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Probiotics for the prevention of ventilator-associated pneumonia

Probiotici u prevenciji pneumonija kod pacijenata na mehaničkoj ventilaciji

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Summary

Ventilator-associated pneumonia is associated with a high rate of all-cause mortality and a prolonged duration of mechanical ventilation and intensive care unit stay. Ventilator associated pneumonia accounts for about half of all antibiotics given in the intensive care unit. Plenty of studies have assessed various kinds of prevention strategies, including pharmacological and non-pharmacological interventions, to prevent ventilator-associated pneumonia over the years. An emerging number of studies has assessed the non-antibiotic approaches for the prevention of ventilator-associated pneumonia in the last few years. One of the frequently used strategy is addition of probiotics in the preventive measures list. Regular consumption of probiotics can modulate immune responses and metabolic processes as well as antioxidant and anti-inflammatory effects. The strongest evidence in favor of probiotics lies in the prevention or treatment of necrotizing enterocolitis, acute infectious diarrhea, acute respiratory tract infections, antibiotic-associated diarrhea, and infant colic. The beneficial effects of probiotics in the prevention of ventilator-associated pneumonia were not yet entirely clarified. Multiple pieces of evidence indicate that the bacteria that populate the gut efficiently modulate the immune response. Treatment with probiotics have shown promising preliminary results to attenuate systemic inflammation, especially in postoperative infections and ventilation performance. This review aims to summarize latest data on the use probiotics to prevent ventilator-associated pneumonia in critical care unit.

Key words: Ventilator-associated pneumonia, probiotics, prevention

Sažetak

Pneumonija kod pacijenata na mehaničkoj ventilaciji (MV) razlog je za visok stepen mortaliteta, produženo trajanje mehaničke ventilacije i produžen boravak u jedinici intenzivne nege. Brojne studije objavljene su sa temom prevencije ovakvih stanja, sa farmakološkog i nefarmakološkog aspekta. Veliki broj studija se bavi neantibiotskim pristupom u prevenciji pneumonija kod pacijenata na MV. Jedan od pristupa je primena probiotika u cilju prevencije pneumonija. Redovna upotreba probiotika modilira imuni odgovor, metaboličke procese, ima antioksidativni i antiinflamatorni efekat. Očigledno je da bakterije crevne sluznice efikasno moduliraju imuni odgovor. Najviše potvrda u prilog probiotika povezano je sa tretmanom nekrotizirajućeg enterokolitisa, akutne infektivne dijareje, akutnih respiratornih infekcija, antibioticima udružene dijareje, infantilnih kolika. Korist od primene probiotika u slučaju pneumonije izazvane MV, nije u potpunosti razjašnjena. Tretman koji uključuje i probiotike pruža obećavajuće rezultate u smanjenju sistemske inflamacije, naročito u postopertaivnim stanjima i kod pacijenata na MV. Ovaj pregledni članak razmatra upotrebu probiotika u prevenciji pneumonija kod pacijenata na MV u jedinici intenzivne nege.

Ključne reči: pneumonija kod pacijenata na MV, probiotici, prevencija

Ventilator-associated pneumonia (VAP) is defined as a pulmonary infection in patients who have been mechanically ventilated continuously for at least a forty-eight-hour period (1). Ventilator-associated pneumonia results from the invasion of the lower respiratory tract and lung parenchyma by microorganisms. Intubation compromises the integrity of the oropharynx and trachea and allows oral and gastric secretions to enter the lower airways. VAP is associated with a high rate of all-cause mortality and a prolonged duration of mechanical ventilation and ICU stay. Hospital-acquired pneumonia (HAP) is pneumonia that develops 48 hours or longer after admission to a hospital in nonventilated patients (2).

In 2016, the American Thoracic Society (ATS) and the Infectious Disease Society of America (IDSA) updated guidelines for the management of HAP and ventilator-associated pneumonia (VAP). VAP is no longer a subtype of HAP as in previous guidelines. HAP and VAP are now

viewed as distinct entities. VAP is further divided into multidrug resistant (MDR) VAP and non-MDR VAP (3).

On account of the high incidence, severity and enormous burdens of VAP, plenty of studies have assessed various kinds of prevention strategies, including pharmacological and non-pharmacological interventions, to prevent VAP over the years. Fortunately, the incidence of VAP has been steadily decreasing in recent years possibly due to the application of the ventilator bundles, such as hand hygiene, oral care, semi-recumbent position, and subglottic secretion drainage system, daily sedation vacations as well as deep vein thrombosis prophylaxis, etc. (4).

An emerging number of studies has assessed the non-antibiotic approaches for the prevention of VAP in the last few years. The term “probiotics”, defined as live nonpathogenic microorganisms that exert a health benefit to the host later, first appeared in 1974 and it might represent a novel non-antibiotic intervention (5). The beneficial effects of probiotics in the prevention of VAP were not yet entirely elucidated, perhaps via modulating intestinal microbiota, adjusting immune response, improving gut barrier function and suppressing pathogenic bacteria overgrowth (6).

The origin of “microbiota” can be dated back to early 1900s. It was found that a vast number of microorganisms, including bacteria, yeasts, and viruses, coexist in various sites of the human body - gut, skin, lung, oral cavity. In addition, the human microbiota, also known as “the hidden organ,” contribute over 150 times more genetic information than that of the entire human genome. Although “microbiota” and “microbiome” are often interchangeable, there are certain differences between the two terms. Microbiota describes the living microorganisms found in a defined environment, such as oral and gut microbiota. Microbiome refers to the collection of genomes from all the microorganisms in the environment, which includes not only the community of the microorganisms, but also the microbial structural elements, metabolites, and the environmental conditions. In this regard, microbiome encompasses a broader spectrum than that of microbiota (7).

The gut microbiome harbors complex communities of bacteria which together fulfill a wide range of functions within the human body. A balanced gut microbiome enhances the host defense against infection by fine tuning the local and systemic immune system, repressing enteric pathogens, and supporting epithelial barrier integrity (8). Conversely, perturbation of the microbiome (called ‘dysbiosis’) appears to have detrimental effects on the host and is associated with a wide range of diseases. In healthy conditions, the gut microbiota exhibits stability, resilience, and symbiotic interaction with the host. There is a lot of research into the definition of a “healthy” gut microbiota and its link to host physiological functions. Gut microbiota is composed of bacteria, yeasts, and viruses. A healthy microbiota community often demonstrates high taxonomic diversity, high microbial gene richness and stable core microbiota (9).

Probiotics are living microorganisms that, when administered in adequate amounts, confer health benefits to the host. Regular consumption of probiotics can modulate immune responses and metabolic processes as well as antioxidant and antiinflammatory effects, with these microorganisms acting as gut microbial modulators. The mechanisms or metabolic pathways through which probiotic supplementation benefits human health are not yet well established (10).

According to the International Scientific Association, probiotics and prebiotics are defined as live microorganisms that, when administered in adequate quantities, confer some health benefits to the host. Probiotic strains exert their antimicrobial properties through the production of ammonia, lactic acid, free fatty chains, hydrogen peroxide, and bacteriocins. Probiotics affect the intestinal ratio of beneficial and harmful bacteria in favor of the growth of beneficial bacteria (11).

Critically ill patients have a hyper-inflammatory response against various offending injuries that can result in tissue damage, organ failure, and fatal prognosis. The origin of this detrimental, uncontrolled inflammatory cascade can be found also within our gut. In detail, one of the main actors is our gut microbiota with its imbalance, namely gut dysbiosis: learning about the microbiota's dysfunction and pathophysiology in the frame of critical patients is of crucial and emerging importance in the management of the systemic inflammatory response syndrome (SIRS) and the multiple organ dysfunction syndrome (MODS). Multiple pieces of evidence indicate that the bacteria that populate our gut efficiently modulate the immune response. Treatment and pretreatment with probiotics have shown promising preliminary results to attenuate systemic inflammation, especially in postoperative infections and ventilation performance. Finally, it is emerging how immunonutrition may exert a possible impact on the health status of patients in intensive care. (12).

In a systematic review and meta-analysis, published in 2020, it was shown that probiotic administration has a promising role in lowering the incidence of VAP, the duration of mechanical ventilation, length of ICU stay, and in-hospital mortality. Nine studies were included in the meta-analysis. The incidence of VAP, duration of mechanical ventilation, length of ICU stay and in-hospital mortality in the probiotic group was significantly lower than that in the control group. Probiotic administration was not associated with a statistically significant reduction in length of hospital stay, incidence of oro-pharyngeal colonization and incidence of diarrhea (13).

A systematic review and network meta-analysis of randomized controlled trials based on a Bayesian framework, published in 2021, the efficacy of synbiotics, probiotics, prebiotics, enteral nutrition or adjuvant peripheral parenteral nutrition (EPN) and total parenteral nutrition (TPN) in preventing nosocomial infection (NI) in critically ill

adults has been questioned. Fifty-five RCTs (7,119 patients) were identified. Primary outcome showed that synbiotics had the best effect in preventing NI than EPN, probiotics followed, whereas TPN significantly increased NI. Subgroup analysis showed that TPN significantly increased NI in intensive care unit (ICU) patients and severe acute pancreatitis (SAP) patients. Secondary outcomes showed that synbiotics were more effective in preventing hospital-acquired pneumonia (HAP), catheter-related bloodstream infection, urinary tract infection and sepsis than EPN. Amongst the treatments, probiotics were most effective for shortening the mechanical ventilation duration, prebiotics were most effective for preventing diarrhea and TPN was the least effective in shortening hospital length of stay. Authors concluded, that amongst the five therapies, synbiotics not only prevented NI in critically ill adults but also demonstrated the best treatment results. By contrast, TPN did not prevent NI and ranked last, especially in ICU and SAP patients (14).

In a systematic review with meta-analysis, published in the European Respiratory Journal in 2022, 15 studies involving 2039 patients were identified for analysis. The pooled analysis suggests significant reduction on VAP in a fixed-effects model. Subgroup analyses performed on the category of clinical and microbiological criteria both support the above conclusion; however, there were no significant differences in duration of mechanical ventilation (MV) or length of ICU stay in a random-effects model. Also, no significant differences in total mortality, overall mortality, 28-day mortality or 90-day mortality were found in the fixed-effects model. Authors concluded, that probiotics helped to prevent VAP without impacting the duration of MV, length of ICU stay or mortality (15).

In a meta-analysis, performed in 2022, a total of 15 studies involving 4,693 participants were included. The incidence of VAP in the probiotic group was significantly lower. The probiotic administration was associated with a significant reduction in the duration of mechanical ventilation, length of ICU stay and incidence of bacterial colonization. No statistically significant differences were observed regarding the incidence of diarrhea and mortality between probiotics group and control group (16).

In another meta-analysis, published in the same 2022 year, a total of 25 randomized controlled trials reporting on 5049 critically ill patients were included. In the intervention group, 2520 participants received probiotics or synbiotics, whereas 2529 participants received standard care or placebo. Pooling data from randomized controlled trials demonstrated a significant reduction in the incidence of ventilator-associated pneumonia in the treatment group. However, in the subgroup analysis, the reduction of incidence of VAP was only significant in patients receiving synbiotics and not significant in those receiving only probiotics. Moreover, sepsis incidence of critically ill patients was only significantly reduced by the addition of synbiotics. The incidence of ICU-acquired infections was significantly reduced by the synbiotics therapy. There was no significant difference in mortality, diarrhea, or length of ICU stay between the treatment and control groups. Authors concluded that synbiotics are an effective and safe nutrition therapy in reducing septic complications in critically ill patients. However, in such patients, administration of probiotics alone compared with placebo resulted in no difference in the septic complications (17).

In a meta-analysis of the effects of probiotics on various parameters in critically ill ventilated individuals, which was published in 2023, 5893 critically ill ventilated subjects were identified; 2912 of them were using the probiotics, and there were 2981 controls. Odds ratio (OR) and mean difference (MD) with 95% confidence interval (95% CI) were calculated to assess the effect of probiotics on different parameters in critically ill ventilated subjects using the dichotomous and contentious methods with a random or fixed effects model. The probiotics caused a significantly lower incidence of ventilator-associated pneumonia, shorter duration of mechanical ventilation, shorter intensive care unit stay, shorter hospital stay, and lower oropharyngeal colonization in critically ill ventilated subjects compared with controls. However, probiotic use had no significant difference in terms of diarrhea incidence and in-hospital mortality in critically ill ventilated subjects compared with controls. As a conclusion, probiotics caused a significantly lower ventilator-associated pneumonia incidence, shorter duration of mechanical ventilation, shorter ICU and hospital stay, and lower oropharyngeal colonization. However, there was no significant difference in terms of diarrhea incidence and in-hospital mortality in subjects who used probiotics compared with controls (18).

A systematic review and meta-analysis of randomized controlled trials with trial sequential analysis, published in 2023, aimed to analyze a beneficial effect of probiotics on clinical or diarrheal outcomes in critically ill patients. Seventy-five studies with 71 unique trials (n = 8551) were included. In the overall analysis, probiotics significantly reduced VAP incidence. However, such benefits were demonstrated only in lower, but not higher quality studies, with significant test for subgroup differences ($p = 0.004$). Additionally, trial sequential analysis (TSA) showed that the VAP benefits of probiotics in the overall and subgroup analyses were type-1 errors. In higher quality trials, TSA found that future trials are unlikely to demonstrate any benefits of probiotics on infectious complications and diarrhea. Probiotics had higher adverse events than control (19).

In another recent systematic review of 10 clinical trials evaluated the effects of probiotics, and two trials evaluated the effects of synbiotics on VAP hospitalized in ICU. Among these trials, 11 had investigated these effects on the adult population and one on children. In total, 2132 individuals were in the probiotic group and 2032 in the placebo group. In total, six clinical trials highlighted the considerable effects of probiotics on the reduction or prevention of VAP ($p < 0.05$), so that the mean prevalence of VAP was lower in the probiotic group (23.89%, ranging from 0.66% to 40.7%) than

the placebo group (38.27%, ranged 0.94% to 53%). However, some studies did not find any effects following probiotic consumption (20).

In a randomized, placebo-controlled study enrolling multi-trauma patients, patients expected to require mechanical ventilation for > 10 days were assigned at random to receive prophylaxis with a probiotic formula (n = 59) or placebo (n = 53). The probiotic formula was a preparation of *Lactobacillus acidophilus LA-5*, *Lactobacillus plantarum, Bifidobacterium lactis* BB- 12 and *Saccharomyces boulardii*) in sachets. Each patient received two sachets twice daily for 15 days: one through the nasogastric tube and one spread on the oropharynx. The incidence of VAP was the primary endpoint. The incidence of other infections and sepsis, and the duration of hospital stay were the secondary endpoints. Administration of probiotics reduced the incidence of VAP (11.9% vs 28.3%) and sepsis (6.8% vs 24.5%). Furthermore, probiotic prophylaxis reduced the time of stay in the intensive care unit (ICU) and the length of hospital stay. The prophylactic use of probiotics with a combination of enteral and topical application to the oropharynx had a positive effect on the incidence of VAP and sepsis, as well as on ICU and total hospital stay in patients receiving protracted mechanical ventilation (21).

In a randomized, double-blind clinical trial, which was performed in 2022 and included 72 children under 12 years of age under mechanical ventilation for more than 48 h., patients were randomly divided into Limosilactobacillus reuteri DSM 17938 probiotic recipients (n = 38) and placebo groups (n = 34). In addition to the standard treatment, both groups received a sachet containing probiotics or a placebo twice a day. Children were screened for VAP based on clinical and laboratory evidence. After adjusting the other variables, it was observed that chance of VAP among probiotics compared to the placebo group was significantly decreased. Also, probiotic was associated with a significantly lower chance of diarrhea than the placebo group. Authors conclude, that probiotic utilization is effective in preventing the incidence of VAP and diarrhea in children under mechanical ventilation in the PICU (22).

In a randomized placebo-controlled trial in 44 ICUs in Canada, the United States, and Saudi Arabia enrolling adults predicted to require mechanical ventilation for at least 72 hours. A total of 2653 patients were enrolled from October 2013 to March 2019. Enteral *L rhamnosus* GG (1 × 1010 colony-forming units) (n = 1321) or placebo (n = 1332) twice daily in the ICU were administered. The primary outcome was VAP determined by duplicate blinded central adjudication. Secondary outcomes were other ICU-acquired infections including Clostridioides difficile infection, diarrhea, antimicrobial use, ICU and hospital length of stay, and mortality. Among 2653 randomized patients (mean age, 59.8 years, 2650 (99.9%) completed the trial (mean age, 59.8 years; 1063 women (40.1%.) with a mean Acute Physiology and Chronic Health Evaluation II score of 22.0 and received the study product for a median of 9 days. VAP developed among 289 of 1318 patients (21.9%) receiving probiotics vs 284 of 1332 controls (21.3%). None of the 20 prespecified secondary outcomes, including other ICU-acquired infections, diarrhea, antimicrobial use, mortality, or length of stay showed a significant difference. Fifteen patients (1.1%) receiving probiotics vs 1 (0.1%) in the control group experienced the adverse event of *L rhamnosus* in a sterile site or the sole or predominant organism in a nonsterile site. The results of the study indicated, that among critically ill patients requiring mechanical ventilation, administration of the probiotic *L rhamnosus GG* compared with placebo, resulted in no significant difference in the development of ventilator-associated pneumonia (23).

In a study of the effects of synbiotic supplementation on enteral feeding tolerance, protein homeostasis, and muscle wasting of critically ill adult patients a consecutive of 42 patients, requiring enteral nutrition (EN), were prospectively randomized to receive the synbiotic capsule (containing a combination of *Lactobacillus, Bifidobacterium, Streptococcus*, and fructooligosaccharides) or placebo (21 patients in each group) for a maximum of 14 days. Enteral intolerance and energy homeostasis were evaluated on a daily basis. Nitrogen balance and 24-h urine creatinine excretion were recorded on days 1 and 14. Mid-arm circumference was recorded every 3 days. Mean EN volume, energy, and protein intake per day were 962.5 ± 533.82 ml, 770 ± 427.05 kcal, and 38.5 ± 21.35 g (fourth day) vs. 590 ± 321.1 ml, 472 ± 256.81 kcal, and 23.6 ± 12.84 g (first day) in the synbiotic group ($p < 0.05$). Changes in the placebo group were not statistically significant. On day 1, nitrogen balance (NB) was - 19.84 ± 8.03 in the synbiotic vs. - 10.99 ± 9.12 in the placebo group ($p = 0.003$). On day 14, NB was - 14.18 ± 13.05 in the synbiotic and - 9.59 ± 7.71 in the placebo group ($p = 0.41$). Mid-arm circumference, 24-h urine creatinine, and creatinine-height index were almost steady in the synbiotic group, while they decreased in the placebo group. Overall, it was concluded that enteral nutrition supplemented with synbiotics has no statistically significant effect on energy and protein homeostasis and muscle mass maintenance of critically ill patients on day 14, but it can increase enteral feed volume and energy and protein intake during the first 4 days of ICU admission (24).

The double-blinded controlled clinical trial clinical trial aimed to investigate the efficacy of synbiotics in improving EFI and oropharyngeal aspiration in patients admitted to the intensive care unit, which was published in 2023, was conducted on 105 critically ill patients admitted to the ICU of a tertiary referral hospital affiliated with a medical university. The patients were randomly assigned to either a synbiotic or control group and underwent 7 days of investigation. The primary end point was reduced gastric residual volume, which is suggestive of an improvement in EFI. The secondary end point included requirement for prokinetics, frequency of aspiration, duration of mechanical ventilation, length of ICU stay, and level of consciousness. It was found out, that synbiotic intervention has resulted in a significantly

diminished requirement for prokinetics, fewer oropharyngeal aspirations, improved volume of bolus administration, and decreased gastric residual volume during the 7-day follow-up period. The patients who received synbiotic had an improved level of consciousness, and hence, better tolerance of enteral feeding (25).

In conclusion, the results of different studies indicate that the administration of probiotics may be useful in reducing the incidence of VAP in critically ill patients. Preventive use of probiotics may be a possible effective non-pharmacological option in reducing the time of stay in the ICU and the length of hospital stay in the ventilated patients. However, the long-run effects of probiotics safety on individuals dictate further studies, especially in special groups of critically ill patients. Large-scale, well-designed, multicenter trials are needed to validate the current findings and take a decision about the effectiveness of different strains of probiotics.

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