Probiotics in Pediatric Critical Illness

Subjects: Microbiology

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In 2002, for the first time, the World Health Organization (WHO) described probiotics as live micro-organisms that, when administered in the necessary quantities, help to maintain the homeostasis of the intestinal flora. In fact, the microbiome is a collection of microorganisms that live in symbiosis with the human body and play a crucial role in regulating the response of the intestinal immune system through production of anti-inflammatory cytokines and inhibition of pro-inflammatory cytokines.

pediatric critical illness | pediatric intensive care unit | children | probiotic | lactobacillus | lactobacillus reuteri

1. Overview

The use of probiotics in critically ill adult and children patients has been growing exponentially over the last 20 years. Numerous factors in pediatriac intensive care unit (PICU) patients may contribute to intestinal dysbiosis, which subsequently promotes the pathobiota's growth. Currently, lactobacillus and bifidobacterium species are mainly used to prevent the development of systemic diseases due to the subverted microbiome, followed by *streptococcus*, *enterococcus*, *propionibacterium*, *bacillus* and *Escherichia coli*, *Lactobacillus rhamnosus GG*, and *Lactobacillus reuteri DSM 17938*. The aim of this article is to review the scientific literature for further confirmation of the importance of the usage of probiotics in intensive care unit (ICU) patients, especially in the pediatric population. A progressive increase in nosocomial infections, especially nosocomial bloodstream infections, has been observed over the last 30 years. The World Health Organization (WHO) reported that the incidence of nosocomial infections in PICUs was still high and ranged between 5% and 10%. Petrof et al. was one of the first to demonstrate the efficacy of probiotics for preventing systemic diseases in ICU patients. Recently, however, the use of probiotics with different lactobacillus spp. has been shown to cause a decrease of pro-inflammatory cytokines and an increase in anti-inflammatory cytokines. In addition, in some studies, the use of probiotics, in particular the mix of Lactobacillus and Bifidobacterium reduces the incidence of ventilator-associated pneumonia (VAP) in PICU patients requiring mechanical ventilation. In abdominal infections, there is no doubt at all about the usefulness of using Lactobacillus spp probiotics, which help to treat ICU-acquired diarrhoea episodes as well as in positive blood culture for candida spp. Despite the importance of using probiotics being supported by various studies, their use is not yet part of the standard protocols to which all doctors must adhere. In the meantime, while waiting for protocols to be drawn up as soon as possible for use in PICUs, routine use could certainly stimulate the intestine's immune defences. Though it is still too early to say, they could be considered the drugs of the future.

2. Probiotics

Interest in the use of probiotics in critically ill patients in ICUs for adults or children has been growing exponentially over the last 20 years with numerous studies each year, but the first trials on the importance of probiotics were carried out about 30 years ago [1].

In 2002, for the first time, the World Health Organization (WHO) described probiotics as live micro-organisms that, when administered in the necessary quantities, help to maintain the homeostasis of the intestinal flora [2]. In fact, the microbiome is a collection of microorganisms that live in symbiosis with the human body and play a crucial role in regulating the response of the intestinal immune system through production of anti-inflammatory cytokines and inhibition of pro-inflammatory cytokines [3][4][5][6].

In addition, the microbiota builds a physical barrier between the outside and inside of our bodies with the help of the caliciform cells, which produce mucus made up of proteins that strengthen the barrier of the intestinal wall [7][8]. Moreover, the enterocytes produce antibacterial substances, such as bacteriocins and lactate, that can inhibit the growth of patho-biota [9][10]. Studies conducted in the past have shown that the loss of normal intestinal flora and its replacement by the growth of pathogenic bacteria (dysbiosis) can lead to the development of critical illnesses [11]. Sepsis has an important impact on the gastrointestinal function and the associated permeability alteration can become a source of systemic infection [12].

The composition of the gut microbiome in ICU patients has previously been shown to play a major role in determining the outcome in those patients. Additionally, enteral nutrition and the use of various drugs, particularly antibiotics, can lead to alteration of the gut microbiome in ICU patients [13][14][15].

Regrettably, despite this solid evidence, probiotics are not part of the standard protocols in the ICU [16].

The most commonly used probiotics are lactobacillus and bifidobacterium species, followed by streptococcus, enterococcus, propionibacterium, bacillus, and *Escherichia coli* [17]. In particular, *Lactobacillus rhamnosus GG* [18] and *Limosilactobacillus reuteri* [19] have been widely used in the treatment of infections of the gastrointestinal tract, inflammatory diseases, and drug-induced diarrhoea in the ICU in both adults and children. In addition to those, probiotics based on certain yeast species, such as *Saccharomyces boulardii* [20] and *Saccharomyces cerevisiae* [21][22], are also widely used, especially in the treatment of diseases of the gastrointestinal tract [20][22].

3. Conclusions

The importance of using probiotics in the PICU is supported by various studies and their use is growing daily. **Table 1** shows the most important studies supporting the use of probiotics mentioned in our article. Despite the scientific evidence, the use of probiotics in PICU patients is not yet part of the standard protocols. This is probably because, although they are safe and evidence confirms their importance in restoring the balance of the microbiota of pediatric and non-pediatric patients, and in assisting standard therapy in the course of even serious infectious

diseases, these are the most fragile patients where the microbiota, although rarely, can induce bacteremia, fungemia, and sepsis. Well-designed multi-center RCTs are needed to address these issues before the routine use of probiotics is recommended in critically ill children.

Table 1. Summary of high-power studies supporting the benefit of probiotics in the pediatriac intensive care unit (PICU).

	Authors	Study and Period	Patient Group	Administrations	Main Results
1	Singhi S. et al.	1991–1996, 1999–2000, 2002–2003 High statistical power	861 episodes of nosocomial bloodstream infection were documented in 841 patients	——	- Increase of frequency of nosocomial infection in the PICU - Increasing trend of resistance to the commonly used cephalosporins.
2	Petrof et al.	Sistemic review 1980–2011 High statistical power	23 randomized controlled trials enrolling critically ill adults, which evaluated probiotics compared with a placebo and reported clinically important outcomes	Probiotics with the conventional prescribed therapy set in the ICU leads	- Using probiotics in preventing systemic diseases leads to a reduction in complications related to infections.
3	Honeycutt TC et al.	Randomized, double-blind, placebo-controlled trial, April 2004–December 200 Low statistical power	61 total pediatric ICU patients: 31 of treatment group vs. 30 of placebo group	One capsule of Lactobacillus rhamnosus strain ones a day vs. one capsule of insulin once a day	- No results in support of the usage of probiotics.
4	Angurana SK et al.	Randomized, double-blind, placebo-	100 children 3 months to 12 years old with	Probiotic group received a multistrain, high-dose probiotic product VSL#3,	- Using probiotics leads to a

	Authors	Study and Period	Patient Group	Administrations	Main Results
		controlled trial, November 2014–October 2015 High statistical power	severe sepsis in the ICUs (probiotic group *n* = 50 vs. placebo group *n* = 50)	which contained Lactobacillus paracasei, *L. plantarum, L. acidophilus, L. delbrueckii, Bifidobacterium longum, B. infantis, B. breve, Streptococcus salium, B. infantis and B. delbrueckii. breve,* and *Streptococcus salivarius*	decrease of proinflammatory cytokines and an increase of anti-inflammatory cytokines.
5	Wang Y. et al.	Systematic review and meta-analysis, from the earliest available date to 30 April 2016. High statistical power	23 trials involving 6269 children in the PICUs, probiotics groups vs. placebo groups	——	- Probiotics lead to lower probability of developing complication and fast healing.
6	Banupriya et al.	Open-label randomized controlled trial, November 2011 and July 2013 High statistical power	150 pediatric patients requiring mechanical ventilation for more than 48 h in the PICU (75 vs. 75 patients)	Mix of Lactobacillus acidophilus, *L. rhamnosus, Lactobacillus plantarum, L. casei, Lactobacillus bulgaricus, Bifidobacterium longum, B. infantis, Bifidobacterium breve*, and *Streptococcus thermophilus* for 7 days or until discharge	- Probiotics lead to a decrease in the incidence of VAP and a decrease in the ICU stay; - Probiotics lead to lower colonisation by potentially pathogenic organisms, Klebsiella, and Pseudomonas.
7	Shimizu et al.	Randomized controlled trial, November 2011–September 2016 Intermediate	72 patients in the PICUs (35 patients receiving synbiotics and 37 patients not receiving synbiotics)	A daily symbiotics administration (in particular, bifidobacterium breve strain yakult, lactobacillus casei strain Shirota, and galacto-oligosaccharides).	- Probiotic lead to decrease of the incidence of VAP and of the incidence of enteritis.

	Authors	Study and Period	Patient Group	Administrations	Main Results
		statistical power			
8	Szajewska H. et al.	Recommendations, developed by the Working Group (WG) on Probiotics of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition, for the use of probiotics for the prevention of antibiotic-associated diarrhea (AAD) in children based on systematic review, 2016			- The incidence of ICU-acquired diarrhoea episodes decreased in children treated with Lactobacillus rhamnosus GG.
9	Kumar S. et al.	Prospective double-blinded, randomised controlled trial, November 2007–October 2008 High statistical power	150 PICU children aged between 3 months and 12 years: placebo group (n = 75) and probiotics group (n = 75)	Probiotics contained *Lactobacillus acidophillus, L. rhamnosum, Bifidobacterium longum, B. bifidum, Saccharomyces boulardi,* and *S. thermophilus*.	- Probiotics lead to less Candida colonisation and reduce a pathological growth of Candida; - Candiduria was less common in the probiotic group.
10	Manzoni et al.	Retrospective study, 2003–2008 Very high statistical power	743 VLBW infants	Lactobacillus GG as a single dose of 3×10^9 CFU/day from the fourth day of life for 4 to 6 weeks	- Probiotics were well tolerated without any adverse effects and did not lead to bacteremia or sepsis episode attributable to Lactobacillus GG.
11	Simakachorn N. et al.	Controlled, double-blind, randomised clinical trial, August 2006–May 2009	94 patients between 1 and 3 years old under mechanical ventilation	Synbiotic blend composed of two probiotic strains, *Lactobacillus paracasei* NCC 2461 and	- Probiotic's formula was as well tolerated as the currently used

WHO

2016, 535, 65–74.

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Authors	Study and Period	Patient Group	Administrations	Main Results
	Intermediate statistical power	requiring enteral feeding	*Bifidobacterium longum* NCC 3001	formula and that it was safe.

High statistical power 0.8–0.9; intermediate statistical power 0.7–0.6; low statistical power < 0.5.

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