



Probiotic Perspectives

Probiotics: An Extraordinary Record of Safety

Humans have safely consumed microbially fermented foods for millennia. Living bacterial or yeast cultures have long been used to create such foods as yogurt, kefir, sauerkraut, kimchee, and miso. In the early 1900s, the Nobel laureate Elie Metchnikoff observed health benefits associated with fermented food consumption and developed the concept of probiotics: living microorganisms that confer health benefits when consumed on a regular basis. Since the idea was first introduced, a vast literature has emerged documenting health-promoting effects of probiotics ranging from improved gastrointestinal health to enhanced systemic immune function. Today, widely used and well researched probiotics such as *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces* species have compiled a solid, recognized record of safety.

Safety Research

Clinical trials

Studies show probiotics not only beneficially impact health, but are extremely safe. Toxicity studies in animals have failed to produce adverse events or bacteremia as a result of probiotic administration. Human research has yielded similar findings. In 1999, a large review study examined data from 143 clinical trials in which probiotics were administered to 7,526 persons. Subjects in the trials ranged from preterm infants to elderly adults and included healthy and chronically ill individuals. In all of the trials, spanning four decades, not a single adverse event was reported. A 2010 review examined results from a separate set of clinical trials involving persons receiving probiotics plus enteral or parenteral nutritional support.

In 1999, a large review study examining probiotic use reported no adverse events in 143 clinical trials.

Of the 53 studies reviewed, only two reported increased rates of non-infectious complications following probiotic use. In one of these trials, an error of randomization led to greater numbers of sicker patients receiving probiotics, which may have

skewed the results. The authors claim a logistic regression was performed to correct for this error, but failed to include this data in the study. In the second trial, it is unclear from the information presented whether differences in adverse event levels between the probiotic and control groups reached statistical significance. The ambiguity of the statistical methodology and reporting in these two studies makes it likely the observed adverse events were chance anomalies. If these studies are excluded as outliers, the combined results of the 1999 and 2010 meta-analyses indicate no adverse events occurred from probiotic use in 194 clinical trials.

Case reports

Despite an excellent safety record in clinical trials, a number of case reports of adverse events following probiotic administration have appeared in the medical literature. Most of these events involved use of the fungal probiotic *Saccharomyces boulardii* in critically ill persons with central or peripheral venous catheters. Fungemia was the primary adverse event reported. Venous catheters are known risk factors for infection as environmental contamination may allow microorganisms (pathogenic or probiotic) to gain entry into the systemic circulation. While *S. boulardii* has an excellent safety profile extending back over 50 years and a remarkable record of efficacy in treating various types of diarrhea, it is advisable to avoid administering this particular probiotic to persons with either central or peripheral venous catheters. A scant number of case reports associate *Lactobacillus rhamnosus* GG with bacteremic complications in seriously ill infants or children. Once again, central venous catheters were present in all published cases and likely contributed to the spread of infection. Although bacteremia is an extremely rare complication of probiotic use, clinicians are advised to exercise caution when administering *L. rhamnosus* to persons requiring central or peripheral venous catheterization.

Upper Safe Levels

Perhaps because of the scarcity of adverse events reported in animal and human

studies, there is currently no established upper safe level of probiotic intake. One can intuitively assess the safe level of intake of probiotics by realizing the intestinal tract harbors an estimated 100 trillion microorganisms. In the context of this staggeringly large intestinal microbial population even very high probiotic doses are unlikely to produce ill effects. The published scientific literature also supports the safety of high-dose probiotic administration. Over the past several decades, the doses of probiotics used in clinical trials have exhibited a clear upward trend. At present, it is not uncommon for researchers to administer hundreds of billions of CFU/day of probiotics in clinical intervention trials.

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One study conducted by Klaire Labs® found administration of 200 billion CFU/day of *Lactobacillus* and *Bifidobacterium* organisms produced no adverse effects in kidney transplant patients. The therapeutic intervention, in fact, reduced the incidence of immunosuppression-associated diarrhea by over 70%. Other clinical trials, especially those using a mixed probiotic formulation called VSL#3, have reported using very high probiotic dosages. In a recent trial, daily administration of 3.6 trillion organisms to persons with inflammatory bowel disease for eight weeks proved to be as safe as placebo and resulted in a significant reduction in disease activity. In light of these data, there do not yet appear to be criteria by which we can establish an upper safe level of probiotic use, but this level is certain to be very high.

Safety During Pregnancy, Nursing, and Infancy

Pregnancy
Intake of any type of medication during pregnancy can be problematic because of potential harm to the developing fetus.

While dietary supplements, like probiotics, are generally far safer than medications, their safety data with regard to pregnancy should be examined. Probiotics can be administered to pregnant women vaginally as well as orally. In 2007, a Cochrane review found vaginal application of probiotic-fermented yogurt during pregnancy reduces the incidence of genital infections by 80%. Genital infection is a primary cause of preterm delivery, which accounts for more than 70% of neonatal and postnatal morbidity and mortality. A more recent study reported pregnant women who consume approximately three ounces per day of probiotic-containing yogurt have a significantly reduced risk of spontaneous preterm delivery. While preliminary, these data suggest vaginal and oral probiotic administration during pregnancy is not only safe, but may represent a therapeutic strategy to prevent preterm labor and delivery. Probiotics have been observed to exert other health benefits in pregnant women. A 2008 clinical trial reported in the *British Journal of Nutrition* found initiating probiotic supplementation and dietary counseling during the first trimester of pregnancy results in significantly better maternal blood glucose control than does dietary counseling alone. A trial from the journal *Pediatrics* reported use of probiotics during pregnancy, coupled with administration of both probiotics and prebiotics to infants, significantly reduces the incidence of respiratory infections during the first two years of life. In 2001, a landmark clinical trial examined the effects of administering *Lactobacillus rhamnosus* both prenatally to pregnant women with a family history of atopy and postnatally to their infants.

While preliminary, data suggests administration of probiotics during pregnancy is not only safe, but may represent a therapeutic strategy to prevent preterm labor and delivery.

After two years, researchers found the incidence of atopic eczema in children who had received probiotics was *half* that of

children who had received a placebo. Follow-ups to this study reveal a remarkable persistence of the probiotic effect. At four years, atopic eczema had developed in 25 of 54 children in the placebo group compared to 14 of 53 children in the *L. rhamnosus* group (relative risk 0.57). At seven years, the cumulative risk of developing eczema was still significantly lower in the *L. rhamnosus* group compared with the placebo group.

Nursing

Infants with atopic disease whose mothers begin taking probiotics during nursing also experience clinical benefits. Probiotic intake during lactation may enhance mammary gland production and secretion of immunoprotective agents such as immunoglobulin A (IgA), thereby conferring a higher degree of immunocompetence to nursing infants. In 1997, a Finnish trial examined the effects of administering 40 billion CFU/day of *L. rhamnosus* to nursing mothers of infants with atopic eczema. After one month, researchers noted a significant decline in inflammatory symptomatology in infants whose mothers had received the *Lactobacillus* probiotic. A more recent trial documented significant reductions in gastrointestinal disturbances and medication use in healthy, breastfeeding infants following administration of *Lactobacillus casei* to nursing mothers. No published trial involving administration of probiotics to nursing mothers has reported adverse events in either mother or infant.

Infancy

Probiotics appear to be not only safe, but highly beneficial when administered directly to infants, including infants classified as low birth weight (LBW) or very low birthweight (VLBW). Probiotics promote colonization of the infant gut with beneficial organisms, inhibit the growth and activity of pathogens, improve the function and integrity of the intestinal mucosal barrier, and favorably modulate immune responses. A recent study found supplementing LBW infants with probiotics significantly reduces feeding intolerance and enhances weight gain. Probiotics have also been shown to effectively reduce the risk of developing necrotizing enterocolitis (NEC), a leading cause of morbidity and mortality in

LBW/VLBW infants. A 2007 meta-analysis of seven randomized, controlled clinical trials found early intervention with probiotics significantly reduces the incidence of NEC and overall mortality in VLBW infants. A 2010 update of this meta-analysis confirmed and extended its findings. The review examined data from 11 clinical trials conducted between 1997 and 2009 involving over 2,000 VLBW infants. Depending on the type of analytical model used (trial-sequence vs fixed-effect), the results revealed a 30-65% reduction in the incidence of NEC following intervention with probiotics. Importantly, probiotics were well tolerated by infants in all of the trials and no adverse events were reported.

References and further information available on request.

Klaire Labs® Probiotics

Klaire Labs® has been at the forefront of providing safe and effective probiotics to clinicians and patients for over 30 years. Klaire has a full line of broad-spectrum, high-potency probiotic formulations that are hypoallergenic, strain-certified, and can be safely used by adults, pregnant and nursing women, children, and infants.