Microbiota Modulation: Can Probiotics Prevent/Treat Disease in Pediatrics?

Hania Szajewska

Department of Pediatrics, The Medical University of Warsaw, Warsaw, Poland

Abstract

A number of metagenomic analyses providing knowledge of the human microbiome have yielded data on the differences between healthy and diseased individuals. Microbiota manipulation, such as through the administration of probiotics, may potentially contribute to improved health outcomes. The objective of this review was to summarize the most recent data on the use of probiotics to treat or prevent diseases in pediatrics. MEDLINE and The Cochrane Database of Systematic Reviews were searched in September 2012 for randomized controlled trials or their meta-analyses published in the last 3 years. To provide examples of current research interests, the focus of the search was on well-studied, common pediatric conditions as well as on some chronic diseases for which the benefits of gut microbiota manipulation are only in the early stages.

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Introduction

Humans have 10 times more microbial cells than human cells, with the highest concentration of microorganisms located within the digestive tract. Up to 1,000 different species have been identified with current microbiological techniques. Whereas many of the microbes are potential pathogens and can cause illness, others maintain health. Though the concept is not new, surprisingly little is known about the exact role and mechanisms by which these microorganisms contribute to human health or disease. However, over the last decade or so, there
has been a remarkable renewal of interest in this topic, at least partially due to recent developments in molecular technology. A number of metagenomic analyses have yielded data on the differences between healthy and diseased individuals. Microbiota manipulation, such as through the administration of probiotics and/or prebiotics, microbial suppression or elimination through the administration of antibiotics, and fecal microbiota transplantation may potentially contribute to improved health outcomes.

The objective of this review was to summarize the most recent data on the use of probiotics in pediatrics. MEDLINE and The Cochrane Database of Systematic Reviews were searched in September 2012 for randomized controlled trials (RCTs) or their meta-analyses published in the last 3 years. To provide examples of current research, the focus of the search was on well-studied, common pediatric conditions as well as on some chronic diseases for which the benefits of gut microbiota manipulation are only in the early stages.

### Common Pediatric Conditions

#### Treatment of Acute Gastroenteritis

**What Is Already Known?**
In 2008, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society of Paediatric Infectious Diseases (ESPID) stated that select probiotics with proven clinical efficacy [e.g. *Lactobacillus GG* (LGG), *Saccharomyces boulardii*] that are administered in appropriate dosages, according to the strain and the patient population, may be used as an adjunct to rehydration therapy for the management of acute gastroenteritis in children [1].

**What Is New?**
In an update to a previously published Cochrane review, Allen et al. [2] pooled data from 63 RCTs (n = 8,014) that evaluated the efficacy of probiotics for the treatment of acute infectious diarrhea in subjects of all ages. Probiotics (as a group) reduced the duration of diarrhea and the risk of diarrhea lasting ≥4 days. The majority of the trials (56 RCTs) were carried out in infants and young children. The most commonly studied probiotics were LGG (13 RCTs) and *S. boulardii* (10 RCTs). This updated Cochrane review confirmed the effectiveness of both LGG and *S. boulardii*.

New data are available for *Lactobacillus reuteri* DSM 17938. A recent RCT was conducted in 74 Italian children aged 6–36 months who were hospitalized...
for acute diarrhea with clinical signs of dehydration. The investigators found that the administration of *L. reuteri* DSM 17938 compared with placebo significantly reduced the duration of watery diarrhea (2.1 ± 1.7 vs. 3.3 ± 2.1 days; p < 0.03), the risk of diarrhea on day 2 (55 vs. 82%; p < 0.01) and on day 3 (45 vs. 74%; p < 0.03), and the relapse rate of diarrhea (15 vs. 42%; p < 0.03). The duration of hospital stay was similar in both groups [3].

Moreover, a number of studies on various probiotics (single or in combinations) were published subsequent to the ESPGHAN/ESPID guidelines. Many, albeit not all, reported a shortened duration of diarrhea in the probiotic(s)-treated group.

Overall, new evidence has confirmed that the probiotics currently supported by ESPGHAN/ESPID – LGG and *S. boulardii* – are effective in reducing the duration of diarrhea. Current evidence clearly indicates that they are not the only effective probiotic microorganisms; however, they are the most studied. In addition to ESPGHAN/ESPID, the American Academy of Pediatrics has supported the administration of probiotics for the treatment of acute gastroenteritis, although no specific microorganisms have been indicated [4].

**Prevention of Antibiotic-Associated Diarrhea**

*What Is Already Known?*

In the pediatric population, antibiotic-associated diarrhea (AAD) occurs in approximately 11–40% of children between the initiation of therapy and up to 2 months after cessation of treatment. Several meta-analyses have shown most of the tested probiotics to be effective in reducing the risk of AAD.

*What Is New?*

The most recent meta-analysis, which pooled data from 63 RCTs involving almost 12,000 participants, indicated a statistically significant reduction in the incidence of AAD in the probiotic groups compared with the control groups (relative risk, RR, 0.58; 95% CI: 0.50–0.68). The number needed to treat (NNT) was 13 (95% CI 10.3–19.1) [5]. One of the systematic reviews showed a benefit of using high doses of *Lactobacillus rhamnosus* or *Saccharomyces boulardii* in children [6].

Overall, recent data have reconfirmed the 2010 opinion of the American Academy of Pediatrics [4] that there is some evidence to support the use of probiotics to prevent AAD (but no evidence to suggest that use of probiotics is beneficial for treatment).
What Is Already Known?
Rotavirus remains a leading cause of nosocomial gastroenteritis, which frequently results in prolonged hospital stays and increased additional medical costs. For prevention of rotavirus infection, vaccination seems to be the most promising strategy. However, the high cost of rotavirus vaccines precludes their widespread use in many settings, thus maintaining interest in other strategies for preventing nosocomial diarrhea. Previously, there was some promising evidence to recommend the use of *Bifidobacterium bifidum* (later renamed *B. lactis*) and *Streptococcus thermophilus* to prevent nosocomial diarrhea [7].

What Is New?
A meta-analysis of 3 RCTs involving 1,092 children documented that compared with placebo, LGG administration for the duration of the hospital stay was associated with significantly lower rates of diarrhea (RR 0.37, 95% CI 0.23–0.59) and symptomatic rotavirus gastroenteritis (RR 0.49, 95% CI 0.28–0.86; fig. 1)

### Table 1
The table below summarizes the results of the meta-analysis:

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Subtotal (95% CI)</th>
<th>Total events</th>
<th>Heterogeneity: Chi² = 2.56, df = 2 (P = 0.28); I² = 22% Test for overall effect: Z = 2.49 (P = 0.01)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1 Diarrhea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hojsak 2010</td>
<td>0.42 [0.25, 0.71]</td>
<td>1</td>
<td></td>
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<tr>
<td>Szajewska 2001</td>
<td>0.20 [0.06, 0.66]</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>0.37 [0.23, 0.59]</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Chi² = 1.26, df = 1 (P = 0.26); I² = 21% Test for overall effect: Z = 4.14 (P &lt; 0.0001)</td>
<td></td>
<td></td>
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<tr>
<td>1.1.2 Rotavirus gastroenteritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hojsak 2010</td>
<td>0.19 [0.01, 4.04]</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Mastretta 2002</td>
<td>0.63 [0.35, 1.16]</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Szajewska 2001</td>
<td>0.13 [0.02, 1.06]</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>0.49 [0.28, 0.86]</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td></td>
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<tr>
<td>Heterogeneity:</td>
<td>Chi² = 2.56, df = 2 (P = 0.28); I² = 22% Test for overall effect: Z = 2.49 (P = 0.01)</td>
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<td></td>
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<tr>
<td>1.1.3 Asymptomatic rotavirus infection</td>
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<tr>
<td>Mastretta 2002</td>
<td>1.30 [0.60, 2.80]</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Szajewska 2001</td>
<td>1.60 [0.52, 4.89]</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1.39 [0.74, 2.62]</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Chi² = 0.09, df = 1 (P = 0.77); I² = 0% Test for overall effect: Z = 1.02 (P = 0.31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences:</td>
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<td></td>
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<tr>
<td>Chi² = 11.16, df = 2 (P = 0.004); I² = 82.1% Favors lactobacillus GG Favors placebo</td>
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</tbody>
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**Fig. 1.** Effect of LGG on healthcare-associated diarrhea. Reproduced with permission from Szajewska et al. [8].

**Nosocomial Diarrhea**

What Is Already Known?
Rotavirus remains a leading cause of nosocomial gastroenteritis, which frequently results in prolonged hospital stays and increased additional medical costs. For prevention of rotavirus infection, vaccination seems to be the most promising strategy. However, the high cost of rotavirus vaccines precludes their widespread use in many settings, thus maintaining interest in other strategies for preventing nosocomial diarrhea. Previously, there was some promising evidence to recommend the use of *Bifidobacterium bifidum* (later renamed *B. lactis*) and *Streptococcus thermophilus* to prevent nosocomial diarrhea [7].

What Is New?
A meta-analysis of 3 RCTs involving 1,092 children documented that compared with placebo, LGG administration for the duration of the hospital stay was associated with significantly lower rates of diarrhea (RR 0.37, 95% CI 0.23–0.59) and symptomatic rotavirus gastroenteritis (RR 0.49, 95% CI 0.28–0.86; fig. 1)
There was no significant difference between the LGG and the control groups in the incidence of asymptomatic rotavirus infection, duration of hospitalization, or duration of diarrhea (fig. 1). In contrast, a recent, double-blind, placebo-controlled RCT performed in 106 children aged 1–48 months found that use of *L. reuteri* DSM 17938 did not significantly affect the risk of developing nosocomial diarrhea, defined as 3 loose or watery stools per day in a 24-hour period that occurred >72 h after admission or rotavirus infection [9]. Another RCT carried out in Brazil found a lack of an effect of *Lactobacillus delbrueckii* H2B20 in the prevention of diarrhea in children hospitalized for a short period [10].

Overall, the available evidence suggests that LGG may reduce the risk of nosocomial diarrhea and may be considered for use in hospitalized children.

**Infantile Colic**

**What Is Already Known?**

Although infantile colic is usually self-limited, it may be very distressing to parents, hence the interest in effective remedies. Previously, it has been documented in an open RCT that compared with simethicone, *L. reuteri* ATCC 55730 improved colicky symptoms in breastfed infants within 1 week of treatment [11]. This strain was found to carry potentially transferable resistance traits for tetracycline and lincomycin. It has since been replaced by a new strain, *L. reuteri* DSM 17938, which was derived from *L. reuteri* ATCC 55730 with no unwanted plasmid-borne resistances.

**What Is New?**

The double-blind RCT by Savino et al. [12] showed that compared with placebo, *L. reuteri* DSM 17938 administered at a dose of $10^8$ colony-forming units (CFU) per day to 46 breastfed infants improved symptoms of infantile colic. By day 21 after randomization, mothers of infants in the probiotic group were significantly more likely than mothers of infants in the placebo group to report a reduction from baseline in the average crying time to <3 h per day (84 vs. 43%). Also, a more recent double-blind RCT found that the administration of *L. reuteri* DSM 17938 at a dose $10^8$ CFU to exclusively or predominantly breastfed infants was associated with treatment success at 1, 2, 3, and 4 weeks after randomization (fig. 2). In addition, throughout the study period, the median crying time was significantly reduced in the probiotic group compared with the control group [13].

Overall, given the lack of effective therapy for infantile colic and the generally good safety profile of probiotics used in otherwise healthy populations, the use of *L. reuteri* DSM 17938 could be discussed with caregivers. Until now, all
studies were carried out in exclusively or predominantly breastfed infants. Studies in formula-fed infants would be helpful. The mechanism of action of *L. reuteri* for treating infantile colic has yet to be elucidated.

### Prevention of Necrotizing Enterocolitis

#### What Is Already Known?
It has been speculated that abnormal patterns of gut colonization in preterm infants may contribute to increased susceptibility to infections and the pathogenesis of necrotizing enterocolitis (NEC). A number of systematic reviews, with or without a meta-analysis, have reviewed data on the effects of the enteral administration of probiotics on the risks of NEC and mortality in preterm infants [14–16].

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**Fig. 2.** *L. reuteri* DSM 17938 for the management of infantile colic. Primary outcome – treatment success (reduction in the daily average crying time $\geq 50\%$). Reproduced with permission from Szajewska et al. [13].
What Is New?

Among them, the most recent is the updated meta-analysis by Deshpande et al. [17] (search date: March 2009), which identified 11 RCTs and involved 2,176 preterm infants. Compared with the control group, preterm neonates in the probiotic group had a reduced risk of NEC (RR 0.35, 95% CI: 0.23–0.55) and all-cause mortality (RR 0.42, 95% CI: 0.29–0.62), but there was no difference between groups in the risk of sepsis (RR 0.98, 95% CI: 0.81–1.18). The major concern with regard to this meta-analysis, as with many other meta-analyses in the area of probiotics, is whether it is appropriate to pool data on different microorganisms.

Overall, certain probiotics (as a group) prevent NEC. Whether probiotic supplementation should become the standard of care is still under discussion. In general, scientific societies are in the position that they have insufficient data to recommend the use of probiotics in infants at risk for NEC, and they have concluded that further research is needed [18, 19]. Before the routine use of probiotics in preterm infants, data regarding which products should be administered, at what dosages, and for how long are needed. In settings in which the incidence of NEC is high, one may consider the use of probiotics – single or in combination. However, care should be taken in choosing those that are the best studied, with the highest effect size and the best safety profile. Of note, some researchers consider that the current evidence justifies the routine use of this intervention [20].

Beyond the Gut – Prevention of Respiratory Tract Infections

What Is Already Known?

Young children attending day care centers are at higher risk of developing a respiratory tract infection (RTI). Both families and the society would benefit from inexpensive effective methods of RTI prevention. While the mode of action of probiotics outside of the gastrointestinal tract is less clear, it has been hypothesized that probiotics may influence the incidence of infections by immunomodulation of local immunity (by maintaining gut wall integrity) and systemic immunity (by enhancing nonspecific and specific arms of the immune system).

What Is New?

A Cochrane review [21] (search date: May 2011) pooled data from 10 RCTs (n = 3,451) that evaluated the efficacy of using probiotics for the prevention of upper respiratory tract infections (URTIs) in subjects of all ages. Probiotics were supe-
rior to placebo in reducing the number of participants experiencing episodes of acute URTI, reducing the rate ratio of episodes of acute URTI, and reducing antibiotic use. The included studies used different types of probiotics, with some administering a combination of probiotics. Inclusion of both adults and children precludes practical implications from this meta-analysis regarding which probiotic(s) to use for preventing URTIs.

Among a number of other probiotic strains studied, LGG seems to be the most promising for preventing RTIs. Initially, LGG efficacy was documented in a double-blind, randomized, long-term study that showed that milk containing LGG moderately reduced the incidence of respiratory infections and antibiotic treatment in children [22]. Two subsequent RCTs add to the evidence. Hojsak et al. [23] recruited 281 children aged 1–7 years who attended day care centers to randomly receive LGG at a dose of $10^9$ CFU or placebo. After the 3-month (November through February) intervention, compared to the placebo group, children in the LGG group had a significantly reduced risk of URTIs (RR 0.66, 95% CI: 0.52–0.82, NNT 5, 95% CI: 4–10), a reduced risk of RTIs lasting longer than 3 days (RR 0.57, 95% CI: 0.41–0.78, NNT 5, 95% CI: 4–11), and a significantly lower number of days with respiratory symptoms (p < 0.001). A more recent Finish double-blind RCT conducted by Kumpu et al. [24] in 501 children aged 2–6 years attending day care centers involved the administration of LGG ($10^8$ CFU) in normal milk or normal milk alone (placebo group) for 7 months (October through April). The investigators found that compared with placebo, administration of LGG reduced the occurrence of respiratory illness in the completed cases subgroup (128 subjects with recovery of LGG in their fecal samples), but not in the total population.

Overall, the role of probiotics in preventing RTIs in children remains to be defined; however, there are substantial grounds to consider LGG as a good candidate.

**Chronic Conditions**

**Overweight and Obesity**

While it is clear that genetic factors are important in determining bodyweight, others such as behavioral and environmental factors also contribute. In 2004, the Jeffrey Gordon group first proposed that there is a link between the type of gut microbiota and the regulation of bodyweight [25], and new research avenues have opened up. Recent advances in understanding the link between gut microbiota and obesity are discussed in detail elsewhere [26]. In brief, sig-
naling molecules produced by gut microbiota might modulate adiposity by regulating the expression of host genes that are crucial in fat storage and oxidation, in gastrointestinal hormone production and barrier function, and in systemic inflammation. There have been several studies published over the last few years showing that the composition of the gut microbiota differs between lean and obese individuals [27]. Differences are apparent within the first week of life, and may precede clinical symptoms. In particular, it has been documented that a shortage of bifidobacteria in early gut microbiota is followed by the later development of overweight and obesity in children [28]. Preliminary data from one RCT showed that administration of LGG had a transient preventive effect on weight gain during the first years of life [29]. The findings are encouraging. Further studies will show whether targeting gut microbiota by the administration of probiotics will reduce the risk of obesity or metabolic syndrome.

**Celiac Disease**

The composition of the gut microbiota differs between individuals with celiac disease and healthy individuals with respect to phylogenetic diversity and an abundance of microbial taxa. For example, some of the most recent data, albeit obtained from a relatively small group of subjects, have shown that gut microbiota of infants at risk for celiac disease exhibits reduced proportions of bacteria of the phylum Bacteroidetes and a high abundance of Firmicutes compared with subjects with a nonselected genetic background [30]. However, other studies have reported a higher abundance of Bacteroidetes [31, 32]. In other conditions characterized by a deranged immune response of the mucosal immune system, attention has been given to the possible role of manipulation of the gut microbiota. It could be envisioned that probiotics/prebiotics may influence the type of immune reactivity to gluten in subjects with celiac disease; however, no such studies to support this view are available yet.

**Type 1 Diabetes**

A recent study found that compared to controls, subjects who just developed type 1 diabetes-related autoimmunity had an aberrant gut microbiome [33]. In diabetes-prone rats, administration of *Lactobacillus johnsonii* delayed the development of diabetes [34]. Furthermore, a meta-analysis of 20 studies demonstrated a 20% increase in the risk of childhood-onset type 1 diabetes...
after caesarean section delivery that cannot be explained by known confounders [35]. Taken together, these human and animal data indicate that gut microbiota may be involved also in the development of type 1 diabetes. The ongoing PRODIA study aims to determine whether the administration of probiotics during the first 6 months of life decreases the appearance of type 1 diabetes-associated autoantibodies in children with genetic risk for this disease [36].

Conclusions

‘The microbes are coming’ [37]. This statement recently made by Gregor Reid speaks for itself. It is clear that the microbiota plays a significant role in the development of a number of conditions. Rapid progress in the field of microbiota science is currently underway. Be alert for new findings.

Disclosure Statement

H. Szajewska has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Arla, Biogaia, Biocodex, Danone, Dicofarm, Nestlé, Nestlé Nutrition Institute, Nutricia, Mead Johnson, Polpharma, and Vitapharma.

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Can Probiotics Prevent/Treat Disease in Pediatrics?


37 Reid G: The microbes are coming. CMAJ 2011;183:1332.