

FELINE INFLAMMATORY BOWEL DISEASE: WHAT'S NEW?

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Inflammatory bowel disease (IBD) is thought to be the most common cause of chronic gastrointestinal signs in cats. IBD describes a stereotypic response of the gastrointestinal tract (GIT) to a variety of disease processes that result in the presence of increased numbers of inflammatory cells, usually lymphocytes and plasma cells, in the lamina propria that lies below the surface epithelium. IBD denotes a heterogeneous group of idiopathic, chronic, relapsing inflammatory disorders affecting the GIT that are immunologically-mediated. Terminology is confusing as a variety of terms, including IBD, have been used to describe patients with chronic intestinal signs where a specific diagnosis has not yet been reached including gastroenterocolitis, chronic intestinal inflammation or chronic inflammatory enteropathy (CIE). For the purposes of this presentation IBD will be defined as intestinal inflammation where the cause is unknown. However, this definition is problematic and perhaps IBD is better defined by chronic, non-resolving immune dysregulation that has become self-perpetuating irrespective of the initiating cause for example chronic inflammation that persists in some cats following apparent successful elimination of *Giardia*. Even at this level there is disagreement as immune cells are normal residents of the intestinal lamina propria so the diagnosis of IBD relies on a (usually subjective) increase in inflammatory cells leading to secondary changes such as villous blunting and fibrosis. It remains unclear whether the increased numbers of inflammatory cells are actively recruited to the lamina propria (inflammation) or represent a failure of lymphocyte death (apoptosis).

Immune dysregulation

The intestinal immune system has to recognise and tolerate non-harmful luminal bacteria, ingested foreign proteins and self-antigens as well as responding appropriately to potentially harmful and invasive organisms. Not surprisingly the regulation of such a complex interplay will fail from time to time creating an inflammatory and reactive environment affecting intestinal motility as well as the ability to digest and absorb nutrients leading to the characteristic signs of weight loss, vomiting diarrhoea and often polyphagia. Interestingly in cats vomiting is far more common than diarrhoea as a presenting sign in cats and around 10% of cats show weight loss as their only presenting clinical sign. Underlying this is the basic genetic make-up that may predispose an individual towards an inflammatory response resulting in certain dog and cat breeds being over-represented e.g. Maine Coon. Much current work is focused on the role of pattern recognition receptors in the aetiopathogenesis of IBD. Currently the most persuasive hypothesis explaining the aetiology of IBD is a complex interplay between environmental factors, such as the intestinal microbiota, and dysregulated host responses in a genetically-susceptible individual.

For cats with a history of chronic GIT disease some form of investigation is warranted as symptomatic and supportive treatment although often apparently resulting in an improvement in clinical signs rarely leads to long term improvement. In younger patients that are clinically well, routine haematology and biochemistry is rarely revealing and often all values lie within the reference interval. Given the list of causes of intestinal inflammation (Table 1) faecal analysis is likely to be the highest yield examination to rule in/out a primary cause. However, results need to be interpreted with care as, for example, the presence of *Campylobacter*, may reflect dysbiosis associated with IBD and/or previous treatment rather than being the cause of the clinical signs hence treatment may not lead to long term improvement.

If faecal analysis is unhelpful then specific blood tests can be of value, usually B₁₂, folate, pancreatic-specific lipase (fPLi) and trypsin-like immunoreactivity (TLI). Failure to identify and correct hypcobalaminaemia has been associated with a poorer response to therapy and delayed recovery in IBD cases; recently oral therapy has been shown to be effective at 250µg/day. In cats, elevated fPLi may also indicate pancreatitis as the primary entity but it is commonly associated with IBD together with cholangiohepatitis as part of the 'triaditis' complex.

Ultimately a clinical diagnosis of IBD is based on:

1. The presence of persistent or recurrent GI signs (NB in cats this may be only variable appetite and weight loss)
2. Inability to identify known enteropathogens or other causes of signs of gastrointestinal disease
3. Histopathologic confirmation of intestinal inflammation requiring biopsies to be acquired either via endoscopy or laparoscopy. In general inflammation increases distally along the small intestine so inclusion of ileal biopsies is recommended either surgically or retrograde via colonoscopy. The challenge in many feline cases is differentiating IBD from chronic alimentary lymphoma (Sabattini *et al* 2016).

Management options

The goal of management is to reduce the level of disease such that minor alteration in disease level remain subclinical. Assessment of true response to treatment is difficult as clinical signs will often wax and wane. This means that any treatment trial will need to be continued for at least twice the cycle time of the clinical signs to show that it is truly effective. The use of clinical activity indices in assessing disease activity in people and a similar system, the feline chronic enteropathy activity index (FCEAI) has been developed for use in cats but its true clinical utility in directing treatment remains unclear. Other markers have also been used such as acute phase protein (haptoglobin, α_1 -acid glycoprotein and serum amyloid A) have also been used to try and monitor response to therapy.

A suggested approach to a known/strongly suspected IBD case would be

1. Strict dietary therapy – diet and water only (no treats tit bits etc.) for 2-3 weeks
2. If no or partial response – metronidazole/tetracycline and diet for further 2-3 weeks
3. If no or partial response – immunosuppression and diet \pm metronidazole/tetracycline

Management options can be broadly grouped into

1. Shorter term symptomatic relief
 - a. Antacids, mucosal protectants, prokinetics, antiemetics
 - b. Probiotics – may also directly impact the underlying immune dysregulation (Rossi et al 2014)
 - c. Antibacterials – management of dysbiosis and immunoregulation
 - i. A variety of antibacterial agents have been suggested including metronidazole, doxycycline, tylosin and sulfasalazine
2. Immunosuppressive agents
 - a. Prednisolone – remains the initial treatment of first choice
 - b. Other agents e.g. ciclosporin, mycophenylate mofetil, chlorambucil, budesonide
3. Diet

Immunosuppressive agents

For patients that do not seem to tolerate traditional glucocorticoid therapy, budesonide a glucocorticoid with a strong first pass metabolism that primarily works locally in the GIT can be considered and has been shown to be as effective as prednisolone (Dye et al 2013). The dose rate for budesonide is poorly established with suggested initial dose of up to 1mg q8hr in cats; the author tends to use 1.5mg PO q24hr in cats as an initial dose rate. In chronic cases 0.75-1mg PO q48-72hrs can be effective. Budesonide is relatively expensive and is only available in 3mg capsules containing enteric coated beads meaning recompounding is necessary and accurate dosing problematic. There are no published studies comparing the efficacy of different adjunctive immunosuppressive therapies with limited studies on individual agents. Routinely the author would use ciclosporin as a first choice as it holds a veterinary license in both cats and dogs and there is published evidence of its efficacy in dogs (Allenspach et al 2006). Chlorambucil can also be highly effective in cats with some cats showing a dramatic response where glucocorticoids have failed. A variety of dosage regimes have been suggested, the author tends to use either 4mg PO /cat for 3 (<4kg) or 4 (>4kg) consecutive days every 3 weeks or 2mg PO/cat q48hr (>4kg) q72hr (<4kg). as a starting dose. Fanconi-like syndrome has been reported in cats on chlorambucil therapy (Reinert & Feldman 2015). Mycophenylate mofetil is being more widely used as an immunosuppressive agent but its safety and efficacy in cats is poorly documented.

Dietary therapy

The benefits of dietary therapy alone (or in combined with drug therapy) in the clinical management of feline IBD is documented. Studies involving both controlled and elimination diets alone or in combination with drug therapy have suggested response in about three quarters of cats (105 individuals). The optimal diet in terms of one novel protein source versus another or the advantage in feeding an intact protein elimination diet versus a hydrolyzed protein elimination diet has not been demonstrated to date. Modifying the dietary n3:n6 fatty-acid ratio may also modulate inflammatory responses by reducing production of pro-inflammatory metabolites. A recent study showed IBD cats have low serum concentrations of 25-hydroxycholecalciferol (Lalor *et al* 2014); the clinical significance of this is unknown

Conclusion

IBD in cats remains a challenging condition to characterise as our understanding of its aetiology remains incomplete in the absence of an identified cause. Management of IBD requires an individualised, usually multimodal plan with the likelihood of significant long term client support being necessary. This does not mean that all patients will be on medication, indeed for many careful dietary management is all that is needed in the

long term. In a significant number of patients, immune regulation and tolerance seems to re-establish and their diet can be gradually returned to a routine maintenance diet.

Table 1 – Causes of intestinal inflammation

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| <i>Intestinal parasitism</i> | Round, whip and hookworms Heavy infestation with tapeworms Giardia Isospora Cryptosporidia Tritrichomonas foetus |
| <i>Infectious agents</i> | Rotavirus Coronavirus <i>Campylobacter jejuni</i> Salmonella Clostridia Enteropathogenic, toxigenic or invasive <i>E.coli</i> <i>Mycobacteria</i> spp. Rare/non UK – <i>Histoplasma</i> spp., Protothecosis (algal), Pythiosis (fungal) Antibacterial-responsive enteropathy |
| <i>Endocrine disease</i> | Hypoadrenocorticism Hyperthyroidism |
| <i>Diet</i> | Intolerance e.g. lactulose Hypersensitivity/allergy |
| <i>Pancreas</i> | Pancreatitis Exocrine pancreatic insufficiency |
| <i>Neoplasia</i> | Lymphoma |
| <i>Idiopathic</i> | Lymphoplasmacytic gastroenterocolitis Eosinophilic gastroenterocolitis Granulomatous gastroenterocolitis |
| <i>Drugs and toxins</i> | |
| <i>End stage chronic kidney disease</i> | |

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