What are the indications for using probiotics in children?

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ABSTRACT
The health benefits of probiotics have been the subject of extensive research. Still, some questions are being repeatedly asked: should one use or not use probiotics? If yes, how and when should probiotics be used? The purpose of this review is to summarise current evidence on specific probiotics’ efficacy and safety to help healthcare professionals make evidence-based decisions on the indications for using specific probiotic strains or combinations in children. To identify relevant data, searches of MEDLINE and the Cochrane Library databases were performed in July 2015 to locate randomised controlled trials or their meta-analyses published in the last five years. The MEDLINE database also was searched for evidence-based clinical practice guidelines, developed by scientific societies. Considering that probiotics have strain-specific effects, the main focus was on data on individual probiotic strains, not on probiotics in general.

INTRODUCTION
Probiotics: myth or miracle? Are probiotics really good for your health? Probiotics: panacea or just a big ‘fad’? These titles from non-medical publications reflect an increasing interest in probiotics not only among medical professionals but also among journalists, non-specialists and laypeople. In many countries, the probiotic industry is big business, often with aggressive marketing causing uncertainty about whether or not to use probiotics. If yes, when and how should probiotics be used?

The purpose of this review is to summarise current evidence on probiotics’ efficacy and safety to help healthcare professionals make evidence-based decisions on the indications for using probiotics in children. To identify relevant data, searches of MEDLINE and the Cochrane Library databases were performed in July 2015 to locate randomised controlled trials (RCTs) or their meta-analyses published in the last five years. The MEDLINE database also was searched for evidence-based clinical practice guidelines, developed by scientific societies. Considering that probiotics have strain-specific effects, the main focus was on data on individual probiotic strains, not on probiotics in general.

CLINICAL EFFECTS OF PROBIOTICS
For a summary of the clinical effects of probiotics in children, see table 3.

Treatment of acute gastroenteritis
Worldwide, acute gastroenteritis remains one of the leading illnesses in children. Rehydration is the key treatment and should be applied as soon as possible. In 2014, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) provided recommendations for the use of probiotics for the treatment of acute gastroenteritis in previously healthy infants and children based on a systematic review. The use of the following probiotics may be considered in the management of children with acute gastroenteritis in addition to rehydration therapy: *Lactobacillus rhamnosus* GG (LGG) (low quality of evidence; strong recommendation) and *S. boulardii* (low quality of evidence; strong recommendation).

In summary, in line with current European guidelines, the use of probiotics with documented efficacy may be considered in the management of acute gastroenteritis.

Prevention of antibiotic-associated diarrhoea
The prevalence of antibiotic-associated diarrhoea (AAD) varies depending on the criteria used to diagnose it, but in children it ranges from about 5% to 40%.3 Evidence from several meta-analyses has consistently shown that most of the tested probiotics significantly reduce the risk of AAD in the general (mainly adult) population. A 2012 meta-analysis pooled data from 63 RCTs involving almost 12 000 participants and indicated a statistically significant reduction in the risk of AAD in the probiotic groups compared with the control groups.
(relative risk (RR) 0.58; 95% CI 0.50 to 0.68). The number needed to treat (NNT) was 13 (95% CI 10 to 19). In children, two of the most effective probiotics for reducing the risk of AAD are *S. boulardii* (six RCTs, n=1653, RR 0.43, 95% CI 0.3 to 0.6) and LGG (five RCTs, n=445, RR 0.48, 95% CI 0.26 to 0.89) (Szajewska et al, under review).

In summary, administration of selected probiotics with proven efficacy may be considered for preventing AAD.

**Prevention of nosocomial diarrhoea**

Rotavirus infection remains the most important cause of severe diarrhoea, including nosocomial diarrhoea, in young children. For prevention of rotavirus infection, vaccination is the best strategy; however, the high cost of vaccination precludes its widespread use in many settings, hence, interest in the use of probiotics. Earlier trials have shown that some probiotics may be effective for preventing nosocomial diarrhoea.

A 2011 meta-analysis of three RCTs involving 1092 children documented that compared with placebo LGG administration for the duration of the hospital stay was associated with significantly lower rates of diarrhoea (two RCTs, n=823, RR 0.37, 95% CI 0.23 to 0.59) and symptomatic rotavirus gastroenteritis (three RCTs, n=1043, RR 0.49, 95% CI 0.28 to 0.86). There was no significant difference between the LGG and the control groups in the incidence of asymptomatic rotavirus infection, duration of hospitalisation or duration of diarrhoea.

One 2012, double-blind, placebo-controlled RCT performed in 106 children aged 1–48 months found that *L. reuteri* DSM 17938 did not significantly affect the risk of developing nosocomial diarrhoea (≥3 loose or watery stools per day that occurred ≥72 h after admission) (RR 1.06, 95% CI 0.7 to 1.5) or rotavirus infection (RR 1.04, 95% CI 0.6 to 1.6).

Most recently, one large (n=727), double-blind, placebo-controlled RCT demonstrated that administration of *Bifidobacterium animalis* subsp. *lactis* BB-12 was not effective in preventing nosocomial infections (gastrointestinal and respiratory infections) occurring >48 h after admission in hospitalised children older than 1 year.

In summary, available evidence suggests that the use of LGG may be considered in hospitalised children to reduce the risk of nosocomial diarrhoea.

**Prevention of infections in children attending daycare centres**

Infants and children attending daycare centres are at high risk of respiratory and/or gastrointestinal infections. One systematic review (search date: July 2014) evaluated the effect of probiotics for preventing acute upper respiratory tract infections (URTIs). Subgroup analysis of RCTs carried out in children showed a reduced number of subjects in the probiotics group compared with the placebo group who experienced at least one episode of URTI (five RCTs, n=1457; OR 0.43, 95% CI 0.29 to 0.63) or at least three episodes (two RCTs, n=332, OR 0.56, 95% CI 0.35 to 0.89). However, the rate ratio of episodes of acute URTI was similar in the probiotic and placebo groups (three RCTs, n=1136, rate ratio 0.77, 95% CI 0.57 to 1.05). Some evidence was of low or very low quality. No indications for use of specific strains were provided.

More informative was a strain-specific systematic review (search date: September 2012) focusing on LGG only. Four RCTs involving 1805 children were identified. Compared with placebo, the administration of LGG reduced the incidence of acute otitis media (four RCTs, n=1805, RR 0.76, 95% CI 0.64 to 0.91; NNT 17, 95% CI 11 to 46), the risk of URTIs (one RCT, n=281, RR 0.62, 95% CI 0.50 to 0.78; NNT 4, 95% CI 3 to 8), as well as antibiotic treatments (four RCTs, n=1805, RR 0.80, 95% CI 0.71 to 0.91). However, there was no difference between the groups in the risk of overall respiratory infections (four RCTs, n=1805, RR 0.84, 95% CI 0.67 to 1.05).

One RCT assessed the effect of a daily administration of *L. reuteri* DSM 17938 (1×10^8 CFU) for 3 months in preventing
diarrhoea in 336 otherwise healthy, Mexican children attending daycare centres. Compared with the placebo group, in the L. reuteri DSM 17938 group there was a significant reduction in the number of episodes of diarrhoea, episodes of diarrhoea per child, mean duration of diarrhoea episodes and days with diarrhoea per child both during the intervention and for the next 3-month follow-up period (the primary outcomes). At both 3 and 6 months, there was a significant reduction in the number of respiratory tract infections (a secondary outcome). Moreover, a cost-effectiveness analysis showed that intervention with L. reuteri DSM 17938 was cost saving for the community. Earlier, another RCT carried out in malnourished Indonesian children found that the consumption of regular calcium milk with L. reuteri DSM 17938 (5×10⁸ CFU) compared with regular calcium milk alone reduced the risk of diarrhoeal disease.

However, a direct comparison of the studies is difficult due to the different study populations and the double intervention used in the latter study.

One double-blind RCT carried out in Croatia in 210 children who attend daycare centres found that that B. animalis subsp. lactis BB-12 given during the 3-month intervention period had no effect on the prevention of gastrointestinal and respiratory tract infections. In summary, available data suggest that some probiotics such as LGG and L. reuteri DSM 17938 may have some effect on community-acquired infections. However, repeat studies are still needed.

### Prevention of allergy

It has been hypothesised that, among other causes, aberrant gut microbiota, due to factors such as mode of delivery (vaginal vs caesarean), use of antibiotics during the early neonatal period and mode of feeding (breast vs formula feedings), contribute to the development of allergic diseases. Prevention of allergic disorders through modification of gut microbiota via the provision of probiotics (and/or prebiotics) is currently being evaluated.

Recently, two independent guidelines were published yielding contradictory recommendations. In 2014, the European Academy of Allergy and Clinical Immunology (EAACI), based on the results of a systematic review of RCTs (search date: September 2012), concluded that there is no evidence to support the use of probiotics (also prebiotics) for food allergy prevention. In 2015, the World Allergy Organization (WAO) guidelines were published. These guidelines are based on the findings from the systematic review (search date: December 2014) by Cuello-Garcia et al. This systematic review identified 29 publications in which 12 various probiotics, single or in combinations, were used; however, except for LGG, none were studied in more than one trial. The authors concluded that there are significant benefits of probiotic supplements in reducing the risk of eczema when used by women during the last trimester of pregnancy (RR 0.71, 95% CI 0.60 to 0.84), when used by breastfeeding mothers (RR 0.57, 95% CI 0.47 to 0.69) or when given to infants (RR 0.80, 95% CI 0.68 to 0.94).
In line with the EAACI, the WAO experts agreed that probiotic supplementation cannot be recommended for reducing the risk of allergy in children. However, the WAO considered that there is a likely net benefit from using probiotics for preventing eczema. Specifically, the WAO suggests: “a) using probiotics in pregnant women at high risk for having an allergic child; b) using probiotics in women who breastfeed infants at high risk of developing allergy; and c) using probiotics in infants at high risk of developing allergy.” All recommendations were conditional and supported by a very low quality of evidence.

One important limitation of the WAO guidelines is the lack of answers to the most important practical questions. Which probiotic(s) should be used to reduce the risk of eczema? When should one start the administration of probiotics with proven efficacy? When should one stop? What is the dose of an effective probiotic?

In summary, probiotics as a group reduce the risk of eczema. However, it would be premature to support the routine use of probiotics for preventing eczema. Data regarding which probiotic products should be administered, at what dosages and the most effective dosing schedule are needed.

Prevention of necrotising enterocolitis
Possibly the most promising indication for the use of probiotics is for preventing necrotising enterocolitis (NEC) in preterm infants. This is based on the assumption that abnormal gut microbiota may be implicated in the pathogenesis of NEC.

A number of meta-analyses consistently have shown that enteral administration of probiotics reduces the risks of NEC and mortality in preterm infants. One of them is the updated Cochrane review (search date: October 2013), which identified 24 RCTs. Compared with the control group, preterm neonates in the probiotics group had reduced risks of NEC stage ≥2 (20 RCTs, n=5529, RR 0.43, 95% CI 0.33 to 0.56) and all-cause mortality (17 RCTs, n=5112, RR 0.65, 95% CI 0.52 to 0.81), but there was no difference between groups in the risk of nosocomial sepsis (19 RCTs, n=5338, RR 0.91, 95% CI 0.8 to 1.03).27 Probiotics also reduced the time until full enteral feeding.28

Based on the findings from this review, probiotics as a class seem to confer a benefit. However, the optimal probiotic formulation (organisms and dose) and the duration of treatment remain unclear. Given the above, one recent, strain-specific, systematic review (search date: December 2014) deserves attention. This review focused on *L. reuteri DSM 17938*.29 Six RCTs (n=1778) were identified. Compared with the control group, the administration of *L. reuteri DSM 17938* significantly reduced the time to full feeds (two RCTs, n=1071, mean difference (MD) −1.34 days, 95% CI −1.81 to −0.86), duration of hospitalisation (three RCTs, n=837, MD −10.77 days, 95% CI −13.67 to −7.86) and risk of late-onset sepsis (four RCTs, n=2347, RR 0.66, 95% CI 0.52 to 0.83). The latter effect had not been documented with regard to other probiotics. There were no significant differences between the groups with regard to all-cause mortality (three RCTs, n=1718, RR 0.79, 95% CI 0.57 to 1.09) and ≥ stage II NEC (three RCTs, n=2181, RR 0.69, 95% CI 0.47 to 1.01).

In summary, probiotics as a group have the potential to reduce the risk of NEC in preterm infants. In settings in which the incidence of NEC is high, one may consider the use of probiotics (single or in combination) that are the best studied, with the highest effect size, and the best safety profile. The safety and efficacy of using probiotics in very-low-birthweight (birth weight <1500 g) and extremely low-birthweight infants (birth weight <1000 g) remain unknown.

*Helicobacter pylori* infection
Unsatisfactory *Helicobacter pylori* eradication rates and therapy-associated side effects remain a problem. A number of systematic reviews and meta-analyses have shown that probiotic supplementation improves eradication rates and/or reduces side effects of *anti-*H. *pylori* treatment.30 31

A 2014 meta-analysis (search date: July 2013) focused on children.32 Compared with the control group, children in the probiotic group experienced an increased eradication rate (seven RCTs, n=508, OR 1.95, 95% CI 1.28 to 3.0) and reduced risk of side effects associated with *H. pylori* eradication therapy (five RCTs, n=393, RR 0.32, 95% CI 0.13 to 0.79). However, it was unclear which probiotics are effective.

A 2015 meta-analysis (search date: February 2015) found that compared with placebo or no intervention *S. boulardii* given along with standard triple therapy significantly reduced the risk of overall *H. pylori* therapy-related adverse effects and increased the eradication rate. However, data in children were limited (eradication rate: two RCTs, n=330, RR 1.13, 95% CI 1.03 to 1.25).33 Of note, while in both analyses the addition of probiotics to standard triple therapy significantly increased the eradication rate, it was still below the desired level (≥90%) of success.

Given the available evidence, the fourth edition of the Maastricht consensus on the management of *H. pylori* infection recommends that “certain probiotics show promising results as an adjuvant treatment in reducing side effects”.34 However, children were not specifically addressed.

In summary, in patients with *H. pylori* infection, supplementation of standard eradication therapy with selected probiotics (such as *S. boulardii*) may alter the eradication rate and/or risk of side effects; however, evidence in children remains limited.

Functional gastrointestinal disorders
Infantile colic
Because of the natural history of colic, which peaks at some point and then subsides, no treatment is generally needed. However, excessive crying is distressing to caregivers, hence, there is interest in effective therapeutic and/or preventive options.

Four independent RCTs showed that use of *L. reuteri* DSM 17938 reduced crying times in breastfed infants with infantile colic.35-38 In contrast, one RCT that involved both breastfed and formula-fed infants did not confirm this effect.39 A 2014 meta-analysis of three RCTs found that compared with placebo the administration of *L. reuteri* DSM 17938 reduced crying time on day 21 by approximately 43 min (MD −43 min/day, 95% CI −68 to −19). This effect was mainly seen in breastfed infants (MD −57 min/day, 95% CI −67 to −46).40

One RCT carried out in Italy in 389 breastfed and formula-fed infants revealed that compared with placebo the administration of *L. reuteri* DSM 17938 daily from day 3 for 90 days resulted in a significant reduction of crying time by approximately 51 min/day at 1 month and 33 min/day at 3 months.41 Thus, preliminary data suggest that *L. reuteri* DSM 17938 may be useful in the prevention of infantile colic.

In conclusion, the administration of *L. reuteri* DSM 17938 is likely to reduce crying times in breastfed infants with infantile colic, but its role in formula-fed infants is less clear. The use of *L. reuteri* DSM 17938 for preventing infantile colic, while promising, needs further evaluation by an independent research team.
Abdominal pain-related functional gastrointestinal disorders

A 2011 meta-analysis evaluated the efficacy of a single probiotic microorganism, that is, LGG, for the treatment of abdominal pain-related functional gastrointestinal disorders (FGDs) in children. Compared with placebo, LGG supplementation was associated with a significantly higher rate of treatment responders (no pain or a decrease in pain intensity) in the overall population with abdominal pain-related FGDs (three RCTs, n=290, RR 1.31, 95% CI 1.08 to 1.59; NNT 7, 95% CI 4 to 22) and in the irritable bowel syndrome (IBS) subgroup (three RCTs, n=167, RR 1.70, 95% CI 1.27 to 2.27; NNT 4, 95% CI 3 to 8). However, no difference was found in the rate of treatment responders between children with functional abdominal pain or functional dyspepsia who received placebo or LGG. The intensity of pain was significantly reduced in the overall study population and in the subgroup of children with IBS. The frequency of pain was significantly reduced in the IBS subgroup only. In one multicentre, crossover RCT performed in 59 children (age range 4–18 years) with IBS, VSL#3 (a mixture of eight probiotic strains) was found to be safe and more effective than placebo in ameliorating symptoms and improving quality of life.

In summary, evidence of the effectiveness of probiotics for the treatment of abdominal pain-related FGDs in the paediatric population is scant and does not support the routine use of probiotics for such treatment.

Functional constipation

Evidence-based recommendations developed by ESPGHAN and NASPGHAN do not support the use of probiotics in the treatment of childhood constipation. This recommendation is based on the findings from five RCTs in which both positive results (Lactobacillus casei rhamnosus Lcr35; Bifidobacterium longum; L. reuteri DSM 17938), as well as negative results (LGG; Bifidobacterium lactis strain DN-173 010) were obtained. None of the findings, whether positive or negative, have been confirmed in repeat trials.

In summary, limited evidence available does not support the use of probiotics in the treatment of constipation in children.

Inflammatory bowel disease

In line with current evidence-based guidelines by the European Crohn’s and Colitis Organisation (ECCO) and ESPGHAN, VSL#3 and Escherichia coli Nissle 1917 may be considered as an effective treatment for maintenance in patients with ulcerative colitis; however, this recommendation is based on limited evidence. With regard to Crohn’s disease, according to ECCO/ESPGHAN guidelines, there is not enough evidence to suggest that probiotics are beneficial for the induction or maintenance of remission.

In summary, limited evidence available does support the use of selected probiotics in the treatment of ulcerative colitis, but not in the management of Crohn’s disease.

DOSE OF PROBIOTICS

For probiotic health effects, the dose of probiotics, which need to be administered in adequate amounts, is essential. The optimal dose of probiotics has not been clearly established and may differ for various probiotics/conditions. Until more data are available, it is prudent to use the treatment regimen (probiotic dose and formulation, duration of treatment) proven to be effective in well-designed and executed RCTs for the same indication.

SAFETY

Overall, probiotics are safe for use in otherwise healthy populations, but caution should be taken in specific patient groups.

Risk factors for adverse events include immunosuppression, prematurity, critical illness, presence of structural heart disease, hospitalisation, presence of a central venous catheter and the potential for translocation of probiotics across the bowel wall. More research is needed before absolute statements on the safety of probiotics in general or individual probiotic strains can be made.

QUALITY OF PROBIOTIC PRODUCTS

Many clinicians have concerns regarding the reliability of some of the products currently on the market. Indeed, a number of studies, including recently described case of fatal mucormycosis in a premature infant associated with contaminated probiotic supplement, have questioned the microbiological quality and labelling of many commercial probiotic products. Healthcare professionals and consumers should be aware of possible variations and that dietary supplements are not regulated as drugs.

CONCLUSIONS

- The best documented is the efficacy of certain probiotics for the treatment of acute gastroenteritis, for the prevention of antibiotic-associated diarrhoea and nosocomial diarrhoea, and for the prevention of NEC; however, in the latter condition it is not clear which probiotic(s) should be used.
- There is some evidence to support the use of certain probiotics to prevent or treat other conditions, such as infantile colic, H. pylori infection, and atopic eczema, but further studies are needed.
- Not all probiotics are equal. The clinical effects and safety of any single probiotic or combination of probiotics should not be extrapolated to other probiotics.
- It is reasonable to use the regimens proven to be effective in well-designed and executed RCTs in a given population.
- The use of products with no documented health benefits should be discouraged.

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Safeguarding patient data

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