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CHRONIC SMALL BOWEL DIARRHEA: A DIAGNOSTIC APPROACH
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Introduction
Diarrhea which has lasted 3 weeks or more is considered chronic. The approach to chronic diarrhea is based on the origin of diarrhea - large bowel or small bowel, and the presence of other specific or localising clinical findings. Differentiation is important as the diagnostic and therapeutic approaches to small and large bowel diarrhea are different. Differentiation is made on the basis of information furnished by the owner in response to questions about faecal characteristics, volume and frequency and related signs such as vomiting, weight loss, tenesmus and dyschezia.

Small bowel diarrhea is a consequence of diseases that affect the small intestine or related structures such as the exocrine pancreas. Some diseases are associated with signs of large and small bowel diarrhea e.g. infectious agents such as *Giardia*, *Trichomonas foetus*, FeLV/FIV, *Salmonella*, *Campylobacter*, histoplasmosis, phycomycoses, algae may cause bloody mucoid loose stool and weight loss.

The approach to patients with chronic small bowel diarrhea who are stable and have no specific localizing clinical findings is usually to:

- Rule out endoparasites and pathogenic bacteria: fecal analysis
- Screen for systemic disease: CBC, profile, UA ± T4, FeLV/FIV, ACTH stim
- Rule out exocrine pancreatic insufficiency: TLI
- Rule out partial obstruction: palpation, radiographs, ultrasound
- Evaluate intestinal structure and function: biopsy (endoscopic / surgical); cobalamin/folate

Signalment and history
Infectious and parasitic diseases are common in young animals, whereas neoplasia and metabolic disorders are more common in middle aged to older animals. Certain conditions are more common in certain breeds e.g. protein-losing enteropathies in the Lundehund and soft coated wheaten terrier.

Small bowel diarrhea is generally associated with weight loss and large stool volume. Failure to thrive, changes in appetite, borborygmi, flatus, abdominal discomfort, ascites and oedema are also more common with small than large bowel diarrhoea.

Laboratory evaluation of chronic small bowel diarrhoea

**Faecal analysis**
*Giardia* (ELISA or IFA), *Coccidia* (routine fecal), *Trichomonas foetus* in cats (‘In pouch’ or PCR), other endoparasites, Fecal analysis for clostridial endospores and endotoxin is fraught with difficulty in interpretation. Culture for *Campylobacter* if bloody mucoid diarrhea. Culture for *Salmonella* in animals with bloody stools, or fever, or chronic undefined diarrhea. Fecal culture cannot be used to diagnose small intestinal bacterial overgrowth. Fecal blood can be detected using appropriate detection systems, but the patient must be on a meat free diet for 72hrs prior to interpretation and drugs such as cimetidine may cause false positive test results.

**Hematology**
Anemia (microcytosis) (MCV < 63fl) in dog: decreased red cell haemoglobin and thrombocytosis are common in dogs with iron deficiency secondary to GI blood loss from intestinal parasites or tumors (Ddx portosystemic vascular anomalies or fibrosing liver disease in young dogs with signs of gastrointestinal disease). Anemia (macrocytosis) (MCV > 53fl) in cat: regenerative anemia, hyperthyroidism, FeLV or cbl/ folate deficiency. Eosinophilia: intestinal parasitism, mast cell tumors, hypoadrenocorticism, eosinophilic enteritis or hypereosinophilic syndrome. Neutrophilia ± a left shift may be encountered in inflammatory or infectious conditions. Lymphopaenia is commonly associated with stress, protein losing enteropathies (Table 1) and immunodeficiency. Lymphocytosis or lack of a stress leukogram in a sick patient is suggestive of hypoadrenocorticism.

**Serum biochemistry**
R/O non-intestinal diseases which cause gastrointestinal signs i.e. kidney disease, renal disease, hypoadrenocorticism. Detect metabolic consequences e.g. hypokalemia, hyponatremia. Hyperkalaemia combined with hyponatremia suggests that an ACTH stimulation test should be performed to detect hypoadrenocorticism or pseudo-hypoadrenocorticism associated with *Salmonella* / whip worms / GI ulceration. Mild to moderate increases in liver enzymes such as ALT (up to 500 IU/l) are common in cats with hyperthyroidism and cats and dogs with intestinal disease. Hypocholesterolemia: dogs with protein losing enteropathy, EPI and other chronic enteropathies. Plasma bile acids and ammonia: liver dysfunction or shunting in patients with GI signs. Hypoglycaemia with signs of gastrointestinal disease should arouse the suspicion of sepsis, liver disease,
hypoadrenocorticism or pancreatic tumor. Hypoalbuminemia and/or hypoglobulinemia: R/O protein losing enteropathies. Hypoalbuminemia with normal or increased globulin concentration has to be distinguished from protein losing nephropathy and liver disease. Chronic diarrhea associated with hypoalbuminaemia usually requires intestinal biopsy to define the cause. Non-intestinal causes of protein losing enteropathy such as congestive heart disease, caval obstruction or portal hypertension should also be considered. When globulin concentrations are normal or elevated, renal and hepatic causes should also be pursued.

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Example</th>
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<tbody>
<tr>
<td>Lymphangiectasia</td>
<td>Primary lymphatic disorder Venous hypertension e.g. right heart failure, hepatic cirrhosis</td>
</tr>
<tr>
<td>Infectious</td>
<td>Parvovirus, Salmonella, Histoplasmosis</td>
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<tr>
<td>Structural</td>
<td>Intussusception</td>
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<tr>
<td>Neoplasia</td>
<td>Lymphosarcoma</td>
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<tr>
<td>Inflammation</td>
<td>Lymphoplasmacytic, eosinophilic, granulomatous</td>
</tr>
<tr>
<td>Endoparasites</td>
<td>Giardia, Ancylostoma</td>
</tr>
<tr>
<td>GI haemorrhage</td>
<td>HGE, neoplasia, ulceration</td>
</tr>
</tbody>
</table>

Table 1: Protein losing enteropathies

Urinalysis
Part of a baseline evaluation to detect or rule out urogenital disorders in patients with signs of intestinal disease. Urate crystalluria may prompt the investigation of hepatic dysfunction as a cause of clinical signs. Urine prot : creatinine for determining if the kidney is involved in the development of hypoalbuminaemia in patients with intestinal signs.

Serology and hormone assays
T₄, FIV and FeLV. ACTH stimulation to confirm hypoadrenocorticism or pseudohypoadrenocorticism where this is suspected from serum biochemistry. An ACTH stimulation test may also be used to screen for atypical hypoadrenocorticism (glucocorticoid insufficiency) in patients with unexplained chronic diarrhea, eosinophilia, inappropriate lymphocytosis. Serology for Histoplasma, pythiosis.

Tests of pancreatic function
Pancreatic function tests are most commonly employed in dogs with chronic diarrhea who are bright and alert with few signs other than chronic diarrhea, occasional vomiting, weight loss or polyphagia and normal to mildly abnormal clinicopathologic test results.

Trypsin-like immunoreactivity (TLI) is a sensitive and specific test for detecting exocrine pancreatic insufficiency (TLI < 2.5 μg/l) in the dog and is performed in dogs with chronic small bowel diarrhea. The TLI assay is species specific and a cat specific assay has recently been developed. Exocrine pancreatic insufficiency is uncommon in cats and is usually associated with chronic diarrhea and polyphagia (feline TLI ≤ 8 μg/l).

Diagnostic imaging evaluation of chronic small bowel diarrhoea

Radiography
Survey abdominal radiographs are low yield in patients with chronic diarrhea. Contrast radiography is useful in evaluating partial obstruction and transit time/ gut length.

Ultrasonography
Ultrasound is useful for detecting intestinal lesions such as intussusceptions, masses and foreign bodies, and for assessing intestinal wall thickness. The results of radiography and ultrasound provide a rational basis for selecting endoscopic biopsy (± duodenal juice analysis) or a laparotomy. Normal or diffusely thickened intestines can initially be evaluated endoscopically while focal lesions usually require guided aspiration or laparotomy.

Tests of intestinal function
When a clinical problem cannot be adequately defined or localised to the small intestine a variety of tests can be used to assess small intestinal function. Intestinal function tests have the potential benefit of allowing an overall assessment of SI function, rather than the small snapshot provided by a biopsy. They should always be critically evaluated in the context of the whole patient.

Cobalamin and folate
The measurement of circulating concentrations of cobalamin and folate may give an indication of the site and cause of intestinal dysfunction. Plasma concentrations of cobalamin and folate are labile and reflect the balance between dietary intake, bacterial utilisation and production, and intestinal absorption and body losses. The interpretation of circulating cobalamin and folate concentrations with regard to small intestinal disease is only valid if exocrine pancreatic insufficiency, dietary supplementation, parenteral administration have been excluded and attention is paid to dietary vitamin content.

Dogs
The finding of a low folate or low cobalamin concentration is useful in supporting the presence of an intestinal problem but is not usually helpful in determining the specific cause. Where low cobalamin is detected and EPI, intestinal obstruction and presumed idiopathic “SIBO”
have been excluded, localisation of the problem to the ileum can be inferred.

Cats
Subnormal concentrations of cobalamin are common in cats with EPI, intestinal (IBD, lymphoma), pancreatic or hepatic disease: The simultaneous presence of disease in the intestines, pancreas or hepatobiliary system in many cats made it difficult to determine the precise cause of subnormal cobalamin concentrations. The circulating half-life of parenteral cyanocobalamin was shorter in two cats with IBD (5 days) than in four healthy cats (12.75 days).
The rapid depletion of circulating cobalamin in cats indicates that cats may be highly susceptible to cobalamin deficiency.

Other function tests
Measurement of fecal alpha-1-antiprotease concentrations is useful for confirming the GIT as the site of protein loss, especially in dogs with hypoproteinemia but minimal diarrhea, and monitoring response to therapy. Breath hydrogen, intestinal permeability testing and measurement of deconjugated bile acids have yet to be shown to be useful in clinical practice.

Intestinal biopsy
Biopsy of the intestine is frequently required to achieve a diagnosis in patients with chronic diarrhea due to malabsorption. In diffuse intestinal diseases and in animals with hypoproteinaemia, endoscopy provides a minimally invasive low risk way of obtaining a biopsy. Endoscopic biopsies are restricted to the mucosa and are small, difficult to process and to orientate, and can be obtained only from the proximal duodenum and occasionally the distal ileum. Thus, surgical biopsies are necessary in patients with focal intestinal lesions and in those whom endoscopic biopsy has not yielded a result. Surgical biopsies should be taken from multiple sites along the small intestine even if the intestine looks grossly normal. A small dermatologic punch aids the surgeon in obtaining full thickness biopsies and biopsy sites are sutured in an appropriate fashion. Other abdominal organs, such as the liver and pancreas, can also be biopsied

The information which can be obtained from intestinal biopsies depends on the expertise of the pathologist. Minimum evaluation should include routine microscopic examination of H&E stained sections. The pathologist should be able to give an indication of villus height and morphology, ratio of crypt to villus and the type and degree of cellular infiltrate and intraepithelial lymphocyte count. Recent studies suggest that changes in mucosal architecture are more significant than subjective alterations in cellularity. Staining for different lymphocyte sub-types, assessment of marker enzymes, electron-microscopy and mucosal enzymology are restricted to specialist centers, but may be useful in sub classifying intestinal disorders and distinguishing inflammation from neoplasia. Specialized detection methods for infectious agents can also be applied e.g. fluorescence in situ microscopy, PCR.