EVIDENCE-BASED GI
AN ACG PUBLICATION

When to Use Prophylactic Antibiotics for Management of Acute-on-Chronic Liver Failure?

Sonali Paul, MD, MS

Assistant Professor of Medicine, Division of Gastroenterology, Hepatology & Nutrition, University of Chicago Medicine, Center for Liver Disease, Chicago, Illinois

Sonali Paul, MD, MS
Associate Editor

Kulkarni AV, Tirumalle S, Premkumar M, et al. Primary Norfloxacin Prophylaxis for APASL-Defined Acute-on-Chronic Liver Failure: A Placebo-Controlled Double-Blind Randomized Trial. Am J Gastroenterol. 2022; 117(4):607-616. PMID: 35041634 https://doi.org/10.14309/ajg.0000000000001611
Correspondence to Sonali Paul, MD, MS, Associate Editor. Email: EBGI@gi.org

STRUCTURED ABSTRACT

Question: Does prophylactic norfloxacin prevent bacterial infections and improve transplant-free survival in patients with acute on chronic liver failure (ACLF)?

Study Design: Double-blind, placebo-controlled trial of 143 patients with ACLF randomized to norfloxacin 400mg daily or placebo for 30 days. Patients were contacted by telephone every 7 days for the first month, and then every 2 weeks for the next 2 months, and asked about infectious symptoms.

Setting: Department of Hepatology, Asian Institute of Gastroenterology in Hyderabad India from October 2019 to May 2021.

Patients: One hundred forty-three patients with ACLF seen in the outpatient setting (within at least 5 days of discharge if recently hospitalized) aged 18 to 75 years old (mean 43.5 years) with a mean Model for End Stage Liver Disease (MELD) of 28 were included in this study. Alcohol was the most common cause of ACLF for both groups. ACLF was defined using the Asian Pacific Association for the Study of the Liver (APASL) criteria defined as an acute hepatic injury resulting in jaundice (total bilirubin 5 mg/dL), coagulopathy (interquartile range [international

ratio] ≥1.5), complicated within 4 weeks by ascites or hepatic encephalopathy in a patient with chronic liver disease or cirrhosis[1]. Exclusion criteria included those with a history of spontaneous bacterial peritonitis, current bacterial infections, renal failure, malignancy, GI bleeding within 7 days, antibiotic exposure within 5 days, hepatic encephalopathy, those receiving prophylactic rifaximin, those who received fluoroquinolones in the last month, and those receiving omega 3 fatty acid lipid emulsions for ACLF. **Exposure**: Participants were randomized to norfloxacin 400 mg daily or placebo for 30 days in addition to standard medical therapy (diuretics, steroids for alcohol-associated or autoimmune hepatitis, hepatitis B/C treatments, beta blockers, lactulose, and nutritional support). **Outcome**: The primary outcome was bacterial infections at days 30 and 90. Transplant-free survival at 30 and 90 days were the secondary outcomes.

Data Analysis: Kaplan-Meier survival analysis used to assess incidence of infections and transplant-free survival at 30 and 90 days. A sub-group analysis of patients with alcohol associated hepatitis receiving steroid therapy was also analyzed.

Results: The incidence of bacterial infections at 30 days was significantly lower in the norfloxacin group at 18% (95% confidence interval [CI] 10-29) compared to the placebo group 34% (95% CI 23-46; *P*=0.03). Similarly, the incidence of infections at 90 days was 46% (95% CI 34-58) and 62% (95% CI 50-73; *P*=0.02) respectively. There were trends towards increased transplant-free survival at both 30 and 90 days in the norfloxacin group compared to placebo, but this did not reach statistical significance. Thirty-day survival was 78% (95% CI 66-87) vs 65% (95% CI 52-76; *P*=0.084), and 90-day survival was 58% (95% CI 46-70) vs 44% (95% CI 32-56; *P*=0.058), respectively.

Patients in the norfloxacin group also had lower incidences of hepatic encephalopathy (32% vs 52% in placebo; *P*=0.01), acute kidney injury (24% vs 37% in placebo, *P*=0.09), and ACLF grade progression (21% vs 42% in placebo; *P*=0.006; Figure 1). Of those receiving steroid therapy for alcohol associated hepatitis, bacterial infections were lower in those receiving norfloxacin at 30 days compared to placebo (10% vs 39%, *P*=0.06) and 90 days (30% vs 69% respectively; *P*=0.03). There were no significant differences in mortality, encephalopathy, or acute kidney injury. Notably, 25% in the norfloxacin group developed urinary Candida compared to only 3% in the placebo group.

Funding: Cipla India Ltd. provided the drugs and placebo but did not fund the trial and was not involved in treatment allocation, data collection, or interpretation.

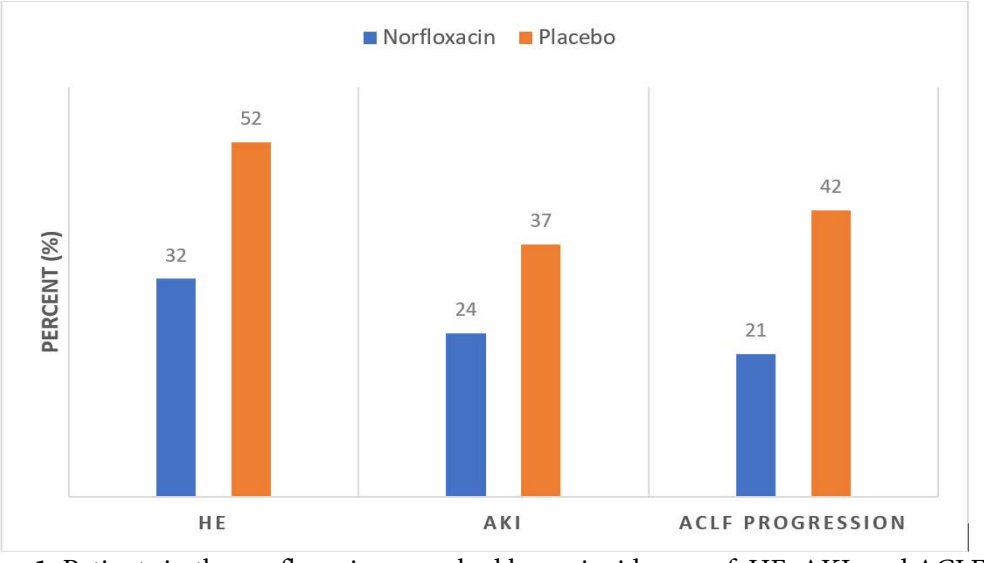

Figure 1. Patients in the norfloxacin group had lower incidences of HE, AKI, and ACLF progression compared to placebo.
ACLF, acute on chronic liver failure; AKI, acute kidney injury; HE, hepatic encephalopathy.

COMMENTARY

Why is this important?

ACLF is a relatively recent described entity in patients with chronic liver disease and portends poor prognosis. ACLF definitions vary (**Figure 2**) but is

Organ	APASL ACLF Research Consortium	EASL CLIF-C ACLF	NACSELD
Liver	Total Bilirubin PT/INR	Total bilirubin PT/INR	--
Kidney	Creatinine	Creatinine/Dialysis	Dialysis
Brain	HE grade	HE grade	HE grade III/IV
Circulatory	Lactate	MAP, vasopressors	MAP, vasopressors
Respiratory	--	PaO_2 or SpO_2 / FiO_2	Mechanical ventilation
Major Organ failure Category	**Predominantly Hepatic failure variables**	**Combination of hepatic and extrahepatic organ failure variables**	**Predominantly extrahepatic organ failure variables**

Figure 2. Definitions of Acute on Chronic Liver Failure[2]

diagnosed with a combination of both hepatic and extrahepatic organ failures. The most recent American College of Gastroenterology Guidelines (ACG) on the Management of ACLF define it as a condition in patients with chronic liver disease (with or without cirrhosis) who have elevated bilirubin and prolonged international normalized ratio. It is associated with the potential for multiple organ failure (kidney, lung, cardiovascular, neurological)_and portends high 3-month mortality without treatment of underlying disease, liver support, or transplantation[2]. The guideline is an invaluable tool that summarizes the current data and management strategies on ACLF and addresses important aspects both from a hepatic and extrahepatic organ perspective.

Infection is a leading cause of mortality in patients with cirrhosis, including those with acute on chronic liver failure. About 40% of patients with ACLF develop bacterial infections which predicts mortality[3]. Therefore, strategies for infection prevention are needed for optimal management of patients with acute on chronic liver failure. The ACG guideline does not recommend routine prophylactic antibiotics for patients with ACLF, although prophylactic antibiotics for primary and secondary spontaneous bacterial peritonitis prophylaxis are recommended without recommending any specific antibiotic regimen.

Key Study Findings

Norfloxacin prophylaxis was found to be safe in preventing bacterial infections at 30 and 90 days and trended toward improved transplant-free survival compared to placebo in patients with ACLF but did not quite reach statistical significance: 30-day survival of 78% vs 65%, P=0.084 and 90-day survival of 58% vs 44%, P=0.058, respectively. Patients receiving norfloxacin also had decreased incidences of hepatic encephalopathy, acute kidney injury, and ACLF progression but did have higher incidence of Candida urinary tract infections. In those receiving steroids for alcohol-associated hepatitis, norfloxacin significantly decreased the risk of bacterial infections at days 30 and 90, but did not have any significant effect on mortality.

Caution

While novel and significant findings, this study has several limitations. First, the study population was very restrictive with only patients with ACLF defined by APASL criteria. Other ACLF criteria exist, such as those by European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) and North American Consortium for the Study of End-Stage Liver Disease (NACSELD) (**Figure 2**), and results may not be applicable when these definitions are applied. The patients studied also predominantly had alcohol-related liver disease, so findings may not relate to other disease states such as nonalcoholic fatty liver disease or viral hepatitis. Those with recent infections, hospitalizations, recent antibiotics, and current hepatic encephalopathy were also excluded which severely limits generalizability to many patients with ACLF.

My Practice

As mentioned previously, infection remains a top concern in patients with ACLF. In my hepatology practice, I follow the current American Association for the Study of Liver Diseases (AASLD) practice guidelines which recommend prophylactic antibiotics (indefinitely) in those with cirrhosis and low ascitic fluid protein (<1.5 g/dL) and evidence of renal dysfunction (creatinine > 1.2 mg/DL, blood urea nitrogen level > 25 mg/dL) or serum sodium level < 130 mEq/L or Child-Turcotte-Pugh score > 9 with bilirubin > 3mg/dL[4]. I also give antibiotic prophylaxis in patients receiving steroids for alcohol-associated hepatitis. My preferred regimen is ciprofloxacin 500 mg daily. While the current data show a benefit of norfloxacin prophylaxis in patients with ACLF, given the restrictive inclusion criteria, it may be difficult to apply this to my patient population.

For Future Research

Use of norfloxacin in addition to other antibiotics that are commonly used in primary prophylaxis such as ciprofloxacin and Bactrim (sulfamethoxazole-trimethoprim) should also be assessed in future studies. Additionally, patients with other types of liver diseases, not just alcohol, should be included in future studies with the use of other ACLF definitions.

Conflicts of Interest

Dr. Paul reports no conflicts of interest.

REFERENCES

1. Sarin SK, Choudhury A, Sharma MK, et al. APASL ACLF Research Consortium (AARC) for APASL ACLF working Party. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific association for the study of the liver (APASL): an update. Hepatol Int 2019; 13(4):353-390.
2. Bajaj JS, O'Leary JG, Lai JC, et al. Acute-on-Chronic Liver Failure Clinical Guidelines. Am J Gastroenterol 2022; 117(2):225-252.
3. Fernandez J, Acevedo J, Wiest R, et al. Bacterial and fungal infections in acute-on-chronic liver failure: Prevalence, characteristics, and impact on prognosis. Gut 2018; 67:1870–80.
4. Biggins SW, Angeli P, Garcia-Tsao G, et al. 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. Hepatology 2021; 74(2):1014-1048.