INFLAMMATORY BOWEL DISEASE IN DOGS AND CATS

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Intestinal inflammation is merely a final common pathway by which many gastrointestinal (GI) diseases manifest. But if no underlying cause of the inflammation can be found, it is then termed idiopathic Inflammatory Bowel Disease (IBD). Thus extensive diagnostic investigations must be performed to exclude the known causes of intestinal inflammation before IBD can be diagnosed. Lymphocytic-plasmacytic enteritis (LPE) is considered to be the most common histological form of IBD in dogs and particularly in cats; eosinophilic gastro-enteritis-(colitis) (EGE) is the next most common form. Neutrophilic inflammation is sometimes seen, especially in cats, but idiopathic granulomatous enteritis is considered uncommon.

Clinical presentation

Idiopathic IBD is probably the most common cause of chronic vomiting and/or diarrhoea in dogs. In cats, vomiting without diarrhoea is considered the more typical presentation, although subtle changes in stool quality may be missed in cats using litter trays or defecating outdoors. There is no confirmed sex predilection for IBD but certain breeds are predisposed to certain types of IBD (LPE – German shepherd, Shar pei, Siamese; EGE - German shepherd). The disease is seen most frequently in middle-age dogs and cats although there is often a history of previous intermittent signs that may have been controlled, at least in part, by dietary manipulation. A diagnosis of idiopathic IBD before the age of one year is unlikely, and the clinician should look again for an underlying cause (e.g. diet or infection) before accepting that the condition is truly idiopathic and beginning immunosuppressive treatment.

Ultimately, IBD is a histological diagnosis, but there are clinical features in the presentation that are characteristic. The signs of IBD are variable and may wax and wane, only sometimes with obvious precipitating events, e.g. ‘stress’, dietary change. Yet the nature and severity of the signs can be crudely correlated to the region affected within the GI tract, to the histological type of inflammation, and to its severity.
An individual case may show some or all of the following signs depending on the type, severity and site of the inflammation:

- Vomiting, haematemesis
- SI-type diarrhoea: large volume, watery, melaena
- LI-type diarrhoea: haematochezia, mucus, frequency and tenesmus
- Abdominal discomfort / pain
- Excessive borborygmi and flatus
- Weight loss
- Altered appetite: polyphagia or decreased appetite / anorexia
- Hypoproteinaemia / ascites (protein-losing enteropathy)
- Hypercoagulability and thrombo-embolic disease

Gastric signs are seen more commonly if there is gastric or upper intestinal inflammation and, in cats, vomiting may be the predominant sign of both gastric and intestinal IBD. LI-type diarrhoea may be due to colonic inflammation, but can also occur secondary to prolonged SI diarrhoea; alternatively both SI and LI may be diffusely inflamed. The presence of blood in the vomit or diarrhoea is associated with more severe disease and, more frequently perhaps, with eosinophilic inflammatory infiltrates. Severe disease is associated with weight loss and even a protein-losing enteropathy (PLE) with consequent hypoproteinemia and ascites. Milder inflammation may not affect appetite but post-prandial pain can be a significant problem even in the absence of other signs. Recently developed clinical scoring schemes allow objective comparison between cases.

**Diagnosis**

The clinical signs of IBD are often suggestive of the diagnosis, but intestinal inflammation must be confirmed by intestinal biopsy and known causes of inflammation must be ruled out. Before intestinal biopsy is undertaken, laboratory tests and imaging examinations are performed. They will not enable a diagnosis of idiopathic IBD to be confirmed, but they hopefully rule out the known causes of intestinal inflammation. The tests that are routinely performed are discussed below.
**Haematology**

In LPE there is sometimes a neutrophilia and occasionally a mild left shift. The presence of an eosinophilia is not a reliable marker of EGE. Anaemia may reflect chronic inflammation or chronic blood loss.

**Serum biochemistry**

There are no pathognomonic changes in IBD, but diseases of other organ systems will be recognised as a cause of the GI signs. Hyperthyroidism should be ruled out in cats by testing serum T4. Hypoalbuminaemia and hypoglobulinaemia are quite common and characteristic of a PLE. Decreased total serum calcium and magnesium partly reflect reductions in protein-bound ions, but true functional hypocalcaemia and hypomagnesaemia (i.e. reduced ionised Ca\(^{++}\) and Mg\(^{++}\)) have been shown in PLEs. Hypocholesterolaemia is suggestive of malabsorption. Mild elevations in liver marker enzymes (ALT, ALP) may reflect liver damage secondary to the intestinal inflammation and uptake of toxins through the damaged intestinal mucosa, and are of no direct consequence. However, in cats, there is a recognised association between IBD, chronic pancreatitis and cholangitis (so-called ‘triaditis’).

**Rectal cytology**

The presence of inflammatory cells is a crude marker of lower intestinal inflammation, but is helpful in the diagnosis of histoplasmosis in endemic countries.

**Faecal parasitology**

Ideally three consecutive samples should be checked for hookworms, whipworms and *Giardia*. In reality it is usually easier to treat empirically.

**Faecal culture**

The isolation of *Salmonella* or *Campylobacter* may be significant. Detection of pathogenic *E. coli* is restricted to specialist laboratories with appropriate pathogenicity genes tested by PCR.

**TLI, folate & cobalamin**

Exocrine pancreatic insufficiency as a cause of signs of malabsorption should be ruled out by measuring serum TLI. Proximal intestinal inflammation may cause folate malabsorption, whereas distal inflammation may lower serum cobalamin. These vitamins are not reliable indicators, but severe reductions of folate and/or cobalamin concentrations do correlate with the severity of intestinal inflammation, and are helpful in determining prognosis, and whether vitamin supplementation is indicated.
Serology

Testing for FeLV and FIV in cats is important as such infections may be associated with chronic diarrhoea syndromes. Serology is not confirmative for FIP, and intestinal biopsy is necessary to confirm transmural FIP-induced granulomas.

Imaging

Plain radiographs are used to look for anatomical intestinal conditions. Contrast studies rarely add further information in IBD unless there is very severe mucosal disease. Ultrasound examination permits the evaluation of the thickness of any mucosal infiltrate, although thickening is not a consistent finding in IBD unless tissue oedema (due to hypoalbuminaemia) is present. The presence of normal layering suggests a benign process, but mucosal striations can indicated dilated lymphatics.

Intestinal biopsy

Endoscopy is the easiest method of biopsy, but has limitations, particularly the inaccessibility of the jejunum (and ileum), and recent evidence suggests a lack of correlation between changes in the duodenum and ileum of individual canine patients. In some cases, especially if there is some doubt as to whether there might be an anatomical intestinal problem (e.g. tumour, intussusception) or extra-intestinal disease (e.g. pancreatitis), exploratory laparotomy and full-thickness biopsy is preferred. However, the risk of wound dehiscence makes endoscopic biopsy the preferred method initially.

The interpretation of GI biopsies will be discussed later so, in conclusion, the diagnosis of IBD depends on the histopathological identification of intestinal inflammation, having ruled out known causes of intestinal inflammation. Only then is it safe to consider treatment of idiopathic IBD.

Treatment

The mainstay of treatment of idiopathic IBD has always been immunosuppression, and the author's preferred choice is prednisolone in combination, in severe cases, with azathioprine (for dogs) or chlorambucil (for cats). Despite the concept that IBD is a loss of immunological tolerance to the normal intestinal flora, antibiotics are not effective alone. Drug therapy will be discussed elsewhere.

In IBD there may also be lack of tolerance to dietary antigens. Highly digestible, restricted fat ‘intestinal’ diets are helpful in the management of IBD. They provide less ‘work’ for the compromised intestine, and hopefully contain the optimum amounts of n3:n6 fatty acids, fibre and micronutrients etc. necessary for general intestinal health. However, hydrolysed diets have shown even great efficacy when intestinal
inflammation is present, although it is not clear whether this then indicates a true dietary sensitivity or a symptomatic effect.

**Prognosis**

The belief that IBD is always successfully managed by immunosuppression is false. Indeed the outcome is often poor in the long-term, and cases that appear to respond well may actually be mis-diagnosed. It is also apparent that the presence of hypoalbuminaemia and hypobalaminemia are indicators of a poor prognosis,
In most cases of acute diarrhoea, a tissue diagnosis is not needed, and intestinal biopsy is very rarely performed. However, historically in chronic diarrhoea, a definitive diagnosis has depended on histological examination of intestinal tissue, although this procedure has major limitations.

Biopsy specimens are collected either endoscopically or surgically (by laparotomy or laparoscopy). The clear advantages of endoscopy to the patient and client are balanced by a number of drawbacks, and the client should always be warned that surgical biopsy might ultimately be required for definitive diagnosis.

The duodenum and proximal jejunum (if possible) are biopsied routinely by endoscopy, and ileal biopsies may be obtained via colonoscopy. At laparotomy, full-thickness biopsies are usually taken from at least three sites, the duodenum, the jejunum, and the ileum, as well as inspecting and biopsying extra-intestinal organs.

.Relative Advantages of Endoscopic and Surgical Intestinal Biopsy

<table>
<thead>
<tr>
<th>Endoscopy</th>
<th>Laparotomy</th>
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<tbody>
<tr>
<td><strong>Advantages</strong></td>
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</tr>
<tr>
<td>Minimally invasive</td>
<td>Allows biopsy of multiple sites</td>
</tr>
<tr>
<td>Allows visualization and biopsy of focal lesions</td>
<td>Requires expensive equipment</td>
</tr>
<tr>
<td>Permits multiple biopsies</td>
<td>Permits large, full-thickness biopsies</td>
</tr>
<tr>
<td>Minimal risk</td>
<td>Allows inspection of other organs</td>
</tr>
<tr>
<td>Steroids can be started early; no convalescence</td>
<td>Offers potential for corrective surgery</td>
</tr>
</tbody>
</table>
Disadvantages

- Requires general anaesthesia
- Requires general anaesthesia
- Technically demanding
- Poses a surgical risk
- Small risk of perforation
- Poses a post-surgical risk of dehiscence
- Permits reliable access only to duodenum
- Requires convalescence
- Jejunum only accessible in cats /small dogs
- Requires delay before steroids
- Ileum only accessible via colonoscopy
- Small, superficial (and potentially crushed) biopsies
- May miss lymphangiectasia, lymphoma

The risk of dehiscence after surgical biopsy is significant, especially if the patient is malnourished and/or hypoproteinaemic, or the surgeon inexperienced. Administration of plasma or colloid may reduce the cardiovascular effects of hypoproteinaemia, but the effect is only transient and really only worthwhile to provide circulatory support during the perioperative period when biopsies are being collected. Best practice is to perform endoscopic biopsy first unless there is evidence that the disease is beyond the reach of the endoscopy; the surgical option is preferred if there is any possibility of extraintestinal disease or focal intestinal pathology. The size and quality of endoscopic biopsies depends not just on the equipment available, but also the pressure exerted by the forceps, which is in part dependent on the operator’s experience. Biopsies should always be taken, even in the absence of gross abnormalities, because microscopic changes may be present. Multiple biopsies (six or more) should be collected, because the size of the specimens, crush artifacts, and fragmentation can make interpretation difficult.

Although histopathological assessment of intestinal biopsies remains the gold standard for diagnosis of intestinal disease, it has marked limitations. Biopsy specimens can be normal by light microscopy, which suggests that sampling or interpretation problems have occurred or that many diseases have a functional rather than a morphological abnormality.
Causes of Chronic Diarrhoea for which SI Biopsy May Be Normal*

- SIBO / ARD
- Dietary indiscretion
- Food intolerance
- Type I hypersensitivity to food (if dog is starved before biopsy)
- Toxigenic / secretory diarrhoea
- Motility disorders/irritable bowel syndrome
- Brush border membrane disease (e.g., hypolactasia)
- Patchy mucosal disease not sampled
- Intestinal sclerosis (if biopsies are not full thickness)
- Undiagnosed EPI or colonic or systemic disease

* Detection of histological abnormalities depends on the size and quality of the biopsy, the quality of processing, and the expertise of the pathologist.

Even when there are histopathological abnormalities present, agreement between histopathologists often is poor, especially when examining endoscopic biopsies; in one study, some histopathologists made a diagnosis of lymphoma after assessing tissues from healthy dogs, and there was only reasonable agreement between five independent pathologists in about half of the samples examined. Thus a standardized approach is required.

The WSAVA GI Standardization Group have produced a standardized template so that there is consistency in descriptions. However, this publication does NOT provide any evidence of the relative importance of each feature. Prospective studies looking at weighted scoring systems are required.
Criteria for Histological Assessment of Endoscopic Intestinal Biopsies

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<tr>
<th>Crypt-Villus Unit</th>
<th>Lamina Propria</th>
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<tbody>
<tr>
<td>Villus height and width</td>
<td>Immune cell density</td>
</tr>
<tr>
<td>Villus clubbing/fusion</td>
<td>Predominant cell type</td>
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<tr>
<td>Crypt depth</td>
<td>Lymphangiectasia</td>
</tr>
<tr>
<td>Mitotic index</td>
<td></td>
</tr>
<tr>
<td>Crypt abscessation/distortion</td>
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<tr>
<td>Crypt to villus ratio</td>
<td>Miscellaneous</td>
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<td>Epithelium</td>
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<tr>
<td>Erosions</td>
<td>Hyperaemia or congestion</td>
</tr>
<tr>
<td>Enterocyte height (flattening, necrosis)</td>
<td>Edema</td>
</tr>
<tr>
<td>Intraepithelial lymphocyte density</td>
<td>Fibrosis</td>
</tr>
<tr>
<td>Goblet cell number, size</td>
<td>Infective agents</td>
</tr>
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</table>

The WSAVA GI Standardization have shown that the experience of the endoscopist, as well as simply the quality and numbers of biopsies can influence the reliability of the histological interpretation. Worryingly there is emerging evidence that ileal biopsies are more likely to be diagnostic than duodenal. As expected, fewer biopsies are needed to reliably detect architectural changes the better their quality (i.e. size, depth and integrity) and more specimens are needed the deeper the lesion.

Therefore the primary clinician should always interpret endoscopic biopsy results cautiously and in light of the clinical presentation; results should be questioned if the tissue diagnosis does not fit the clinical picture or if the response to apparently appropriate therapy is poor. In some cases, repeat biopsy (e.g., by exploratory laparotomy) may be required. Cytological examination of endoscopic biopsy squash preparations or mucosal brushings are only an adjunct to histopathological examination.

However, even if the limitations of biopsy, especially endoscopic biopsy, and histopathology are ignored, the question remains as to the value of a histopathological diagnosis. There are no pathognomonic changes on histology for food allergy, ARD/SIBO and so the diagnosis is based on the response to empirical treatment. Therefore, treatment trials (antibiotics, exclusion diet) can be justified before biopsy is performed.
Even a diagnosis of intestinal inflammation cannot be used to diagnose IBD as there are many causes of intestinal inflammation:

- Chronic infection
  - *Giardia* sp.
  - *Histoplasma* sp.
  - *Toxoplasma* sp.
  - *Mycobacteria* sp.
  - Protothecosis
  - Pythiosis
  - Pathogenic bacteria (*Campylobacter*, *Salmonella* spp., pathogenic *Escherichia coli*)
- Food allergy
- Small bowel inflammation associated with other primary gastrointestinal diseases
  - Lymphoma
  - Lymphangiectasia
- Idiopathic causes
  - Lymphocytic-plasmacytic enteritis (LPE)
  - Eosinophilic gastroenterocolitis (EGE)
  - Neutrophilic enteritis
  - Granulomatous enteritis

Alimentary lymphoma and lymphangiectasia in dogs can be diagnosed by biopsy, although full-thickness samples are more reliable. However, in older cats the most common form of alimentary lymphoma (small cell, villus lymphoma) is not always reliably differentiated from severe lymphoplasmacytic enteritis. Immunophenotyping and even clonality testing may be necessary. Yet the prognosis for both conditions treated with prednisolone and chlorambucil is almost identical, suggesting an absolute histological diagnosis is not necessary as it does not alter treatment.

Biopsy of solid tumours is indicated and should be diagnostic.
Challenging clinical cases
Problems with intestinal inflammation

• How do we diagnose it?
  – Clinical & histological definition
• Is it idiopathic IBD?
  – Beware!
• How do we treat it?
  – Conventional and new therapies
• How do we monitor it?
  – New markers of inflammation
• What is the prognosis?
  – Can we explain treatment failures?
Idiopathic IBD ?
11.001181 Sheba - history

- 7 year-old NF German shepherd dog
- 2008 diarrhoea started
  - Low cobalamin
  - Oxytetracycline (OTC) & low fat diet
  - Diarrhoea controlled for a year
- 2009 relapse
  - Endoscopic biopsy confirmed LPE
  - Prednisolone and OTC
- 2010 diarrhoea worsening again
  - Azathioprine added to prednisolone in 2000
- March 2011 owner stopped treatment because of steroid side-effects
- October 2011 referred by another practice
Sheba – problem list

- Severe weight loss 26 kg (ideal 35 kg)
  - BCS 1/5
- Variable appetite
- Muscle atrophy
- Severe scale
  - Secondary pyoderma
- Diarrhoea
  - Watery
  - 1-2 x per day
  - No blood
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<td>6 - 18 x10⁹/l</td>
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<tr>
<td>Monocytes</td>
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<tr>
<td>Dynamic bile acids</td>
<td>within reference range</td>
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</table>
11.001181 Sheba

- TLI 3.4 5.0 – 35 µg/l
- Folate 10.0 3.5 – 8.5 µg/l
- Vitamin B$_{12}$ 39 215 – 500 ng/l

- Faecal x 3 negative endoparasites
  negative culture
11.001181 Sheba - investigation

- Abdominal radiographs
  - NAD
  - Poor detail because thin
- Abdominal ultrasound
  - Intestinal wall thickness WNL
  - Pancreas visible
11.001181 Sheba - investigation

- Upper GI endoscopy
  - Multiple small gastric ulcers
  - Irregular duodenal mucosa
11.001181 Sheba - diagnosis

- Endoscopic biopsy
  - Normal stomach ??
  - Lymphoplasmacytic enteropathy with marked plasma cell component
08.05356 Bomber

- 6 year old male Bulldog
- History of urolithiasis
  - No further info’ on uroliths
  - Treated with u/d for 8 weeks
  - Developed diarrhoea
  - Treated with w/d
  - Re-presented in June 2008 after diarrhoea for 3 months
08.05356 Bomber

- June 2003
  - Watery diarrhoea
  - Poor appetite
  - Slightly depressed
  - Severe weight loss
    - From 29 to 18.9 kg
08.05356 Bomber

- June 2008
  - Faecal negative for ova and Campylobacter
  - Albumin low - numbers not reported
  - Neutrophils increased - numbers not reported
  - TLI 17.6 (5-35 μg/l)
  - Cobalamin <100 (275-590 ng/l)
  - Bile acids WNL

- Treated with
  - i/d
  - r/d
08.05356 Bomber

- July 2008
  - No improvement
  - Referred for endoscopic biopsy elsewhere
    - Grossly normal
    - Biopsy report
      - “Mild gastritis with superficial fibrosis”
      - “Enteritis, moderate, lymphoplasmacytic”
      - “Colitis, mild”
      - “Probably inflammatory bowel disease”
08.05356 Bomber

- Treatment
  - Intermittent IV fluids
  - 20 mg prednisolone q12h
  - 1 1/2 x 25 mg azathioprine
  - 200 mg metronidazole q8h
  - Hydrolyzed z/d diet
08.05356 Bomber

- August 2008
  - No improvement
  - Lab results (interesting ones only!) whilst on pred.

- HCT 31.8 mild anaemia
- Total WBC 15.3 x 10^9/l WNL
- PMNs 13.6 x 10^9/l mild mature neutrophilia
- Albumin 16 g/l low (27-38 g/l)
- ALP 940 iu/l raised (23-212 iu/l)
- ALT 35 iu/l WNL (10-100 iu/l)
08.05356 Bomber

- August 2008
  - Collapsed once and had two seizures
  - Referred to another vet school
    - Treated symptomatically for seizures
    - Sent home on same treatment for GI disease
  - Referred to Bristol
    - Advised to wean off prednisolone and azathioprine before appointment
038.05356 Bomber

- October 2008
  - Referral appointment
  - Off all treatment except z/d
  - No further seizures
  - Brighter but still watery diarrhoea
  - Weight 18 kg
  - BCS 1/5

“You are our last hope”
<table>
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<th>08.05356 Bomber</th>
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<th>Ref. Ranges</th>
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<td>3.5 - 7.0 mmol/l (mg/dl)</td>
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04.05421 Thunder

- 10 year old male Black labrador
- Previous vomiting
- Soft stool
- Appetite OK
- Progressive weight loss
  34 → 27 kg
Perhaps the greatest advance in gastrointestinal (GI) therapeutics in the past decade is not a drug, but the realisation that ‘if the gut works’ one should ‘use it’. In starvation the intestinal mucosa atrophies and the animal is more susceptible to bacterial invasion from the lumen. The understanding that enterocytes largely use luminal glutamine for energy metabolism and that colonocytes use volatile fatty acids (butyrate and propionate derived from fibre fermentation) has led to many attempts at dietary manipulation to improve ‘intestinal health’. Enteral nutrition, either voluntary or by tube feeding, is believed to reduce morbidity and mortality and is much simpler and safer than parenteral nutrition. Increasingly sophisticated systems of tube feeding and available foods make nutritional support a simple reality for practitioners. The use of exclusion diets, including hydrolysed diets, probiotics and nutraceuticals is discussed elsewhere.

Symptomatic control of vomiting caused by intestinal disease can be gained by using anti-emetics and prokinetics, but drug therapy for chronic enteropathies encompasses the use of antibacterials, antidiarrhoeals, and anti-inflammatory/immunosuppressive agents. A specific diagnosis may lead to specific treatment, but a number of symptomatic treatments are frequently used. Indeed, the risk of polypharmacy is very real in animals with GI disease. Antiparasiticides are used very frequently for treatment and prophylaxis, and empirical treatment.

**Vitamin B₁₂**
Cobalamin deficiency is also recognised as an important consequence of chronic small intestinal disease, and in itself has metabolic consequences that can lead to anorexia and further gut damage. Parenteral supplementation is indicated. Weekly injections of 1-2 mg per dog or 250 μg per cat for 4-6 weeks are given, or until serum concentrations are supra-normal to ensure intracellular stores are replete.

**Antibacterials**
Despite the relative safety of antibacterials, the risks of inducing antibiotic resistance are real, and the use of antibiotics in acute GI disease should be restricted to times of clear need. A chronic enteropathy where antibacterials are used was formerly termed small intestinal bacterial overgrowth, but is more literally termed antibiotic-responsive diarrhoea (ARD).
In ARD, the clinical benefit of antibiotics is clear, but how these products work for years without the development of resistance and why supposedly sub-therapeutic doses are also effective has called into question their mode of action. It seems very unlikely that they sterilise the gut, but they may exert a pressure on the ecosystem excluding potential pathogens, perhaps by inhibiting adherence rather
than killing the organism. Alternatively they may be directly anti-inflammatory, as they are used in man to treat various skin disorders and arthritis.

**Antidiarrhoeals**
Suspensions of inert substances such as kaolin and pectin can be effective in controlling mild diarrhoea. Historically they were believed to 'coat and protect' the intestinal mucosal. It now seems likely that their efficacy depends on their ability to bind water and toxins, and a direct anti-secretory effect.

**Immunosuppressive agents**
Immunosuppression is used to treat idiopathic inflammatory bowel disease (IBD)

* Corticosteroids
Prednisolone (and methylprednisolone) remain(s) the first-choice immunosuppressive agent in dogs and cats. Equipotent doses of dexamethasone have similar immunosuppressive effects, but have more deleterious effects on brush border enzyme activity and so dexamethasone is not recommended.

* Novel steroids
Prednisolone suppression of the HPA axis and the consequent side-effects have led to attempts to find safer steroids. Budesonide has been given to dogs and cats with IBD with some success. The correct dose is uncertain, but an empirical dose of 3 mg q12h in large dogs and 1 mg q12h in cats of an enteric-coated formulation in 3 mg capsules (Entocort CR, Budenofalk) has been suggested. The value of this preparation in animals is unclear, especially as steroid hepatopathy still seems to be a problem in dogs.

* Azathioprine
This is an effective immunosuppressive agent (*Imuran*, 2 mg/kg/day in dogs). Its major use is as a steroid-sparing drug in patients suffering iatrogenic Cushing's. Bone marrow toxicity is uncommon in dogs, but will occur quite rapidly (1-2 weeks) in some individuals. They probably lack an enzyme (thiopurine methyltransferase, TPMT) necessary to degrade its active metabolite, 6-mercaptopurine. This enzyme is low in about 10% of dogs but in almost 100% of cats. This explains why the safety of azathioprine in cats has been questioned and why, if used, the dose (0.3 mg/kg/day) is so much lower than in dogs.

* Chlorambucil
Azathioprine is not a good choice for feline IBD, whilst oral chlorambucil (2 mg/cat every 4-5 days) usually in combination with prednisolone is an effective and relatively safe.

* Cyclosporine
This anti-rejection drug is beginning to find uses in veterinary medicine to treat immune-mediated diseases. Preliminary studies in idiopathic canine IBD have shown variable success.
Anti-inflammatory drugs

In general, non-steroidal anti-inflammatory drugs (NSAIDs) are toxic to the GI mucosal barrier. In addition, intestinal absorption predisposes to renal toxicity, particularly in dehydrated, diarrhoeic patients. However, systems that deliver NSAIDs to the colon are useful in treating colitis.

5-Aminosalicylic acid (5-ASA) derivatives

Sulphasalazine (Azulfidine, Salazopyrin) is indicated for the treatment of idiopathic colitis. Within the drug, a diazo bond (binding a sulfa-moiety to 5-ASA) is cleaved by colonic bacteria. This releases free 5-ASA, which acts locally in high concentrations as an anti-inflammatory. Unfortunately a major side-effect, keratoconjunctivitis sicca, is well recognised. Sulphasalazine may inhibit TMPT activity, and myelosuppression is a greater risk if it is used concurrently with azathioprine.

Olsalazine (Dipentum) is two 5-ASA moieties again released by colonic bacteria. It has been used successfully in dogs, although KCS has still been reported, and the dose is one half the dose of sulphasalazine. A newer derivative, balsalazide (Colazide) is also pro-drug (4-aminobenzoyl-β-alanine-5-ASA) releasing free 5-ASA, but has not been tried in animals. Slow-release enteric formulations of 5-ASA (mesalazine, Pentasa) are available but premature release may cause absorption and nephrotoxicity in dogs and cats.
PROBIOTICS & NUTRACEUTICALS – WHAT IS THE EVIDENCE?

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Definitions

A **nutraceutical** is a product isolated or purified from food that is generally sold in a medicinal form not usually associated with food, and that is shown to have a physiological benefit or provide protection against chronic disease.

A **prebiotic** is a naturally occurring substance often added to food that usually, through its fermentation to volatile fatty acids, enhances intestinal health and the growth of potentially beneficial bacteria.

A **probiotic** is a live micro-organism that, when administered in adequate amounts, confers a health benefit on the host.

Nutraceuticals

The term nutraceutical originated as a hybridization of *nutrition* and *pharmaceutical* and included any dietary supplement; there is still no regulatory definition. Even vitamin supplements can be considered nutraceuticals, and there is clear a wealth of evidence of their value. Today ‘functional foods’ are fed to promote health, whilst the term nutraceutical is applied to supplements added to the diet in order to modify health problems.

Although fashionable for the treatment of chronic conditions such as osteoarthritis, there is only limited evidence of the benefit of such nutraceuticals (e.g. glucosamine, shark’s cartilage, green-lipped mussels). These products either supplement glycosaminoglycans, potentially modifying cartilage composition, or are anti-oxidants potentially reducing inflammation. There is no evidence that these products are of benefit in GI disease.
**Prebiotics**

Prebiotics are a form of nutraceutical that have been developed to improve GI health. More commonly they are actually incorporated within the diet as, typically, they are partially digestible fibres, e.g. ispaghula (plantain), chicory, inulin, beet pulp. Their bacterial fermentation releases volatile fatty acids which are energy sources for colonocytes: feeding of a fibre-free diet results in colonic changes and diarrhoea. As well as being incorporated within diets, prebiotics can be supplemented separately and even given in combination with probiotics, termed synbiotics.

Prebiotics may provide the right environment for the growth of so-called ‘beneficial’ or probiotic bacteria. There is good evidence that addition of dietary fibre does alter the colonic flora, although the evidence for an effect in the small intestine is generally lacking. Fructooligosaccharides (FOS), mannan oligosaccharides (MOS), gum Arabic (acacia gum) and beta-glucan potentially inhibit pathogenic bacteria and have positive effects on mucosal barrier integrity, immunoregulation and the innate immune system, although most effects have been shown experimentally, and clinical benefits are harder to demonstrate.

**Probiotics**

Lactobacilli and *Bifidobacteria* are frequently claimed to have probiotic activity, but *E. coli*, *Enterococcus* and non-bacterial *Saccharomyces* may also be probiotic. However, is significant scepticism as to the efficacy of any probiotics because of a lack of supportive evidence, fuelled by historical evidence that commercially available products contained:

- inactive organisms because of a very short shelf-life
- insufficient organisms to evade the acidic gastric environment
- organisms that failed to colonise the intestine permanently
Newer products have improved numbers and viability, but it is now clear that permanent colonisation rarely if ever occurs; probiotic organisms can be cultured from stool for as long as they are being given, but for only a few days after their oral administration is stopped.

Possible mechanisms for probiotic activity include:

- production of antimicrobial metabolites
- competitive interactions (receptor binding)
- interaction with epithelial function, e.g. improved intestinal permeability
- immune modulation

The rationale for using probiotics in intestinal disease, and in particular in IBD, is that bacteria are involved in its pathogenesis. There is considerable interaction normally between the healthy intestine and the millions of organisms representing several hundred species of bacteria. The presence of pathogens or at least the disturbance of the normal flora may exacerbate inflammation. Bacterial species vary in their ability to drive intestinal inflammation: various *Bifidobacterium* and *Lactobacillus* species have no pro-inflammatory activity and so are frequent choices as probiotics.

Evidence of efficacy is now beginning to emerge both in experimental models of intestinal inflammation and in human cases of inflammatory bowel disease (IBD):

- Prevention or reduction of durations of rotavirus or antibiotic-associated diarrhoea
- Reduction of cancer-promoting enzymes and/or putrefactive metabolites in the gut
- Beneficial effects on microbial aberrances in intestinal inflammation
- Normalization of stool consistency
- Prevention or alleviation of allergies in infants
- Prevention of respiratory tract infections

However, although effects have been shown in companion animals there has yet to be significant proof of clinical benefit in naturally occurring intestinal disease. Most information is available for the probiotic
Enterococcus faecium SF68 (Fortiflora®). It has been shown to have immunomodulatory effects in dogs, increasing faecal IgA and anti-distemper antibodies, and in cats, increasing CD4+ counts. Yet clinical benefit has not been shown in studies of feline herpesvirus recrudescence and canine giardiasis, although it was shown that co-administration with metronidazole did not affect SF68 viability. The most convincing positive effect of SF68 has been a reduction in diarrhoea in cats entering an animal shelter in the USA: the prevalence of diarrhoea persisting two or more days was nearly 21 per cent of all cats fed placebo, versus 8% in cats given SF68.

These studies give some hope that probiotics may be beneficial, yet it has been shown in experimental rodent models of IBD, that their performance varies with the individual organism given. Thus it appears that strain-specific probiotics may be required not only for the species but perhaps even for the type of intestinal disease being treated. Thus probiotics may become a simple adjunct to conventional treatment of intestinal disease in dogs and cats as soon we can give the appropriate strain(s) at the right dose and at the right time. Until then, the empirical administration of live yoghurt is likely to be of little benefit.