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Saccharomyces boulardii: A New Probiotic Approach in Veterinary Medicine

The use of *Saccharomyces boulardii* has been established for multiple indications in human patients. With a better understanding of the impact of antibiotics on the intestinal microbiota, as well as increasing concerns surrounding antimicrobial resistance, a closer look at the yeast's potential impact on veterinary medicine is warranted.

KEY POINTS

- Indiscriminate use of antibiotics promotes development of antibiotic resistance, which poses a critical problem in public healthcare.
- Antibiotics cause alterations in intestinal microbiota, resulting in loss of microbiota function.[1] Antimicrobial-associated dysbiosis may predispose patients for atopic, inflammatory, and autoimmune diseases.[2,3]
- Antibiotic-associated diarrhea (AAD) is a common presenting sign in veterinary and human medicine and occurs in up to 25% of human patients.[4] In veterinary studies, 56% of healthy dogs receiving metronidazole[5] and up to 85.7% of cats receiving amoxicillin-clavulanate[6] developed worsening fecal scores. Administration of the probiotic yeast *Saccharomyces boulardii* helps in protection against and management of AAD in dogs.[7]
- In dogs with inflammatory bowel disease (IBD) managed with standard therapy (ie, diet, antibiotics, and steroids) and concurrent administration of *S boulardii*, clinical signs improved faster and more significantly than dogs managed with standard therapy alone.[8]

Antibiotics

Judicious Use

The indiscriminate overuse of antibiotics promotes antimicrobial resistance and transfer of resistance genes to pathogenic bacteria.[1,9] In 2014, the World Health Organization published a global report[10] with alarming data on the increase of antimicrobial resistance by specific pathogens. Resulting limited treatment options for bacterial infections and the subsequent potential for worse clinical outcomes and death pose a major problem in both human and veterinary medicine.

A study in healthy dogs evaluated the effect of a 7-day treatment with amoxicillin, an antibiotic commonly used in small animal veterinary practice. After 4 to 7 days of treatment, most dogs shed *Escherichia coli* resistant to several antibiotics.[11] Therefore, due to the alarming emergence of antimicrobial resistance, a more judicious use of antibiotics is recommended.

Effects on Intestinal Microbiota

Antimicrobial agents also have pervasive effects on resident intestinal bacteria, which can result in dysbiosis,[12] an alteration in microbiota diversity and composition.

Several studies have shown negative effects on the intestinal microbiome after antibiotic treatment in humans and animals. In one such study, cats receiving amoxicillin-clavulanate for 7 days were observed to have a decreased number of intestinal bacterial species, and the overall distribution of specific taxa had not recovered 7 days after antibiotic cessation.[6] Another study revealed dogs treated with tylosin—an antibiotic commonly used for canine chronic enteropathy—for 14 days also had significantly decreased microbiota diversity and alterations in

microbiota composition, particularly an increase in *E coli*-like sequences. Several bacterial taxa did not recover 14 days after antibiotic cessation, when the last fecal sample was collected in this study.[13] Similar bacterial alterations with increased *E coli* have also been seen in dogs receiving metronidazole. Major disruptions in intestinal metabolism—including levels of bile acids and tryptophan—were observed and persisted until 4 weeks after cessation of metronidazole.[5]

Health Effects of Dysbiosis & Duration of Effects

The intestinal microbiome works as a metabolic organ and fulfills a variety of functions; a balanced microbiome is essential for host health. The microbiota modulates the host immune system, protects the host from invading pathogens, and provides nutrients to the host by metabolizing and fermenting various dietary components.[14,15] Intestinal dysbiosis causes alterations in composition or diversity of bacteria as well as loss of microbiota function.[1] Negative effects from loss of microbiota function include overproduction and translocation of bacterial toxins, pro-inflammatory stimulation of the immune system, reductions in beneficial bacterial metabolites (eg, short-chain fatty acids [SCFAs], secondary bile acids), and increased intestinal permeability.

Clinical signs vary between individuals and can range from mild GI signs to an increased risk for systemic diseases (eg, diabetes mellitus, obesity).[2,16] Although clinical signs caused by antibiotic exposure usually resolve within days to weeks, alterations in diversity and composition can persist for longer periods. Studies in human medicine showed that alterations in intestinal microbiota and increased presence of bacterial resistance following antibiotic treatment can persist up to 4 years.[17] Antimicrobial-associated dysbiosis is suspected to predispose patients for development of atopic, inflammatory, and autoimmune diseases, as well as IBD, asthma, or obesity in humans.[2,3]

▲ MYCEQUIN™ chewable tablets for dogs from Nutramax Laboratories Veterinary Sciences, Inc. contain NMXAAD™ Proprietary blend of 10 billion CFUs (colony-forming units) of *Saccharomyces boulardii* plus beta-glucan. Beta-glucan is an immune-modulating compound that enhances innate defenses and stimulates both cell-mediated and humoral immunity. Beta-glucan has been shown beneficial in dogs with IBD.

General recommendation for MYCEQUIN use is 1 daily with antibiotics to help protect against antibiotic-associated gastrointestinal signs and 2 daily for chronic gastrointestinal conditions.

Saccharomyces boulardii as a Probiotic

Differences from Bacteria

S boulardii is a yeast strain first isolated in 1920 from the outer skin of tropical fruits in Indochina[18] and, in recent decades, has garnered much interest as a probiotic agent. Probiotics are live microorganisms that, when consumed in adequate amounts, confer a health benefit to the host.[19] *S boulardii* has favorable probiotic properties that differentiate it from bacterial probiotics.[20] While bacteria are prokaryotes, yeasts are eukaryotic cells, which are up to 10 times larger than bacterial cells. Because of their differing cell wall structure, yeast cells are recognized by different host receptors than bacterial cell wall components, thus causing different antigenic responses. Yeast cells are resistant to low pH, bile salts, and GI enzymes, and *S boulardii* also has an optimal growth temperature similar to body temperature. These features allow for transit through the acidic stomach and are favorable to optimal colonization of the colon.[21] An important property of yeast is its natural resistance to antibiot-

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ics, which allows it to be administered concurrently with antibiotics. In addition, administration of yeast does not promote development of antimicrobial resistant bacteria.

Mechanisms of Action of *S boulardii*

Several studies investigated the properties of *S boulardii* and found an extensive spectrum of mechanisms of action. *S boulardii* directly inhibits the growth of several pathogens (eg, *Salmonella typhimurium*, *Yersinia enterocolitica*) and has toxin-inhibiting properties through production of proteases able to degrade *Clostridium difficile* toxins and *E coli* endotoxin.[18]

In mice, treatment with *S boulardii* promoted faster restoration of the intestinal microbiota after disruption due to antibiotic treatment.[22] Administration of *S boulardii* in humans was associated with increased intestinal SCFAs,[23] which have anti-inflammatory properties, regulate intestinal motility, and are known to be an important source of energy.[15] By increasing IgA levels and reducing pro-inflammatory responses, *S boulardii* is also able to modulate immune responses.[18]

In human medicine, major indications for the use of *S boulardii* are AAD and IBD (see **Human Global Guidelines for Probiotics and Prebiotics**). Clinical efficacy of *S boulardii* has also been observed in unclassified acute diarrhea, enteral-nutrition–related diarrhea, traveler's diarrhea, irritable bowel syndrome, *C difficile* infection, and reduction of side effects of *Helicobacter pylori* therapy.[18]

In a study of healthy dogs receiving lincomycin, AAD was prevented in all dogs concurrently receiving *S boulardii*.

Research in Veterinary Medicine

Antibiotic-Associated Diarrhea

AAD is defined as otherwise unexplained diarrhea that occurs in association with the administration of antibiotics. An estimated 25% of human patients treated with antibiotics develop diarrhea.[4] While the exact incidence is currently unknown in veterinary medicine, antibiotic-associated GI side effects, including diarrhea, vomiting, and hyporexia, are believed to occur frequently and can result in owners discontinuing the course of antibiotics prematurely with implications for development of antimicrobial resistance.[6,24]

In numerous studies in human medicine, *S boulardii* significantly reduced the development of AAD.[18] In a veterinary study of healthy dogs receiving lincomycin at 150 mg/kg IM (approximately 7 times the recommended dose in dogs), AAD was prevented in all dogs concurrently receiving *S boulardii* at 20 billion CFUs/day. In the control group that only received lincomycin without *S boulardii*, 75% of the dogs developed diarrhea with a mean duration of 6.5 days. In dogs that received *S boulardii* as soon as diarrhea occurred, a significantly shorter duration of diarrhea was observed with a mean duration of 2.9 days.[7]

Inflammatory Bowel Disease

IBD is characterized by a histologically confirmed inflammation of the GI tract with chronic recurrent GI signs.[25] Animals with IBD require multimodal therapeutic approaches, and achieving relief of clinical signs can be challenging. Although the pathophysiology of IBD differs in humans and small animals, treatment with *S boulardii* in humans with IBD was associated with significantly reduced colonic permeability and relapse rate as well as significantly improved stool scores.[18]

One veterinary study investigated the effects of *S boulardii* in 20 dogs with chronic enteropathy confirmed as IBD. The dogs received *S boulardii* versus placebo concurrent to regular IBD therapy consisting of diet, antibiotics, and steroids ± other immunosuppressants. Clinical signs, evaluated with the canine chronic enteropathy clinical activity index (CCECAI), improved significantly in dogs administered *S boulardii* compared with dogs given placebo. The body condition scores increased significantly only in the *S boulardii* group.[8]

AAD = antibiotic-associated diarrhea
IBD = inflammatory bowel disease
SCFAs = short-chain fatty acids

HUMAN GLOBAL GUIDELINES FOR PROBIOTICS AND PREBIOTICS

AAD and IBD are listed as evidence-based indications for adults and/or children in the *Guidelines on Probiotics and Prebiotics* published by the World Gastroenterology Organisation. Specific indications in children are acute gastroenteritis, prevention of AAD, and reduction of side effects from treatment for *Helicobacter pylori*. Recommended dose of *S boulardii* in children for the prevention of AAD is 5-10 billion CFUs/day.[26]

Implications

These results indicate that *S boulardii* is a promising probiotic agent that can be used for protection against and management of AAD and in addition to standard therapy in dogs with IBD. Further studies are warranted to evaluate the efficacy of *S boulardii* against other GI diseases in small animals.

Future Directions in Probiotic Research

Research on the intestinal microbiome has grown tremendously in recent years. The intestinal microbiome is a highly complex organ that affects the host's metabolism and immune system; therefore, a balanced microbiome is crucial for host health.

Therapies for the modulation of the intestinal microbiome are currently limited, mostly because of technical difficulties in evaluating the complex multiple immune and metabolic interactions between the microbiome and the host. It has become clear that individual probiotics have strain-specific effects on the host. For the best clinical outcome, probiotic products should be chosen based on scientifically proven effects for the particular clinical disorder.

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