Targeted Temperature Management in ALF.

Recommendation. We suggest not routinely using induced moderate hypothermia (< 34°C) for critically ill ALF patients who are at risk of developing intracranial hypertension (Conditional recommendation, very low quality of evidence).

Rationale. Moderate hypothermia has been successful in decreasing ICP and has been reported to help to bridge to liver transplant in some uncontrolled studies (24–26). Its use in ALF remains controversial, as two studies have demonstrated both absence of benefit and harm (27, 28). A retrospective cohort study of ALF patients in the U.S. Acute Liver Failure Study Group with grade III or IV hepatic encephalopathy found that therapeutic hypothermia in ALF was not associated with increased bleeding or infections. Although young acetaminophen ALF patients may benefit, therapeutic hypothermia did not consistently affect 21-day survival (28). In a multicenter RCT (n = 46), patients with ALF, high-grade encephalopathy, and ICP monitoring were randomized to targeted temperature management groups of 34°C or 36°C (control) for a period of 72 hours. The primary outcome was a sustained elevation in ICP greater than 25 mm Hg. There were no significant differences between the groups in the primary outcome during the study period (35% vs 27%; p = 0.56) (RR, 1.31; 95% CI, 0.53–3.2). Furthermore, both groups had similar occurrence rate of adverse events and overall mortality (41% vs 46%; p = 0.75; RR, 0.89; 95% CI, 0.44–1.80; **Supplementary Table 3*c***, http://links.lww.com/CCM/H302). This study did not confirm an advantage of induced moderate hypothermia in patients with ALF (29).

Treatment of Hepatic Encephalopathy.

Recommendation. There was insufficient evidence to issue a recommendation on using lactulose, rifaximin, flumazenil, branch-chain amino acids, carnitine, zinc, probiotics, and L-ornithine L-aspartate (LOLA) in critically ill ALF patients with hyperammonemia.

Recommendation. We suggest using nonabsorbable disaccharides in critically ill ACLF patients with overt hepatic encephalopathy (Conditional recommendation, low quality of evidence).

Rationale. Nonabsorbable disaccharides (NADs) (i.e., lactulose, lactitol) are used as first-line agents for the treatment of hepatic encephalopathy. In a meta-analysis of 38 RCTs (n = 1,828), Gluud et al (14) found that NADs, compared with placebo/no intervention, reduce hepatic encephalopathy (24 RCTs [n = 1,487]; RR, 0.58; 95% CI, 0.5–0.69) and serious liver-related adverse events such as liver failure, variceal bleeding, serious infections, spontaneous bacterial peritonitis (SBP), and hepatorenal syndrome (24 RCTs [n = 1,487]; RR, 0.47; 95% CI, 0.36–0.6). Treatment was also associated with a reduction in mortality in patients with overt encephalopathy (RR, 0.36; 95% CI, 0.14–0.94; **Supplementary Table 4**, http://links.lww.com/CCM/H302), although not in patients with minimal hepatic encephalopathy. The quality of evidence was downgraded because the population studied was cirrhotics with hepatic encephalopathy, and most trials were at high risk of bias for lack of blinding. Thus, a conditional recommendation was issued.

Recommendation. We suggest using enteral polyethylene glycol (PEG) as an alternative to lactulose in critically ill ACLF patients with overt hepatic encephalopathy (Conditional recommendation, low quality of evidence).

Rationale. A single center RCT (n = 50) demonstrated that using 4 L of PEG enterally over 4 hours led to faster hepatic encephalopathy resolution compared with standard therapy with lactulose (30). Thirteen of 25 patients in the standard therapy arm (52%) had an improvement of one or more in hepatic encephalopathy score, compared with 21 of 23 evaluated patients receiving PEG (91%) (RR, 0.18; 95% CI, 0.04–0.72; **Supplementary Table 5**, http://links.lww.com/CCM/H302). The median time for hepatic encephalopathy resolution was 2 days for standard therapy and 1 day for PEG group. PEG safety profile and balanced electrolytes make it an attractive alternative to lactulose in the ICU setting. However, volume of 4 L may be a concern for aspiration, especially in advanced grades of encephalopathy and should be used cautiously.

Recommendation. We suggest using oral rifaximin as adjunctive therapy in critically ill patients ACLF patients with overt hepatic encephalopathy (Conditional recommendation, low quality of evidence).

Rationale. Rifaximin is an oral nonsystemic antibiotic with less than 0.4% absorption. In a RCT (n = 120) comparing rifaximin (550 mg bid) and lactulose with lactulose and placebo in which 80% of patients had severe hepatic encephalopathy, patients who received rifaximin demonstrated an increased proportion of complete encephalopathy reversal and improvement