ID CONSULT

Prebiotics, Probiotics Are Useful Now

Prebiotics and probiotics might offer a way to both prevent and treat disease by enhancing the body's natural immune defense mechanisms.

Recognition that certain naturally occurring bacteria in the gut might be beneficial to health dates back to the early 1900s, when Nobel laureate Dr. Eli Metchnikoff reported that peasants who consumed sour milk with live *Lactobacillus bulgaricus* lived longer than other people. Now, emerging data suggest that supplementation with health-associated bacteria, also known as "probiotics," can prevent or reduce diarrhea caused by altered gut flora from antibiotics or rotavirus.

BY CHRISTOPHER J. HARRISON, M.D.

In addition, "prebiotics," the nondigestible oligosaccharides that stimulate growth of existing probiotic bacteria, also have drawn interest. Prebiotic supplements that do not contain added probiotics could avoid some of the problems associated with probiotics, such as difficulty maintaining live organisms until administration and potential bacteremia in immunosuppressed individuals.

Present in breast milk, prebiotics enhance the growth of existing probiotic bacteria strains *Bifidobacteria* and *Lactobacillus,* which predominate in the guts of breast-fed infants. The gut flora of bottle-fed infants, in contrast, tend to comprise primarily *Enterobacteriaceae* and *Clostridia*.

Several studies—some supported by infant formula manufacturers—show that adding prebiotic galacto-oligosaccharides and fructo-oligosaccharides to cow's milk formula can result in intestinal flora in bottle-fed infants similar to that in breast-fed infants. This, in turn, results in a reduced intestinal load of more pathogenic bacteria in the infant.

Mucosal and systemic immunity also appear to be enhanced with prebiotic supplementation, possibly reducing subsequent immune-mediated disease such as asthma and allergies. In one prospective, placebo-controlled study, 102 infants at high risk for atopy were fed prebiotic-containing formula (galacto- and long-chain fructo-oligosaccharides) or formula with a placebo (maltodextrin). The atopic dermatitis rate was 9.8% for infants receiving prebiotics, compared with 23.1% for placebo (Arch. Dis. Child. 2006;91:814-9).

A growing data set suggests that pre- and probiotic supplementation in infancy can enhance IgA responses to antigenic challenge, and favorably influence T-helper cell balance, thus reducing inflammatory and/or allergic responses. One prebiotic, lactulose, is commercially available in liquid form under various brand names and is approved for treating constipation.

Whether to routinely prescribe lactulose or other prebiotics for non–breast-fed infants remains an unanswered question. Stay tuned for more data.

Meantime, I believe the data on probiotics are sufficient to support several clinical uses. I advise using a product called Lactinex, which contains both *Lactobacillus acidophilus* and *Lactobacillus bulgaricus,* as antidiarrheal prophylaxis during prolonged antimicrobial therapy, particularly with broad-spectrum agents. I also recommend it during shorter antibiotic courses if mom says that her child always develops diarrhea while on antibiotics.

Lactinex comes in tablet or packet form, with 1 million colony-forming units per tablet or 100 million per packet. The granules can be mixed with food or formula. I advise one packet per day for all ages. Older children can take two to three tablets, three to four times a day.

In the 1990s, my colleagues and I conducted a study in children on a broad-spectrum antibiotic where a 30% reduction in daily stool number and 50% fewer diarrhea days occurred with Lactinex, compared with placebo supplements. The study, funded by an antibiotic manufacturer, was not published because of higher-than-expected diarrhea rates in controls. But, it encouraged me about the potential benefit of probiotics.

Another option for acute diarrhea is *Lactobacillus GG,* a widely studied probiotic strain sold commercially under the brand name Culturelle. A 2001 literature review revealed that probiotics significantly lowered the risk (odds ratio 0.43) of diarrhea lasting more than 3 days, particularly with rotavirus. Of individual strains, only *Lactobacillus GG* showed consistent effect (J. Pediatr. Gastroenterol. Nutr. 2001; 33[suppl. 2]:S17-25).

But other data suggest benefit for other probiotic organisms. A randomized study of 201 healthy, non–breast-fed day care infants aged 4-10 months compared *Lactobacillus reuteri* or *Bifidobacterium lactis* with placebo, revealing significantly fewer episodes of fever (11%, 27%, and 41%, respectively) and diarrhea (13%, 2%, 31%). Duration of diarrhea was also shorter with the probiotics (Pediatrics 2005; 115:5-9).

Other exciting data include reductions in atopic disease among children whose mothers took prenatal *Lactobacillus GG* (Lancet 2001;357:1076-9), enhanced immune response to typhoid immunization in adults given *Lactobacilli* (FASEB J 1999;13:A872 [abstr]), and reduced incidence/severity of necrotizing enterocolitis in very-low-birth-weight newborns receiving *Lactobacillus acidophilus* plus *Bifidobacterium infantis* (Infloran) (Pediatrics 2005;115:1-4).

To be sure, not all pre- and probiotic studies have had positive outcomes. But, excluding immunosuppressed individuals, risk is minimal from these naturally occurring organisms, so why not use them? I predict that we'll be hearing more about this in the future. ■

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Fluconazole Prophylaxis in NICU Not Linked to Resistance

BY DIANA MAHONEY
New England Bureau

TORONTO — Fluconazole prophylaxis for invasive candidiasis in extremely low-birth-weight infants is not associated with the emergence of fluconazole-resistant *Candida* species, Dr. C. Mary Healy said at the annual meeting of the Infectious Diseases Society of America.

In infants weighing less than 1,000 g at birth, 42 days of fluconazole prophylaxis (FP) has been shown to reduced *Candida* colonization and invasive candidiasis, "but the possibility that [this regimen] could lead to a resistant *Candida* species is an ongoing concern," said Dr. Healy of Baylor College of Medicine in Houston. "The worry is that FP will cause overgrowth and infection by inherently less susceptible species, particularly *C. glabrata*."

To evaluate the impact of FP on the incidence of invasive candidiasis (IC), as well as IC-related mortality and fluconazole susceptibility of *Candida* isolates, Dr. Healy and her colleagues reviewed data from the neonatal intensive care unit (NICU) at the Women's Hospital of Texas in Houston for infants treated both before and after the implementation of an FP strategy in 2002.

For the purposes of this investigation, IC was defined as the presence of a *Candida* species isolated from blood or cerebrospinal fluid in NICU infants.

Since April 2002, as per hospital protocol, extremely low-birth-weight infants younger than 5 days in the NICU of the Women's Hospital of Texas have been eligible to receive intravenous FP at a dose of 3 mg/kg for 6 weeks on a dosing schedule that varies by age: every third day for the first 3 weeks, every second day for the subsequent 2 weeks, and daily for the final 2 weeks, said Dr. Healy.

Using pharmacy and electronic records, Dr. Healy and her colleagues reviewed the demographic, clinical, and laboratory data for all of the NICU infants of any birth weight during the first 4 years of FP implementation and compared it with that of infants who were in the NICU in 2000-2001, before the use of FP.

Between April 2002 and March 2006, 362 extremely low-birth-weight infants in the hospital's NICU received FP, along with 47 infants with a body weight greater than 1,000 g who were started on the preventive therapy at the discretion of the neonatologist. The median body weight of the 409 infants was 775 g, the median gestation was 26 weeks, and the median dose they received was 13 mg/kg over 29 days.

Twenty-nine percent of those infants receiving FP completed the 6-week protocol. Fifty-nine percent discontinued the therapy because IV access was no longer needed, 7% died from non IC-related causes, 2% transferred to other hospitals, 2% had breakthrough infections, and 1% had transient elevation of liver transaminases, which resolved when FP was discontinued, Dr. Healy reported.

Comparing infants who developed IC during the pre- and post-FP time periods, there were 19 cases in 2000-2001 and 22 cases in 2002-2006.

"Infants [who developed IC] during the FP period were of significantly greater gestational age and had significantly higher birth weight than those who developed it before FP," said Dr. Healy. "There was also a strong trend toward them being older, although this did not reach significance." There was no difference in prenatal or perinatal complications, nor were there differences in complications of prematurity.

With respect to potential resistance, "our findings are reassuring," said Dr. Healy. "The IC species distribution remained stable both before and after FP implementation. In the IC cases prior to FP, *C. albicans* was identified in 14 infants, *C. parapsilosis* in 3, *C. tropicalis* in 1, and *C. glabrata* in 1. After FP, the species distribution was *C. albicans* in 13 infants, *C. parapsilosis* in 6, *C. tropicalis* in 1, and *C. glabrata* in 2. "It's particularly reassuring that *C. glabrata* is no more common now than it was before FP," she said.

Similarly, the minimum inhibitory concentrations (MICs) for fluconazole were consistent. "Even though, as you would expect, MICs were higher for *C. glabrata* isolates than for *C. albicans,* we have not yet detected any resistant isolates."

The treatment of IC was the same during both periods—all of the infants received amphotericin B for similar durations, and three also received caspofungin since 2002—and there was no significant difference in the duration of IC between the two periods.

Regarding the overall impact of FP on IC in the NICU, "when we look at infants of any birth weight since the FP protocol was established, the IC rate has been halved, from 0.6% to 0.3%," said Dr. Healy. "These rates become more impressive when we look at our target population of extremely low-birth-weight infants, in whom the IC rate decreased 3.6-fold, from 7% to 2%."

Dr. Healy reported having no conflicts of interest related to this presentation. ■