Invasive Infections and Probiotics Uses in Children

Subjects: Allergy

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According to the revised definition of the International Scientific Association for Probiotics and Prebiotics (ISAPP), probiotics are “live microorganisms that when administered in adequate amounts, confer a health benefit on the host”. During the last two decades, interest in probiotic supplements that modify the microbiota to confer health benefits has been growing, leading to the widespread use of many different types of probiotics in both community and healthcare settings.

Keywords: probiotics ; invasive infections ; sepsis ; preterm

1. Introduction

According to the revised definition of the International Scientific Association for Probiotics and Prebiotics (ISAPP), probiotics are “live microorganisms that when administered in adequate amounts, confer a health benefit on the host” [1]. During the last two decades, interest in probiotic supplements that modify the microbiota to confer health benefits has been growing, leading to the widespread use of many different types of probiotics in both community and healthcare settings.

Nevertheless, the probiotic’s market continues to grow rapidly worldwide, also due to the perception of their safety [2]. The general assumption that probiotics are safe derives from a long history of probiotic use and mixed data from clinical trials, and animal and in vitro studies [3]. However, only a few systematic safety studies have been carried out, particularly in vulnerable populations, and most of the existing published studies on probiotics have not specifically reported safety, leaving uncertainties regarding their potential risks [4][5]. In 2018, a systematic review of 384 randomised controlled trials assessing probiotics and prebiotics found that safety outcomes for these interventions in the literature were often missing, insufficient, or inconsistent; of the 384 trials, 106 (28%) did not provide any information related to harms, and 311 (81%) did not mention adverse events in the abstract [6].

Increasing evidence raises concerns about the probiotics’ opportunistic potential of causing bloodstream and deep-seated infections, especially in high-risk groups such as preterm neonates and critically ill patients [7][8]. A Cochrane review assessing the efficacy and safety of probiotics’ use in children with antibiotic-associated diarrhoea concluded that, although no serious adverse events were observed in the included studies, observational case reports and case review have reported serious adverse events in debilitated or immunocompromised children with underlying risk factors, including central venous catheter use and altered intestinal permeability [9].

Unlike adult patients, who are described to develop both systemic and deep-seated infections such as liver abscess [10], endocarditis [11][12], pleural empyema [13], and retropharyngeal abscess, children seem to develop primarily systemic bloodstream infections after probiotics’ administration [14].

2. Facts

Most patients were younger than 2 years old. More specifically, 21 patients out of 49 (43%) were neonates (age < 1 month), while the other 18 (37%) were aged between 1 month and 2 years. Of the remaining patients, 4 (8%) were aged between 2 and 12 years, and only 2 (4%) between 12 and 18 years, while for 4 patients (8%), their age was not reported. The female/male ratio was 0.36 (16 female and 29 male). Males were more prone to develop invasive infections compared to females, with an OR of 3.01 (p = 0.08). Most of the patients (45/49) were receiving probiotics at the onset of the infection, with a median treatment duration of 10.0 days (IQR 1–21.5), while 4 cases did not take any probiotic supplements. For these patients, the invasive infection was reported to be caused by contaminations of probiotics administered to another child admitted in the same room.

All children except one had at least one condition facilitating the development of invasive infection, with prematurity and intravenous catheter use being the most frequently reported predisposing factors (55% and 51%, respectively). Gastrointestinal pathologies such as short bowel syndrome, enteral/parental nutrition, intestinal inflammation, and abdominal surgery were described in 23 cases (46.9%). Respiratory support, congenital heart disease, and genetic syndromes were present respectively in 9 (18.3%), 6 (12.2%), and 4 (8%) patients. Two patients were undergoing chemotherapy, one for acute lymphoblastic leukaemia, the other for acute myeloid leukaemia. Less frequent underlying conditions were cystic fibrosis, malnutrition, burns, immunosuppressive treatment, and renal failure.

The treatment of the invasive infections was specified for 41 patients. The median treatment duration was 12 days (IQR 10–14.5). Treatment drugs varied largely, including more frequently ceftriaxone, ampicillin, gentamicin, penicillin, ampicillin/sulbactam, vancomycin, and levofloxacin for bacterial infections and amphotericin B, fluconazole, and micafungin for fungal infections.

While most patients had a favourable outcome, three of them (6%) died. In two cases, the fatal outcome was considered to be related to multiple comorbidities rather than to probiotic infection itself.

Two of these were neonates taking probiotics according to a routine protocol for premature babies. One of the new-borns, a premature baby born at 27 weeks of gestational age, died after sepsis from *Limosilactobacillus reuteri* on the second day of life. The other new-born (27 weeks of gestational age) developed a *Saccharomyces boulardii*-related sepsis. The fungus appeared cleared after 72 h of antifungal therapy, but the baby died of an unrelated cause (cardiac problem).

The third case of death occurred in a 5-month-old baby with congenital heart disease receiving probiotics (*Bacillus clausii*) for watery diarrhoea; despite intensive antibiotics treatment, he finally succumbed to multidrug-resistant sepsis with multiorgan failure.

Three case reports [15][16][17], describing a total of four patients, suggested that a probiotic supplement taken by one hospital inpatient may spread to neighbouring patients, to whom it is not directly administered, leading to sepsis. In three cases, the etiological agent was confirmed by the identification, by molecular analysis, of the same probiotic strain compared with the probiotic administered to the neighbouring patient. In the other case, correlation was demonstrated by the isolation of the same microorganism in blood culture and CVC tip culture [17].

It has been suggested that contamination of vascular catheters may be responsible for such cases [18].

3. Invasive Infections Associated with the Use of Probiotics in Children

This review summarised all the reported cases of paediatric patients who developed an invasive infection related to probiotics' use. To our knowledge, this is the first review that focused specifically on the paediatric population. We were able to identify 49 documented paediatric cases of reported invasive infection caused by microorganisms used as probiotic supplementation.

Results of this review in terms of causative microorganisms (*Lactobacillus* spp. followed by *Saccharomyces* spp. and *Bifidobacterium* spp.) are slightly different from those reported in a previously published review in 2018 [14]. That study included 93 cases (both children and adults), identifying *Saccharomyces spp.* (50.5%) as the most frequent cause, while *Lactobacillus* spp. and *Bifidobacterium* spp. were present in 27.9% and 12.1% of cases, respectively. A higher frequency of fungemia in the adult population could explain this difference, since in that study, only 8 out of 34 patients with Saccharomyces-associated infection were children.

Previous reviews on the safety of probiotics have not found severe adverse events after the use of probiotics. In a review of 19 RCTs, including more than 2800 infants taking probiotics to prevent NEC, no cases of bacteraemia were reported, and the authors concluded that consumption of such products has a negligible risk to consumers [19]. Similar findings were reported by Borriello et al., who underlined the low risk in probiotics' supplementation also in immunocompromised hosts [20]. In a retrospective study of two Italian neonatal units, no isolation of *Lactobacillus* species was reported in more than 5000 surveillance and clinical cultures [21]. The low incidence of severe adverse events could be explained by high standards of probiotics' preparation, high standards of wards' hygiene and care, and finally, by the fact that the great majority of children in these RCT's did not have multiple comorbidities simultaneously.

We are aware that the incidence of probiotic-related infection cannot be compared between RCTs and case reports. Despite that, this review highlights how the risk of invasive infection during probiotic supplementation, although rare, should not be ignored, especially in patients with predisposing risk factors.

Findings on our review in terms of predisposing factors are largely in line with a previous systematic review [14]. Our review suggests that, in the paediatric population, prematurity is the major risk factor for developing a severe infection after probiotics' use. The 2018 review [14] including adults showed that extreme ages are the most involved, with 35.5% of probiotics-associated infections occurring after 60 years and 26.7% in children younger than one year, of whom about 66% were premature. This could be explained by the systematic use of probiotics in premature children to prevent NEC (although trials on the NEC are mostly small, and some with high risk of bias, as stressed by the Cochrane review) and late-onset sepsis [19][22], but also by the susceptibility of their immature immune system to infections [23].

Similarly, intravenous catheters were identified as a frequent predisposing factor for developing invasive infections during probiotics' use, also in the previous review [14]. In 23 cases (46.9%), patients had a pre-existing intestinal disease, such as short bowel syndrome, enteral/parental nutrition, intestinal inflammation, abdominal surgery, and diarrhoea, making intestinal comorbidity one of the most relevant predisposing factors for the development of probiotics-related infection. This could be explained by the extensive use of probiotics in patients with intestinal disorders, which may have an increased risk of probiotic translocation through the damaged intestinal mucosa. Several studies [24][18][25] suggest that a friable mucosa could potentially decrease adherence of the Lactobacillus and increase intestinal permeability, thereby potentiating migration of the organism across the intestinal mucosal barrier. Translocation may result in the transfer of bacteria to other organs, causing bacteraemia, septicaemia, and multiple organ failure [26].

Other high-risk groups included children with respiratory support (18.3%), congenital heart disease (12.2%), and genetic syndromes (8%), with less frequent underlying conditions being cystic fibrosis, malnutrition, burns, immunosuppressive treatment, chemotherapy for hematologic malignancies, and renal failure. Malignancy and immunosuppression related to HIV or immunosuppressive drugs were more common in the adult population [14]. More studies are needed to further elucidate the risk of invasive infections after probiotic use in these categories of patients.

Although most cases had favourable outcomes with appropriate antimicrobial therapy, children required hospitalisation and antimicrobial therapy. In addition, this review highlights three reported fatal cases, occurring in small children, of which two were premature babies taking probiotics according to a routine protocol for premature babies. In these cases, the cause of death was related to the underlying disease rather than to probiotic infection itself.

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