

Are probiotics safe? *Bifidobacterium* bacteremia in a child with severe heart failure

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SUMMARY

Although few cases of bacteremia or sepsis caused by probiotics have been reported, it is important to consider their pathogenic potential, especially in some categories of patients. We report a case of *Bifidobacterium* spp bacteremia in a child with heart disease, undergo-

ing probiotic supplementation to prevent antibiotic-associated diarrhea.

Key words: probiotics, *Bifidobacterium*, bacteremia, children; heart disease.

INTRODUCTION

Probiotics are live microorganisms that confer a health benefit on the host by improving intestinal microbial balance [1]. Although they are generally considered safe, they can rarely cause invasive human infections [2, 3]. We report a case of *Bifidobacterium* spp bacteremia in a child with heart disease, undergoing probiotic supplementation to prevent antibiotic-associated diarrhea (ADD).

CASE REPORT

Our patient is a child with a diagnosis of congenital light mitral regurgitation and *ostium secundum* defect. At the age of five months she started with respiratory problems and progressive clinical deterioration. An ultrasound test revealed dilated cardiomyopathy and severe mitral regurgitation with heart dysfunction and reduced ejection frac-

tion (EF 38%). She presented progressive clinical worsening, recurrent respiratory infections, signs and symptoms of heart failure and poor weight gain. To control the progressive valvular disease, she underwent a mechanic valve replacement surgery at fifteen months of age. Given the poor ventricular function with cardiac arrest and sub-optimal post-operative haemodynamic response, the child needed to be put on extracorporeal membrane oxygenation (ECMO). A broad spectrum empirical antimicrobial therapy with meropenem (20 mg/kg IV every 8 hours), teicoplanin (10 mg/kg IV every 12 hours the first three doses, then every 24 hours), amikacin (20 mg/kg/day IV) and fluconazole (10 mg/kg/day IV) was started. At the same time, treatment with probiotics was started to prevent ADD. After seven days she was decannulated from ECMO; two days later the sternum was closed. The day after the removal of ECMO, she presented high fever (>38°C) with increased inflammatory markers. Cultural tests resulted negative and she continued with the ongoing antimicrobial therapy, changing teicoplanin with linezolid (10 mg/kg IV every 8 hours). The child's clinical condition improved and antibiotic therapy was discontinued after 16 days. On day 17

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after surgery, she developed fever again, general discomfort and feeding intolerance, without any specific signs or symptoms of infection. Laboratory tests showed neutrophilic leucocytosis (white blood cell count -WBC- 17140/mm³, 60% neutrophils) and increased inflammatory markers (C-reactive protein -CRP- 74 mg/L). Treatment with vancomycin (10 mg/kg IV every 6 hours), meropenem (20 mg/kg IV every 8 hours), amikacin (18-20 mg/kg/day IV) and fluconazole (10 mg/kg/day IV) was empirically initiated. Temperature was still high (38°C) on day 20 after surgery and CRP and WBC count increased to 189 mg/L and 17200/mm³ (54% neutrophils), respectively. Gram positive, non-sporulating and irregular rods grew on blood culture obtained from a central venous line (CVC) on day 17 after surgery. After 96 hours of incubation blood culture resulted positive for *Bifidobacterium* spp. No further studies were carried out to identify the specific bacterial strain in the blood, nor antibiotic susceptibility testing was performed. No other organisms were detected in other cultures. We checked the composition of the probiotics that the child received and we documented the presence of *Bifidobacterium longum*. Probiotics and amikacin were discontinued. The other antibiotic therapies were not replaced, because considered appropriate for this kind of infection. The patient improved and repeated blood cultures resulted negative. She became afebrile after six days of treatment, with improved clinical condition and resolution of the infection.

■ DISCUSSION

Probiotic microorganisms are typically members of the genera *Lactobacillus*, *Bifidobacterium* and *Streptococcus*. These bacteria are obligatory or facultative anaerobic organisms, which are usually non-motile, with a wide spectrum of morphologies and a fermentative metabolism. Their biological features enable them to predominate and prevail over potential pathogenic microorganisms in the human digestive tract. These potentially harmful bacteria may translocate across the intestinal epithelium and could result in disease in humans [2].

Probiotic bacteria are commonly administered orally and can be delivered as treatments or supplements [1].

Probiotics and prebiotics confer a health benefit

when given for various indications. Main clinical applications in pediatric patients seem to be prevention and treatment of acute infectious diarrhea and AAD, treatment of necrotizing enterocolitis (NEC) in low birth weight (LBW) newborns, chronic inflammatory bowel disease (IBD), prevention and treatment of infantile colic [1, 4]. Probiotics seem useful also in critically ill children in the prevention of fungal colonization and invasive candidiasis and in the reduction of sepsis, feeding intolerance and duration of hospitalization in preterm infants [2].

The most frequently used probiotic strains are *Lactobacillus* and *Bifidobacterium*. A daily intake of 10⁶-10⁹ colony forming units (CFUs) is reported as the minimum effective dose for therapeutic purposes. Probiotic treatment promotes changes of the composition of gut flora and enhancement of the immune response: mucosal immunity activation, cytokine production, IgA secretion, phagocytosis and inhibition of pathogen attachment and damage due to microbial toxin. They also have a physical barrier function and a trophic effect on the intestinal mucosa, stimulating the proliferation of normal epithelium and making the environment unsuitable for the growth of pathogens [2, 5].

Although no serious adverse events were observed among otherwise healthy children, some authors have questioned the safety of probiotic therapy, especially in children with underlying risk factors including the use of CVC, alterations in the integrity of the intestinal mucosa, prematurity state, malignancies and immune deficiencies [2]. *Bifidobacterium* spp is a very uncommon cause of human infection and only sporadic infections have been previously described in paediatric patients [3, 6-13]. Relevant data of these cases are reported in Table 1. As described, in children *Bifidobacterium* species bacteraemia is almost always related to the administration of probiotics or food added with them. By contrast, in adults the role of probiotic administration remains largely unknown [3, 9].

In our case the following reasons could make *Bifidobacterium* spp bacteremia a possible and reasonable diagnosis:

- 1) the bacterium was detected from the blood when inflammatory markers increased;
- 2) the use of CVC and/or the previous cardiac surgery (with ECMO) may have led to the translocation of *Bifidobacterium* spp from the gut;

Table 1 - Characteristics of reported paediatric cases of *Bifidobacterium* species bacteremia.

Age	Gender	Underlying condition	Antibiotic or immunosuppressive therapy prior to the onset of bacteremia	Clinical presentation	Blood culture findings	Antibiotic therapy	Probiotic use	Outcome
2 weeks [9]	Male	Prematurity, spontaneous gut perforation	penicillin and gentamicin	Sepsis	<i>B. longum</i>	cefotaxime, gentamicin	Yes	Recovered
5 weeks [9]	Female	Prematurity, leaky gut after NEC	ampicillin and gentamicin	Sepsis (hypotension, metabolic acidosis)	<i>B. longum</i>	ampicillin, gentamicin, metronidazole	Yes	Recovered
2 weeks [9]	Male	Prematurity	ampicillin and gentamicin	Apnea, bradycardia, temperature instability	<i>B. longum</i>		Yes	Recovered
3 weeks [9]	Male	Prematurity		Sudden infant death syndrome prior to hospital admission	<i>B. longum</i> (obtained post-mortem)		NA*	Death
2 weeks [10]	Female	Prematurity, low birthweight	amoxicillin and gentamicin	Sepsis and ileus (3 episodes)	<i>B. infantis</i>	ceftazidime and vancomycin 7 days, then imipenem 7 days	Yes	Recovered Surgical resection
10 days [10]	Female	Prematurity, low birthweight	amoxicillin and gentamicin	Sepsis shock, coagulopathy, ileus	<i>B. infantis</i>	ceftazidime, amikacin, metronidazole	Yes	Recovered Surgical resection
10 days [6]	Female	Prematurity, low birthweight omphalocele		Bilious gastric fluid and increased inflammatory markers	<i>B. breve</i>	ampicillin-sulbactam (then meropenem) and amikacin	Yes	Recovered
2 weeks [8]	ND	Prematurity, low birthweight		Sepsis, distended abdomen	<i>B. infantis</i> , <i>B. longum</i>	cefotaxime, vancomycin and metronidazole	Yes	Recovered
2 weeks [11]	Female	Prematurity, respiratory assistance		Periumbilical redness with pus, marbled and pale skin, distended abdomen	<i>B. longum</i>	flucloxacillin, gentamicin	Yes	Recovered
3 weeks [11]	Male	Prematurity, respiratory assistance		Suspected nosocomial infection	<i>B. longum</i>	amoxicillin, gentamicin	Yes	Recovered
10 days [11]	Female	Prematurity, respiratory assistance		Acute necrotizing enterocolitis	<i>B. longum</i>	amoxicillin-clavulanic acid, gentamicin	Yes	Serial laparotomy
8 days [12]	Male	Prematurity, cloacal exstrophy, omphalocele and imperforate anus		Abdominal distension, bilious gastric fluid	<i>B. breve</i>	cefazolin, vancomycin	Yes	Recovered
2 years [7]	Male	Acute lymphoblastic leukemia, chemotherapy	prednisone, vincristine, doxorubicin and L-asparaginase	Abdominal discomfort and distension	<i>B. breve</i>	piperacillin-tazobactam, vancomycin and gentamicin, then only penicillin	Food added with probiotics	Recovered
10 days [13]	Female	IUGR**, postoperative omphalocele		Increased CRP and WBC count	<i>B. breve</i>	Not known	Yes	Recovered
23 days [13]	Male	Preterm, Down syndrome, frequent vomiting and stagnant bowel		Fever, vomiting, increased CRP and WBC count	<i>B. breve</i>	Not known	Yes	Recovered (Hirschsprung disease)

* NA=Not available; ** IUGR=Intrauterine Growth Restriction.

3) no other organisms were detected in cultures from other tissues.

Our experience confirms that *Bifidobacterium* spp, generally considered non-pathogenic, can be the cause of severe infections. Similar cases are reported in literature in patients with underlying risk factors (bacteremia, sepsis, abscesses of different locations, pneumonia, pericarditis and urinary tract infections) [3, 14]. The source of infection can be associated with haematogenous spread, aspiration of oral secretions, diagnostic procedures, acupuncture therapy, administration of probiotics and alteration in the integrity of intestinal mucosa [14]. The impact of the ingestion of probiotics is still unclear in patients with underlying diseases or immunosuppression [3]. For this reason, probiotics should be used carefully, especially in critically ill patients.

The antibiotic susceptibility of bifidobacteria is of interest for the treatment of those rare cases where bifidobacteria are pathogenic agents. They are generally susceptible *in vitro* to many antibiotics such as beta-lactams, erythromycin, clindamycin, tetracycline, linezolid and vancomycin, which are commonly employed in treating infections from Gram-positive organisms. Penicillin has been shown to be effective against *Bifidobacterium* spp and it is the drug of choice when treating this kind of infections. Patients with bacteremia have been successfully treated with ampicillin (associated or not with aminoglycoside) or oxacillin. Eventually, broad-spectrum antibiotics have been administered in patients with bacteremia, as in our case, with a positive clinical response [14, 15].

■ CONCLUSIONS

Up to now, treatment with probiotics has appeared to be safe and infections caused by *Bifidobacterium* spp may be overlooked, underreported or misinterpreted as mediated by organisms normally populating the microbiota. However, isolated cases of severe infections by probiotic agents have been reported in children, especially in the context of host susceptibility, as in case of recent surgery, malignancy or immunodeficiency. For this reason the role of probiotics should be better investigated and carefully managed by health care personnel.

Conflict of interest: none

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