corresponding to 50% of all cases of cirrhosis, according to the World Health Organization (WHO). Alcoholic liver disease (ALD) is multifaceted, with several cofactors influencing its progression. Patients abusing alcohol can simultaneously have viral hepatitis B or C, or a genetic disease, such as alpha-1 antitrypsin deficiency or haemochromatosis.

Alcohol consumption is usually assessed in pure grams per day and has a direct relationship with liver damage. Daily alcohol consumption of >30g for men and >20g for women is considered the cut-off volume at which there is a risk of developing alcohol-related liver disease. Besides volume, the pattern of consumption is also a significant factor, with heavy episodic drinking (HED) defined as an intake of 60g or more of pure alcohol on at least one occasion in the past 30 days. Regarding HED, there is scarce information on the threshold to be applied to this pattern of drinking. Although the relationship between alcohol consumption and ALD is well defined, it must be acknowledged that severe disease only develops in a fraction of those who consume excessive amounts of alcohol. Nonetheless, the disease course is very much influenced by the pattern of drinking, with periods of abstinence or heavy drinking clearly altering its progression.

ALD can present in different stages, ranging from steatosis to more severe disease, such as the clinical syndrome of alcoholic hepatitis, or decompensated liver cirrhosis, which is sometimes complicated by liver cancer. In the setting of alcoholic hepatitis, several scores, such as the Maddrey discriminant function, Glasgow alcoholic hepatitis score (GASH) and ABIC, may be used to evaluate disease severity, predict short-term survival, and decide on the need for specific treatment. Later on, the Lille score, which includes the reduction in serum bilirubin levels at day 7, evaluates the response to prednisolone after one week, in order to decide whether to continue or stop treatment. Despite being a frequent disease, the different aspects of ALD mean that its management still poses many difficulties and pitfalls. In this article we discuss frequent mistakes in ALD, based on the current guidelines and some paradigmatic real-life cases.

Mistake 1 Not recognizing alcoholic hepatitis in a patient who has multiple chronic liver disease aetiologies

A male patient with longstanding cirrhosis and documented chronic hepatitis C (non-viraemic after treatment one year before) is admitted to the emergency department with haematemesis but no haemodynamic compromise. As anticipated, oesophageal variceal bleeding is confirmed and successfully managed by band ligation. A straightforward case, right? During rounds the next morning you pay a little more attention to the patient. He is presenting with jaundice (total bilirubin 5.4 mg/dL) and mildly elevated transaminase levels (with an AST:ALT ratio >2), is a little more thrombocytopenic than you would expect (45,000/mcL) and leukocytosis is slightly more pronounced than anticipated (12.4 x10⁹/ cell/L). Over the days that follow, his bilirubin level goes up (19 mg/dL) and his INR and creatinine levels also worsen. The patients is now in grade III-IV hepatic encephalopathy. Now you start to wonder: has anything gone wrong? Why is he in acute-on-chronic liver failure (ACLF)? Is he infected? What about alcohol? In fact, his previous registries state he misused alcohol and was referred to a rehabilitation program a couple of years earlier. On admission, the patient denied he was misusing alcohol, but his wife confirms he had gone back to drinking heavily. So is this alcoholic hepatitis?

Alcoholic hepatitis is a clinical syndrome. Most of its clinical features are present in this patient (jaundice, AST:ALT elevation 2-5 times the upper limit of normal (ULN) in a ratio of 2:1 and an inflammatory response syndrome). The clinical picture frequently worsens with progression to ACLF and is associated with complications such as gastrointestinal bleeding, encephalopathy and hepatorenal syndrome. In fact, the presenting symptom may well be one of these complications. Histologically-proven severe alcoholic hepatitis is estimated to comprise 6% of patients with decompensated cirrhosis and up to a quarter of ACLF patients. Diagnosis based on classic clinical criteria such as those mentioned above were found to misdiagnose alcoholic hepatitis in up to 25% of cases, thus addressing the question of alcohol consumption is essential.

Questionnaires such as CAGE and AUDIT (alcohol use disorders inventory test), or the shorter version AUDIT-C, will help identify harmful and hazardous drinkers with good sensitivity and specificity. A thorough anamnesis will help tie up the loose ends, but as discussed later, liver biopsy can...
A diagnosis of cirrhosis was unclear and elastography was performed using FibroScan® (ECHOSENS, France). It revealed a coefficient of 47 kPa, which is an elevated value that is sometimes prove valuable in confirming alcoholic hepatitis.\(^2\) In summary, always think alcohol otherwise you will miss a few cases, and as demonstrated further on, you will miss the chance to implement specific therapies that have a direct impact on patient survival.

**Mistake 2 Interpreting elevated liver stiffness values and thrombocytopenia as cirrhosis/severe fibrosis in patients who are actively drinking alcohol**

A few years ago, a 38-year-old female was admitted with an altered mental status in the setting of excessive alcoholic intake. She had no previous history of liver disease but stated a prolonged 80g/day alcohol consumption pattern. In the setting of macrocytosis, mildly elevated transaminase levels (AST>ALT) and elevated total bilirubin levels, this drinking pattern supported the diagnosis of alcoholic hepatitis (Maddrey score of 23). The patient also presented with mild thrombocytopenia and equivocal abdominal ultrasound findings (diffuse hyperechogenicity, hepatomegaly and mild ascites), but no oesophageal varices nor other stigmata of portal hypertension. A diagnosis of cirrhosis was unclear and elastography was performed using FibroScan® (ECHOSENS, France). It revealed a coefficient of 47 kPa, which is an elevated value that is strongly suggestive of the presence of cirrhosis. However, after discharge and several months of sustained abstinence, liver stiffness values decreased to 8 kPa and no stigmata of cirrhosis were identifiable. In addition, the platelet count, which was low at admission (102,000/mcL), normalized after 3 weeks of abstinence.

Alcohol intake has been associated with elevated liver stiffness, with studies showing an average decline in liver stiffness values of 10% with abstinence.\(^2\) Thus, the presence of stiffness may be overestimated by liver stiffness values by as much as 27%.\(^2\) Recently, however, Thiele et al. published the results of a prospective study comparing two elastography techniques (FibroScan® and Aixplorer® [SuperSonic Imagine, France]) for assessment of alcohol-induced liver fibrosis and cirrhosis.\(^2\) Both techniques showed high accuracy (>0.92), with high negative predicted values (NPVs) and modest positive predicted values (PPVs) using 9.6 kPa and 10.2 kPa as the cut-off values for diagnosing significant fibrosis, and 19.7 kPa and 16.4 kPa for diagnosing cirrhosis. In this study, active alcohol consumption did not influence liver stiffness. On the other hand, significant inflammation and congestion, as is found in alcoholic hepatitis, may indeed explain the elevated liver stiffness in alcoholic patients.\(^2\) Fernandez et al. demonstrated a positive correlation between AST and liver stiffness levels, which may be more pronounced in advanced stages of fibrosis.\(^2\) Another probable consequence of this inflammatory milieu that sets in the alcoholic hepatitis liver is an increase in sinusoidal resistance and flow, resulting in portal hypertension even in the absence of cirrhosis.\(^2\) This may be explained by both functional modifications, driven by TNF overproduction, and architectural changes, such as sinusoidal capillarization and perisinusoidal fibrosis.\(^2\)

Another well-known toxic effect of alcohol is direct (but reversible) myelosuppression, probably due to the effect of accumulated reactive aldehydes on hematopoietic stem cells, leading to ineffective megakaryopoiesis, which in conjunction with a reduced platelet lifespan, results in worsening thrombocytopenia.\(^2\) Summing up, liver stiffness values and thrombocytopenia should always be interpreted carefully in the setting of active alcohol intake, especially if they indicate the possibility of significant fibrosis/cirrhosis. It is thus always best to repeat measurements after abstinence and putative inflammation decrease.

**Mistake 3 Interpreting elevated iron parameters as a possible haemochromatosis, in patients actively consuming alcohol**

During my first year of residency, we received a patient who flew from Angola for evaluation of hepatic encephalopathy. He was abusing alcohol, with obvious cirrhosis manifested with ascites and grade II hepatic encephalopathy. He also had a transferrin saturation of 55% and a ferritin level of 352 ng/ml, so I hypothesised he would have haemochromatosis alongside alcoholic cirrhosis. Obviously I was wrong, and the not-so-inexpensive HFE gene test produced a negative result.

The discovery of the genetic base of haemochromatosis has brought some clarification to the once confusing high prevalence of siderosis in ALD.\(^2\) Iron metabolism markers, such as ferritin and transferrin saturation, have been shown to be elevated in one to two thirds of ALD patients.\(^2\) This reflects an iron overload state that may be, at least in part, explained by negative regulation of hepcidin.\(^2\) Actually, ALD patients heterozygous for the C282Y mutation in the HFE gene failed to show increased hepatic iron stores when compared with ALD patients homozygous for the wild-type allele.\(^2\) The same is not so clear for patients carrying the H63D mutation.\(^2\) Conversely, the finding that haemochromatosis patients are often excessive drinkers is explained by the fact that alcohol acts a potent co-factor in the development of cirrhosis. In fact, it has been shown in a series of C282Y homozygous haemochromatosis patients that 7.1% of those consuming >60g alcohol/day had cirrhosis compared with 61% of those drinking >60g alcohol/day.\(^2\) Thus, although we can state that there is an association between haemochromatosis and alcohol abuse, this is not cause and effect but rather an aggregation of co-factors in advanced liver disease patients.

From a clinical point of view it is valuable to remember that the magnitude of ferritin elevation is considerably lower in ALD patients (10–500 µg/L) when compared with homozygous haemochromatosis patients (500–10,000 µg/L).\(^2\) The same is true for transferrin saturation: ALD (20–60%) and homozygous haemochromatosis (60–100%).\(^2\) Even if we take this difference into consideration, one may find only a very modest PPV for cut-offs values such as transferrin...
Mistake 4 Not performing a liver biopsy when other aetiologies (known or unknown) may be partly responsible for the clinical picture

In 2016, a 45-year-old African male with a recent diagnosis of chronic hepatitis B was admitted to our hospital. He had a history of abusive alcohol consumption that had been aggravated the previous week, following a generous celebration of his team’s soccer championship victory. Clinical and laboratory stigmata of alcohol consumption were present (parotid gland hypertrophy, palmar erythema, macrocytosis, aminotransferase levels twice the ULN with an AST:ALT ratio of 2:1 and gamma-glutamyltransferase [GGT] elevation), although there was no systemic inflammatory response syndrome (SIRS) and total bilirubin levels were 9.5mg/dL. These features shed doubt on whether alcohol consumption was the key player in the patient’s presentation or other features such as HBV could be responsible. A liver biopsy revealed aspects of fibrosing cholestatic hepatitis, with no aspects of alcoholic steatohepatitis, and as the HBV DNA level was 3,466IU/mL the patient was started on tenofovir, with improvement.

In recent years many noninvasive techniques, some of which have already been addressed, have conquered a space in clinical management, relinquishing liver biopsy for somewhat equivocal cases. In the setting of ALD, namely alcoholic hepatitis, guidelines advocate liver biopsy for severe cases or whenever a concurrent aetiology may contribute to the clinical picture. Figure 1 shows the classic histopathology findings in alcoholic hepatitis. However, availability of the transjugular route is often necessary, since the majority of patients with severe alcoholic hepatitis have evidence of severe coagulopathy. Reviewing the cohorts of ALD patients submitted for liver biopsy, it was found that 5–25% of those patients may not show histological features of ALD, especially if clinical doubt was stated, but almost none revealed a different diagnosis. Thus, liver biopsy will be valuable in confirming alcoholic hepatitis in three quarters of patients who have clinically doubtful features. As for the rest, it will mostly ensure the need for further diagnostic measures, though in some cases it may reveal a course-changing diagnosis.

In one of the studies, in which liver biopsy was done only in patients with a Maddrey’s Discriminant Function (MDF) >32, it was found that 25% had just cirrhosis with no evidence of alcoholic hepatitis. This distinction may be important when deciding on whether to treat with corticosteroids or whenever data from clinical trials is being interpreted. Furthermore, please note that liver biopsy has prognostic significance. The Alcoholic Hepatitis Histologic Score (AHHS) takes into account the degree of fibrosis, neutrophil infiltration, type of bilirubinostasis and presence of megamitochondria, and is independently correlated with 90-day mortality. Patients with low AHHS scores (<3 points) have 3% mortality in contrast to patients with high scores (>6 points) who have 51% mortality. So, keep in mind that you might need to think outside the box and, when in doubt, remember that liver biopsy (frequently via a transjugular route) is possibly a good choice.

Mistake 5 Considering a patient with alcoholic hepatitis ineligible for corticosteroid therapy based on the diagnosis of infection at initial evaluation

A 52-year-old patient was admitted in 2016 with a clear-cut picture of alcoholic hepatitis—it was his first manifestation of liver disease. He had an MDF of 92, a Glasgow score of 9, and a MELD score of 22. An initial work-up was done to screen for infection, and a pulmonary infection was diagnosed on the basis of the chest film and a positive pneumococcal antigen urine test. At this point it was decided not to start corticosteroids because of the ongoing infection. In the following days there was a marked worsening of all liver function parameters. The days went by and despite apparent infection control, corticosteroids were consistently put aside because of the fear of uncontrolled sepsis. By then bilirubin levels had reached 25mg/dl and encephalopathy worsened to grade III-IV. The patient was discussed again with the complete hepatology team and prednisolone was started at a dose of 40mg/day. Marked improvement ensued, and the Lille score evaluated at 1 week was 0.15, so treatment was continued at the same dose for a total of 4 weeks, with tapering for the following 2 weeks. The patient was discharged with a bilirubin level of 2mg/dl.

Corticosteroid therapy remains the best evidence-based therapy for severe alcoholic hepatitis, with multiple trials showing that prednisolone reduces 28-day mortality. Patients with the most severe alcoholic hepatitis, as set by a high MDF (>32 points) or concomitant hepatic encephalopathy, are the ones who benefit most from corticosteroids. This group can be further stratified into responders by a Lille model score <0.45 by day 7. The recent STOPAH trial showed that corticosteroids do not seem to influence medium-term (90 day) and long-term (1 year) mortality. That said, besides organ support and general measures, corticosteroid therapy is currently the only truly effective therapy that can be offered to patients with severe alcoholic hepatitis, as pentoxifyline failed to demonstrate any improvement in patients’ outcomes. The major setback is obviously the increased risk of infection and worsening/lack of efficacy in the setting of concomitant complications, such as gastrointestinal haemorrhage and hepatic encephalopathy. Thus, when evaluating a candidate for corticosteroid treatment, a complete and thorough sepsis work-up should be undertaken. If the sepsis work-up is negative then therapy should not be postponed based on elevated inflammatory markers, since in alcoholic hepatitis they are a sign of SIRS and not always occult infection. A different issue is when we face an active infection, which used to deter us from using corticosteroids. However, Louvet et al. elegantly demonstrated that patients whose infection is diagnosed on initial evaluation and successively controlled by appropriate antibiotic therapy may be given corticosteroids without increasing mortality. Interestingly, when infection develops during corticosteroid therapy, it is associated with a higher mortality, but this is only significant in the group of responders. In conclusion, a thorough sepsis work-up should be performed and treatment with corticosteroids given to those who are eligible (MDF >32 points or concomitant hepatic encephalopathy).

Mistake 6 Failure to address alcohol consumption and subsequent patient enrolment in an alcohol rehabilitation program

In 2002, a 38-year-old male patient was admitted with clinical evidence of severe alcoholic hepatitis. The patient had started drinking at the age of 14, and had since been drinking about 200g of alcohol a day, with frequent episodes of binge drinking. The patient was unemployed, divorced and had little social support. Two years before, he experienced a similar episode that resolved with corticosteroid treatment and abstinence.
However, abstinence was not sustained and he relapsed with heavy drinking, which was probably the cause of the present episode. Again, the patient recovered with supportive treatment and abstinence. This time he was transferred to an alcohol rehabilitation clinic where he remained for 4 weeks. This course of action was very effective; the patient managed to become abstinent and remains so at present. He also got a job, got married, gained an extra 10 kilos in weight, and currently has no clinical evidence of cirrhosis, apart from an irregularity of the liver margins and heterogeneity visible on ultrasound. His elastography values vary from 7.2–9.9 Kpa.

In this case, the mistake was not to do a proper referral to an alcohol rehabilitation clinic at the time of the first episode. However, alcoholic patients often refuse to be referred, claiming that they will be able to maintain abstinence by themselves. The lack of admission that they need help is itself a bad prognostic sign, particularly if there is evidence of dependence and not just excessive consumption. This is one of the reasons why it is so important to address alcohol consumption using standardized units for consumption estimation and questionnaires like CAGE and AUDIT to assess abuse and dependence. An active effort to address consumption should always be undertaken whenever a diagnosis of ALD is made, independently of whether it is a simple steatosis in the primary care setting, compensated cirrhosis in an outpatient clinic or severe alcoholic hepatitis in a medical ward or ICU. Enforcing abstinence is the next step. Abstinence, as stated in most guidelines, is the major therapeutic goal for patients with ALD because it produces a reduction of morbidity and mortality across the entire disease spectrum. Although medical therapy in the setting of alcohol dependence should always be undertaken by an experienced multidisciplinary team, some evidence supports the effect of brief motivational interventions, within both the primary care and hospital setting, on reducing alcohol consumption. This motivational intervention is in the hands of the patient’s physician and should be followed whenever a patient shows insight and willingness, by appropriate referral to an accomplished alcohol rehabilitation program.

### Mistake 7

**Withholding transplant solely based on absence of prolonged abstinence**

A few years ago, a 59-year-old male patient with cirrhosis who had a longstanding follow-up at another outpatient clinic was admitted for spontaneous bacterial peritonitis, hepatic encephalopathy and refractory ascites. The cirrhosis had been classified as cryptogenic after a thorough investigation, although the aetiologies suspected were somewhat difficult to prove. In this case the suspects were alcohol (he stated he had been a ‘bon vivant’ at the Portuguese colony of Mozambique, but admitted only moderate active alcohol consumption) and nonalcoholic steatohepatitis (NASH; thanks to long-standing and poorly controlled diabetes and metabolic syndrome). Nevertheless, his liver function was rapidly deteriorating as demonstrated by a fast rising MELD score (from 13 to 21 points). Despite our uncertainties about what caused the cirrhosis and whether there would be ongoing alcohol misuse, he was referred for hepatic transplantation. The process went smoothly. As for the aetiology, well... we later got the histopathology report on the explant confirming the patient had hepatic schistosomiasis.

In previous decades, a 6-month period of abstinence has been proposed and widely implemented as a precondition for the standard of care in most solid organ transplantation programs. This period of prolonged abstinence is based on the concept that the longer the patient is consuming alcohol, the lower the risk of relapse after transplantation. In fact, it has been estimated that the post-transplant risk of relapse decreases by 5% for each month of pre-transplant abstinence. Furthermore, for some patients the recovery of liver function after the 6-month abstinence period is so good that they no longer need a liver transplant. Although the 6-month rule is widely used, some groups have challenged it, demonstrating good or at least equivalent outcomes for patients who have not been abstinent for 6 months prior to transplantation. Moreover, it seems that alcohol use in post-transplant patients is independent of liver disease aetiology and in some cohorts did not affect survival. In addition, and although there is some evidence that a shorter abstinence period (i.e. <6 months) is associated with increased relapse rates, other factors such as social support, depression and family history also play a significant role.

What is more, it appears obvious that the greater the severity of liver decompensation (i.e. as assessed by the MELD score) the lower the odds of having a prolonged abstinence period (or reaching one) and, therefore, of offering that patient a chance for survival via liver transplantation. This point led to international guidelines published in 2016 dropping the *sine qua non* aspect of the 6-month rule and enforcing the need for early pre-transplant and continuous post-transplant multidisciplinary alcohol treatment. Nevertheless, most national guidelines and transplant centres’ praxis are still far from incorporating this changes. So this is the take-home message: abstinence is greatly desirable and there is no doubt that the longer the patient is abstinent the better, in some cases even reverting the need for transplantation, but the risk for alcohol misuse after transplantation is multifactorial and its impact on survival unclear. While thinking about the suitability of a patient with ALD for liver transplantation, please be advised that some patients may not have enough time on their side to achieve and maintain abstinence.

### References

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