ROLE OF BACTERIA IN CHRONIC COLITIS
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Inflammatory bowel disease (IBD) is the term applied to a group of poorly understood enteropathies that commonly affect animals and people. IBD in both people and animals is increasingly considered a consequence of uncontrolled intestinal inflammation in response to a combination of environmental, enteric luminal constituents (principally microbial and dietary) and immunoregulatory factors in genetically susceptible individuals.

In people, genetic susceptibility is linked increasingly to defects in genes involved in sensing and killing of bacteria (e.g. NOD2, ATG16L1) that in the presence of the enteric microflora may lead to up-regulated mucosal cytokine production, delayed bacterial clearance and increased bacterial translocation, promoting and perpetuating intestinal inflammation. While the mucosa-associated flora is implicated frequently as a pivotal factor in the development of IBD in people and animals, the specific bacterial characteristics that drive the inflammatory response are still being defined.

In dogs, the clinical responses of Boxer dogs and French Bulldogs with granulomatous colitis (GC; also known as histiocytic ulcerative colitis, HUC) to enrofloxacin, and a subset of dogs (e.g. German Shepherd) with idiopathic chronic diarrhea to antibiotics such as tylosin or oxytetracycline, points to a similar interaction of host susceptibility and microflora. The E. coli strains isolated from the colon of Boxer dogs with GC/HUC are broadly similar to those in healthy dogs, and the numbers of cultivable aerobic and anaerobic bacteria in the duodenal juice of dogs with antibiotic responsive enteropathy are similar to dogs that respond to food or immunosuppression suggesting that affected individuals are susceptible to their resident microflora rather than obligate pathogens, but this remains to be determined.

Recent advances in molecular microbiology have enabled the analysis of complex bacterial communities without bacterial culture. Culture-independent analyses of bacterial 16S rDNA libraries indicates that only @30% of the fecal flora appears cultivable, and there is significant variation in the flora in different gastrointestinal segments and luminal contents versus the mucosa of healthy individuals. Our understanding of the role of bacteria in IBD is rapidly moving beyond the detection of pathogens such as Campylobacter and Salmonella to in-depth analysis of the resident microflora (microbiome) that may perpetuate inflammation in an IBD susceptible individual.

This presentation will present an in depth overview of the mucosal bacteria associated with chronic colitis in dogs and cats.

The results of the principal studies covered in this presentation are summarized as follows:
Granulomatous Colitis in Boxer dogs
Granulomatous colitis (GC) of Boxer dogs, also known as Histiocytic Ulcerative Colitis (HUC), was first described by Van Kruijningen in a kennel of Boxer dogs in 1965. The clinical hallmarks of the disease are severe large bowel diarrhea that is often accompanied by profound weight loss, anemia and hypoalbuminemia. GC/HUC, although rare, occurs world-wide with reported cases originating from Australia, Japan, North America and Europe. Boxer dogs are most commonly affected. The pathognomonic lesion of GC/HUC in Boxer dogs is mucosal infiltration with large numbers of macrophages staining positively with period-acid-Schiff (PAS), and is usually accompanied by mucosal ulceration and loss of goblet cells. Evaluation of colonic biopsies from GC affected Boxer dogs by fluorescense in situ hybridization (FISH) with...
eubacterial and E.coli rDNA probes has revealed the presence of intramucosal *E. coli* in affected individuals. Clinical response to antibiotics was observed in 7/7 dogs within 2 wks of enrofloxacin given at a mean dose of 7 mg/kg/d for a mean duration of 9.5 weeks, and was sustained in 6 dogs (mean disease-free interval to date of 45 months). Post-enrofloxacin FISH was negative for *E. coli* in 4/5 dogs. *E. coli* resistant to enrofloxacin were present in the FISH positive dog that relapsed clinically. These findings suggest that *E. coli* invasion plays a critical role in the initiation and/or progression of GC/HUC in Boxer dogs. Unfortunately, antibiotic resistance is an increasing problem and we have documented enrofloxacin resistant *E. coli* in 6/6 Boxers that were empirically treated with enrofloxacin prior to definitive diagnosis. The empirical use of enrofloxacin to treat undefined colitis is discouraged, and culture based antimicrobial susceptibility testing is required to optimize response of Boxers with enrofloxacin resistant *E.coli*.

**Granulomatous Colitis in French Bulldogs**

We have recently discovered that GC in French bulldogs is associated with intramucosal *E. coli* and clinical response to fluoroquinolone antimicrobials. Thus, GC in French bulldogs is phenotypically, histologically, and microbiologically analogous to GCB.

Since GC/HUC in dogs is remarkably breed-specific it may be due to a heritable anomaly in Boxers and French Bulldogs dogs that confers susceptibility to invasion and persistence of *E. coli* within the colonic mucosa. Further studies are ongoing to identify the host and bacterial factors related to invasion and persistence of *E. coli* in GC/HUC susceptible Boxers and French Bulldogs. Please contact the author if you are interested in participating in a prospective clinical study.

**Canine Lymphocytic - plasmacytic colitis**

The colonic mucosa of 23 dogs undergoing evaluation for signs of gastrointestinal disease (endoscopic biopsies) and 18 dogs without signs of intestinal disease (full thickness biopsies) was evaluated using a standardized histopathological scoring system. The number and spatial distribution of mucosal bacteria was determined by FISH with probes to 16S rDNA and an antibody to *Brachyspira* spp. The mucosal flora of healthy and inflamed colon hybridized with probes to *Bacteroides/Prevotella, Clostridium, Enterobacteriaceae, Streptococcus* and *Helicobacter* spp. 16S rDNA sequence analysis showed *Helicobacter* spp had highest homology to *H. canis, F. rappini,H. hepaticus* and *H. cinaedi. Brachyspira* were not detected in any samples. The number of mucosa-associated bacteria and Enterobacteriaceae was lower in dogs with colitis and was inversely correlated with severity. Colitis was associated with a significant reduction in the proportion of *Clostridium* spp relative to total bacteria and Enterobacteriaceae. The relationship of the abnormal flora to the pathogenesis of “lymphoplasmacytic” colitis remains to be established. It is noteworthy that the majority of dogs with lymphoplasmacytic duodentis (who also have evidence of similar microbial shifts) respond to dietary therapy rather than antibiotics.

**Implications for patients with chronic colitis**

1. Rule out known enteropathogens and parasites up front
2. Base therapy on the patient profile: breed, clinical evaluation, histopathology
3. Do not immunosuppress until other avenues are exhausted
4. Dietary manipulation is a good starting point for most dogs with idiopathic lymphoplasmacytic colitis, with supplemental tylosin (15mg/PO BID) the usual next step.
5. The presence of neutrophils and or macrophages increases the likelihood of an
infectious agent (bacteria, fungi, algae) and these should be ruled out / detected with additional testing e.g. PAS stain, Giemsa, Steiner, FISH

**Further Reading:**