A Research Update for the Veterinarian from the **Ralston Purina Company** St. Louis, Mo., USA



Purina Research Report

In this issue:

Many cases of this syndrome in dogs and cats likely are secondary to an underlying disease that should be managed by addressing the primary disease process.

Fructooligosaccharides (FOS) Small intestinal bacteria were not affected by dietary supplementation with FOS.

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Of the three non-steroidal antiinflammatory drugs tested, none induced severe gastroduodenal lesions.

Feeding a hydrolyzed protein diet to dogs with IBD was associated with moderate to marked improvement in clinical signs.

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Microalbuminuria may someday prove to be an excellent means of tracking progress in IBD patients.

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Small Intestinal **Bacterial** ergrowth/

Karen L. Johnston VMD, MRCVS, PhD

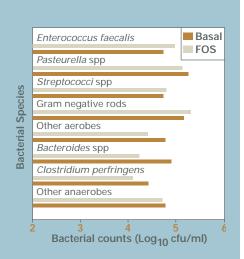
Small intestinal bacterial overgrowth (SIBO) is a clinical syndrome in human medicine. It is associated with symptoms of vomiting, diarrhea, or weight loss caused by an abnormal accumulation of small bowel bacteria. A similar syndrome has been reported to occur in dogs and cats. The diagnosis of SIBO relies on documenting higher numbers of proximal small intestinal bacteria than are normal for a particular species. 67,20 It is essential, therefore, to understand the normal physiology of the proximal small intestine with regard to microbial numbers and common bacterial species. To this end, this article reviews the intestinal physiology of the healthy dog and cat relative to the clinical syndrome of SIBO in small animal internal medicine. continued on page 2

Effect of FOS on Bacteria in Healthy Cats

Source: Sparkes AH. Papasouliotis K. Sunvold G. et al Am J Vet Res 1998;59:431-435.

Small intestinal fluid samples from healthy cats fed diets with or without fructooligosaccharide (FOS) were quantitatively and qualitatively cultured to identify aerobic, anaerobic and total bacterial counts. As reported previously from this laboratory as well as by others, high numbers of bacteria were identified, with counts as high as 7.56 (log 10 cfu/ml) total aerobes and 6.57 total anaerobes in the proximal small intestine of healthy cats.

Of the 66 bacterial species identified, six occurred with frequency. The graph shows mean counts from the most prevalent bacteria cultured from the proximal small intestine of healthy cats fed diets with or without FOS. The investigators found considerable variation in bacterial counts within individual cats over several collections, independent of diet or other variables. While dietary fibers can alter colonic microflora, FOS had no apparent effect on the total number or composition of small intestinal bacteria.



Small Intestinal Bacterial Overgrowth

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The proximal small intestine of man is generally considered to be fairly sterile. Certainly, anaerobic bacteria are extremely uncommon, thus finding greater than 10⁴ cfu/ml (colony forming units/ml) of anaerobic bacteria would indicate small bowel bacterial overgrowth. Likewise, total bacteria at a level greater than 10⁵ cfu/ml is abnormally high for humans and also would lead to the diagnosis of SIBO.⁵

However, it is well recognized that there are considerable species differences in normal intestinal microflora. Unlike the situation in man, both dogs and cats normally have large numbers of small intestinal microbes. Interestingly, anaerobic species appear to be as common as aerobic species, including bacteria such as *Clostridium perfringens*, *Bacteroides* and *Bifidobacterium* species. At least 24 papers have been published which describe the small intestinal bacterial flora of healthy dogs or cats.

These reports represent research from several different countries over a span of 30 years. The animals which have been used for the studies are from different environments, and they constitute numerous breeds being fed many different diets. Although a variety of culture methods have been employed in these studies, general trends surface on inspection of the data. Excluding studies in which duodenal fluid has been severely diluted with saline, the majority indicate that both the healthy dog and cat normally have a luxuriant small intestinal flora. Bacterial numbers over 109 cfu/ml have been found in healthy dogs and total bacterial numbers greater than 10⁸ cfu/ml have been found in healthy cats.13

With this information, it is clear that the diagnosis of SIBO in small animals should not hinge, as it does in human medicine, upon the culture of small intestinal bacteria at a level greater than 10⁵ (cfu/ml) or anaerobic bacteria greater than 10⁴ (cfu/ml). Rather, it appears that small intestinal bacterial counts greater than 10⁹ cfu/ml or 10⁸ cfu/ml would be required before diagnosing the presence of SIBO in dogs or cats, respectively. Use

of the criteria extrapolated from humans rather than based on canine or feline physiology can lead to inappropriate conclusions. Indeed, one study determined that SIBO was an extremely common cause of small bowel disease because 51% of patients referred for investigation of intestinal disease were found to have small bowel bacterial counts greater than 10⁵ (cfu/ml). ¹⁶ A

... both dogs and cats normally have large numbers of small intestinal microbes.

disease prevalence of this magnitude should certainly be questioned, a thought expressed by numerous veterinary gastroenterologists.^{8,17}

Although there have been no published reports describing clinical disease found in association with intestinal microbes greater than 10° (cfu/ml), it is likely that the SIBO syndrome does exist in companion animals. It will likely occur, as it does in other species, secondary to either motility disorders,

Advances in Nasogastric Feeding Safety

Source: Thomas BW, Falcone RE. Confirmation of Nasogastric Tube Placement by Colorimetric Indicator Detection of Carbon Dioxide: A Preliminary Report. J Am Coll Nutr 1998;17:195-197.

Nasogastric or nasoesophageal feeding tubes can be rapidly and safely placed without anesthesia in patients that require nutritional supplementation. A danger in placing and using these tubes lies in the inadvertent placement of the tube, and subsequent food, into the trachea instead of the esophagus. Currently, survey radiographs are used to assure correct placement of these feeding tubes. A recent study in human critical care patients evaluated measurement of CO₂ emerging from nasoenteric or endotracheal tubes as a simple means of confirming correct placement of the feeding tube. Tubes were

placed deliberately into the trachea or esophagus, with enteric placement confirmed by radiography. All transtracheal insertions showed immediate and unambiguous color changes consistent with the presence of carbon dioxide while none of the nasoenteric tubes showed such changes. The results from this study suggest the CO₂ indicator* may provide a rapid, less expensive means of confirming

the correct placement of nasoenteric feeding tubes compared to radiographs.

❖

* The CO_2 indicator used in this study was the Easy-CapTM (Nellcor, Inc., Hayward, CA).



impaired immunological defenses, structural defects or luminal disorders which lead to an environment conducive to the excess proliferation of microbes. For example, one dog with intestinal obstruction developed an aerobic bacterial count of 10¹¹ (cfu/ml) (Leisewitz A, 1998. Personal communication). Management should therefore be aimed at addressing the underlying disease process that led to the bacterial proliferation.

It is well-established in both human and experimental animal medicine that an abnormal small intestinal flora can damage the enterocytes either directly or indirectly. Bacteria are able to adhere to enterocytes and damage the cells through

the production of enzymes, such as proteases and glycosidases. Furthermore some bacteria have the ability to cleave brush border proteins which are important to digestion and absorption of key dietary nutrients.³ Some bacteria are able to deconjugate bile acids which can lead to fat malabsorption. The free bile acids also can directly damage the enterocytes.¹⁰ Bacterial

metabolism of other dietary nutrients, such as cobalamin and taurine, have been widely described and can be clinically important as deficits can lead to megaloblastic anemia or possibly dilated cardiomyopathy, respectively.^{2,14} As the metabolic properties of bacteria can vary significantly, specific clinical signs may relate to the type of bacteria within the small bowel. For example, if the microbial milieu in the bowel contains a high preponderance of *Bacteroides* species, serum cobalamin may be lowered.²¹ Or the bacterial flora may contain high levels of Clostridium, Bacteroides, Bifidobacterium, or Eubacterium species which are exceedingly competent at the deconjugation of bile acids.¹⁹ In this

leconjugation of bile acids.¹⁹ In this scenario the patient may suffer from steatorrhea

Studies are lacking which describe intestinal damage in dogs or cats with culture proven total bacterial counts greater than the 10° or 10° cfu/ml found in healthy dogs and cats. However, there are

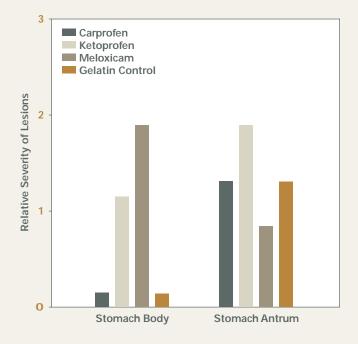
excellent studies describing changes to subcellular organelles in canine enterocytes before and after antimicrobial therapy.⁴ As the normal intestinal milieu contributes to intestinal transit time as well as enterocyte migration up the villus tip, it is no surprise that changes occur in enzyme activities of the enterocyte related to the intestinal flora.^{1,15} Further studies are needed to determine the type of damage which may occur in animals with true SIBO.

It is clear that the intestinal microbes are an active metabolic entity within the intestinal lumen. Indeed, ancillary tests for the diagnosis of SIBO rely on quantifying those various metabolic properties. Examples of these tests include breath hydrogen analysis, serum vitamin levels, and serum levels of unconjugated bile acids. These procedures are used in humans and experimental animals against an uncontested diagnostic cut-off value of total bacteria greater than 10⁵ cfu/ml and have proven useful.9,11,12 However, the effect of the higher bacterial counts of dogs and cats on the sensitivity and specificity of these must be carefully

Endoscopy of the Gastroduodenal Mucosa After Carprofen, Meloxicam and Ketoprofen Administration in Dogs

Forsyth SF, Guilford WG, Haslett SJ, Godfrey J. J Small Anim Pract 1998;39:421-424.

Non-steroidal anti-inflammatory drugs (NSAIDs) are administered for a variety of reasons, however, these drugs can cause adverse side effects. Amongst these are gastrointestinal lesions such as hemorrhage or ulceration. Three NSAIDs or a gelatin placebo were administered with food for 28 days. The graph shows the mean score (scale of 0 to 6+) for histologic evaluation of biopsies taken on day 28 of the study. The data represent six dogs on each treatment. This study suggested that carprofen, ketoprofen and meloxicam produced relatively mild lesions of the gastric mucosa that were not significantly different from those found in dogs fed a placebo.



evaluated to ascertain appropriate use in veterinary medicine.

Treatment options for a disease which has not been well documented to occur in companion animals are speculative at best. Antimicrobial agents are clearly the treatment of choice for human patients with primary SIBO. However, secondary SIBO is best viewed as a symptom

The finding of SIBO should prompt a search for an underlying disorder.

rather than a diagnosis, and should be managed by addressing the underlying disease process.¹⁸

In summary, small intestinal bacterial overgrowth, defined as the finding of small intestinal microbes greater than 10° cfu/ml, has not been reported in companion animal medicine. It is likely that the disease does exist secondary to an underlying disorder of the small bowel and it may even exist as a primary entity.

However, it is clear that the diagnosis should not be based, as it is in human medicine, upon the finding of small bowel bacterial numbers greater than 10⁵ cfu/ml, or on other tests that were validated using these numbers. The finding of SIBO should prompt a search for an underlying disorder rather than simply addressing the resultant increase in bacterial numbers. Further research is needed to evaluate the role that a luxuriant flora effects upon the mammalian host.

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Diarrhea in Cats with Feline Immunodeficiency Virus

Source: Papasouliotis K, Gruffydd-Jones TJ, Werrett G, et al. Assessment of intestinal function in cats with chronic diarrhea after infection with feline immunodeficiency virus. Am J Vet Res 1998;59:569-574.

Bacterial overgrowth has been implicated in the pathogenesis of chronic small bowel diarrhea in immunocompromised humans and animals. Between 50% and 100% of human immunodeficiency virus (HIV) infected people and nearly 90% of simian immunodeficiency virus (SIV) infected monkeys with diarrhea were determined to have small intestinal bacterial overgrowth (SIBO) on the basis of breath hydrogen testing and intestinal fluid cultures. Despite this, indications of SIBO could be detected in only one cat (10%) among 10 feline immunodeficiency

virus (FIV) infected cats with chronic diarrhea. This cat's abnormal breath hydrogen lactulose test result was suggestive of SIBO; however, intestinal cultures for this cat, as well as the other nine tested, fell within the limits of counts from healthy cats. Of the measures of intestinal function evaluated in this study, no consistent abnormalities were detected. Neither carbohydrate malassimilation, increased permeability nor SIBO appear to be significant contributors to the gastrointestinal dysfunction commonly observed in FIV-infected cats.





A hydrolyzed protein diet appeared beneficial for patients with IBD.

Dietary Trial in Dogs with Inflammatory Bowel Disease Utilizing a Hydrolyzed Protein Diet

The effects of feeding a highly digestible diet containing a hydrolyzed soy protein (Purina CNM HA-Formula™) was evaluated in six dogs with inflammatory bowel disease (IBD). The diagnosis was based on history, physical examination, fecal flotation, fecal smear, and serum B12, folate and trypsin-like immunoreactivity. Gastroduodenoscopy and biopsy were performed prior to and after 8-14 weeks of dietary therapy. All owners completed a questionnaire every two weeks during the 10 week study. Dogs were fed the test diet twice daily, with total intake calculated to meet energy requirements (132*BW_{kg} 0.75). No other therapy was required for four of the dogs. One dog was treated for concurrent EPI; another was treated with diet alone for 4 weeks, then with metoclopramide to further decrease frequency of vomiting. There was a poor correlation between histologic

abnormalities and the gross appearance of the gastrointestinal mucosa, and between the clinical response of the dogs and their biopsy findings. The results of this study indicate that the feeding of a hydrolyzed single protein source diet to dogs with IBD was associated with moderate to marked improvement in clinical signs.

Stanley L. Marks, University of California-Davis, School of Veterinary Medicine, and D.P. Laflamme, Ralston Purina Company.

Signalment	History	BCS (9pt)*	Fecal Score (0-100)**	Clinical Outcome	Additional Therapy	Chg BW (kg)	Post fecal score
2.5 yr M Coonhound	6 mo. history vomiting & diarrhea (lg. & sm bowel), wt. loss (6kg)	3	50-75	Complete Resolution	NONE	+6.6	100
9 yr F Collie	3 mo. history vomiting & diarrhea (sm bowel), wt. loss (6kg)	6	0	Complete Resolution	NONE	+0.5	100
2 yr FS Puli	18 month history of intermittent vomiting	4	100	Moderate Improvement	Metoclo- pramide	-0.7	100
1.5 yr FS Rhodesian Ridgeback	18 mo. history vomiting & diarrhea (lg. & sm bowel), wt. loss (4kg)	3	25	Complete Resolution	NONE	0	100
3 yr F German Shepherd	3 mo. history vomiting & diarrhea (lg. & sm bowel), wt. loss (6kg)	3	10-25	Moderate Improvement	NONE	0	50
2.5 yr MC Dalmatian	6 mo. history vomiting & diarrhea (lg bowel)	7	50	Moderate Improvement	NONE	0	100

^{*} BCS (Body Condition Score, values 1-9): 1 = emaciated, 5 = ideal, 9 = grossly obese ** Fecal Score: 0 = very loose, 100 = formed, very hard

ResearchAbstracts

Gastric Emptying of Diets Varying in Macronutrient Composition in Cats

OBJECTIVE: To determine the rate of gastric emptying of diets differing in macronutrient composition on both a caloric and gram basis.

METHODS: Gastric emptying, of four diets differing in macronutrient composition, was measured using gamma scintigraphy in 20 cats. Each cat received all four diets. Twenty cats were trained to meal feed by giving them adlibitum access to food for 15 minutes twice daily. Cats were accommodated to each diet for at least two weeks before scanning. On test days, diets were labeled with 3 to 4 mCi of 99mTc-disofenin. Gastric images were then taken with a large field of view gamma camera equipped with a low energy parallel hole collimator linked to

Macronutrient Composition of E)iets (as a % Protein	% of cal CHO	ories) Fat
Diet 1 (high fat)	13%	8%	79%
Diet 2 (high protein and fat)	31%	12%	57%
Diet 3 (high CHO)	18%	44%	38%
Diet 4 (high protein)	52%	15%	33%

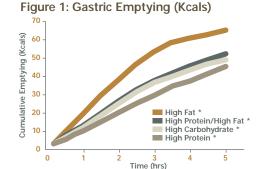
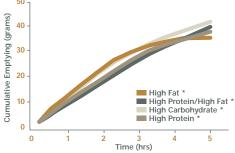


Figure 2: Gastric Emptying (grams)



* Width of lines includes Standard Error of the Mean

Dietary fat does not delay gastric emptying in cats.



a nuclear medicine computer. Images were taken at times: 0, 15, 30, 45, 60, and at every 30-minutes out to 6 hours. Each cat was scanned three times at least two days apart for each diet.

RESULTS: Figure 1 shows gastric emptying of kcals over time for the four diets; Figure 2 represents the same data only expressed as grams rather than kcals. On a caloric basis, the high fat diet emptied significantly faster than the other three diets from 45 minutes until the end of the experiment (p<0.01) and the high protein diet emptied the slowest starting at two hours (p<0.05). On a gram basis, the two diets with the highest amounts of protein emptied the slowest starting at two hours (p<0.05). This data would suggest that fat does not delay gastric emptying in the cat, especially on a caloric basis. 🔀

LA Foster, JJ Hoskinson, JM Goggin, MD Butine. Kansas State University.

Microalbuminuria Correlates with Intestinal Histopathological Grading in Patients With Inflammatory Bowel Disease

(adapted from: Mahmud N, McDonald GSA, Kelleher D, Weir DG. Gut 1996;38:99-103.)

There are various methods used to diagnose inflammatory bowel disease (IBD) including various subjective scoring systems. Most of the objective laboratory measures that may be used are difficult, invasive, expensive or have other limitations. Microalbuminuria has been shown to be a marker of IBD based on correlation with erythrocyte sedimentation rate and C-reactive protein in human patients with active disease. Microalbuminuria, defined as elevations in urine albumin above normal yet below the detection limits of the semiquantitative urine dipstrips, may also be increased in other inflammatory

conditions and following myocardial infarction. To determine whether or not microalbuminuria correlated with degree of intestinal inflammation, a study was conducted to evaluate urinary albumin levels and histological determinations of colonic inflammation in IBD patients.

Forty-two patients with either Crohn's colitis or ulcerative colitis were evaluated. Patients with active IBD had higher concentrations of microalbuminuria, in 12-hour urine collections, compared to those in remission although all patients exceeded the normal reference range. Patients with more extensive colonic disease had increased concentrations compared to those with localized disease.

There was a strong positive correlation between microalbuminuria and intestinal histopathological score in patients with localized or extensive disease.

[Editor's note: Adaptation of this assay to veterinary medicine may provide a simpler, less invasive means of monitoring patients with IBD.]

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