

Probiotics: Should We Use Them Proactively in Critical Illness?

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Critical illness is a heterogeneous disease, a culmination of varied etiologies.¹ Despite the development of multiple interventions backed by sound physiological rationale, there are only a few, which have stood the test of time and are in current practice.² Most interventions are targeted toward reducing unacceptably high mortality in intensive care. Although mortality is an important patient-centric outcome, other clinical outcomes such as infections, duration of mechanical ventilation, length of ICU stay, and length of hospitalization among others are also worth pursuing. Microbiome alterations or dysbiosis are common in critical³ illnesses. The depletion of commensal microbiota and overgrowth of pathogenic microbes may result in susceptibility to myriad infections such as nosocomial infections, ventilator-associated pneumonia (VAP), and inflammatory conditions. Probiotics have been postulated to reduce the incidence of VAP and other infections.⁴ Probiotics consist of a family of bacteria,⁵ supplemented exogenously to replenish normal commensals that competitively inhibit pathogenic microbes within the gut. Probiotics are considered a relatively safe, inexpensive and useful intervention for a wide variety of diseases, infections, inflammatory conditions, and autoimmune diseases. Probiotics are presumed to reverse dysbiosis and thus offer benefits in a wide variety of illnesses. Despite strong physiological rationale, most available literature has failed to provide convincing evidence, favoring the use of probiotics in critical illnesses.⁶

In this editorial, we examine the review "Probiotics in critically ill patients; an umbrella review" performed to evaluate the role of probiotics in critical illness outcomes.⁷ The study included a comprehensive search of published systematic reviews till September 2020, in multiple databases such as PubMed, Embase, ScienceDirect, and Cochrane, targeting the adult critically ill patient population and use of probiotics. The authors included 20 systematic reviews which were further assessed for risk of bias using the risk of bias in systematic reviews tool (ROBIS). The authors found that commonly reported outcomes with the use of probiotics included VAP, overall mortality, hospital, intensive care unit (ICU) mortality, length of hospital and ICU stay, duration of mechanical ventilation, and incidence of nosocomial pneumonia and other infections. These are standard outcomes in critical care research. However, the authors also reported trials of probiotics for uncommon outcomes such as antibiotic use, septic complications, sleep quality and quantity, and modulation of inflammatory molecules. Most SRs were judged to have a high risk of bias in the selection of studies and synthesis. The authors concluded that probiotics may be useful in reducing the rate of VAP, nosocomial pneumonia, duration of antibiotic use, and mechanical ventilation

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but were inconsistent in reducing overall mortality and length of hospitalization.

This is concerning; VAP is widely considered as one of the factors associated with increased mortality and length of hospitalization. Theoretically, a decrease in the incidence of VAP should translate into a reduction in overall mortality and length of hospitalization. However, most published systematic reviews do not reveal any reduction in mortality with the use of probiotics. There could be several explanations for the discordant results of the impact of probiotics on critical illness outcomes. First, the drug might be ineffective for decreasing mortality. Yet, the signals seen in most studies demonstrate some trend, albeit insignificant, toward reduced rates of mortality. Second, the association of VAP with mortality may be lesser in magnitude than predicted in earlier studies. This would reduce the mortality slightly but not significantly. Third, the optimal dose, duration, and timing of probiotics are yet to be established; the dose, duration, and timing of administration of probiotics in clinical studies are variables. Fourth, the studies may be of low quality and underpowered for mortality outcome, thus failing to provide a conclusive answer. Fifth, as mentioned by the authors, prevailing heterogeneity of probiotics and nonstandard definitions of critical outcomes such as VAP limits the inclusion criteria and leads to dilution of the targeted population which could benefit. These explanations seem plausible in explaining the discordant results seen in the umbrella review. However, these concerns are common in most critical care trials and research. Recently, adaptive designs have been used which enrich the patients with a high likelihood of benefit; these may potentially identify groups of critically ill patients in which the use of probiotics could be beneficial. The umbrella review does indicate that the role of probiotics in critical illness needs to be evaluated with better design.

In the recently published systematic review of probiotics in critical care patients, the authors found either significant association or general trend favoring probiotics for almost all outcomes.⁴ But, when the authors combined six trials (including 785 patients) with a low risk of bias, a nonsignificant trend was seen for the reduction of VAP toward probiotics.

Contrary to the conclusion of this umbrella review and others, the largest multicenter study on the use of probiotics, which was published after the study period, failed to show any benefit for all outcomes—including VAP—in a broad critically ill patient population.⁸ Moreover, the study found lactobacillus bacteremia in patients with serious underlying comorbidities, raising concerns of harm. This is the largest study enrolling 2,653 randomized adult critically ill patients across 44 ICUs in different parts of the world. It included a broad patient population—medical, surgical, and trauma—with significant severity and within 72 hours of ICU admission. The primary outcome was the incidence of VAP, while secondary outcomes were infections and mortality. The study reported no significant difference between intervention and placebo arm in either of the outcomes and concluded that the use of *Lactobacillus rhamnosus GG* (probiotic) for the prevention of VAP in critically ill patients requiring mechanical ventilation was not supported. The study is methodologically robust with safeguards against biases—compared to previous studies of probiotics in a similar study population. However, despite the above strength, the inherent limitations of this research topic, which were elaborated earlier, persist albeit to a smaller extent. Perhaps the studied population was too sick to benefit from the use of probiotics. As shown by a large study in neonates, the correct selection of population along with optimum dose, duration, and timing of probiotic administration may still be effective in reducing infections and mortality.

Systematic reviews and meta-analyses are the cornerstones of synthesizing available scientific knowledge and are considered the pinnacle of the evidence-based medicine⁹ pyramid. They form the basis of recommendations that are issued as guidelines from multiple societies in each aspect of healthcare. Recent years have witnessed an explosion of these in all disease conditions primarily owing to easy accessibility to published studies and improvement in technology. However, the ability of the general clinician to critically appraise the published reviews is greatly lacking and thus he/she may fall prey to prevailing biases. The credibility of a published systematic review depends largely upon the methods and quality of included studies. If the quality of included studies is low, the confidence in effect estimates will be low and so would

be the conclusions. On the other hand, systematic reviews provide a more precise evaluation of existing gaps in the literature and an informed direction for future research.

The current umbrella review offers a comprehensive view of the available literature assessing the role of probiotics in adult critical illnesses. It summarizes the key outcomes in critical illness for which probiotics could be useful. However, unless new evidence emerges, the results of the recent large multicenter trial dissuade the use of probiotics in routine clinical practice and encourage their use in trial settings.

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REFERENCES

1. Pirracchio R, Gropper MA. Heterogeneity in intensive care: low severity does not mean low risk! *Anesthesiology* 2019;130(2):190–191. DOI: 10.1097/ALN.0000000000002537.
2. Santacruz CA, Pereira AJ, Celis E, Vincent J-L. Which multicenter randomized controlled trials in critical care medicine have shown reduced mortality? A systematic review. *Crit Care Med* 2019;47(12):1680–1691. DOI: 10.1097/CCM.0000000000004000.
3. Wischmeyer PE, McDonald D, Knight R. Role of the microbiome, probiotics, and “dysbiosis therapy” in critical illness. *Curr Opin Crit Care* 2016;22(4):347–353. DOI: 10.1097/MCC.0000000000000321.
4. Batra P, Soni KD, Mathur P. Efficacy of probiotics in the prevention of VAP in critically ill ICU patients: an updated systematic review and meta-analysis of randomized control trials. *J Intensive Care* 2020;8:81. DOI: 10.1186/s40560-020-00487-8.
5. Madsen K. Probiotics in critically ill patients. *J Clin Gastroenterol* 2008;42 (Suppl 3) Pt 1:S116–S118. DOI: 10.1097/MCG.0b013e31817283cb.
6. Theodorakopoulou M, Perros E, Giamarellos-Bourboulis EJ, Dimopoulos G. Controversies in the management of the critically ill: the role of probiotics. *Int J Antimicrob Agents* 2013;42 (Suppl): S41–S44. DOI: 10.1016/j.ijantimicag.2013.04.010.
7. Naseri A, Seyedi-Sahebari S, Mahmoodpoor A, Sanaie S. Probiotics in Critically Ill Patients: An Umbrella Review. *Indian J Crit Care Med* 2022;26(3):339–360.
8. Johnstone J, Meade M, Lauzier F, Marshall J, Duan E, Dionne J, et al. Effect of probiotics on incident ventilator-associated pneumonia in critically ill patients: a randomized clinical trial. *Journal of the American Medical Association* 2021;326(11):1024–1033. DOI: 10.1001/jama.2021.13355.
9. Foroutan F, Guyatt G, Alba AC, Ross H. Meta-analysis: mistake or milestone in medicine? *Heart* 2018;104(19):1559–1561. DOI: 10.1136/heartjnl-2018-313042.