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Letter on "Synbiotics modulate gut microbiota and reduce enteritis and ventilator-associated pneumonia in patients with sepsis: a randomized controlled trial"

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See related research by Shimizu et al., https://ccforum.biomedcentral.com/articles/10.1186/s13054-018-2167-x.

Recently a very interesting article was published by Shimizu et al. [1] about the use of synbiotic (pro- and prebiotic) therapy in patients with sepsis in the intensive care unit. We were looking forward to this randomized trial, because conclusive and high evidence data is still sparse on this topic in intensive care medicine. However, we believe that the paper has some methodological flaws that impair the validity of the study:

First, the study was performed single blinded to the participants (who were severely ill and ventilated at the time of study entry) but not blinded to the treating physicians and was not compared to placebo, therefore bearing a high risk of performance bias [2].

Second, the randomization was done in a 1:1 ratio with permutation blocks, but the allocation sequence was generated by the corresponding author of the study without further clarification. This uncertainty is not meeting good clinical practice standards, and in our opinion, automatized generation of randomization sequences should be used.

Third, in the methods of the study, the authors define that patients receiving other probiotics, or were expected to be discharged or transferred out of the ICU within 3 days after admission, were excluded. However, of the 127 patients screened for eligibility, 50 patients were excluded because they received probiotic therapy before inclusion or were "too severely ill to survive," which in our understanding does not match the exclusion criterion "expected to be discharged or transferred out of the ICU." In the study, it is not presented how the intensivists defined the severity of the disease and the probability of survival and the consecutive exclusion from the study.

Fourth, the analysis of the microbiota was done with rectal swabs in this study. As previous studies have shown that the microbiota present in the rectal swabs differs strongly from colonic lumen or mucosal samples collected by colonoscopy, rectal swabs may be not a true representation of the colonic microbiota especially in critically ill patients [3]. We are aware that a full colonoscopy in critically ill patients is not feasible, but retrieving samples by rectoscopy could be a reasonable compromise. Furthermore, the study samples were analyzed using a proprietary 16S- and 23S-PCR system (Yakult Intestinal Flora-SCAN (YIF-SCAN)), where a diagnostic advantage for the detection of the study probiotics (Yakult BL Seichoyaku) cannot be excluded. Using full 16S rRNA microbiome sequencing would be a more objective analysis method.

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Authors' response

Kentaro Shimizu

We thank Dr. Reisinger and Dr. Stadlbauer for their insightful comments. As they pointed out, this was a single-blinded study in which the physicians were not blinded because it was difficult to create a placebo of Oligomate (the prebiotics used), which contains 55% or more galacto-oligosaccharide and is manufactured by the action of enzymes on lactose [4]. We used a 1:1 ratio with permutation blocks, but we did not automate the generation of randomization. These are limitations of the present research, and we expect the next step will be a double-blinded study. In response to the third comment, excluded patients were as follows: severely ill patients who could not be started enteral nutrition within 3 days of admission and non-severely ill patients who were able to eat after extubation and did not require enteral nutrition. In this research, the blood lactate level (median (IQR)) was 3.2 (1.7–5.7) mmol/L, and we thought that enteral nutrition could be provided with caution in patients treated with adrenergic agents, in accordance with the current guidelines [5]. Because patients with feeding intolerance were reported to have a higher rate of bacteremia and mortality [6], we used synbiotics when enteral nutrition could be tolerated.

In response to the fourth question, we agree with the comment that "rectal swabs may not be a true presentation of the colonic microbiota." However, our preliminary research reported that the percentages of *Bacteroidetes* and *Firmicutes* from swab samples showed significant serial dynamic changes, and an extreme imbalance was associated with prognosis in critically ill patients [7]. Swab samples may change and be representative of the current colonic microbiota in accordance with the clinical situation.

In addition, our study was a quantitative research study of the main subset of microbiota, and other whole bacteria were not evaluated as described in the limitations. However, many 16S rRNA microbiome research studies only include proportions, and not quantities, and so it is difficult to evaluate true changes in bacterial counts by assessing proportional changes alone. It was reported in critically ill patients that the number of obligate anaerobes was significantly decreased and that the decrease of obligate anaerobes and the increase of facultative aerobes were associated with bacteremia and mortality [8]. Assessment of both proportions and quantities in microbiome research should be included in further study.

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