Proceeding of the NAVC
North American Veterinary Conference
Jan. 8-12, 2005, Orlando, Florida

UPDATE ON SMALL INTESTINAL BACTERIAL OVERGROWTH AND ANTIBIOTIC-RESPONSIVE DIARRHEA

Alex J. German, BVSc, PhD, CertSAM, MRCVS
Department of Veterinary Clinical Sciences
University of Liverpool, United Kingdom

INTRODUCTION

The normal SI bacterial flora is a diverse mixture of aerobic, anaerobic and facultative anaerobic bacteria. This flora increases numerically from duodenum to colon, and a number of factors control the overall populations including luminal patency, motility, substrate availability, bacteriostatic and bacteriocidal secretions and an intact ileocolic valve. The resident bacterial flora is an integral part of the healthy SI; a stable enteric flora prevents colonization by pathogens, and stimulates the development of the enteric immune system. Indeed, the host response to a bacterium is likely to be as important as the intrinsic pathogenicity of the organism. Loss of tolerance to the normal bacterial flora may precipitate intestinal inflammation and abnormal intestinal function.

Small intestinal bacterial overgrowth is the uncontrolled proliferation of resident bacteria, and is defined by an increase in the absolute number of bacteria in the upper small intestine during the fasted state. The upper limit for normal bacterial numbers has been defined in humans, but was then extrapolated to dogs. Much controversy remains about what represents a normal resident bacterial flora in dogs, and the exact numbers have not yet been adequately defined (1). SIBO in humans arises secondary to underlying disorders that interfere with the numerous control mechanisms on bacterial numbers. All of these factors can potentially lead to **secondary SIBO** in dogs and cats. The term **idiopathic SIBO** was used to describe an antibiotic-responsive condition of large-breed (especially German shepherd) dogs, in which no underlying cause could be recognized. However, it is doubtful whether a genuine overgrowth exists in these cases, and the alternative name of **idiopathic antibiotic-responsive diarrhea (ARD)** is now preferred (2,3). This condition has similarities with the recently described tylosin-responsive diarrhea in dogs (4). Idiopathic ARD has not been documented in cats. Therefore, it is better that we consider that there are the two separate syndromes (e.g. secondary SIBO and idiopathic ARD), each with differing etiologies and pathogenesis.

ETIOLOGY AND PATHOGENESIS

SIBO can arise secondary to diseases that result in excess substrate in the intestinal lumen (e.g. EPI, motility disorder, blind loop), diseases that affect the clearance of bacteria (e.g. partial obstruction, abnormal motility) or to morphological or functional derangement of the mucosa. The increased numbers of bacteria compete for nutrients, produce 'toxic substances' (e.g. e.g. hydroxylated fatty acids and deconjugated bile salts) and can damage the mucosal brush border leading to alterations in enzyme activity.

A number of hypotheses exist as to the cause of idiopathic ARD, although many now believe that the importance lies in the various host:bacterial interactions that can occur. In this regard, normal mucosal health is maintained by the mucosal barrier, which limits exposure of luminal factors (including the bacterial flora) to the underlying mucosal immune system. Therefore, the disease may manifest either if the mucosal barrier is disrupted, if the enteric flora itself changes, if dysregulation occurs in the response of the immune system to this flora, or a combination of the above. Studies into GSDs with idiopathic ARD have highlighted that there may be mucosal barrier defects (e.g. permeability changes and IgA deficiency), as well as alterations in intestinal immune system homeostasis (e.g. increased numbers of IgA plasma cells and $CD4^+$ T cells; increased expression of certain cytokines) (5,6). Thus, it is tempting to speculate that this represents immune dysregulation and loss of tolerance to endogenous bacterial antigens. Such a hypothesis is supported by the fact that antibacterials lead to resolution of clinical signs, and decreased cytokine expression, but not a decline in bacterial numbers (5). Finally, it is also possible that qualitative changes in the intestinal flora may underlie this syndrome and a hitherto unidentified pathogen may be involved, e.g. intestinal *Helicobacter* sp. or enteropathogenic *E. coli* (1,2). Therefore, the predisposition of GSDs to this syndrome could be explained by genetic susceptibility to infection as a result of expression of particular MHC polymorphisms.

DIAGNOSIS

The most common clinical signs are small intestinal diarrhea and weight loss, although other signs (e.g. vomiting, appetite alterations, excessive borborygmi and abdominal discomfort) may also occur. In cases of secondary SIBO, other signs pertaining to the underlying condition may be present. Physical examination may be unremarkable, although abdominal palpation may demonstrate the underlying cause in some cases of secondary SIBO. Further, EPI can be diagnosed by measuring serum TLI concentration < 2.5μg/l, whilst disorders causing partial obstruction are best detected with diagnostic imaging.

A number of tests have been used to diagnose SIBO, including direct (quantitative culture of duodenal juice) and indirect (hydrogen breath tests, serum markers e.g. folate, cobalamin, unconjugated bile acids) methods. However, whilst it is logical to assume that a genuine increase in bacterial numbers occurs in secondary SIBO, few studies have documented its exact magnitude, and therefore it is difficult to apply an exact cut-off in the clinical setting. The indirect tests have also not been properly validated in the diagnosis of secondary SIBO. Therefore, for secondary SIBO it is better to concentrate the diagnostic effort on identifying the underlying process, rather than in demonstrating the SIBO.

Recent studies have suggested that quantitative culture of duodenal juice and all of the indirect tests do not reliably identify cases of idiopathic ARD (3, 7, 8,9). Therefore, response to treatment remains the best approach, provided that it is performed after thorough investigations to eliminate other diseases. The criteria for diagnosing idiopathic ARD are as follows:

- No other etiological cause identified (based on the results of the preliminary diagnostics and histo-pathological assessment).
- A positive response to an antibiotic trial (e.g. resolution of clinical signs including weight gain).
- Relapse of signs upon withdrawal of treatment, and remission on reintroduction of antibiotics.

TREATMENT

Therapy for secondary SIBO is best directed at the underlying disorder if appropriate. With the exception of EPI, most secondary SIBO cases do not need specific therapy for the SIBO, unless response is poor, or the underlying disease cannot be corrected. Experimental studies have shown that bacterial numbers in EPI cases decline with pancreatic enzyme supplementation alone (probably because of a reduction in available substrate), suggesting that this problem will disappear of its own accord (10). However, in some clinical cases, concurrent antibacterial therapy is necessary, although it is not clear whether this is effective against the secondary SIBO, or a concurrent idiopathic ARD (given similar breed predispositions).

For idiopathic ARD, an appropriate antibacterial should be administered for an initial period of four weeks. If signs relapse at this stage then a longer course may be required, and many cases required long-term (or lifelong) therapy to maintain remission of signs.

The choice of antibacterial is controversial (2); most GSDs with idiopathic ARD respond well to. Other cases may respond better to other antibacterials including tylosin or metronidazole. Interestingly, bacterial numbers do not decline significantly when oxytetracycline is administered, despite resolution of clinical signs suggesting that this drug is not 'sterilising' the small intestine. Instead it may provide a selection pressure to the bacterial microflora or may be having other (immunomodulatory?) effects. For secondary SIBO, other drugs are more appropriate e.g. tylosin, metronidazole or fluoroquinolones, the latter of which is used humans on account of their effects on Gram-negative organisms.

Adjunctive therapy may be helpful in cases of both secondary SIBO and idiopathic ARD. This includes the feeding of a highly digestible, fat restricted diet. Some diets contain prebiotics (e.g. fructo-oligosaccharides) but, whilst these can modulate colonic microflora in small animals (11), the effect on small intestinal bacterial populations in clinical cases is questionable (12).

PROGNOSIS

The prognosis for secondary SIBO depends upon whether the underlying cause can be adequately treated.

The prognosis for idiopathic ARD is guarded; many cases relapse after therapy is discontinued, and then require lifelong treatment. However, some cases may improve spontaneously as the animal enters adulthood.

REFERENCES

1. Johnston SE. Small Intestinal Bacterial Overgrowth. Vet Clin N Am Sm Anim Pract 1999;29:523-550.
2. Marks SL. Editorial. Small intestinal bacterial overgrowth in dogs – less common than you think? J Vet Intern Med 2003;17:5-7.
3. German AJ, Day MJ, Ruaux CG, Steiner JM, Williams DA, Hall EJ. Comparison of direct and indirect tests for small intestinal bacterial overgrowth and antibiotic-responsive diarrhea in dogs. J Vet Intern Med 2003;17:33-43.
4. Westermarck E. Tylosin-responsive diarrhea in dogs. Proceedings of the 13th ESVIM Congress, Upsala, Sweden, 2003; p 58-59.
5. German, AJ, Helps CR, Hall EJ, Day MJ. Cytokine mRNA expression in mucosal biopsies from German shepherd dogs with small intestinal enteropathies. Dig Dis Sci 2000:45;7-17.
6. German AJ, Hall EJ, Day MJ. Immune cell populations within the duodenal mucosa of dogs with enteropathies. J Vet Intern Med 2001;15:14-25.
7. Rutgers HC, Batt RM, Elwood CM, Lamport A. Small intestinal bacterial overgrowth in dogs with chronic intestinal disease. J Am Vet Med Assoc 1995;206:187-193.
8. Simpson JW. Observations on the diagnostic value of three different methods of assessing small intestinal bacterial overgrowth (abstract). Proceedings of the 1999 BSAVA congress, Birmingham UK, p 311.
9. Walkley HM, Neiger R. Accuracy of three non-invasive tests to diagnose small intestinal bacterial overgrowth in dogs (Abstract). J Sm Anim Pract 2000;41:478.
10. Simpson KW, Batt RM, Jones D, Morton DB. Effects of exocrine pancreatic insufficiency and replacement therapy on the bacterial flora of the duodenum in dogs. Am J Vet Res 1990;51:203-206.
11. Sparkes AH, Papasouliotis K, Sunvold G, Werrett G, Gruffydd-Jones EA, Egan K, Gruffydd-Jones TJ, Reinhart G. Effect of dietary supplementation with fructooligosaccharides on fecal flora of healthy cats. Am J Vet Res 1998;59:436-440.
12. Sparkes AH, Papasouliotis K, Sunvold G, Werrett G, Clarke C, Jones M, Gruffydd-Jones TJ, Reinhart G. Bacterial flora in the duodenum of healthy cats, and effect of dietary supplementation with fructo-oligosaccharides. Am J Vet Res 1998;59:431-435.