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Invited Review-pharmacology across disciplines

Probiotics and antibiotic-associated diarrhea in children: A review and new evidence on *Lactobacillus rhamnosus* GG during and after antibiotic treatment

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ABSTRACT

Antibiotic associated diarrhea (AAD) is a common complication in childhood in the outpatient and inpatient settings. This review provides up to date information on the use of probiotics in the prevention and treatment of AAD, including that from Clostridium Difficile, in children. The most recently systematic reviews and subsequently published randomized controlleds trials are considered. Different single and multistrain probiotics are described; a specific recommendation for the use of *Lactobacillus Rhamnosus* GG (LGG) and *Saccharomyces boulardii* (Sb) emerges. New information on LGG survival under amoxicillin/clavulanate therapy in children is also provided. This information is relevant in view of the frequent use of this molecule in children, its association with AAD, and LGG's sensitivity to penicillin that might make this probiotic ineffective. In spite of a demonstrated positive effect of specific strains of probiotics on AAD, safety issues still remain among which the risk of associated severe infections and of antibiotic resistant gene exchange.

Contents

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Table 1
Incidence of AAD in children exposed to different oral antibiotics [5,7].

Antibiotic	Incidence of AAD%
Penicillin G and V	1.2–3
Penicillin A and M	11
Amoxicillline	1.2
Amoxicilline + Clavulanate	19.8–23
Cephalosporins	9
Macrolides	8
Trimethoprime/Sulfamethoxazole	6
Erythromycin/Sulfafurazole	16

1. Antibiotic associated diarrhea: who and when

Antibiotics are the most widely prescribed drugs in the paediatric population, being administered to more than 50% of subjects between birth and 18 years of age [1]; furthermore they justify 24–27% of prescriptions in children, with amoxicillin, azithromycin and amoxicillin/clavulanate being the most used [2].

However antibiotic therapy must be used with caution as it may result in a wide range of adverse events, including antibiotic associated diarrhea (AAD) [2].

Almost any oral and intravenous antibiotic has been associated to diarrhea in children [1], however the risk of AAD is higher when antibiotics against anaerobes are utilized [3].

AAD is a frequent complication observed both in the outpatient and inpatient settings that develops in up to a third of all patients treated with antibiotics [4], and in particular in 11–62% of children and in up to 80% of hospitalized toddlers [5].

AAD is normally defined as 3 or more liquid stools in 24 h that occur in subjects during or even within 6–8 weeks after antibiotic treatment [6]. However different definitions have been used in pediatric and adult trials ranging from 1 to 3 abnormally loose stools per 24–48 h [6]. To correlate the development of diarrhea to the medication used, it is important to exclude other etiologies such as infectious gastroenteritis [6].

Dominique Turck et al. in 2003 published a prospective study on 650 outpatient children enrolled during a consecutive 11-month period who were exposed to oral antibiotic therapy [5]. Only 11% developed diarrhea, however AAD was more frequent in the diaper-wearing group involving 18% of children aged less than 2 years [5]. Certain antibiotics and in particular amoxicillin and clavulanate had a higher risk of AAD compared to others (p 0.003) and showed a 2.43 relative risk of AAD in all children, and a relative risk of 3.5 in those aged less than 2 years [5]. Table 1 summarizes the incidence of AAD during oral antibiotic therapy in children; data is extracted from two studies, one evaluating just penicillins, and the second one considering different antibiotic types.

AAD may be caused by different mechanisms: a direct toxic effect of antibiotics on the intestine, an altered digestive function secondary to reduced concentrations of gut bacteria, and the overgrowth of pathogenic microorganisms [8].

Clinically AAD may either be mild or, on the contrary, fulminant; the last clinical picture is known as pseudomembranous colitis, which develops usually in patients with chronic conditions and is normally due to a causative agent often identified as Clostridium difficile (CD) [9]. A relative recent study reported an increasing incidence of pseudomembranous colitis among hospitalised children in the United states between 2003 and 2012 [10].

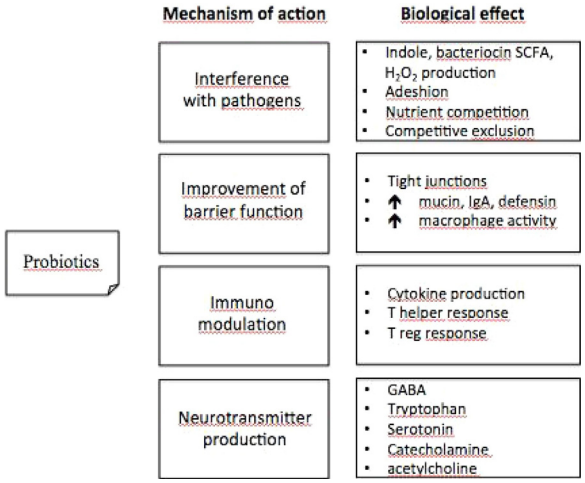

Fig. 1. Probiotics'mechanism of action.

2. Probiotics

Probiotics are non pathogenic live microbial preparations that, when administered in adequate amounts, are able to alter the host's gut microflora by improving its intestinal microbial balance, with beneficial effects [11].

They are usually composed of non pathogenetic bacteria that already occupy the human digestive system, therefore are generally considered safe [12]. Probiotics microorganism should not only be capable of surviving passage through the digestive tract but also have the capability of proliferating in the gut [13]. A benefit to the host must be proven to be above and beyond a placebo [12].

Probiotics may be presented as foods, supplements, drugs, medical foods, medical devices or cosmetics and nowadays different strain and formulations are produced [12].

Probiotics' mechanism of action (Fig. 1) is exerted through modulation of the content of gut microbiota, maintenance of the integrity of the gut barrier, prevention of bacterial translocation and modulation of the local immune response by the gut-associated immune system [14]; however probiotics' effects are strain and dose specific [14].

Different health conditions have proven to have beneficial effects with probiotic assumption such as lactose intolerance, hypercolesterolemia, traveler's diarrhea, acute rotavirus diarrhea, radiotherapy induced diarrhea, respiratory infections and others [15]. However only in AAD, CD-associated diarrhea, and respiratory tract infections are the effects of probiotics considered "evidence-based" [15].

3. Probiotics and AAD

Probiotics have been experimented in AAD; the rationale for the use of these products relies on the hypothesis that AAD is caused by dysbiosis that is triggered by antibiotic use and that the low virulence microbes contained in these preparations favorably modulates and normalizes the unbalanced indigenous gastrointestinal microbiota [16].

Studies conducted in adults demonstrated that both probiotics and fermented products have a modest effect in preventing AAD

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