

The ABC's of Probiotics

Probiotics – “good” bacteria for the gut – have a worldwide market of about \$6 billion dollars annually [*European Urology*. 2005;47:288-296]. Probiotics are “living micro-organisms, which upon ingestion in certain numbers, exert health benefits beyond inherent basic nutrition”, and until recently served mainly as feed additives in pig and poultry production. Now, manufacturers produce a wide variety of probiotics for small animals, packaged in foods, tablets, capsules, pastes, powders, and liquids.

Knowing probiotic basics helps when considering supplementation. As simple as ABC, important things to know involve their Atttributes, Bacteria, and Concerns.

Attributes

Anti-inflammatory: Inflammatory bowel conditions increase intestinal permeability, which non-pathogenic bacteria can reverse. They achieve this by normalizing colonic microflora and restoring tight junctions. They produce bacteriocins that target pathogenic microbes and blocking their tenacious adhesion to intestinal surfaces. In addition, evidence indicates that probiotics such as bifidobacteria can help normalize the ratio of anti- and pro-inflammatory cytokines. Probiotics differentially modulate dendritic cells in the gut, producing transforming growth factor-beta (a tolerogenic cytokine) and interleukin-10 (IL-10). IL-10 down-regulates pro-inflammatory cytokines, thereby improving epithelial permeability and protecting against potentially severe and systemic inflammation. Certain probiotic strains also favorably modulate Cox expression, shifting the profile toward Cox-1 and away from Cox-2.

Anti-infective: Compromised gut barrier function allows luminal organisms and endotoxin to reach distant extra-intestinal sites, a process called “bacterial translocation”. Critical illness, broad-spectrum antibiotic overuse, and overgrown pathogenic bacteria accentuate intestinal permeability and foster bacterial translocation. Research on probiotics highlights their capability to protect against sepsis and urogenital and post-operative infections (i.e., cholangitis and pneumonia) and lower the need for surgery in cases of acute pancreatitis.

Anti-diarrheal: Probiotics offset the risk of antibiotic-associated diarrhea and treat certain infectious diarrheas. *Lactobacillus acidophilus* reduces the number of clostridial organisms in dogs; which may dampen the zoonotic risk from organisms such as *Clostridium difficile*. Even radiation-induced diarrhea can improve with probiotics.

Anti-oxalate: A 2004 study in *Veterinary Microbiology* suggests that intestinal lactic acid bacteria in dogs and cats can increase oxalate degradation and decrease its absorption, potentially reducing oxalate urolithiasis.

Anti-cancer: *In vivo* and *in vitro* evidence indicates that probiotics may inhibit colon carcinogenesis. Recent research sheds light on the protective effects of fermentation products on intestinal epithelial tight junctions, which are susceptible to damage by tumor promoters. Good barrier integrity minimizes exposure of rapidly dividing cells of the colon to luminal contents rich with carcinogens. Weakened tight junctions compromise cell-to-cell signaling needed for epithelial control over the fate of individual cells. Once cancer develops, the loss of tight junction integrity amplifies the metastatic potential of epithelial cancers.

Allergy and atopy control: Intestinal microflora play an important role in the induction of oral tolerance. Dendritic cells in the gut adjust the balance between tolerance and active immunity to antigens from food and microbes. Depending on the bacterial strains they “sense” in the intestinal microflora, dendritic cells’ maturation signals for the gut-associated lymphoid tissue differ. That is, the interleukins they elaborate will either induce tolerance or stimulation from the immune system.

Prenatal administration of probiotics given to mothers with family history of atopic diseases, along with 6 month administration to their infants, effectively prevented the early atopic diseases in high risk children. Also, treatment with lactobacillus GG significantly reduced symptoms in IgE-sensitized infants with atopic eczema/dermatitis syndrome.

Augments immunity: Probiotics enhance both mucosal and systemic immunity, increasing neutrophil bactericidal activity, phagocytosis, and oxidative burst. They stimulate macrophage production and activation, and increase IgA and IgG concentrations. Bacteria such as *Lactobacillus acidophilus* increases lymphocyte numbers in the gut. Research indicates that non-pathogenic *Enterococcus faecium* affords immune benefits in puppies, potentially potentiating protective immunity against infections during critical and stressful stages of life.

Bacteria

The most intensively studied organisms are the lactic acid bacteria (lactobacilli and bifidobacteria), and *Saccharomyces boulardii*. Most probiotic strains originate as normal mammalian commensal flora, or those which have existed in fermented foods for generations worldwide. Properties of a successful probiotic include the ability to 1) survive digestive tract transit; 2) adhere to epithelial cells; 3) colonize in the target organ; 4) secrete anti-pathogenic substances; 5) inhabit the host safely; and 6) remain stable during storage.

Dead or alive? While live probiotics offer clear benefits, the effects of heat-killed or dead bacteria are mixed. New data suggest that the protective effects of probiotics arise not only from their metabolites or their ability to colonize the

colon, but can also be mediated by their own DNA. That is, certain nucleotide patterns derived from probiotics (CpG-DNA motifs) can modulate the host's innate immune responses through engagement of receptors involved in cell signal induction and pro-inflammatory cytokine responses. However, in one study, subjects experienced diarrhea after ingesting dead probiotics, causing early termination of one study looking at live versus heat-killed *Lactobacillus rhamnosus* for atopic disease.

Concerns

As with most "natural" supplements, nagging problems with quality control persist. For example, a 2003 study by Weese and Arroyo in *Canadian Veterinary Journal* [2003;44:212-215] revealed that none out of nineteen commercial pet foods claiming to include probiotics actually contained all of the organisms listed on the package. Other question concerning probiotics surrounds their 1) Potential infectivity, especially in immunocompromised hosts; 2) Possible transmission of bacterial resistance to pathogenic organisms through gene transfer; and 3) Limited species-specific proven safety and efficacy based on well-designed randomized controlled trials.

Determining the optimal bacterial species and strains, dosages, and clinical settings for probiotics in small animals will take more time, but meanwhile, their relative safety and evidential support are favorable indicators.