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When can infants and children benefit from probiotics?

The latest studies indicate that probiotics can help with colic, eczema, and certain types of diarrhea. They may also help with upper respiratory infections and IBS pain.

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PRACTICE RECOMMENDATIONS

› *Recommend a trial of* Lactobacillus reuteri *for breastfed infants with colic.* (A)

› *Consider* Lactobacillus *and* Bifidobacterium *species for the prevention of upper respiratory infections (URIs) and to shorten the course of URI illness.* (B)

› *Do not recommend probiotics for the prevention of respiratory or gastrointestinal allergies.* (A)

› *Consider probiotics for the reduction of abdominal pain in pediatric irritable bowel syndrome, as well as to reduce diarrhea associated with antibiotic use and acute gastroenteritis.* (A)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE ▶ Ms. B, a 26-year-old woman, presents to your office with her 3-year-old son for a well-child examination. During the course of the conversation, she asks you if she should be giving her child probiotics to improve his general health. Many of her friends, who also have their children in day care, have told her that probiotics, "are nature's way of fighting infection." Her son currently takes no medications, and has no history of asthma or recent gastrointestinal disturbances. He was treated for 2 ear infections last winter, approximately 3 months apart. His physical exam is normal and, after today, his immunizations will be up to date. How should you respond?

The use of probiotics as over-the-counter treatments for a variety of conditions continues to grow, with retail sales of functional probiotic foods and supplements topping $35 billion worldwide in 2014.[1] In children, claims of benefit for gastrointestinal (GI) disorders, colic, and allergy prevention, as well as prevention and treatment of upper respiratory infections (URIs) have existed for over 10 years.[2-4] The human gut flora develops rapidly after birth and is known to be influenced by route of delivery (vaginal vs cesarean), type of feeding (breast vs formula), and other environmental factors.[5] The use of probiotics to influence the types of bacteria in a child's intestinal tract continues to be an area of active research. (For more on probiotic formulations, see **TABLE 1**.)

This article summarizes recent research on probiotic use in infants and children. New data support the use of probiotics for the treatment of colic and atopic eczema; however, the data on using probiotics in the management of URIs is less robust and mixed. And while probiotics improve irritable bowel syndrome (IBS) stomach pain, they do not help with related diarrhea or constipation. All of these data are summarized in **TABLE 2**.[6-29]

L reuteri improves symptoms in breastfed infants with colic

Infant colic is a relatively common condition known to nega-

TABLE 1

Common probiotic products for infants and children*

Various preparations are marketed for use in infants and children, and they are available as liquids, chewable tablets, and powders. Solid forms of probiotics maintain the microorganisms in a freeze-dried state, which is typically stable for months. What follows is a sample of some of these preparations.

Product	Form, dose, and probiotic (CFU)	Approximate cost ($)	Probiotic species
Culterelle Kids	One chewable tablet or packet daily; 5 billion/dose	$18.52/30 packets or tablets	*Lactobacillus rhamnosus*
Florastor Kids Daily Probiotic Supplement	One packet daily; 5 billion/packet	$16.98/20 packets	*Saccharomyces boulardii*
Gerber Soothe Probiotic Colic Drops (0.17 ounces)	Liquid 10^8/5 drops daily	$23.47/25-day supply	*Lactobacillus reuteri*
Ultimate Flora for Kids	1 chewable tablet daily; 1 billion/tablet	$12.74/60 tablets	*Lactobacillus acidophilus, Bifidobacterium infantis, Bifidobacterium bifidum, Bacillus coagulans*
Walgreens Children's Probiotic	One tablet or packet daily; 1.5 billion/dose	$19.99/30 packets or $16.49/30 chewable tablets	*L rhamnosus, L acidophilus*

CFU, colony forming units.
*Information obtained from www.walmart.com and www.walgreens.com as of September 15, 2016.

tively impact maternal mental health and the mother/child relationship.[6] Numerous randomized controlled trials (RCTs) over the years have demonstrated mixed results with using probiotics to decrease crying times, with differences noted between infants who are solely breastfed and those who are not.[7]

In the most recent meta-analysis of 6 studies (n=427) that focused only on the probiotic *Lactobacillus reuteri*, breastfed infants with colic receiving a daily dose of 10^8 colony forming units (CFU) cried an average of 56 fewer minutes/day than those in the control group (95% confidence interval [CI], -64.4 to -47.3; *P*=.001) at day 21 of treatment.[8] Although 2 studies in this meta-analysis included a small number of mixed-fed and formula-fed infants, the majority of trials do not show benefit for these infants. Trials assessing the use of *L reuteri* for prevention of colic have not shown positive results.[7]

Probiotics may help prevent and shorten the course of URIs

The mechanisms by which probiotics may prevent or shorten the course of URIs are not obvious. Current theories include boosting the immune function of the respiratory mucosa, acting as a competitive inhibitor for viruses, and secreting antiviral compounds.[9] Multiple reviews published in the last 3 years, however, add to the evidence that the apparent benefit is real.

A 2013 meta-analysis assessed data from 4 RCTs (N=1805), which used *Lactobacillus rhamnosus* as the sole probiotic for prevention of URIs. In treated children, otitis media incidence was reduced by 24% (relative risk [RR] 0.76; 95% CI, 0.64-0.91) and risk of URI was reduced by 38% (RR 0.62; 95% CI, 0.50-0.78).[10] The number needed to treat (NNT) was 4 for URI prevention, and the authors noted that adverse events were similar in the treatment and control groups.

A 2014 systematic review and meta-analysis of 20 RCTs examining duration of illness included 10 studies dedicated to pediatric subjects (age 12 months to 12 years).[11] There were significantly fewer days of illness per person (standardized

TABLE 2

What the evidence tells us about probiotic use for these conditions in children

Condition	Prevention*	Treatment*	Probiotic species	Typical daily dose (CFU/d)
Colic (breastfed)[6-8]	0	+	*Lactobacillus reuteri*	100 million
Atopic eczema[13-17]	+	0	*Lactobacillus rhamnosus, Lactobacillus paracasei, Bifidobacterium lactis*	3-6 billion
URI[9-12]	+	+	*Lactobacillus* and *Bifidobacterium* spp	2-10 billion
IBS[18-20]	Not studied	+	*L rhamnosus* VSL#3†	6 billion 450-900 billion
AAD[21-24]	+	+	*L rhamnosus, Saccharomyces boulardii*	20 billion
AID[23-29]	Not studied	+	*L rhamnosus, S boulardii, Bifidobacterium bifidum, Bifidobacterium infantis*	10 billion

AAD, antibiotic-associated diarrhea; AID, acute infectious diarrhea; CFU/d, colony forming units per day; IBS, irritable bowel syndrome; URI, upper respiratory infection.

* 0=no effect; +=positive effect.

†*Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus bulgaricus,* and *Streptococcus hermophiles.*

mean difference -0.31; 95% CI, -0.41 to -0.11) and each illness episode was shorter by three-quarters of a day (weighted mean difference -0.77; 95% CI, -1.5 to -0.04) in participants who received a probiotic vs those who received a placebo. Probiotics used in these studies belonged to the *Lactobacillus* and *Bifidobacterium* genera.

A 2015 systematic review of 14 RCTs assessing the benefits of probiotics, particularly *Lactobacillus* and *Bifidobacterium* strains, on URI occurrence and symptoms, showed mixed results.[12] Seven of 12 studies found lowered rates of URI and otitis media incidence, 7 of 11 RCTs reported a significant reduction in severity scores for URI, and 4 of 8 RCTs reported significant reductions in school absenteeism between the probiotic and control groups. In a summary statement, the authors noted that "at least one beneficial effect of prophylactic probiotics was observed in the majority of RCTs," and that "none of the studies reported any serious adverse events."

Perinatal probiotics: No benefit for allergic conditions—except eczema

Allergic disease is on the rise and continues to plague children with reduced quality of life, potentially life-threatening reactions, and missed activities, including school. The gut microbiome likely influences a child's allergic propensity through its effects on T-helper cells, transforming growth factor (TGF), and immunoglobulin A (IgA)—all known components of the allergic response. As the hygiene hypothesis suggests, the quantity and types of bacteria that inhabit the GI tract early in life play a significant role in determining a person's later allergic responses.[13]

In a 2013 meta-analysis of 20 trials (N=4866), researchers looked specifically at probiotic use and the diagnosis of asthma and incident wheezing. Single and combination products of *Lactobacillus* and *Bifidobacterium* given prenatally and/or postnatally were included in the studies. The authors found no evidence to support a protective association between perinatal use of probiotics and diagnosed asthma (RR=0.99; 95% CI, 0.81-0.21) or childhood incident wheezing (RR=0.97; 95% CI, 0.87-1.09; 9 trials, 1949 infants).[14]

In a more recent meta-analysis (2015) conducted to inform the World Allergy Organization, 29 studies were evaluated to assess

Lactobacillus reuteri **decreased crying in breastfed infants with colic by nearly an hour a day.**

the impact of probiotics on allergic symptoms of the skin, respiratory system, and GI tract.[15] No significant benefit was noted for any allergic condition except for eczema. Probiotics reduced the risk of eczema when given during the last trimester of pregnancy (RR=0.71; 95% CI, 0.60-0.84), when used by breastfeeding mothers (RR=0.57; 95% CI, 0.47-0.69), and when given to infants (RR=0.80; 95% CI, 0.68-0.94).

A 2014 systematic review and meta-analysis (N=2797) explored probiotic use specifically for the prevention of eczema.[16] The pooled relative risk for all the studies was 0.74 (95% CI, 0.67-0.82). Evidence was strongest for probiotics containing the *Lactobacillus* species *rhamnosus* and *paracasei,* as well as for *Bifidobacterium lactis*. No benefit was noted with *Lactobacillus acidophilus* or other *Bifidobacterium* species. These newer reviews on eczema prevention contrast with an older Cochrane review published in 2008 (12 RCTs, N=781), which did not show significant benefit for the treatment of eczema.[17]

Probiotics improve IBS stomach pain, but not diarrhea or constipation

IBS is a functional disorder of the GI tract that affects up to 20% of children and teenagers and leads to a significant decrease in quality of life.[18] Current theories of causation include bacterial overgrowth and neuronal hyperactivity, which may be amenable to change with supplemental probiotics.

A 2015 systematic review of non-pharmacological treatments for functional abdominal pain disorders identified 4 studies dedicated to IBS in children.[19] A subgroup analysis of 3 RCTs (n=309) that looked at giving *L rhamnosus* to 5- to 17-year-olds with IBS showed improved abdominal pain (according to various pain scales) compared to the placebo group. Study participants received at least 3 x 10^9 CFU twice a day for 4 to 8 weeks. Relative risk for improvement was 1.7 (95% CI, 1.27-2.27) with an NNT of 4. None of these studies showed significant improvement in either frequency or severity of diarrhea or constipation.

A separate crossover RCT (N=59) compared placebo to VSL#3, a product containing 8 probiotics (*Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, L acidophilus, Lactobacillus plantarum, L paracasei, Lactobacillus bulgaricus,* and *Streptococcus hermophiles*), given in age-dependent doses for 6 weeks to children aged 4 to 18 years.[20] The frequency and intensity of abdominal pain were measured on a 5-point Likert scale. The group treated with VSL#3 dropped 1.0 ± 0.2 points vs 0.5 ± 0.2 points in the control group ($P<.05$) and reported an improved quality of life.

These agents reduce antibiotic-associated diarrhea

Antibiotic-associated diarrhea (AAD) occurs in 5% to 30% of children who receive antibiotic therapy.[21] It occurs most frequently with the use of cephalosporins, penicillin, fluoroquinolones, and clindamycin, and is likely caused by an alteration of the normal gut flora. Colitis caused by *Clostridium difficile* remains the most serious antibiotic-associated GI complication.

A systematic review of the specific probiotic *Saccharomyces boulardii* conducted in 2015 analyzed data from 6 RCTs (n=1653) to determine the effect of co-administration of this probiotic with antibiotics.[22] The pooled relative risk for AAD in children receiving the probiotic was 0.43 (95% CI, 0.3-0.6) compared to antibiotics alone. The absolute risk of AAD dropped from 20.9% to 8.8%, translating to a NNT of 8. Two of the RCTs specifically looked at rates of *C difficile* infection (n=579). *C difficile* infection rates dropped by 75% (RR=.25; 95% CI, 0.08-0.73) in the treatment group. This dramatic treatment effect was not seen in studies involving adults.

A similar systematic review focusing on *L rhamnosus* conducted in 2015 pooled data from 5 RCTs (n=445) to see if the probiotic would decrease AAD in children if it was co-administered with antibiotics.[23] The relative risk for AAD in this treatment group was 0.48 (95% CI, 0.26-0.89) with an absolute risk reduction of 13.4% (23% compared to 9.6%), translating to an NNT of 7.

A Cochrane review published in 2015 included 23 studies (N=3938) and found similar results with an RR for AAD of 0.46 for treated children (95% CI, 0.35-0.61).[24] Doses of probiotics ranged from 5 to 40 billion

CFU/day. Although many probiotic species were used in these studies, *S boulardii* and *L rhamnosus* were cited as having the strongest data to support use in this context.

Probiotics reduce the duration, frequency of acute infectious diarrhea

Diarrhea remains the second leading cause of death among children one to 59 months of age worldwide.[25] Current World Health Organization recommendations include oral rehydration salts, continued feeding to avoid dehydration, and zinc to decrease the duration and severity of illness.[26] Multiple studies in adults confirm that a variety of probiotics decrease both the duration and severity of diarrhea in acute gastroenteritis.[27]

The authors of a 2013 systematic review of probiotics for the treatment of community-acquired acute diarrhea in children less than 5 years of age analyzed data from 8 RCTs (N=1755).[28] Various probiotics were used including *Lactobacillus* species, *Streptococcus thermophilus*, *Bifidobacterium* species, and *Saccharomyces boulardii* for between 4 and 10 days. Six of these studies (n=1164) measured diarrhea duration and found a 14% reduction (95% CI, 3.8%-24.2%) in days of illness for those children treated vs those receiving placebo. Five studies (n=925) measured the difference in stool frequency on Day 2 of illness and reported a reduction of 13.1% (95% CI, 0.8%-5.3%) in the number of stools in the treated group vs the placebo group.

This review augments a Cochrane meta-analysis of 63 studies (N=8014) published in 2010.[27] Fifty-six of these studies included infants and children. Pooled analysis of the varied probiotic treatments showed a mean reduction in duration of diarrhea of just over a day (24.76 hours; 95% CI, 15.9-33.6 hours; n=4555, trials=35) and decreased stool frequency on Day 2 of treatment (mean difference 0.80; 95% CI, 0.45-1.14; n=2751, trials=20). The authors concluded that probiotics "have clear beneficial effects in shortening the duration and reducing stool frequency in acute infectious diarrhea."

Pediatric society weighs in. In 2014, the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition issued guidelines regarding probiotic use for the treatment of acute gastroenteritis.[29] In addition to rehydration therapy, these guidelines recommend the use of *L rhamnosus* and/or *S boulardii* as first-line treatments. Lower quality evidence is available for the use of *L reuteri*.

CASE ▶ In response to Ms. B's query about starting her young son on probiotics, you tell her that studies have shown that probiotics are safe for children when given in appropriate doses. They have been shown to help children recover from diarrheal illnesses and can help reduce the number of colds and ear infections when taken regularly. The reason you are giving them determines which strains you should use. You recommend giving her child a formulation of probiotic that contains *Lactobacillus* or *Bifidobacterium* with a dose range of 2 to 10 billion CFUs taken daily to reduce the risk of her child getting another ear infection. **JFP**

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▶ *Lactobacillus rhamnosus* reduced the incidence of otitis media and upper respiratory infections by 24% and 38%, respectively.

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