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Controversies in the management of the critically ill: the role of probiotics

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ABSTRACT

Probiotics are commercially available, viable, non-pathogenic micro-organisms that, when ingested in sufficient quantities, exert a health benefit to the host derived through modification of the gut flora, local release of antimicrobial factors, maintenance of integrity of the gut barrier, competition for epithelial adherence, prevention of bacterial translocation, and modulation of the local immune response. In critically ill patients, probiotics appear to lead to decreased susceptibility to antibiotic-associated diarrhoea, *Clostridium difficile* infections, ventilator-associated pneumonia, necrotising enterocolitis, acute severe pancreatitis, sepsis and multiple organ dysfunction syndrome as well as a shortened duration of infections. Current scientific evidence supporting the use of probiotics is not conclusive and is mainly derived from single-centre, not very well designed trials that are limited by many factors including small sample sizes, heterogeneity in the probiotic strains used, effectiveness of the combined strains, optimum dose regimens, frequency and duration of administration, and certainly incomplete knowledge of the mechanism of action of each strain. Probiotics appear to be well tolerated, whilst adverse events are very rare. The most commonly reported adverse events include bacteraemia, fungaemia and sepsis. At present, based on the available evidence and although helpful and relatively safe for certain disease conditions, routine use of probiotics in the critically ill is not recommended.

1. Introduction

The human gastrointestinal tract is colonised by a vast variety of micro-organisms such as bacteria, fungi, protozoa and viruses [1]. Through mutual interactions, these micro-organisms maintain a delicate balance with the host cells and play a crucial role in host biology, function, physiology and immune response and maintain host health. Micro-organisms that are involved in promoting health benefits to the host are classified as probiotics. According to a Joint Working Group of the Food and Agriculture Organization of the United Nations and the World Health Organization (FAO/WHO), probiotics are defined as 'live microbes which when administered in adequate amounts confer a health benefit to their host' [2]. Furthermore, a probiotic must survive gastric acid and bile in order to reach the small and large intestines to exert its effect [3]. Commercially available probiotics include both bacteria and yeasts and are found as a single microbial strain or as a mixture of multiple strains. The most commonly used bacterial probiotics include various species of *Lactobacillus*, *Bifidobacterium* and *Streptococcus* as well as *Lactococcus lactis*, select non-pathogenic strains of *Escherichia coli* Nissle 1917 and *Bacillus* spp., and some *Enterococcus* spp. The most commonly used yeasts are *Saccharomyces boulardii* and *Saccharomyces cerevisiae*. These agents have been increasingly studied as an alternative treatment strategy for various disease states, many of which affect critically ill patients, including antibiotic-associated diarrhoea (AAD), *Clostridium difficile* infection (CDI), ventilator-associated pneumonia (VAP), necrotising enterocolitis (NEC), acute severe pancreatitis, and sepsis and multiple organ dysfunction syndrome (MODS).

2. Gut microbiota

To understand better the role that probiotics have in influencing health, it is important to have an appreciation of the origin and function of the normal intestinal microbiome (commensal microbiota) [4]. Human gut colonisation starts at birth when micro-organisms from maternal body surfaces and the environment are acquired by

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the infant [5]. These early colonisation events affect the overall phylogenetic composition of the gut microbiota and the subsequent immune system of the adult [6]. During the neonatal period this microbial community inhabiting the gut is unstable and variable, but around the age of 3 years the stable adult microbial composition of the gut emerges [7,8]. The majority of bacteria that colonise the human gut belong to the bacterial phyla Firmicutes, Bacteroidetes and Actinobacteria [9,10]. Microbial diversity at the phylum level is common, whereas more complexity is seen at the genus, species and subspecies levels [11]. The microbiota of an individual amounts to almost 500 different bacterial species, which represent a unique signature for that individual and are important for the development of normal intestinal morphology [11]. This diversity per individual is explained by a number of factors, including birth mode, genotype, age, living environment, diet, biogeographical location, nutrition and health status of the individual [12]. The gut microbiota stimulate epithelial cell proliferation and differentiation in the small and large intestines, provide a physical barrier against invading pathogens, assist digestion, produce important nutrients (short chain fatty acids, vitamins and amino acids), produce energy, promote nutrient intake, are vital to immune system development, and maintain a chronic and immunologically balanced inflammatory response [13,14].

3. How probiotics exert their activity

Probiotics can provide a beneficial effect without actually colonising the gastrointestinal tract. Some probiotics become part of the established intestinal microflora, some temporarily re-model the microbial community and others exert transient effects as they pass through [13]. The effectiveness of probiotics relies on their ability to survive the acidic environment of the stomach and the alkaline environment of the duodenum and their ability to adhere to the colonic mucosa. In general, probiotics enhance gut barrier function, stimulate antimicrobial peptide production by host cells (defensins and cathelicidins), produce antimicrobial factors including short chain fatty acids, bacteriocins and microcins, compete for epithelial cell binding, affect immunoglobulin (Ig) production, and promote a potent type-1 immune response [15–22].

The mechanism by which probiotics exert their benefits to the host varies by specific probiotic strain and mostly depends on the clinical situation present [23,24]. Commercially, the most commonly used bacterial probiotics are *Lactobacillus*, *Bifidobacteria*, non-pathogenic *E. coli* Nissle 1917 and *S. boulardii*. There are multiple strains of each species and for this reason a probiotic formulation may contain one or more strains. Clinical trials have used various formulations and strains and the overall conclusion is that strain specificity and disease setting is important, whilst dosage, and route, duration and frequency of administration must also be considered carefully.

4. Critical illness and the gut microbiota

There are ca. 500 different species of microflora that are part of the normal intestinal microbiota of the human gut. There are 10 times as many bacteria in the gastrointestinal tract as there are cells in the human body, making the gastrointestinal tract the most colonised organ. The species and number of these gastrointestinal bacteria play important roles in determining health and disease outcomes. Critical illness creates a hostile environment in the gut that changes the normal intestinal microbiota and favours the growth of pathogens. The hostile environment is created by changes in nutrient availability, gut motility, pH, oxygen concentration, redox state, presence of catecholamines and osmolality as well as broad-spectrum antibiotic activity. In this environment, probiotics remain viable and $>10^7$ CFU/mL reach the intestine, adhered to the modified hostile intestinal mucosa of the critically ill, and interfere with the growth of potential pathogens and reverse disease status [25]. Studies evaluating probiotics in the critically ill are extremely diverse in terms of strains used, dose regimen, route of administration and most important outcome. For example, in a systematic review of eight randomised controlled trial (RCTs) and 999 patients, it was concluded that probiotics have no beneficial effect in terms of intensive care unit (ICU) length of stay, incidence of pneumonia and mortality [26]. In contrast, in a RCT that included 65 critically ill, mechanically ventilated trauma patients, administration of a multi-strain probiotic and prebiotic therapy for 15 days resulted in a reduction in ICU length of stay and ventilator days as well as a reduction in rates of infection, systemic inflammatory response syndrome (SIRS), severe sepsis and mortality [27]. Another randomised trial that included 20 brain-injured patients who were given probiotic and glutamine for 5–14 days showed a reduced median number of infections per patient, reduced overall incidence of infection, and reduced ventilator days [27].

5. Antibiotic-associated diarrhoea

The reported incidence of AAD is 5–25%, with the risk being higher when using aminopenicillins, cephalosporins and clindamycin [28,29]. Antibiotic use shifts the equilibrium in the gut microbiota to an increase in facultative anaerobes, thus causing a decrease in short chain fatty acid production and an increase in proteolytic activity [30,31]. This shift leads to large watery bowel movements. The use of probiotics aims at restoring the normal microbiota of the gut. Three large single-strain meta-analyses suggest that *S. boulardii* is the most effective micro-organism for preventing AAD [14,32,33]. In these meta-analyses, the pooled relative risk ratio was ca. 0.5, with the number needed to treat in order to prevent one case of AAD at 10; in one of them the relative risk for AAD was 0.43, whilst in the included studies different probiotic strains were used at different doses and durations. According to the conclusions, administration of probiotics has a significant effect against AAD, highlighting, however, that higher doses and not the duration of treatment were associated with better efficacy. A recently published meta-analysis that included 82 RCTs and more than 10,000 patients looked at the ability of probiotics to prevent AAD and concluded that probiotic usage did have an effect in preventing diarrhoea [34]. In this meta-analysis, the pooled relative risk ratio was 0.58, with the number needed to treat in order to prevent one case of AAD at 13, whilst probiotics used in the included studies were mainly *S. boulardii*, *Lactobacillus* and *Bifidobacterium* spp.

6. *Clostridium difficile* infection

CDI is not only the most common nosocomial infection in hospitals but represents a severe side effect of antibiotic therapy, exhibiting significant morbidity and mortality. *Clostridium difficile* is a spore-forming, anaerobic bacterium that germinates when there is a disturbance in the normal gut microbiota. Probiotics that have been studied so far in this clinical situation include *S. boulardii* and *Lactobacillus* GG. Increased interest in probiotic usage comes from the observations that *S. boulardii* degrades *C. difficile* toxins A and B, destroys the colonic receptor site for *C. difficile*, and increases the antitoxin secretory IgA levels in the intestine [35]. A systematic review of four RCTs evaluating the prevention of *C. difficile* associated-diarrhoea (CDAD) proposed only in the subgroup analyses potential efficacy in patients with CDAD and those with high-dose vancomycin therapy, whilst a small study has shown a significant reduction in CDI when administering probiotic therapy

[36,37]. Another randomised clinical trial has studied the efficacy of *S. boulardii* in patients with confirmed CDI along with antibiotic treatment (low-dose vancomycin or high-dose vancomycin or metronidazole) [38]. Patients treated with probiotics and high-dose vancomycin had significantly decreased recurrent CDI rates.

7. Ventilator-associated pneumonia

Selective gut decontamination has been used as a method to reduce VAP mortality in critically ill patients, but an increased antimicrobial resistance rate has been observed. Probiotics were proposed as an alternative in order to maintain the normal gut microbiota and to eliminate pathogenic bacteria from the nasal cavity. Oral administration of probiotics results in delayed colonisation of the respiratory tract by *Pseudomonas aeruginosa* leading to reduced rates of VAP [39]. A meta-analysis of five RCTs that used probiotics to prevent VAP concluded that probiotic administration led to a significant reduction in the incidence of VAP and length of ICU stay but with no significant differences in either ICU or hospital mortality or incidence of diarrhoea [40]. In another RCT that included 146 mechanically ventilated patients, the group treated with probiotics was less likely to develop VAP, received less antibiotics, and had a reduced incidence of CDAD [41]. None of the studies reported any adverse effects.

8. Necrotising enterocolitis

There is accumulating evidence that perinatal antibiotics as well as bacterial colonisation patterns play a pivotal role in the pathogenesis of NEC [42]. Probiotics are used to remodel the microbiota of the invaded gut and, as is shown from three meta-analyses and two clinical trials, use of multiple species of *Bifidobacterium* and *Lactobacillus acidophilus* was associated with reduced rates of NEC and decreased mortality [43–47]. However, a recently published systematic review reported that probiotic administration offers less cogent but positive results to patients with NEC and sepsis [48].

9. Acute severe pancreatitis

It is estimated that up to 20% of patients with acute pancreatitis will proceed to pancreatic necrosis. This condition is complicated by infections mainly due to intestinal barrier failure and bacterial translocation. This alone increases the mortality rate to 30%. A number of clinical trials have shown that administration of probiotics can prevent or reduce the rate of infectious complications and minimise the need for surgical intervention in acute necrotising pancreatitis [49–51]. The large, multicentre, double-blinded, controlled PROPATRIA study that included 296 patients with presumed severe pancreatitis yielded a higher incidence of mesenteric ischaemia and mortality for the group that was given a multispecies probiotic preparation [52].

10. Sepsis and multiple organ dysfunction syndrome

The use of probiotics has been studied in critically ill septic patients with head trauma, severe pancreatitis, and following liver transplantation and abdominal surgery. In a RCT in critically ill, mechanically ventilated trauma patients, administration of a multistrain probiotic–prebiotic commercial formula for 15 days was associated with a reduction in ICU length of stay and ventilator days as well as a reduction in rates of infection, SIRS, severe sepsis and mortality [27]. In patients with MODS, probiotic administration modifies and/or remodels the gut microbiota. Animal model studies have shown that administration of probiotics improves gut barrier function and reduces the population of pathogenic bacteria [53]. However, in clinical trials in critically ill patients with MODS who were treated with either viable multi-strain probiotics or non-viable probiotics, there was a significant increase in the systemic IgA and IgG concentrations only in those patients who received viable probiotics, whilst the MODS scores remained unaltered [54].

11. Safety of probiotics

Probiotics are marketed as dietary supplements and as such they do not need to fulfil safety and efficacy norms set by the US Food and Drug Administration (FDA). Probiotics do have theoretical risks, which include transferring of antibiotic resistance genes, translocating from the intestine, causing adverse reactions, and having toxic and metabolic effects. The reported complications are rare, usually encountered in the critically ill, immunocompromised patients, premature neonates and transplant recipients [55]. The majority of studies have shown that probiotics are well tolerated and quite safe to be used. The PROPATRIA study brought up issues of safety monitoring that need to be revisited. Surveillance for possible adverse events is needed in high-risk groups [52].

12. Conclusions

Probiotics appear to have a promising role in the ICU setting and offer some benefit when used in specific clinical conditions. The benefits are clearly strain- and disease-specific and the success of one probiotic in one clinical situation does not presuppose success in another. Interpretation of available studies is limited by small sample sizes, heterogeneity in the probiotic strains used, effectiveness of the combined strains, optimum dose regimens, frequency and duration of administration, and certainly incomplete knowledge of the mechanism of action of each strain. Although a great number of studies have been performed, the existing data do not offer assistance in making conclusive remarks at this point.

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