

American Journal of Gastroenterology
**Additional analyses for the published Primary Norfloxacin Prophylaxis for APASL-
 Defined**
Acute-on-Chronic Liver Failure: A Placebo-Controlled
Double-Blind Randomized Trial
 --Manuscript Draft--

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To the Editors-in-Chief at American Journal of Gastroenterology

Dear Doctors Bajaj and Long,

We would very much appreciate your consideration of our correspondence on the very interesting article:

Primary Norfloxacin Prophylaxis for APASL-Defined Acute-on-Chronic Liver Failure: A Placebo-Controlled Double-Blind Randomized Trial

Published online on 17.1.2022

For the authors' key outcomes, we have used their data to perform additional analyses using a dichotomous outcome rather than Kaplan-Meier, which may be more suitable for a short-term outcome. These increase the *P* value for both infection and mortality, making the latter a significant outcome. Given the potential risks of prophylactic antibiotics regarding increased incidence of anti-microbial resistance, we believe our analyses strengthen the message of the authors' manuscript.

Many thanks for your consideration.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'A. O'Brien'.

Professor Alastair O'Brien on behalf of all authors

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Dear sirs,

We read with interest the results from the Primary Norfloxacin Prophylaxis for APASL-Defined Acute-on-Chronic Liver Failure: A Placebo-Controlled Double-Blind Randomized Trial published online January 17, 2022 in the American Journal of Gastroenterology¹. We note the authors conclusions that norfloxacin prophylaxis was safe and effective in preventing bacterial infections. The trial team are to be congratulated on completing a double-blind placebo-controlled study in Acute-on-Chronic Liver failure (ACLF) patients and their findings are important. However, given concerns around the risks of anti-microbial resistance, physicians might be reluctant to prescribe prophylaxis in the absence of a mortality benefit.

Therefore, although we appreciate the authors pre-planned analyses, we believe that a different, perhaps more conventional, approach to a short-term study would have given stronger evidence to guide decision-making on antibiotic prophylaxis in ACLF. If we assume that prevention of a dichotomous outcome (diagnosis of infection or not) is more important clinically than assessment of the precise day that the patient was diagnosed with infection, then analysing the data presented at 30 days using an exact test on the contingency table (e.g., an exact version of a Chi-squared test), we calculate that the mid *P* value is 0.002. This is a substantially more significant result than the *P* value presented of 0.03. Furthermore, when analysed similarly, mortality at 6 months is also nominally statistically significant ($p=0.03$). We believe these analyses strengthen the important clinical message of Kulkarni et al's manuscript, especially considering the lack of effective treatment options in ACLF. We hope to provide further clinical data regarding the use of antibiotic prophylaxis from our ASEPTIC trial which is currently recruiting (Primary Antibiotic prophylaxis using co-trimoxazole to prevent Spontaneous bacterial Peritonitis in Cirrhosis).

Reference:

1. Kulkarni, A. V., et al. (2022). "Primary Norfloxacin Prophylaxis for APASL-Defined Acute-on-Chronic Liver Failure: A Placebo-Controlled Double-Blind Randomized Trial." *Am J Gastroenterol*. 2022;00:1–10. <https://doi.org/10.14309/ajg.0000000000001611>

Authors: Dominic Crocombe*, Nick Freemantle# and Alastair O'Brien**, on behalf of the ASEPTIC trial team - Primary Antibiotic prophylaxis using co-trimoxazole to prevent Spontaneous bacterial Peritonitis in Cirrhosis: Trial Registration - EudraCT # 2019-000581-38 and REC # 19/SC/031

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