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Prophylactic Antibiotics Do Not Improve Mortality in Severe Alcoholic Hepatitis Treated with Corticosteroids

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Editor-in-Chief

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LIVER

This summary reviews Louvet A, Labreuche J, Dao T, et al. Effect of Prophylactic Antibiotics on Mortality in Severe Alcohol-Related Hepatitis. JAMA 2023; 329 (18): 1558-66. doi: 10.1001/jama.2023.4902

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STRUCTURED ABSTRACT

Question: Does amoxicillin-clavulanate decrease 60-day all-cause mortality among patients with severe alcoholic hepatitis treated with oral prednisolone?

Design: Multi-center, double-blind, placebo-controlled randomized controlled trial (RCT).

Setting: Twenty-five centers in France and Belgium between June 2015 and May 2019.

Patients: Included patients were: (a) age 18-75 years old; (b) consumption of $\geq$ 40 grams/day of alcohol (about 3 standard drinks/day) for women or $\geq$ 50 grams/day of alcohol (about 4 standard drinks/day) for men; (c) clinical diagnosis of alcohol-related hepatitis with new onset jaundice; and, (d) biopsy-proven alcoholic hepatitis with Maddrey score $\geq$ 32 and Model for End-stage Liver Disease (MELD) score $\geq$ 21. Multiple exclusion criteria

included type 1 hepatorenal syndrome. Patients being treated for diagnosed infection with antibiotics could be included after a 7-day wash-out period after completing antibiotics.

Interventions/Exposure: Amoxicillin 1g plus clavulanate 125mg orally 3 times a day vs identical placebo tablets for 30 days. All patients received 40mg per day of oral prednisolone for 30 days. Patients were evaluated in person weekly for the first 4 weeks, then at day 45, day 60, day 90, and day 180.

Outcome: The primary endpoint was 60-day all-cause mortality from date of randomization. Multiple secondary endpoints included all-cause mortality at 90-day and 180-day follow-up, incidence of infection or hepatorenal syndrome at 60-day follow-up.

Data Analysis: Intention-to-treat analysis with log-rank test using data from last available follow-up.

Funding: French Public Health Ministry

Results: Among 292 randomized patients, mean age was 52.8 (SD 9.2 years); 27% female; 18%-22% had previously been treated with antibiotics and were enrolled after a 7-day washout period. Thirteen percent had prior overt hepatic encephalopathy episodes. For the primary endpoint, there was no significant difference in all-cause 60-day mortality between the amoxicillin-clavulanate group vs placebo group: 17.3% vs 21.3%, *P*= 0.33; hazard ratio: 0.77 (95% confidence interval [CI]: 0.45-1.31). Cumulative incidence of infection was lower in the amoxicillin-clavulanate group at 60 days: 29.7% vs 41.5%; subhazard ratio: 0.62 (95% CI: 0.41-0.91, *P*= 0.02). (**Figure 1**). There were no significant differences in other secondary outcomes.

COMMENTARY

Why Is This Important?

Alcoholic hepatitis is associated with an increased risk of bacterial infection compared to patients with decompensated cirrhosis due to alcohol who do not have severe hepatitis.[1] This may be due to the relative immunosuppression associated with the high-grade systemic inflammation found in patients with alcoholic hepatitis. Furthermore, alcoholic hepatitis patients who don't get corticosteroids are less likely to get bacterial infections compared to patients who do get corticosteroids, which can worsen immunosuppression.[1] Considering that 25%-30% of alcoholic

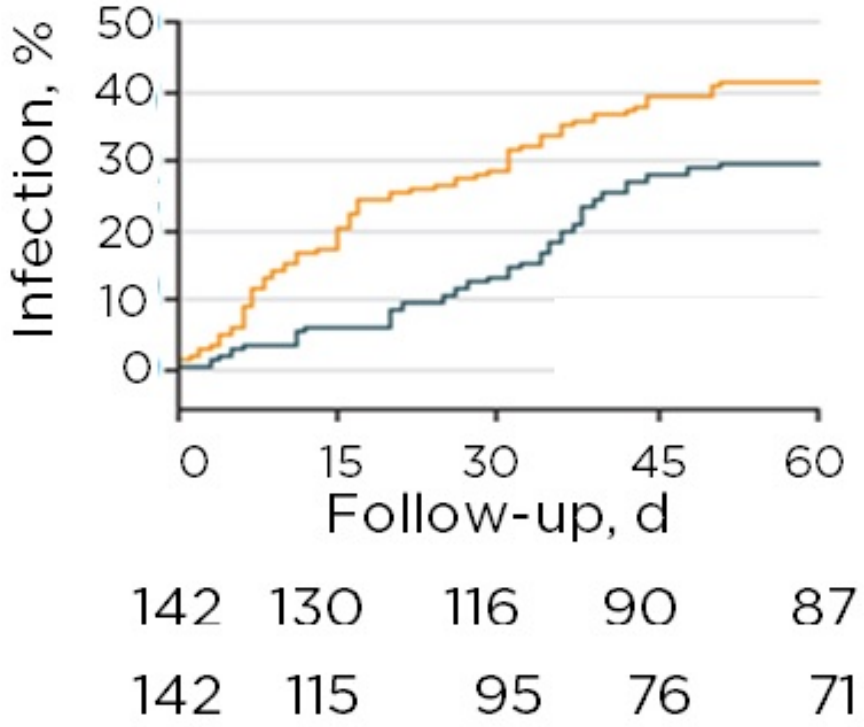

Figure 1. Cumulative incidence of infection at 60 days

hepatitis patients receiving corticosteroids are diagnosed with infections and that infections are associated with adverse outcomes like liver failure and hepatorenal syndrome, the use of prophylactic antibiotics has been proposed.

This RCT, the AntibioCor trial, confirmed the diagnosis of alcoholic hepatitis with biopsy and completed 180-day follow-up while assessing the most important outcome, all-cause mortality, along with the secondary outcome of incidence of infection. The investigators should be commended for their excellent study design and diligence to address new treatment beyond supportive care.

Key Study Findings

There was no significant difference in all-cause 60-day mortality between the amoxicillin-clavulanate group vs placebo group: 17.3% vs 21.3%, *P*=0.33; HR: 0.77 (95% CI: 0.45-1.31).

Cumulative incidence of infection was lower in the amoxicillin-clavulanate group at 60 days: 29.7% vs 41.5%; subhazard ratio: 0.62 (95% CI: 0.41-0.91, *P*= 0.02).

Caution

Approximately 20% of study patients previously treated with antibiotics were enrolled after a 7-day washout period with no antibiotics. The study protocol did not make any recommendations about whether or not to discontinue corticosteroids at day 7 if the Lille score $\geq$ 0.45. Since the sample size was calculated based on an absolute reduction in 60-day mortality of

14%, it's possible that the study was undersized to identify smaller, but still clinically important, reductions in mortality with prophylactic antibiotics.

My Practice

Although I'm a general gastroenterologist, I treat these patients on our inpatient service. Per advice from my hepatology colleagues and consistent with guidelines,[2-4] I usually prescribe corticosteroids if the Maddrey discriminant function (MDF) is $\geq$ 32 and MELD score >20, although I realize that corticosteroids have only proven benefit up to 28 days. If the Lille score is $\geq$0.45 at day 7, then I usually discontinue corticosteroids since they are associated with multiple side effects, including an increased risk of infection. I do not routinely use pentoxifylline per guidelines.[2-4]

Given the results of the AntibioCor trial, I will continue this approach and will not use prophylactic antibiotics in these patients. Based on the post hoc analysis of the ATTIRE trial[5] and guideline recommendations,[2-4] I also do not use prophylactic antibiotics for patients admitted with decompensated cirrhosis to reduce hospital-acquired infections. However, I do monitor these patients carefully for infection since they are at increased risk of infection and initiate antibiotics when appropriate. I also de-escalate antibiotic coverage based on culture and sensitivity if possible.

For Future Research

Although some anti-inflammatory medications are being studied for treatment of alcoholic hepatitis, there are no new treatments on the near horizon.

Conflict of Interest

Dr. Schoenfeld reports no conflicts of interest.

The authors of this article are active on social media. Tag them to discuss their work and this EBGI summary: @mathurinphilip1 (Philippe Mathurin).

REFERENCES

1. Forrest Ewan, Bernal W. The Role of Prophylactic Antibiotics for Patients with Severe Alcohol-Related Hepatitis. JAMA 2023; 329 (18): 1552-53.
2. Singal AK, Bataller R, Ahn J, Kamath PS, Shah VH. ACG Clinical Guideline: Alcoholic Liver Disease. Am J Gastroenterol 2018; 113 (2): 175-94.
3. Bajaj J, O'Leary J, Lai JC, et al. Acute-on-Chronic Liver Failure Clinical Guidelines. Am J Gastroenterol 2022; 117: 225-52.
4. Crabb DW, Im GY, Szabo G, et al. Diagnosis and Treatment of Alcohol-Associated Liver Diseases: 2019 Practice Guidance from the American Association for the Study of Liver Diseases. Hepatology 2020; 71: 306-33.
5. Kutmutia R, Tittanegro T, China L, et al. Evaluating the Role of Antibiotics in Paitients Admitted to Hospital with Decompensated Cirrhosis: lessons from the ATTIRE trial. Am J Gastroenterol 2023; 118 (1):105-113.