

Investigation and Management of Chronic Diarrhoea

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General Principles

Chronic diarrhoea is defined as an increase in the liquid content, frequency or volume of faeces that has occurred for greater than 3 weeks.

Differential Diagnoses for Chronic Diarrhoea

The list below is not exhaustive but reflects the more commonly diagnosed conditions.

Primary Gastrointestinal Disease

Infectious causes

Bacterial – Campylobacter, Salmonella

Parasitic – Cryptosporidium, Giardia

Viral – unlikely to cause chronic diarrhoea

Fungal – Histoplasmosis (USA)

Chronic enteropathy

Food responsive

Antibiotic responsive (metronidazole, tylosin, oxytetracycline)

‘True’ Inflammatory Bowel Disease [IBD] (i.e. a chronic enteropathy that is not food or antibiotic responsive and immunosuppression is required)

Neoplasia – most like diffuse (lymphoma)

Chronic intussusception

Irritable Bowel Syndrome [IBS]? This is considered a multifactorial functional disorder of the gastrointestinal tract in humans characterised by intermittent abdominal pain with constipation and/or diarrhoea. There is much debate about the existence of this condition in dogs and publications are limited.

Non Gastrointestinal Disease

Pancreatic disease – exocrine pancreatic insufficiency, pancreatitis, neoplasia

Hepatic disease

Renal failure

Endocrine disease – hypoadrenocorticism, hypothyroidism (uncommon), (hyperthyroidism in cats).

Cardiac disease – congestive heart failure

Neoplasia

Systemic infection

Drugs/toxins

When investigating the cause of diarrhoea, a logical approach, a little patience and careful management of client expectations are essential.

Investigation of Chronic Diarrhoea

Back to Basics

1. Signalment. Various diseases are more common in certain age groups or breeds. For example, if a young Boxer or French bulldog presented to you with large intestinal diarrhoea, you need to consider the possibility of granulomatous colitis. Clinical suspicion might alter your diagnostic pathway.
2. Classify the type of diarrhoea. It is important to differentiate whether the diarrhoea is large intestinal, small intestinal or both. The type of diarrhoea might be suggestive of different differentials and might change your diagnostic pathway.
3. Take a FULL history. Pertinent questions include whether the patient has been abroad, whether it is regularly wormed and what product is used. Quite often, cases of diarrhoea have already been managed in a number of different ways prior to presentation to you. What, if any, were the responses to the treatments used previously? Are there any other systemic signs, for example vomiting, weight loss or skin changes?

4. Perform a FULL physical examination including rectal examination. Take note of any effusions, presence of dehydration etc. Does the patient require urgent management prior to embarking on further diagnostics? A rectal examination is always indicated in cases of diarrhoea to check for local lymphadenopathy, presence of masses in the colon/rectum.

General Investigations

Haematology

Whilst unlikely to provide you with a specific diagnosis, a haematology is a vital starting point to establish how stable the patient is and perhaps offer some clues as to possible differentials.

- Anaemia/polycythaemia
 - The presence of anaemia might be suggestive of a chronic gastrointestinal bleed. Is there any evidence of iron deficiency such as microcytosis? If the PCV is increased, is the patient dehydrated, or could the patient have essential polycythaemia?
- Neutrophilia
 - Neutrophilia is a non-specific finding common to many inflammatory diseases and is common in patients with chronic diarrhoea. If there is absence of a stress leukogram, then this might raise concern for presence of (atypical) hypoadrenocorticism.
- Eosinophilia
 - Eosinophilia should not be ignored if persistent. Differentials include hypoadrenocorticism, neoplasia, hypersensitivity, parasitic disease.
- Lymphocytosis
 - Again a non-specific finding, but might be suggestive of atypical hypoadrenocorticism or neoplasia (lymphoma / leukaemia).

Biochemistry

A full biochemical profile is important to rule out many systemic diseases such as renal and liver disease. It is worth noting that liver enzymes are often mildly increased with primary gastrointestinal disease and do not always indicate underlying hepatic disease.

- Proteins
 - Look at both the albumin and the globulin levels. In protein losing enteropathy, it is most common for both to be low (panhypoproteinaemia), though sometimes the globulin might be normal or increased due to inflammatory or neoplastic disease. Hypoalbuminaemia might also indicate protein losing nephropathy, hepatic failure or general inflammatory disease (albumin is an acute phase protein).
- Electrolytes
 - Typically, electrolyte derangements occur as a consequence of diarrhoea, rather than the cause. If the sodium: potassium ratio is low, this might be indicative of hypoadrenocorticism. Atypical hypoadrenocorticism is also being recognised more frequently now so a normal sodium: potassium ratio does not exclude this differential.
- Renal parameters. Mild azotaemia might be a consequence of dehydration due to diarrhoea and a urine sample is always warranted to check the specific gravity. In cases of severe renal disease or nephrotic syndrome, diarrhoea might occur as a result of azotaemia.
- Liver parameters. Liver enzymes are commonly mildly increased in gastrointestinal disease due to ascending inflammation into the biliary tree. Hepatic failure and cholestasis can also lead to diarrhoea.
- Calcium – often low in gastrointestinal disease. This is commonly attributed to hypoalbuminaemia. Ionised calcium is also found to be low in some cases, which has been primarily attributed to hypovitaminosis D. Hypovitaminosis D has been associated with a poor prognosis in dogs with chronic enteropathy (Titmarsh et al 2015).
- Cholesterol – often low in gastrointestinal disease

Urinalysis

- USG and UPCr are important parameters to establish, especially in azotaemic patients or patients with hypoalbuminaemia.
- Examine the possibility of a urinary tract infection

Faecal analysis

- The benefits of performing a faecal analysis can be debated at length! This is because interpretation is challenging. Some infectious agents are shed intermittently and therefore not present in all samples; on the other hand many animals are asymptomatic carriers of organisms that have the potential to cause diarrhoea.
- For example *Giardia* and *Cryptosporidium*, *Campylobacter spp.* and *Salmonella spp.* can be detected in the faeces of healthy animals. These infections can also be implicated in the cause of chronic diarrhoea in dogs.
- If such an infection is identified in a diarrhoeic patient, then it might be worth treating, though often there is another cause for the diarrhoea and the infection is an incidental finding.
- A five day course of fenbendazole should also be performed in patients with negative faecal analysis to exclude parasitic disease from the list of differentials with a reasonable degree of certainty. Most cases of *Giardia* can be managed with fenbendazole alone.

More Specific Investigations

Cobalamin / vitamin B12

Cobalamin is absorbed in the distal ileum and requires intrinsic factor for absorption. Intrinsic factor is predominantly released from the exocrine pancreas, and therefore is lacking in patients with exocrine pancreatic insufficiency (EPI). Cobalamin is present in many foods and therefore dietary insufficiency is relatively uncommon, though this can occasionally occur in patients fed a vegetarian or vegan diet.

The most common causes of hypocobalaminaemia include malabsorptive disease of the distal small intestine and EPI. A congenital lack of cobalamin has been reported in several breeds, most commonly Border Collies. This is due to a mutation affecting the cobalamin receptor in the distal ileum. Chronic malnutrition can lead to hypocobalaminaemia; the ileal cells become damaged due to inadequate nutrition and cellular changes lead to inability to absorb cobalamin. Ileal resection can lead to cobalamin malabsorption. Animals with hypocobalaminaemia require supplementation which has traditionally been administered parenterally. There have been some recent publications documenting success of oral supplementation in patients with chronic enteropathies and hypocobalaminaemia (Toresson et al. 2016), though this has yet to be documented in other causes of hypocobalaminaemia.

Folate

Folate is absorbed in the proximal small intestine (duodenum) and therefore a low folate level can occur in malabsorptive disease of the proximal small intestine. This occurs seemingly less frequently compared to hypocobalaminaemia and the benefits of supplementing folate are poorly documented. Historically, a high folate level was considered suggestive of small intestinal bacterial overgrowth 'SIBO'. This condition is poorly characterised, the terminology is rarely used nowadays and the value of a high folate level is questionable.

Trypsin-Like Immunoreactivity (TLI)

A TLI should always be performed in cases of chronic diarrhoea. It is a sensitive and specific test for EPI.

ACTH stimulation test

A serum basal cortisol value greater than 55nmol/l rules out hypoadrenocorticism with a reasonable degree of certainty. Values <55nmol/l are not helpful in assessing adrenal function, and an ACTH stimulation test is required (Lennon et al. 2007). An ACTH stimulation test should be performed to exclude hypoadrenocorticism early in your diagnostic pathway.

Canine Pancreatic Lipase / DGGR lipase

Serum Spec PL (cPLI) and DGGR lipase are considered to be the most sensitive and specific biochemical assays for diagnosis of acute and chronic pancreatitis in dogs. In some dogs with chronic diarrhoea, increased pancreatic lipase values are due to chronic pancreatitis alone, reflecting the primary cause for diarrhoea. In a number of dogs with chronic diarrhoea however, increased cPLI concentration is identified together with chronic enteropathy, and the cause for this is unknown. Assuming the increased cPLI value reflects chronic pancreatic inflammation, this might have occurred as part of a generalised primary condition affecting both the intestine and pancreas independently. Alternatively, inflammation could have originated in the gastrointestinal tract and extended towards the pancreas through the pancreatic duct causing secondary pancreatitis. The significance of the pancreatic inflammation and its contribution to the diarrhoea is difficult to establish. One study demonstrated that dogs diagnosed with IBD that

have a concurrent increase in cPLI are less likely to respond favourably to corticosteroids compared with those with a normal cPLI, and therefore ultimately have a worse prognosis (Kathrani et al. 2009).

Where Next?

At this point you need to take a step back and think about whether your patient is clinically well or in need of urgent management/investigations. In patients that are clinically well, therapeutic trials are justified. In patients that are generally unwell, hypoproteinaemic etc., therapeutic trials are not appropriate (other than immediate stabilisation such as fluid support), and further investigations should be pursued.

If your patient is clinically well....

A true food trial with a single diet fed exclusively is a vital part of the investigation and management of dogs with chronic diarrhoea. In the majority of cases, it is not appropriate to perform invasive investigations before excluding a food responsive enteropathy.

More than 50% of dogs that have a chronic enteropathy will respond to dietary management alone (Allenspach 2007), and they tend to respond within the first 10-14 days. A hydrolysed diet would make a sensible starting point for patients with large or small intestinal disease. This is because the protein source is hydrolysed so is not as antigenic compared to a larger protein. Many clinicians recommend a highly digestible novel protein diet as an alternative to a hydrolysed diet, which has also been shown to have good outcomes (Allenspach 2007). The choice of initial diet is often based around clinician preference, but a hydrolysed protein diet or a true novel protein should always be attempted, and must be fed absolutely exclusively.

A high fibre diet could be considered to manage large intestinal diarrhoea, though a hypoallergenic diet would be the first selection.

If a food trial fails and your patient is still systemically well, then you can consider an antibiotic trial. If your patient is tolerating the diet trial, then it is advised to continue on the same diet since there might be a partial response, which could be improved further with the addition of antibiotics. Metronidazole, Tylosin, oxytetracycline are antibiotics that have been shown to demonstrate efficacy in certain dogs with diarrhoea. Availability and cost often influence the antibiotic that is selected. Oxytetracycline is perhaps more likely to cause multi-resistance and Tylosin has been shown to resolve diarrhoea in patients that have failed other antibiotics (Tylosin responsive diarrhoea).

Other possible treatments

Sulfasalazine has been used for management of large intestinal diarrhoea in dogs. There is limited efficacy for the use of this drug, though historically has been used relatively commonly with anecdotal success. The evidence is weak and side effects are common so this is not commonly advised.

There is increasing evidence for faecal microbiota transplants in both humans and dogs for management of chronic enteropathies and other conditions. At present the evidence is anecdotal in dogs, but this is a promising treatment tool.

Probiotics are commonly prescribed in dogs with diarrhoea, though their efficacy is widely debated. A detailed discussion about probiotics is beyond the scope of this lecture, but there was a recent publication (Rossi G. et al., 2014) which documented a protective effect of VSL#3 (a multi-strain probiotic product) in dogs with IBD.

Imaging and Collection of Biopsies?

If your patient still has diarrhoea despite treatment trials or if your patient is systemically unwell prior to treatment initiation, *further investigations* are warranted:

Imaging

Abdominal radiography can be useful especially if there is evidence for a chronic foreign body, though ultrasound is typically more useful for gastrointestinal disease. The intestines might appear completely normal, yet they can be very abnormal histologically. It is important to assess for presence of fluid and to examine all abdominal organs, for evidence of neoplasia for example.

Collection of Biopsies

Collection of gastrointestinal biopsies is only indicated in patients where non-gastrointestinal causes of diarrhoea have been excluded and when clinical signs are continuing despite adequate anthelmintic, dietary and antibiotic trials. A patient that is unwell with their disease might warrant an endoscopy sooner than systemically well patients.

It is ideal to collect endoscopic biopsies rather than full thickness biopsies via laparotomy in the majority of cases. There are a few situations in which laparotomy might be indicated:

1. If there is a focal lesion which might be inaccessible via endoscopy
2. If the disease (ultrasonographically) is affecting the outer layers (serosa and muscularis layers) rather than mucosa and submucosa.
3. If biopsies are required from multiple locations (e.g. liver, pancreas)
4. In cases where you are suspicious of lymphangiectasia, there is an argument that full thickness biopsies are warranted since endoscopic biopsies are not always fully representative in such cases. Most of these cases are hypoproteinaemic, potentially increasing the risk of full thickness biopsies, so the decision for laparotomy is questionable.

When collecting endoscopic biopsies, it is important to collect 10-15 samples from each relevant location in case only marginal samples are achieved (Washabau et al. 2010). In dogs demonstrating signs of small intestinal disease, it is important to attempt to access the ileum for analysis, not just the duodenum (Casamian-Sorrosal 2010 and Procoli et al., 2013).

Interpretation of Biopsy Results

The main benefit of biopsies is to differentiate lymphoma, inflammatory disease and presence of lymphangiectasia. Detailed discussion of lymphoma and lymphangiectasia are beyond the scope of this presentation and the main focus is on presence of inflammatory disease.

Histopathology might be normal, without evidence of inflammatory or structural disease that can be seen on light microscopy. This could be due to a number of reasons:

- Antibiotic responsive diarrhoea
- Food intolerance
- Brush border membrane disease
- Disease identifiable at the electron microscopic level only
- Motility disorder
- Patchy disease
- EPI

Hopefully a number of these conditions will have been excluded earlier in the investigative pathway.

Management of IBD

Histopathology commonly identifies inflammatory disease of various types and severity; the different types of inflammation likely represent different aetiologies and pathological processes. Further research is required to identify more specific treatment recommendations based on histopathological findings.

At this point in the management of a case of chronic diarrhoea, it is important to review whether the patient has received adequate and appropriate anthelmintic, dietary and antibiotic trials. If these have been performed and the clinical signs warrant treatment, the next step is to initiate treatment with immunosuppressive drugs. I would recommend starting prednisolone at an immunosuppressive dose (2mg/kg/day).

If the patient fails management with prednisolone alone, a number of different second immunosuppressive drugs are available. Ciclosporin has been demonstrated to have effect in steroid resistant dogs with chronic enteropathy (Allenspach 2006), and chlorambucil has been shown to be more effective compared to azathioprine when used in conjunction with prednisolone (Dandrieux 2013), though this was a retrospective study and prospective controlled studies are warranted.

Prognosis

The outcome for dogs with chronic diarrhoea is variable and depends on the underlying cause. If chronic diarrhoea is a consequence of a food responsive or antibiotic response enteropathy, the prognosis is generally excellent. In patients with alimentary lymphoma, the prognosis is generally poor (not all cases). IBD and lymphangiectasia have variable prognoses, depending on response to treatment.

Some patients with IBD will respond favourably to management; immunosuppressive treatment can sometimes be weaned and eventually discontinued. These patients might require long term dietary management or intermittent treatment with appropriate antibiotics and/or immunosuppression. A small proportion of dogs might not require any ongoing specific management, though this is uncommon.

A number of patients with IBD will fail treatment and ultimately require euthanasia due to an unacceptable quality of life. Negative prognostic indicators include presence of hypoalbuminaemia (especially when there are associated clinical signs), hypcobalaminaemia and increased Spec PL. The histological score has been variably associated with outcome, though is not currently considered a prognostic indicator.

There is a vast amount of current research into the pathogenesis of chronic enteropathies in dogs. The investigative and management strategies are likely to evolve in the future; novel treatment options are being explored which will hopefully improve the quality of life and survival of these patients.

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