



# In search of a roadmap towards improving care of patients with cirrhosis and ascites, could a platform trial design transform clinical research?

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The authors of “*Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases*” are to be congratulated on their exhaustive assessment of the data published on patients with cirrhosis and ascites and their guidelines represent a pragmatic, evidence-based, common-sense approach (1). This was evidently a considerable effort. A commentary of the whole document represents too broad a challenge for me, and I have thus focused my article on four areas, two from the guidelines, infection and fluid resuscitation, one that was not but I believe we ignore at our cost, secondary prevention attempts at alcohol cessation, and finally my hope for the future of clinical research in decompensated cirrhosis.

Infections in patients hospitalized with decompensated cirrhosis are a major challenge with a high mortality and correctly these guidelines support early antibiotic prescription in suspected infection as mortality risk increases in septic patients if there is delayed appropriate antibiotic therapy. However, given this increased risk of infections, clinicians also prescribe broad-spectrum antibiotics to cirrhosis patients without infection to prevent hospital-acquired infections (HAI), as we observed in the Albumin to Prevent Infection in Chronic Liver Failure (ATTIRE) trial with 50% receiving antibiotics at trial entry and only

27% diagnosed with infection (2). Antibiotic overuse is a major driver of antimicrobial resistance (AMR) which represents a truly global threat to overall health-care (3) and, compared with other chronic diseases, patients with cirrhosis have increased hospitalizations, longer stays, more invasive procedures, and readmissions, all increasing AMR risk. This has led to high levels of resistance in cirrhosis patients in certain geographical locations which is reflected in the recommendation of empirical use of carbapenems or daptomycin, antibiotics of last resort, in these areas. This emphasises the need to reduce unnecessary antibiotic prescriptions to prevent these life-saving drugs becoming ineffective. Further analyses of the ATTIRE patients not considered by their clinicians to have an infection revealed no differences in subsequent HAI comparing antibiotic treated to nonantibiotic treated (approximately 20% for both) (4,5). Twenty-eight-day mortality was significantly higher in antibiotic-treated patients, likely reflecting their increased disease severity and when we matched groups using propensity scoring, there were no differences in HAI or mortality. The patients prescribed antibiotics in the absence of infection were more unwell than those not, and this action was no doubt taken to prevent infections in patients considered at high risk of sepsis. However, there was no reduction in HAI, nor renal dysfunction and no impact on survival. These data support a policy of prompt

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de-escalation or discontinuation of empirical antibiotics guided by culture sensitivities at 24–48 hours after commencement if no infection and an improving patient. However, these guidelines, consistent with all others, put the focus on early aggressive antibiotic prescribing and use of broader spectrum agents if patients are not responding to treatment. In an era of worsening AMR, with a figure of 35% incidence quoted in certain areas (5), there is also a responsibility to include recommendations on appropriate antibiotic de-escalation or discontinuation in all cirrhosis guidelines, which are sadly lacking.

The section on acute kidney injury and hepatorenal syndrome (HRS) is particularly good but was written before the results of the CONFIRM (6) and ATTIRE (2) trials had been published in full and before terlipressin had been approved for use in the United States by the Food and Drug Administration. The CONFIRM trial with 300 participants was the largest randomized, placebo-controlled trial to date that has investigated the efficacy of terlipressin in reversing HRS. It showed that the percentage of patients who had HRS reversal was approximately twice as high in those who received terlipressin than among those who received placebo, which was statistically significant. ATTIRE demonstrated no significant differences in the composite primary end point (infection, renal failure, or death) between targeted albumin infusions to maintain a serum level >30 g/L and standard care, with 777 patients randomised, despite the albumin group patients receiving a median 10 times as much albumin as standard care and overall, nearly 3 times as much. The overall lack of efficacy to prevent renal dysfunction and mortality in ATTIRE alongside the increased adverse events that were also seen in both trials, support the need for a re-appraisal of current albumin fluid resuscitation regimens. The recommended dosing schedules for albumin infusions have not changed in 20 years and increasingly studies identify cardiac dysfunction in advanced cirrhosis. The future use of non-invasive methods to assess fluid volume and cardiac function, such as point-of-care ultrasonography (POCUS) assisted physical examination prior to intravenous fluid therapy may be able to guide precision fluid resuscitation that could lead to improved outcomes.

Similar to other cirrhosis and ascites guidelines there is no comment on alcohol use disorder. There are other guidance documents, but perhaps we should consider an integrated approach. Alcohol induced cirrhosis remains the major cause of decompensated cirrhosis in most countries. Continued alcohol consumption is the principal trigger

that takes a patient from stable cirrhosis to decompensation and dramatically shortens life expectancy. Conversely, unlike most other treatments mentioned in all cirrhosis guidelines, except for liver transplantation, cessation has the potential to dramatically improve outcomes. Within the UK, the majority of alcohol services provide extended brief interventions to patients admitted to hospital, but at discharge, it is the patient's responsibility to engage in community psycho-social services. Yet very few actually do so because they remain unwell or cannot afford to travel to the treatment centre and many lead chaotic lives. Even in a randomised controlled trial in which patients were offered an alcohol appointment, if this was delayed >48 hours from discharge, only 28% attended (7). There is evidence to support addition of pharmacotherapy for 6 months e.g., acamprosate yet none of these are licensed to aid alcohol cessation in cirrhosis patients within the UK, as they are metabolised by the liver. Intuitively cirrhosis patients have the most to gain from abstinence as even modest alcohol consumption is extremely harmful, however they have not been included in the majority of trials. Therefore, most alcohol-induced cirrhosis patients will not receive ongoing psycho-social support or adjuvant pharmacotherapy, thus missing a precious opportunity to help these people. Sadly, the STOPAH trial reported 1-year rates of complete abstinence following hospital admission with alcoholic hepatitis of only 37% (8) and hospital admissions and death rates secondary to alcohol induced liver cirrhosis continue to rise.

It has been my experience that the separation of alcohol use disorder treatment provision from prescribing diuretics, beta-blockers, antibiotics and albumin represents a common mindset amongst physicians. The relative lack of efficacy for many of the treatments described in this excellent paper compared to long-term alcohol cessation would suggest this approach is unwise. Our inclination to medicalize cirrhosis results, in part, from a lack of training but also lack of interest in addiction treatment, and perhaps the continued debate around the use of prednisolone in alcoholic hepatitis rather than commenting on the disappointing cessation rates reflects this. However, a partnership approach with other health care professionals offers an opportunity to shift the balance to "treating the cause" rather than the complications and to co-develop clinical trials to improve outcomes. Future cirrhosis guideline writing committees may wish to include alcohol use disorder specialists to encourage joint working.

To conclude, many sections of these guidelines conclude

correctly with a need for clinical trials to provide better evidence. Yet trials in advanced cirrhosis are enormously challenging, as we found with ATTIRE. In the UK (approximately 60 million people), liver disease is common with an estimated 60,000 people with cirrhosis and in England and Wales in 2020, there were 9,666 liver deaths with a further 5,445 deaths from primary liver cancer (<https://fingertips.phe.org.uk/profile/liver-disease>). Nevertheless, we have found recruitment to 3 national trials in cirrhosis a substantial logistical challenge [ASEPTIC (9), BOPPP (ClinicalTrials.gov Identifier: NCT03776955) and CALIBRE (10)]. Extremely large trials, such as those that might be required for a non-inferiority study to examine shorter courses of antibiotics, would be even more difficult. This is compounded by the low socio-economic status and frequent alcohol use disorder seen in our patients, which are groups of society rarely included in clinical trials. A further difficulty is that many of the pharmacotherapies described in these guidelines, apart from terlipressin, are off-patient, and so there is no incentive for industry to support this research. My great hope for the future would be to emulate the fantastic multi-disciplinary approach during the COVID pandemic that led to the UK RECOVERY Platform (<https://www.recoverytrial.net/>). If this could be achieved in partnership across several countries, or a continent, there would be a sufficient patient population to examine the efficacy of potential beneficial/harmful therapies in patients with ascites, such as non-selective beta-blockers, proton pump inhibitors, statins or further trials of albumin use, perhaps using a multi-stage drop-the-losers design for multi-arm clinical trials design (11). This would require substantial investment and teamwork (and Brexit makes it harder for the UK's involvement in Europe) but such a transformative approach might lead to the next guidelines having a better evidence-based clinical practice recommendations to research recommendations ratio and lead to improved clinical care in these very unwell patients.

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