# No Effect in Alcoholic Hepatitis of Gut-Selective, Broad-Spectrum Antibiotics on Bacterial Translocation or Hepatic and Systemic Inflammation

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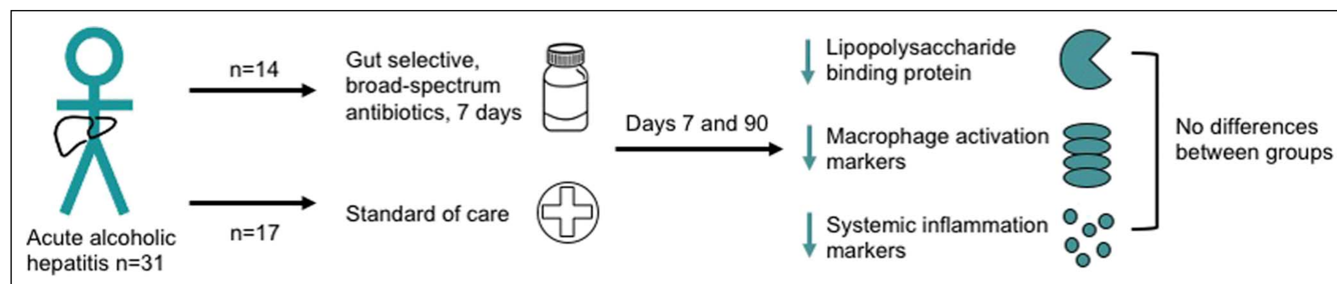
INTRODUCTION: **In alcoholic hepatitis (AH), translocation of gut bacteria may drive hepatic macrophage activation and systemic inflammation. We investigated the effect of oral non-absorbable, broad-spectrum antibiotic treatment on bacterial translocation and liver and systemic inflammation in AH.**

METHODS: **We consecutively recruited 31 patients with AH. Fourteen were given vancomycin 500 mg, gentamycin 40 mg, and meropenem 500 mg once daily for 7 days. Seventeen patients were a reference group receiving standard-of-care. Circulating markers of bacterial translocation and inflammation were measured at baseline, by day 7 and 90. Gut bacteriome profiling was performed before the intervention and at day 7.**

RESULTS: **At study entry, blood lipopolysaccharide-binding protein was multifold higher than normal, remained unchanged at day 7, but decreased at day 90 ($P < 0.001$) with no difference between the study groups. The macrophage activation markers sCD163 and sCD206 showed the same pattern ($P < 0.001$, day 90), still without group differences. The systemic inflammation markers tumor necrosis factor—alpha, interleukin (IL)-6, IL-8, and IL-10 showed similar dynamics without group differences. There was no difference in 90-day mortality (total of 6 deaths) between the groups. The remnant gut bacteriome was markedly diversified by the intervention with growth of bacterial species rare for human flora.**

DISCUSSION: **In patients with AH, gut-targeted antibiotic treatment does not change markers of bacterial translocation and liver and systemic inflammation. This suggests that bacterial translocation is less important once the inflammatory process is established or that bacteriome reduction is less important than composition.**




**SUPPLEMENTARY MATERIAL** accompanies this paper at http://links.lww.com/CTG/A494 and http://links.lww.com/CTG/A495.

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LIVER

## INTRODUCTION

The prognosis and treatment of acute alcoholic hepatitis (AH) have remained poor and essentially unchanged for decades despite numerous clinical trials, which emphasizes the need to explore new treatment targets.

In AH, the composition of bacteria in the gut is disturbed and overgrowth of pathogenic or proinflammatory species is associated with a poor prognosis (1–3). Furthermore, there is increased translocation of bacteria and bacterial fragments such as lipopolysaccharide (LPS) from the gut to the liver because of an increased permeability of the intestinal wall. The load of LPS can be gauged from the blood concentration of LPS-binding protein (LBP), produced by the liver in response to LPS exposure. In the liver, these gut-derived factors activate resident and recruited macrophages to orchestrate liver and systemic inflammation (4–7). Hepatic macrophage activation can be estimated in peripheral blood samples by the shedded, lineage-specific haemoglobin scavenger receptor soluble CD163 (sCD163) and the mannose receptor (sCD206). We and others have previously shown that plasma sCD163 predicts mortality in patients with AH and is related to LPS translocation (8,9). Systemic inflammation in these patients is characterized by increased circulating proinflammatory factors such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-6, and IL-8 and anti-inflammatory factors such as IL-10 (10). Thus, a reduction of the gut bacterial load may be a way to reduce bacterial translocation and hepatic and systemic inflammation in patients with AH.

In this proof of concept study, we therefore aimed to effectively reduce gut bacterial flora by oral administration of a combination of 3 oral, nonabsorbable antibiotics for 1 week. This antibiotic cocktail has previously been shown to greatly reduce the number of anaerobic bacteria and eradicate *Coliforme*, *Enterococcus*, and *Bifidobacteria* to below the detection limit by standard culture methods (11). We hypothesized this intervention to reduce LPS translocation, macrophage activation, and systemic inflammation in a cohort of patients with AH.

## MATERIALS AND METHODS

### Patients

We performed a prospective, sequential intervention cohort study with consecutive enrollment, and recruited 31 patients when diagnosed with AH from the Department of Hepatology and Gastroenterology, Aarhus University Hospital. The first 14 patients were included in the intervention group and the following 17 patients in the reference group. The diagnosis was based on a combination of physical and laboratory criteria: a history of excessive alcohol ingestion (>40/60 g female/males per day) until at least 3 weeks before admission and acute jaundice (developed over at most 2 weeks, serum bilirubin > 80 μmol/L). As recommended in the national guidelines, a liver biopsy was performed in case of di-

**Table 1. Baseline clinical and biochemical characteristics in the intervention and reference groups**

| | Intervention Baseline | | Reference Baseline | | Intervention Day 7 | | Reference Day 7 | |
|---|---|---|---|---|---|---|---|---|
| | Median | IQR | Median | IQR | Median | IQR | Median | IQR |
| Sex: F/M | 5/9 | | 8/9 | | 5/9 | | 8/9 | |
| Age (yr) | 57 | 23 | 55 | 10 | | | | |
| BMI | 29 | 6.8 | 25 | 7 | | | | |
| Weight (kg) | 84* | 12 | 76 | 12 | | | | |
| Height (cm) | 175 | 13 | 169 | 17 | | | | |
| ALT (U/L) | 34 | 22 | 49 | 37 | 82 | 63 | 50 | 46 |
| Sodium (mmol/L) | 131** | 10 | 134 | 6 | 138* | 7.5 | 133 | 4.5 |
| Bilirubin (μmol/L) | 230* | 231 | 139 | 86 | 168 | 155 | 104 | 77 |
| Alkaline phosphatase (U/L) | 231 | 103 | 152 | 161 | 219 | 125 | 151 | 170 |
| Hemoglobin (mmol/L) | 6.8 | 2.3 | 6.4 | 1.3 | 7.1 | 2.2 | 6.8 | 1.4 |
| Creatinine (μmol/L) | 77 | 105 | 63 | 22 | 81* | 45 | 51 | 18 |
| INR | 2 | 0.3 | 1.6 | 0.6 | 2 | 0.7 | 1.3 | 0.6 |
| Albumin (g/L) | 21 | 5 | 22 | 6 | 24 | 6 | 24 | 8 |
| CRP | 23 | 38 | 17 | 21 | 17 | 23 | 15 | 27 |
| Thrombocytes ($*10^9$/L) | 102 | 53 | 173 | 80 | 117 | 173 | 200 | 285 |
| MELD | 23* | 7 | 18** | 6 | 22* | 7 | 14 | 7.5 |
| GAHS | 9 | 2 | 8 | 2 | 8.5 | 1.5 | 7.5 | 1 |
| Child-Pugh score | 11.5 | 2 | 11 | 2 | 10.5 | 2 | 10.5 | 2 |

ALT, alanine aminotransferase; BMI, body mass index; CRP, C-reactive protein; GAHS, Glasgow AH Score; IQR, interquartile range; MELD, Model of End-Stage Liver Disease.
*$P < 0.05$ between intervention and reference group same day. **$P < 0.05$ between baseline and day 7 within groups.

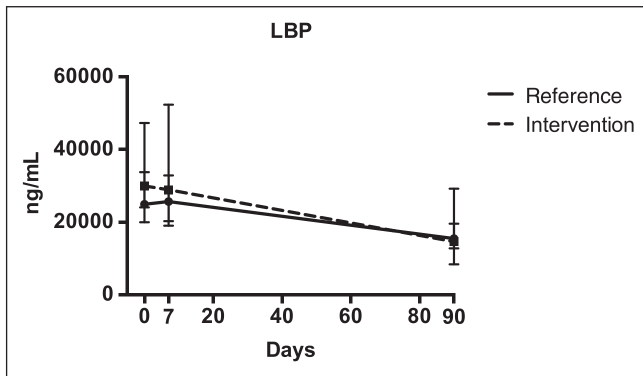


Figure 1. LBP did not change in response to the intervention. Plasma LBP was measured by ELISA at study entry and after 7 and 90 days in a cohort of patients with AH (n = 14) receiving 7 days of oral, broad-spectrum, nonabsorbable antibiotics. These values are compared with a cohort receiving standard-of-care (n = 17). AH, alcoholic hepatitis; ELISA, enzyme-linked immunosorbent assay; LBP, lipopolysaccharide-binding protein.

agnostic doubt. Patients were excluded if they had viral hepatitis, autoimmune liver disease, bile duct obstruction, or liver tumors as diagnosed by standard clinical blood tests and ultrasound. Other exclusion criteria were any other cancer, presence of an uncontrolled infection, on-going gastrointestinal bleeding or bleeding within the previous 3 months, or any immune-modulating therapy within the past 8 weeks. Further exclusion criteria included administration of antibiotics within 3 months before study inclusion, and known allergies toward the used antibiotics, including previous allergic reactions related to beta-lactam antibiotics, aminoglycosides, or vancomycin. Patients were treated according to standard clinical practice following stratification by the Glasgow AH Score (GAHS). Those with a GAHS $< 9$ were given moderate hyperalimentation (a daily energy consumption of 35- to 49-kcal/kg body weight and a daily protein intake of 1.2–1.5 g/kg) and standard supportive medical care, and those with a GAHS $\geq 9$ received prednisolone 40 mg/d. The patients were followed for 90 days, and blood samples were obtained at study entry before initiation of intervention and at days 7 and 90. In the intervention group, stool samples were obtained before the intervention and on day 7 or at clinical indication within the 90-day follow-up period. The stool was cultured for fecal pathogens (all patients baseline; in the intervention group also day 7) and stored for sequencing (n = 6, intervention group). Biochemical data and clinical characteristics were collected on each study day. All patients provided written, informed consent before participation, and the study was approved by the local ethics committee (j. no. 1-10-72-1-15) and reported at clinicaltrials.gov (1-10-72-1-15).

### Intervention

In the intervention group, the following antibiotic regime was administered orally, once daily for 7 days following diagnosis: vancomycin 500 mg powder for concentrate; gentamicin 40 mg solution; and meropenem 500 mg powder for concentrate. The 3 drugs were dissolved and combined into a cocktail with approximately 100 mL of apple juice. These drugs were chosen because of their negligible systemic absorption owing to their hydrophilic nature and their combined very broad spectrum of activity against bacteria.

### Immunological analyses

The plasma concentration of LBP was measured by enzyme-linked immunosorbent assay (kit numbers HK315, Hycult Biotech, Uden, the Netherlands) following the manufacturer's instructions. We measured sCD163 and sCD206 in plasma samples on a BEP-2000 enzyme-linked immunosorbent assay analyzer (Dade Behring, Eschborn, Germany) as previously described in detail (12,13). Plasma cytokines TNF-alpha, IL-6, IL-8, and IL-10 were quantified by multiplex (Meso Scale Disagnostics, V-PLEX Custom Human Cytokine, Meso Scale Diagnostics Rockville, MD).

### Bacterial and fungal sequencing

Stool samples were sequenced in the intervention group (before treatment, n = 6, after treatment n = 3) by BiomCare using polymerase chain reaction for DNA amplification of the selected variable regions of the bacterial 16S rRNA gene and fungal internal transcribed spacer rRNA region, respectively. The product from polymerase chain reaction was normalized using

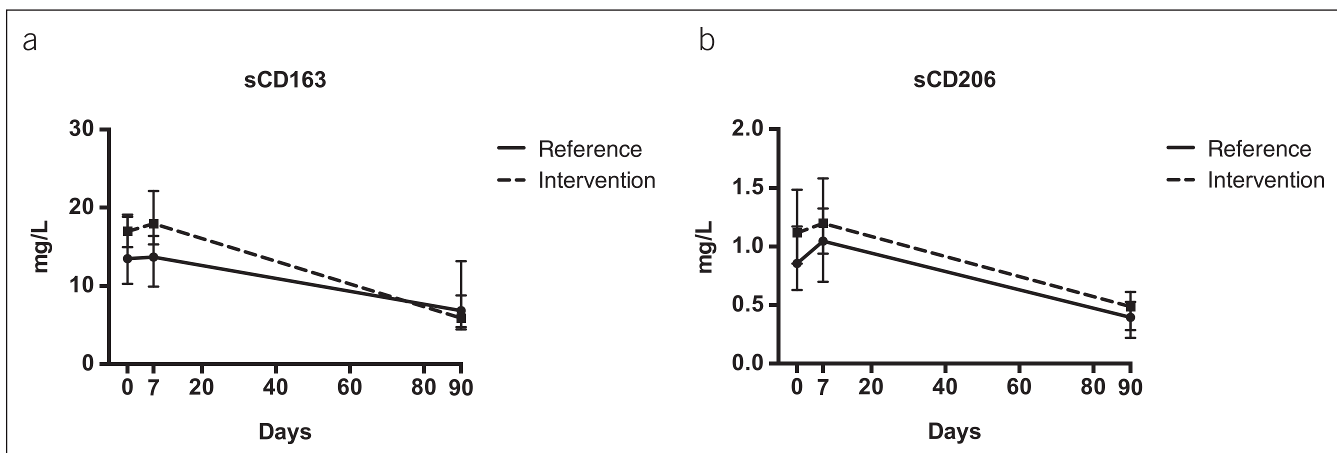


Figure 2. The intervention did not change the course of hepatic macrophage activation markers during AH. The macrophage activation markers soluble (s) (**a**) CD163 and (**b**) sCD206 were measured by ELISA in a cohort of patients with AH (n = 14) receiving 7 days of oral, broad-spectrum, nonabsorbable antibiotics. Baseline to day 7 in the intervention group ($P = 0.037$). No difference between the groups. AH, alcoholic hepatitis; ELISA, enzyme-linked immunosorbent assay.

LIVER

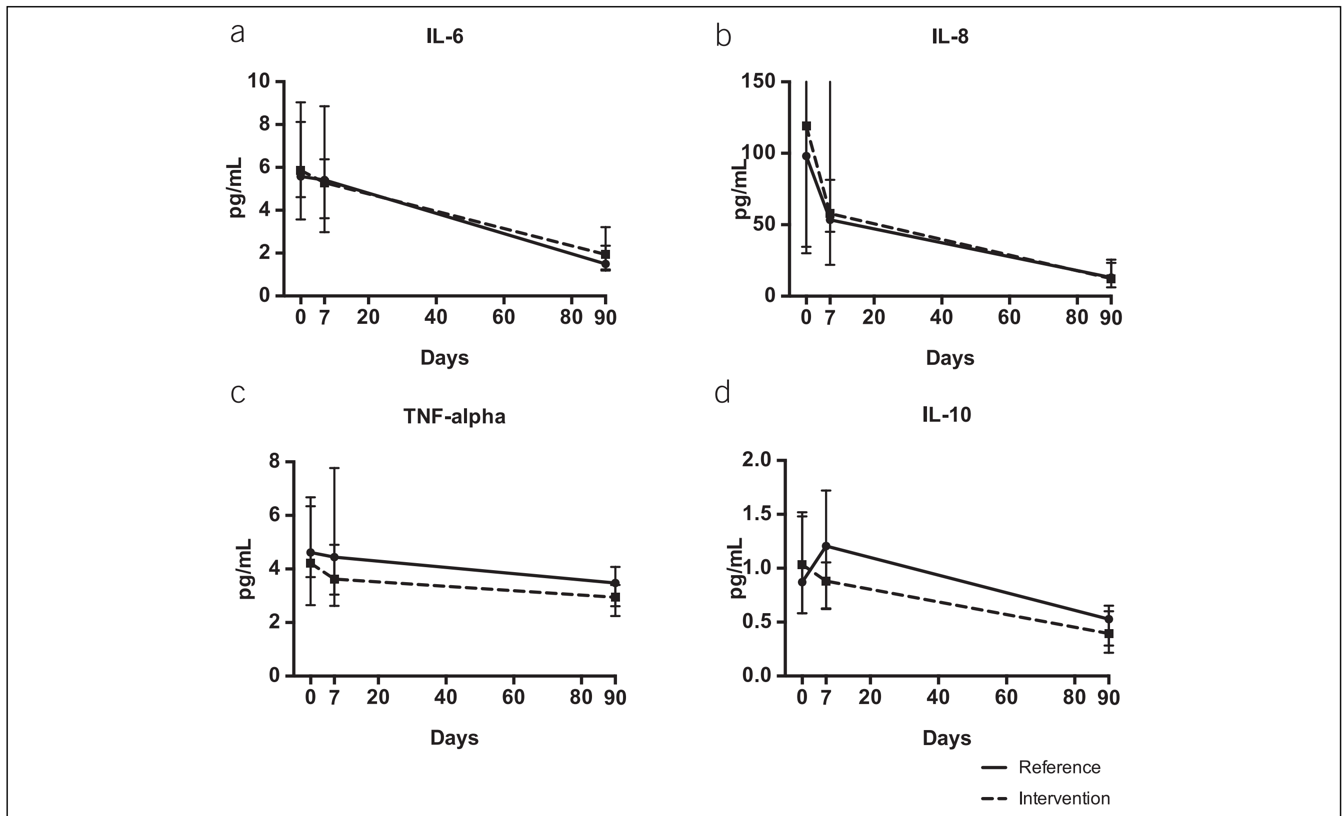


**Figure 3.** No changes in systemic inflammation markers from the intervention. Markers of systemic inflammation, (a) IL-6, (b) IL-8, (c) TNF-alpha, and (d) IL-10 were measured in plasma using mesoscale multiplex in the cohort of patients with AH receiving 7 days of oral, broad-spectrum, gut-selective antibiotics and compared with a cohort receiving standard of care. The dynamics in cytokines were measured at study entry and after 7 and 90 days and the groups compared. Baseline to day 90: IL-6 and IL-8 $P = 0.005$, both, TNF-alpha $P = 0.074$ and IL-10 $P = 0.060$. No difference between the groups. AH, alcoholic hepatitis; IL, interleukin; TNF, tumor necrosis factor.

SequalPrep Normalization Kit followed by sequencing on an Illumina MiSeq platform using v3 chemistry and multiplexing of up to 384 samples per run. Microbiome profiling was performed using the software DADA2, and taxonomy was assigned using reference data from the Ribosomal Database Project database. For 16S sequencing, alpha- and beta-diversities and relative abundances at the phyla level are compared in the intervention group from before to after treatment.

### Statistical analyses

The Wilcoxon rank-sum test was used to examine the study entry data differences between the study groups. An analysis of variance for repeated measurements with Greenhouse-Geisser correction for sphericity was performed for a comparison of protein levels over time. To ensure normally distributed variables, logarithmic transformation was used where appropriate. Normality was evaluated by histograms and Q-Q plots. A 2-tailed $P$ value of $<0.05$ was considered statistically significant. STATA version 11.2 (StataCorp LP, College Station, TX) was used for the data analyses.

## RESULTS

### Patient characteristics

Age and sex distributions were similar in both groups (Table 1). The patients in the reference group had slightly lower bilirubin and Model of End-Stage Liver Disease score (Table 1). One patient in each group acquired an infection at day 7, in the reference group pneumonia and in the intervention group sepsis with *Staphylococcus aureus*. None developed *Clostridium difficile* infection as verified by fecal cultures. During the 90-day follow-up, 3 patients in each group died.

### The intervention did not change LBP

At study entry and in both groups, LBP levels were 2 times the upper normal reference. It did not change at day 7 but normalized at day 90 without difference between the groups (Figure 1).

### The intervention did not change hepatic macrophage activation markers

At study entry in both groups, sCD163 was 10-fold higher and sCD206 3-fold higher than the upper normal levels without differences between the groups (Figure 2). At day 7, sCD163 was slightly higher in the intervention group ($P = 0.037$), although the difference in increase was not different between the groups ($P = 0.88$). At day 90, sCD163 and sCD206 fell in both groups and indiscriminately between the groups (day 0–90) (Figure 2).

### The intervention did not change systemic inflammation

TNF-alpha, IL-6, IL-8, and IL-10 were not different between the groups at entry, at day 7, or at day 90. At day 90, IL-6 and IL-8 fell ($P = 0.005$, sign-rank) and TNF-alpha ($P = 0.074$) and IL-10

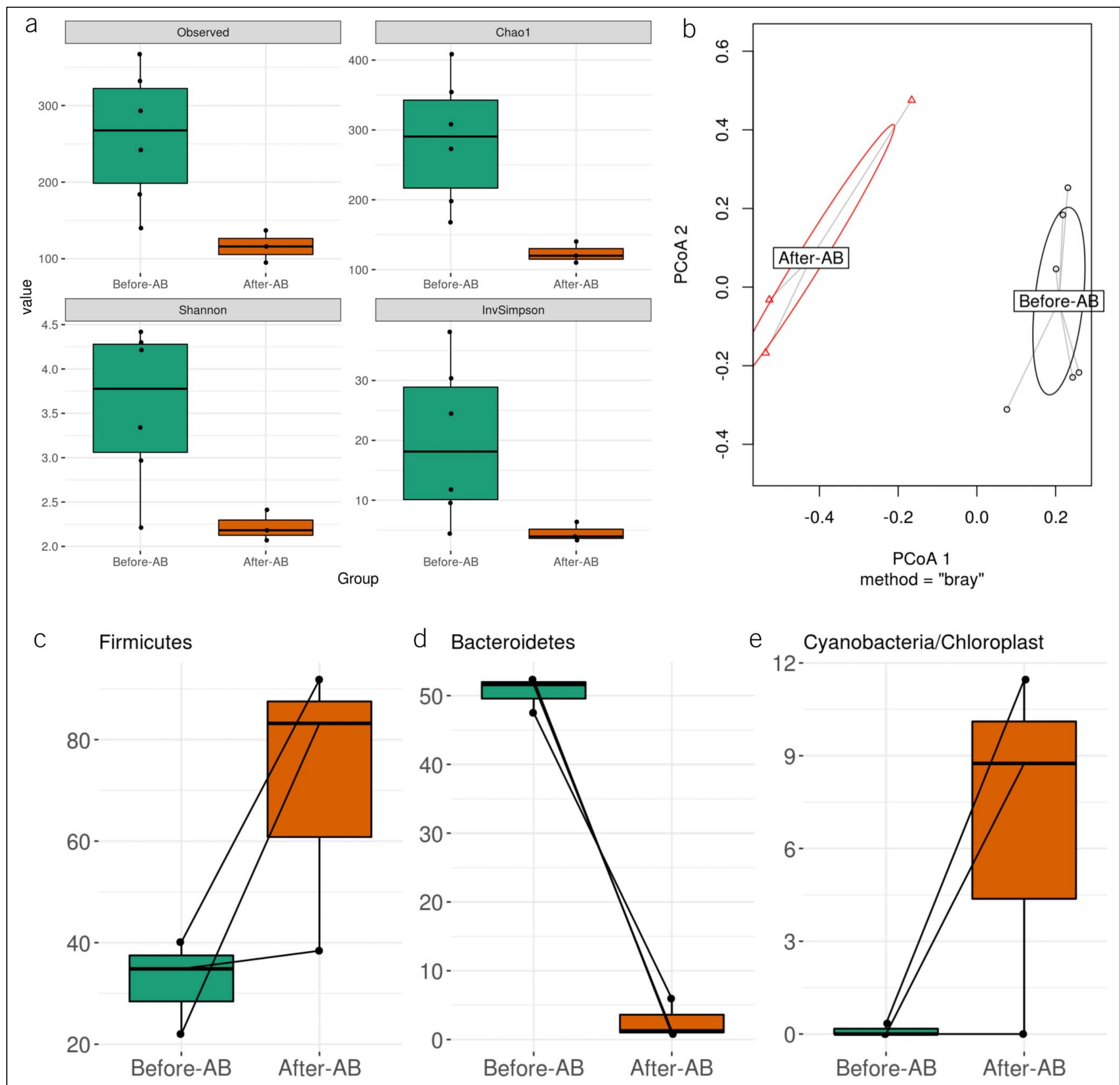


**Figure 4.** Broad-spectrum, gut-selective antibiotics increase gut flora diversity and allows for growth of rare species. Stool samples from patients with AH (n = 6) were analyzed by 16S sequencing at study entry, before the intervention (**a**, **b**) and after 7 days of daily antibiotics and compared. (**a**) Alpha-diversities (not significant), (**b**) beta-diversity visualized as PCoA ($P < 0.05$), and (**c**–**e**) relative abundances (not significant). AH, alcoholic hepatitis; PCoA, principal coordinate analysis.

($P = 0.060$) showed a similar trend in the reference group. This reduction was not different comparing the intervention group to the reference group (delta 90–0, rank-sum). The dynamics in all cytokines during the 90-day follow-up were the same in both groups (analysis of variance) (Figure 3).

### The intervention decreased alpha- and increased beta-diversity

All fecal cultures for pathogens were negative, both before and after treatment. The intervention decreased the alpha-diversity of the remnant gut bacteriome from before the intervention to day 7 as measured both by the Chao and the Shannon index (Figure 4a). The beta-diversity both at the genera and class level was increased (Bray-Curtis, ADONIS $P < 0.05$) from before to after the intervention (Figure 4b). At the phyla level, the relative abundance of *Bacteroidetes* decreased after the intervention, whereas *Firmicutes* and *Cyanobacteria/Chloroplast* increased (Figure 4c–e). Fungal sequences were detectable in only 3/6 patients, and thus, no effect could be attributed to the intervention. Of note, however, the intervention decreased the relative abundance of *Candida* (see Figure, Supplementary Digital Content 1, http://links.lww.com/CTG/A494).

## DISCUSSION

In this study of patients with AH, heavy and effective oral dosing with nonabsorbable antibiotics had no effect on markers of bacterial translocation, hepatic macrophage activation, or systemic inflammation. The results refute our *a priori* hypothesis and may influence our understanding of the importance of the interplay between gut microbiota and inflammation for the disease course in patients with AH.

The cocktail of antibiotics we used has previously been used in healthy persons and shown to effectively and reproducibly eradicate the gut bacteriome to below the detection limit by culture-based methods (11). We did not repeat direct verification of the intervention effect, but we performed 16S RNA sequencing to show how the intervention in our patients radically changed the remnant gut bacteriome. The beta-diversity was markedly shifted in all directions, also indicated by an increased variance among the samples after treatment. Also, there were reductions in alpha-diversity in both richness and evenness. These findings reflect the much-reduced gut bacteriome allowing the sparse growth of rare bacteria. In support, we saw a marked increase in cyanobacteria, which are rare gut bacteria that were undetectable before the intervention. Although 16S RNA sequencing offers only relative measures, the described findings confirm the intervention to markedly reduce the gut bacteriome quantitatively, but also that total eradication was not obtained. These compositional alterations were similar to those reported for other patient groups (14–16).

As a surrogate measure of bacterial translocation, we measured LBP in plasma, which was not reduced more rapidly in the intervention group than during the spontaneous course of the disease. Two studies from the 80s and 90s used a single orally ingested, nonabsorbable antibiotic, paromomycin sulphate for patients with AH and cirrhosis; one reported an intervention-induced reduction in endotoxemia, whereas the other did not (17,18). Their studies and our findings likely reflect that fragments of the killed bacteria, particularly from Gram-negative species, still translocate through the gut wall. Likewise, the intervention effectively reduced viable Gram-negatives, as even the hard-lived *Proteobacterium* did not have a growth spike. LBP may not be a perfectly sensitive marker for liver LPS exposure, but LPS is not directly quantifiable in a meaningful way. Other markers of bacterial translocation are available, but there is no reason to suspect these to respond differently.

In the same way, we observed no effect of the intervention on either the macrophage activation markers or the measured cytokines, which is in line with the lack of signs of effect on bacterial translocation. Another possible explanation for the unchanged inflammation markers could be that the intervention was first established at the time of full-blown disease. The hepatic and systemic inflammation is florid when such patients are admitted, and thus, it may be too late to interrupt the self-perpetuating immune activation process by targeting the factors that may have initiated it. This is also supported from our previous publication showing sustained elevation of sCD163 levels in patients with AH (19).

The normal gut bacteriome exerts important metabolic functions and homeostatic immune modulations. Even in diseases such as AH where the gut bacteriome is pathologically altered, it probably maintains some beneficial functions, which we risk losing by removing all gut bacteria. Furthermore, an increased risk of sepsis with multiresistant organisms has been described following broad-spectrum, not radical antibiotic therapy (20); we observed 1 case of nonmultiresistent Staphylococcus sepsis in the intervention group. We can only speculate whether this was related to the intervention or to the high infection susceptibility of these patients.

We did not measure systemic concentrations of the orally ingested nonabsorbable antibiotics because the available data suggest systemic uptake to be negligible. Theoretically, uptake might be higher due to a higher permeability of the gut barrier in AH. This is the case during *Clostridium difficile* infections with overt gut barrier defects, but only modestly observed in patients with decompensated liver cirrhosis treated with the nonabsorbable antibiotic rifaximin (21,22). Thus, we believe that the systemic uptake is negligible.

As demonstrated, near-complete eradication of the gut bacteriome was not beneficial and possibly modulation of the bacteriome is preferable. This can be performed by means of prebiotics or transplantation of healthy fecal microbiota. One patient with AH with severe disease in a case report of fecal transplantation survived (23). The first, small, and not readily transparent fecal microbiota transplantation trial in patients with AH also seems to indicate a possible beneficial effect (24). Moreover, there is evidence for bacteriophages alleviating alcoholic liver disease (25).

The major strength of this study is the well-characterized cohort of patients with AH from a single Danish tertiary liver center. Weaknesses include the low number of patients and the low number of fecal samples secured only in the intervention group, leaving the study at risk of type 2 statistical errors. Furthermore, the patients were not randomized, which might have assured more even disease severity between the groups. However, based on our data, we recalculated the power analysis, and assuming that there in fact is a statistically significant effect of the intervention on markers of inflammation (LBP) at day 90, it would require a study with $n > 1,000$ in each group to prove it. Thus, the proof-of-concept design of $n = 14$ was chosen because we were looking for clinically relevant effects. Furthermore, such broad-spectrum antibiotics must be used restrictively because of risk of inducing antimicrobial resistance, *Clostridium difficile*, or a *Candida* superinfection. Also, the number of patients participating should be limited because of a theoretical risk of making matters worse by inducing a translocation storm of bacterial fragments in the process of killing the bacteria. This is relevant because in cirrhosis patients with recurrent HE, a 5-day treatment course of oral broad-spectrum antibiotics worsened their Model of End-Stage Liver Disease score (26).

In conclusion, our data indicate that gut-selective, broad-spectrum antibiotics do not hold the promise to reverse the destructive inflammatory chain of bacterial translocation, hepatic macrophage activation, and systemic inflammation in patients with established AH.

## CONFLICTS OF INTEREST

**Guarantor of the article:** Thomas Damgaard Sandahl, MD, PhD.
**Specific author contributions:** S.S., H.V., and T.D.S: designed the study. S.S., T.L.L., L.L.E., and T.D.S.: included the patients and acquired the data. S.S., H.V., H.G., and T.D.S.: analyzed and interpreted the data. S.S., H.V., and T.D.S.: drafted the manuscript. All authors critically revised the manuscript and approved the final version including the authorship list.
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Research (http://ufm.dk/en/research-and-innovation/councils-and-commissions/former-councils-and-commissions/the-danish-council-for-strategic-research) (TRAIN 10–092797).
**Potential competing interests:** S.S., T.L.L., L.L.E., H.G., H.V., and T.D.S. declare that they have no conflicts of interest.
The trial was reported at clinicaltrials.gov (1-10-72-1-15).

## Study Highlights

### WHAT IS KNOWN

- ✓ The gut is leaky in patients with alcoholic hepatitis (AH).
- ✓ Bacterial translocation is considered an important driver of hepatic and systemic inflammation in AH.

### WHAT IS NEW HERE

- ✓ Hepatic and systemic inflammation is not ameliorated by broad-spectrum gut-targeted antibiotic treatment.
- ✓ Gut-targeted antibiotic treatment reduces gut bacterial flora in AH.

### TRANSLATIONAL IMPACT

- ✓ Our study does not support the use of broad-spectrum, gut-targeted antibiotics as a treatment strategy for alcoholic hepatitis.

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