3. In patients with cirrhosis, we suggest avoiding PPI unless there is a clear indication, such as symptomatic gastroesophageal reflux or healing of erosive esophagitis or an ulcer, because PPI use increases the risk of infection (very low quality, conditional recommendation).

Key concept statements

1. Nonselective beta-blockers (NSBB) may decrease bacterial translocation, but patients with ACLF have difficulty tolerating clinically relevant doses.
2. Rifaximin may prevent complications of cirrhosis other than HE.
3. Concentrating or avoiding IV medications that require large sodium loads can improve volume status in patients with ACLF.

Summary of evidence

SBP prophylaxis. It is clear that secondary SBP prophylaxis decreases the risk of recurrent SBP and therefore improves outcomes (108). Daily treatment is needed to decrease the rate of MDR infections. Although most data document the utility of daily norfloxacin, in areas where this is not available, daily ciprofloxacin or trimethoprim-sulfamethoxazole may be used. No study has ever documented superiority of one regimen over another. Cohort studies with subgroup analysis of different types of SBP prophylaxis and randomized trials in the Middle East have shown that rifaximin may be at least as effective as other antibiotics used for SBP prophylaxis and possibly superior, but bacterial resistance patterns may be different in those countries (109,110). Once a resistant infection occurs in a patient on SBP prophylaxis, there is no guidance on how to proceed with SBP prophylaxis. Although the risk-benefit ratio of secondary SBP prophylaxis is clear, recent data have shown that patients admitted to the hospital on primary prophylaxis have a worse outcome than admitted patients taking secondary SBP prophylaxis (56). Of note, primary prophylaxis was studied and recommended in an era when transplant occurred at a lower MELD in patients with progressive liver disease from hepatitis C virus, and now that patients wait longer for transplant, we may need to re-evaluate the indications and drugs used for primary SBP prophylaxis.

PPI therapy. PPIs have been shown to increase the rate of infections in patients with cirrhosis (111–113). Because infections are the number one cause of ACLF in North America and Europe, it is imperative to decrease the rate of infections in our patients with cirrhosis. Because PPIs impair the oxidative burst of neutrophils, they further impair immune function in patients with cirrhosis. PPIs have a major but reversible impact on the gut microbiome, which is also associated with complications in patients with cirrhosis (17,114). As a result, it is important to only treat patients with PPIs who have an indication that cannot be adequately treated with other types of acid blockade and discontinue or change them once healing has been achieved. For example, PPIs are needed to heal gastrointestinal ulcers and erosive esophagitis and treat gastroesophageal reflux not responsive to H2 blockers (115).

NSBB. In a nonrandomized study, patients with ACLF had a lower mortality if they were admitted on an NSBB than if they were not (116). In one randomized controlled trial (RCT), carvedilol improved 28-day but not 90-day transplant-free survival in admitted patients with ACLF compared with placebo (117). NSBB are clearly indicated for both primary and secondary variceal hemorrhage prophylaxis (118), and although they may decrease bacterial translocation, it is difficult in clinical practice for patients with ACLF to tolerate clinically meaningful doses of NSBB.

Statins. Statins have been shown to decrease the rate of hepatic fibrosis, hepatic decompensation, and mortality in patients with cirrhosis; every year of statin exposure cumulatively and independently decreased mortality in patients with CTP-A and -B cirrhosis (119–121). Although little is known about statins in ACLF in humans, in a recent rat model study of lipopolysaccharide-induced ACLF, pretreatment with simvastatin reduced portal pressures, inflammation, and oxidation and led to improved survival (122). However, one must be concerned about dose-related hepatotoxicity of statins in patients with ACLF, given the recent randomized study of patients with CTP-B and -C cirrhosis that showed an increase in alanine aminotransferase (ALT) in patients randomized to 40 mg per day of simvastatin that was not seen in patients randomized to 20 mg per day or placebo (123).

Rifaximin. Rifaximin decreases the rate of overt HE recurrence. Rifaximin has also been studied for SBP prophylaxis compared with placebo and oral quinolone therapy (110). In a meta-analysis, rifaximin was superior to no antibiotics, but equivalent to an oral quinolone for SBP prophylaxis, although most studies included were small, not randomized, or did not allow rifaximin for treatment of HE (110).

Sodium content of IV medications. When choosing antibiotics in patients with a history of ascites, one should also consider the sodium content. At a minimum, always ask pharmacy to concentrate all IV medications, whenever possible or administered in 5% dextrose instead, whenever feasible.

NONINFECTIOUS PRECIPITATING FACTORS

Alcohol-associated hepatitis

Recommendations

1. In patients with severe alcohol-associated hepatitis (Maddrey discriminant function [MDF] ≥ 32; MELD score > 20) in the absence of contraindications, we recommend the use of prednisolone or prednisone (40 mg/d) orally to improve 28-day mortality (moderate quality, strong recommendation).
2. In patients with severe alcohol-associated hepatitis (MDF ≥ 32; MELD score > 20), we suggest against the use of pentoxifylline to improve 28-day mortality (very low quality, conditional recommendation).

Key concept statements

1. AAH leads to ACLF as a result of a combination of a severe SIRS and sepsis.

Summary of evidence

AAH is a major cause of ACLF worldwide. Most patients with ACLF in the CLIF consortium study either had alcohol use, AAH, or infection as the precipitating event (36). Similar precipitating events were noted in a study from Asia (124). Thus, active alcohol use, AAH, and bacterial infections are most frequently associated with the development of ACLF (125). At this time, it is unclear whether alcohol-related ACLF is a specific form of alcohol-associated liver disease or represents a later stage of severe AAH. Nevertheless, it is important that AAH be optimally treated to reverse ACLF. In addition, the alcohol use disorder needs to be treated.