The Evidence for Use of Probiotics in Children

Medscape: Dr. Thomas, can you share with us some background about this report?

Dan W. Thomas, MD: The decision to examine the issue of the medical uses of probiotics and prebiotics was the result of recognition of a growing number of products, as well as increased use of these agents by a broad segment of the population. The report attempted to summarize the evidence about the health benefits of these products and dietary supplements added to food products marketed to children, including infant formula. Additionally, we examined the role of these agents in the potential treatment of gastrointestinal (GI) and non-GI disease. Review of the report and comments were solicited from the committees and sections of the AAP. Additionally, representatives from the Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), US Food and Drug Administration (FDA), US Department of Agriculture, and the Canadian Paediatric Society participated in the report's development. A complete list of participants is included in the report.

Medscape: The clinical report includes definitions of a number of terms. However, it appears that the most relevant of these agents are probiotics and prebiotics. Can you discuss some of the data regarding use of these agents by children?

Dr. Thomas: Prebiotics are supplements or foods that contain viable microorganisms that cause alterations in the microflora of the host and stimulate favorable growth of probiotic bacteria. Human milk contains substantial quantities of prebiotics, and prebiotics and probiotics have also recently been added to infant formulas. Human
milk and formula therefore are examples of functional foods -- a modified food that provides a health benefit that cannot be attributed to the nutrients in that food (see the Table for terms). The most studied probiotic bacteria to date include *Lactobacillus rhamnosus* GG (LGG), *Bifidobacterium lactis*, and *Streptococcus thermophilus*. Live yogurt, which contains probiotics, is the most common example of a functional food. The list of products containing probiotics is rapidly expanding and clinicians can access the most up-to-date information at www.usprobiotics.org. It should be noted that this is an industry-maintained Website.

**Table. Definitions of Agents**

<table>
<thead>
<tr>
<th>Probiotic</th>
<th>A supplement or food containing a sufficient number of viable microorganisms to alter microflora and has the potential for health benefit</th>
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<tr>
<td>Prebiotic</td>
<td>A nondigestible food ingredient that selectively stimulates favorable growth and/or activity of 1 or more indigenous probiotic bacteria</td>
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<tr>
<td>Symbiotic</td>
<td>A product containing both probiotics and prebiotics. Synergy of a specific probiotic for a probiotic in the product is not essential. May be separate supplements or added to food</td>
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<tr>
<td>Postbiotic</td>
<td>A metabolic byproduct generated by a probiotic microorganism that influences biologic functions</td>
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<tr>
<td>Functional food</td>
<td>Any modified food that provides a health benefit beyond that ascribed to any specific nutrients it contains</td>
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Medscape: What is the mechanism of action of these agents?

**Dr. Thomas:** At birth, infants have a sterile GI tract, but bacterial colonization occurs rapidly with different organisms predominating in formula-fed and breast-fed infants. In resource-rich countries such as the United States, those differences are not as pronounced. In healthy persons, the composition of intestinal microflora does not usually change significantly after infancy. The acquisition of these microflora contributes to the intestinal mucosal defense system, which is an integral part of the body’s sophisticated immunoregulatory network. The immunoresponsiveness of the GI defense system is affected by an infant's diet, bacterial colonization, and early exposure to infectious pathogens and antibiotics. The development of a number of allergic conditions, such as eczema, and autoimmune conditions, like diabetes or inflammatory bowel disease, may be affected by dysregulation or interference with the early development of the intestinal mucosal defense system. The infant's early diet and intestinal microbes are likely to play a pivotal role in overall health. Probiotics and dietary prebiotics likely exert positive effects on the development of the mucosal immune system.

Medscape: Can you summarize the report's conclusions regarding the overall safety of these agents?

**Dr. Thomas:** While there have been anecdotal reports of serious infection, including sepsis, with use of these products, most of those cases occurred in ill, pre-term infants and older immunocompromised children or those with indwelling medical devices. Studies in healthy infants and children have found the agents to be both safe and well tolerated. In the United States, products marketed as dietary supplements, such as probiotics, do not require approval by the FDA. Infant formulas, however, must be made in compliance with manufacturing practices regulated by the Infant Formula Act of 1980 and are under the auspices of the FDA. All ingredients in infant formula must be in accordance with FDA food-additive regulations that require that they be generally regarded as safe (GRAS). Prebiotics and probiotics added to infant formulas in the US are classified as GRAS. Other organizations, including the Committee on Nutrition of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition and the Food and Agriculture Organization of the United Nations World Health Organization, while acknowledging the safety of probiotics in general, have recommended centralized product oversight and monitoring. It should be emphasized that while these products are generally recognized as safe, evidence of their overall efficacy has yet to be established and human milk remains the best food for young infants. There is no evidence that would support a recommendation of infant formula supplemented with probiotics in place of human milk.

**Role of Probiotics in Disease**

**Common Gastrointestinal Conditions**
Medscape: Dr. Thomas, can you summarize some of the major findings in the report in each of the therapeutic areas discussed? First, what is the role of these agents in prevention and treatment of acute gastroenteritis (AGE)?

Dr. Thomas: A number of randomized controlled trials (RCT) of probiotics in AGE have been conducted. Rotavirus was the most common cause of acute diarrhea in these studies. While the results indicate that there is modest benefit with use of probiotics to prevent AGE in infants and children, the available data do not support routine use to prevent nosocomial rotavirus diarrhea in children attending daycare. Rotavirus vaccine is likely to be a much more effective agent in preventing rotavirus infection although there may be special circumstances, such as long-term care facilities, where use of probiotics may be useful in prevention. In the treatment of AGE, however, the data are positive. There is evidence from well-conducted RCTs to support the use of probiotics, specifically LGG, in the management of acute infectious diarrhea. Probiotics have been found to shorten the duration of diarrhea by about 1 day and to decrease the number of diarrheal stools. They also shorten the time necessary for intravenous hydration when this is required. Probiotics seem to be more effective when given early in the course of diarrhea and are most effective in healthy infants and young children with watery diarrhea due to viral gastroenteritis, such as rotavirus, but not invasive bacterial infections.

Medscape: Another common cause of diarrhea in young children is the use of antibiotics. What does the report say about use of probiotics in the prevention and treatment of antibiotic-associated diarrhea?

Dr. Thomas: Prevention of diarrhea due to antibiotic use is another area where a meta-analysis of RCTs indicates a benefit from probiotics. In most of the studies, a probiotic was initiated at the same time as the antibiotic, resulting in a substantial reduction in development of diarrhea. Approximately 1 in 7 cases of antibiotic-associated diarrhea was prevented by the use of a probiotic. However, there have been no published RCTs examining probiotics for the treatment of antibiotic-associated diarrhea in children, including *Clostridium difficile* antibiotic-associated diarrhea, and therefore their use presently cannot be recommended for pediatric patients.

Medscape: Can you discuss the report’s recommendations regarding use of probiotics in other GI conditions such as infantile colic and irritable bowel syndrome?

Dr. Thomas: Colic is a common yet incompletely understood condition primarily affecting babies younger than 4 months of age. No studies have examined the use of probiotics in prevention of this condition and only 1 RCT has looked at the potential use these agents in treatment of colic, and that study included only breast-fed infants. While the results were encouraging, finding less crying within 1 week of initiation of *Lactobacillus reuteri* when compared with simethicone, probiotics cannot yet be routinely recommended. There are also limited data examining use of probiotics in irritable bowel syndrome. One study did find that LGG reduced abdominal discomfort and distention in a group of 50 children. Studies of efficacy in treating constipation have been less positive, however, and they are not recommended at this time for treatment of this condition in children.

Serious Gastrointestinal Disease

Medscape: What about use in more serious GI conditions such as inflammatory bowel disease (IBD) or necrotizing enterocolitis (NEC)?

Dr. Thomas: This is an important issue because it is recognized that as many as half of all children with IBD routinely use alternative medicines, including probiotics. Data from RCTs of adults with chronic ulcerative colitis (CUC) are encouraging. A recent Cochrane review reported that adults with mild-to-moderate CUC received comparable benefit from probiotics as compared with anti-inflammatory drugs such as mesalamine. While there has been a single RCT in children with newly diagnosed CUC that had promising results, more research is needed and probiotics cannot be routinely recommend at this time. Another recent Cochrane review examining the potential role of probiotics in maintaining remission in adults with Crohn disease concluded there was, as yet, no proven benefit. At this time, their use cannot be recommended for children with Crohn disease.

There is evidence to support the use of probiotics to prevent NEC in preterm infants weighing more than 1000 g at birth. However, there remain many unanswered questions over the use of probiotics for prevention of
NEC, including overall safety. Further study is recommended before routine utilization of probiotics for this purpose can be recommended.

**Use in Non-Gastrointestinal Disease**

*Medscape:* The clinical report also discussed use of probiotics for non-gastrointestinal conditions, particularly atopic disease. Can you share some of these recommendations?

**Dr. Thomas:** A Cochrane review in 2007 concluded that there was insufficient evidence to warrant routine supplementation of probiotics to either pregnant women or infants for prevention of allergic disorders in infants.\[^6^\] That position was reiterated in a 2010 review that concluded that there was not enough evidence to support the use of probiotics, prebiotics, or synbiotics in the prevention or treatment of allergic dermatitis in children.\[^7^\] A 2007 large RCT in Finland treated pregnant women with atopic disease with a combination of probiotics and prebiotics during pregnancy that was continued in their infants after delivery.\[^8^\] The study did not document a reduction in the cumulative incidence of allergic disease in these infants, although they did find a lower incidence of IgE-mediated allergic disease, including eczema. While interesting, this study requires confirmation.

*Medscape:* The clinical report also discussed use of these agents in prevention and management of extraintestinal, primarily respiratory, infection. Can you describe these results?

**Dr. Thomas:** A few studies have examined the potential for these agents to reduce respiratory symptoms in children, particularly those attending daycare. A study in 2001 conducted in daycare centers in Finland compared children randomly assigned children to receive milk with and without LGG.\[^9^\] While there were trends favoring fewer days of absence from child care as well as fewer diagnoses of infection or use of antibiotics in children fed milk with LGG, the differences were not significant. No studies have found a benefit from administration of probiotics to treat these infections.

**Recommendations for Use of Probiotics**

*Medscape:* While the report makes clear that human milk is the preferred food for infants, what would you suggest primary care providers advise parents who choose to bottle-feed? Should infant formula supplemented with probiotics be recommended?

**Dr. Thomas:** No one can answer this question at this time. The health benefits of feeding infant formula containing probiotics and/or prebiotics are unproven. In essence, this report challenges industry and healthcare researchers to conduct high-quality, evidence-based studies to answer these questions.

*Medscape:* And what about advice to parents of older children who would like to give probiotics to their child?

**Dr. Thomas:** Outside of the specific situations outlined in this report where there is evidence of benefit, the answer to this question, too, is relatively unknown and will have to await further research.

**References**