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Problem Orientated Medicine for Advanced Practitioners

Mini Series

Session 3: Gastrointestinal Disease – Vomiting (When It Is and When It's Not!) and Diarrhoea (How to Stem the Flow!)

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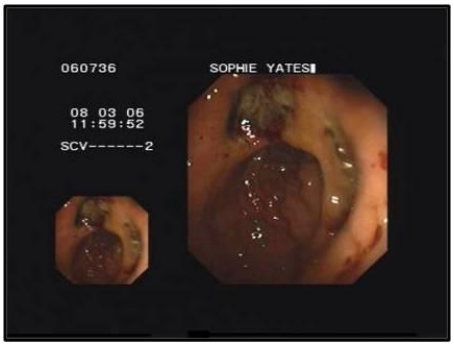


Oesophageal Disease

The Oesophagus forms the connection between oropharynx and stomach. Its main function is to propel food from one to the other. The Oesophagus is divided into the cervical, thoracic and abdominal oesophagus. It begins at the upper oesophageal sphincter (comprised of cricopharangeus and thyropharangeus musles). The cervical oesophagus lies dorsally to the left of the trachea, the thoracic oesophagus also lies dorsal to the trachea but crosses at the carina to lie on the right. The oesophagus passes in the midline between the caudal lung lobes and the short abdominal portion lies between the diaphragm and stomach.

Oesophagus has several layers , adventitia, muscularis, submucosa and mucosa. In the dog the muscular layer is composed of two oblique layers of striated muscle. Approx 10cm proximal to the cardia the muscle fibre orientation changes, the inner layer becoming transverse and the outer layer longitudinal. The cardia is composed of outer striated muscle and inner circular smooth muscle. In the cat the muscular layer cranial to the case of the heart is composed of striated muscle and caudal smooth muscle. The oesophageal gastric sphincter is composed of smooth muscle alone.

Causes of Oesophageal Disease

Physiology

Swallowing is a coordinated controlled series of events.

1. Oral phase – food is prehended and formed into a bolus, it is then propelled to the base of the tongue, which stimulates a series of pharangeal contractions which move the bolus into the laryngopharynx, as other pharyngeal openings are closed. These events are initiated by activation of various sensory receptors in the layngopharynx, nerve fibres of which are located in the trigeminal, glossopharangeal and larangeal nerves.
2. The cricopharangeal and thyropharangeal muscles relax to allow passage of the bolus of food into the oesophagus, the sphincter closes promptly after passage and remains closed
3. The second or oesophageal phase of swallowing starts . a primary peristaltic wave/muscle contraction carries food into the stomach. This is stimulated as above, a secondary peristalitic wave stimulated by local oesophageal distension carries food into the stomach
4. The third phase of swallowing is relaxation of the acrdia allowing passage of food into the stomach. The gastroesophageal sphincter then contracts to prevent reflux.

Clinical history

Oesophageal disease with regurgitation can be difficult to distinguish from true vomiting unless a careful history is taken. Unfortunately many patients may appear in referral caseload that have been extensively investigated for vomiting that are truly regurgitating.

Regurgitation is a passive process, no abdominal effort or retching is involved. It is unlikely that bile will be observed. White or clear mucus may be observed associated with semi digested food.

Questions I ask

Regurgitation/vomiting

1. Can you describe what happens during the 'vomit'
2. What does it look like
3. Is there **yellow/brown** bile associated with it (clients will describe anything as bile)
4. What is in the 'vomit'
5. Does he look nauseous
6. Does he retch
7. How long after feeding – this can infact be very variable
8. Does water produce the same effect
9. Smart phone video?

	Regurgitation	Vomiting
Passive	x	
Bile associated		x
Nausea		x
Slime/mucus	x	
Cough/RT infection associated	X sometimes	

Problems identified in animals with oesophageal disease

Passive regurgitation

Associated respiratory infection due to aspiration

Weight loss

Other associated clinical signs

There may be associated vomiting in the case of oesophagitis which can be confusing, but should not stop investigation of regurgitation. Signs of endocrine disaease (eg hypothyroidism, hypoadrenocorticism). Muscle weakness – myasthenia, myositis, mypopathy, neuropathy. Recent GA (stricture due to regurgitation)

Investigating the oesophagus

Routine laboratory tests

Routine laboratory screening including a haematology and biochemistry profile, and urinalysis can aid in the identification of a number of common systemic diseases that may result in neuromuscular weakness and hence poor oesophageal function, egs derangement in electrolyes, alteration in CK. CK elevation may be vastly increased in inflammatory myopathies but normal in endocrine myopathies. Tyroid and adrenal status should be considered.

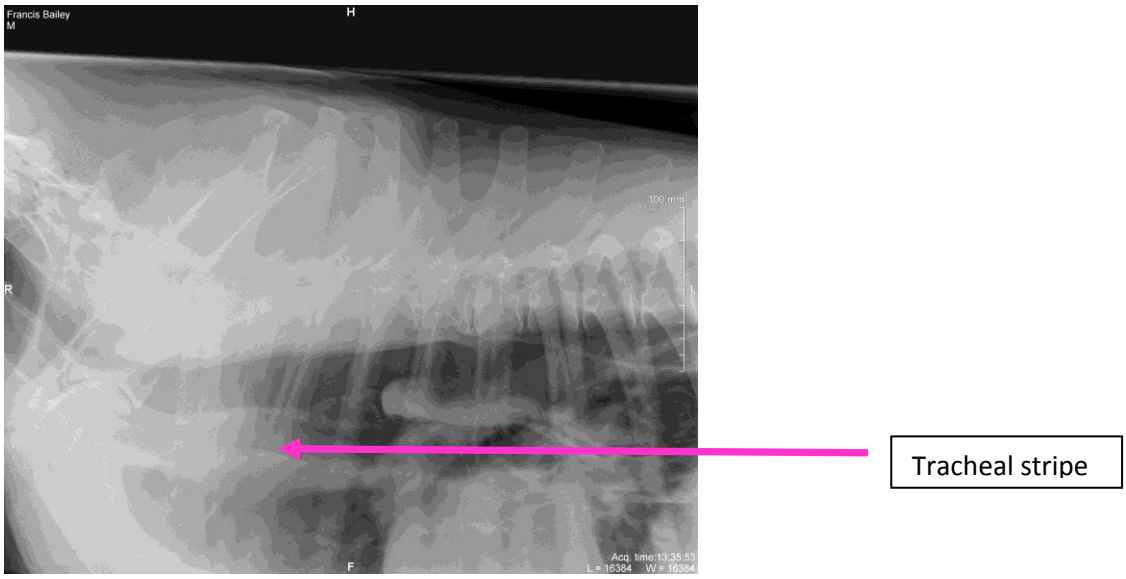
Miscellaneous Laboratory Screening

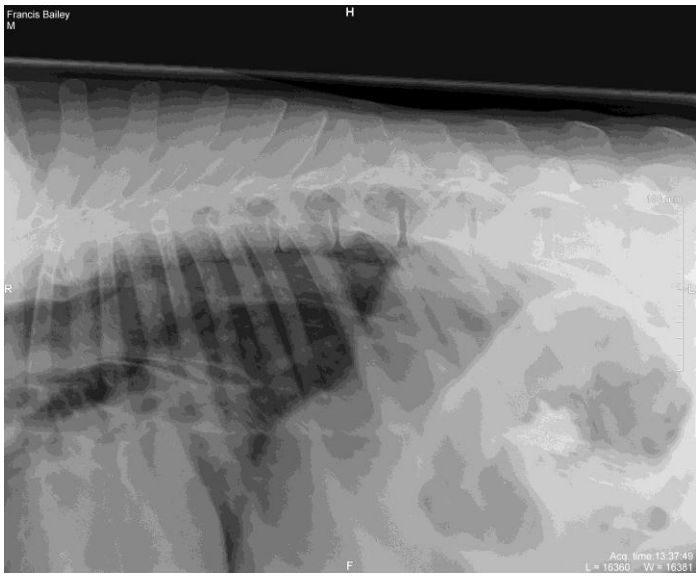
The acetylcholine receptor antibody test should be performed in all cases of acquired dysphagia. This test is not useful for congenital dysphagia as an immune basis is unlikely. The gold standard for the diagnosis of acquired Myaesthenia gravis remains the demonstration of serum AChR antibodies against native AChR by immunoprecipitation radioimmunoassay. This assay involves precipitation of serum IgG and IgM antibodies that bind to solubilized AChR complexed with a high-affinity peptide agonist, 125I-labeled α-bungarotoxin. The precipitate's γ-emission reflects the amount of AChR bound to immunoglobulin. The assay is specific, sensitive and documents an autoimmune response against muscle AChRs. A positive AChR antibody titer, is not predictive of the degree of weakness. Within an individual, AChR antibody levels correlate with the disease severity, but antibody levels between patients are highly variable and do not correlate well with severity. False negatives may occur and consideration of repetition of the test 4-6 weeks later especially if the titre is >).3 should be considered.

Imaging

Radiography

Conscious lateral chest and cervical radiographsradiograph will deterirmine many causes of oesophageal disease. Any sedation or GA can effect the amount of air in the oesophagus and give a false diagnosis of megaoeophagus. Although massive dilation of the oesophagus would be highly suggestive.

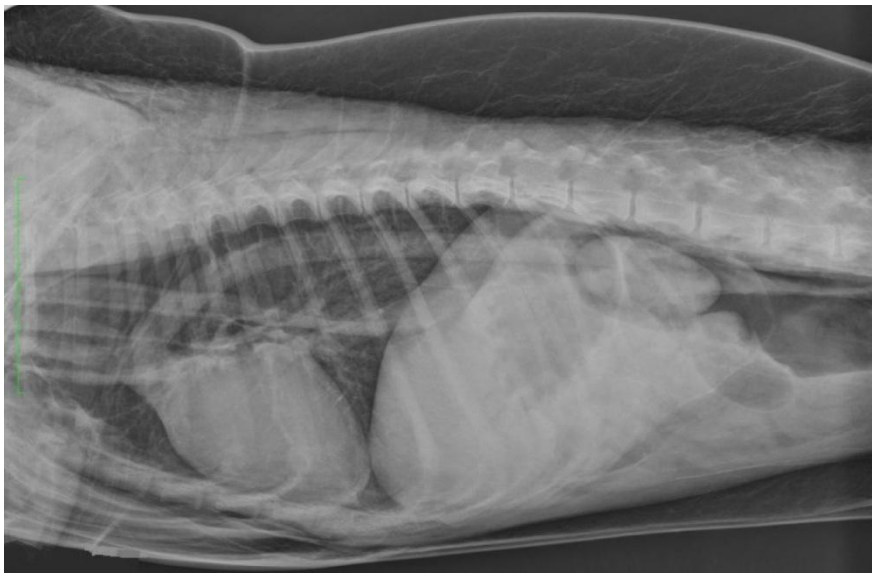




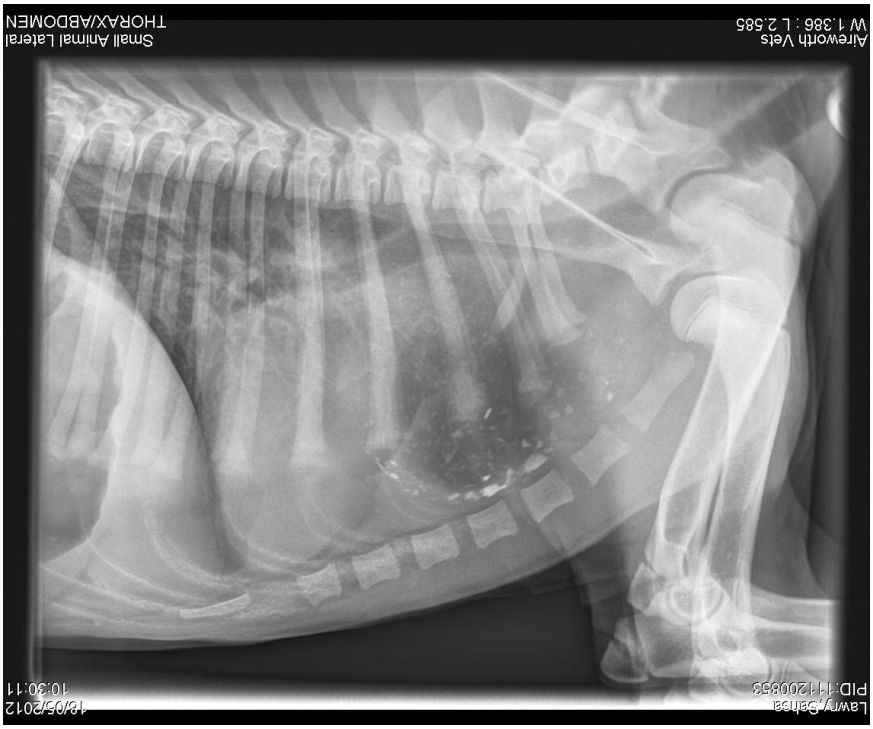
Radiographic signs of oesophageal disease

- Increased visibility
- Tracheal stripe sign – present due to superimposition of the oesophageal and tracheal walls and the longus colli muscle ventral to the 5 and 6 thoracic vertebrae
- Dilation with air fluid or food
- Pneumomediastinum, structures of the mediastinum clearly visible, structures not normally seen eg blood vessels
- Mediastinal space occupying lesion
- Ventral displacement of the trachea and heart
- Increased lucency of the thoracic region
- Ill defined pulmonary consolidation located ventrally
- Pleural fluid

Pneumomediastinum



Oesophageal diverticulum



Contrast investigation

I prefer conscious barium swallow under fluoroscopic imaging as there is less risk of aspiration.

Contrast videofluoroscopy involves real-time capture of images of the animal as it is swallowing liquid barium or barium-soaked kibble and is one of the most important procedures for assessing the functional integrity of the swallow reflex. Videofluoroscopy allows imaging of events that make up a swallow and measurement of the timing of these events in relation to one another. Additionally, the movement of certain anatomic structures is measured in relation to a fixed point to assess function further. One problem with videofluoroscopy is that animal positioning is not standardized in veterinary medicine. Alterations in body position (sternal versus lateral recumbency) do not appear to affect measurements of pharyngeal constriction ratio or the timing of swallowing in healthy dogs; however, cervical oesophageal transit is significantly delayed when dogs are imaged in lateral recumbency.

The fluoroscopic swallow study typically involves assessment of five swallows each of 5 to 10 ml of liquid barium (60% weight per volume) followed by five swallows of canned food mixed with barium and finally 5 swallows of kibble soaked in barium. The timing of the swallow can be determined easily when the swallow video is viewed frame by frame, with each frame representing 1/30th of a second .

The frame in which the epiglottis is observed to close over the larynx is considered as the starting point for all time measurements, and frames are counted until the observation of maximal contraction of the pharynx, opening of the proximal oesophageal sphincter (PES), and closing of the PES. The swallow is considered completed when the epiglottis is observed to reopen, which usually takes five or six frames in healthy dogs.

Normal and cases of abnormal swallow are presented

Electrodiagnostic Testing

Electrodiagnostic evaluation, including electromyography and measurement of motor and sensory nerve conduction velocities, does not provide a specific diagnosis in most cases but can supply important information as to the severity, distribution, and character of a myopathic or neuropathic disease process and assist in selecting the optimal anatomic site for biopsy. The health status of the animal must be taken into consideration because the lengthy procedure is performed under general anesthesia.

Oesophageal Manometry

Oesophageal manometry measures pressure within the oesophageal lumen and sphincters and provides an assessment of the neuromuscular activity that dictates function in health and disease. Manometric techniques have improved in a stepwise fashion from a single pressure channel to the development of high-resolution manometry with up to 36 pressure sensors. Advances in computer processing allow pressure data to be presented in real time as . This spatiotemporal plot provides objective measurements of the forces that drive food and fluid from the pharynx to the stomach. This diagnostic modality has been performed in fully awake dogs and provides a sensitive functional assessment of Oesophagus.

Oesophageal pH/Impedance Testing

Oesophageal pH/impedance testing is a useful diagnostic tool that is used to diagnose acid and non-acid reflux in animals with suspected gastroesophageal reflux, unexplained oesophagitis, or hiatal hernias. The technology of oesophageal pH testing has advanced in recent years, and there are several choices of oesophageal pH probes. The catheter-free Bravo pH Monitoring System from Medtronic is the first catheter free system used to measure oesophageal pH in human patients and dogs that are suspected of having gastrooesophageal reflux, it allows people and animals to maintain their regular diet and activities during pH testing. The Bravo system is an alternative to the traditional pH transnasal pH catheter that can cause patient discomfort, and is easily dislodged by dogs and cats. The main disadvantage of the Bravo system is that one can only record oesophageal pH, and the system does not utilize impedance technology that allows one to measure both acid and non-acid

reflux. Oesophageal pH testing has been extensively utilized in awake and anesthetized dogs in an effort to identify risk factors for gastrooesphageal reflux and asses antacid agents and there efficacy.

Cases
Fleur Ferrari - megaoeophagus
Henry Farrow 31 Oct 2009 myaesthenia
Talisker Scott

Treating Oesophageal Disease

Treating underlying conditions

If an underlying condition such as hypothyroidism, polymyositis, hypoadrenocorticism etc is identified this should be treated, however return of oesophageal function is variable. Ot is of interest that spontaneous remission of canine myaesthenai gravis has been reported in a series of 53 dogs 47 underwent remission in a mean time of 6.4 months. This is obviously important pronostically. Treating oesophagitis is addressed below along with treating gastric ulceration

Gastric disease

Gastritis and inflammatory bowel disease. Is discussed later with inflammatory bowel disease

***Helicobacter* infection in dogs and cats, significance and treatment decisions**

Gastric *Helicobacter*- like organisms (GHLOs) were first described in dogs and cats in 1881, the association between *Helicobacter pylori* infection, gastritis and gastric ulceration was reported by Warren and Marshall in 1983.

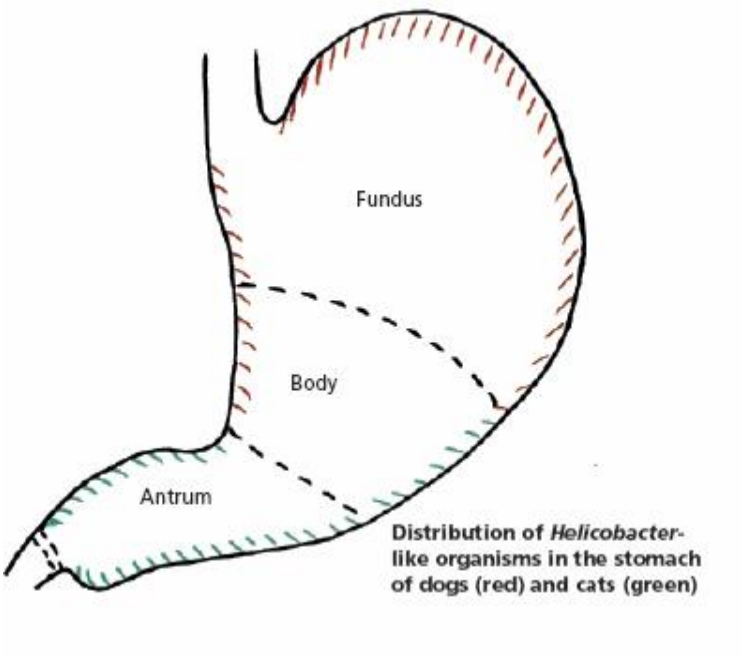
GHLO's are micriaerophilic Gram-negative bacteria which are highly motile. They are of spiral shape and vary between 1 and 8mm in length and have up to 20 terminal flagellae. More than 30 different types of GHLOs have been recorded.

KNOWN SPECIES OF *HELICOBACTER* FOUND IN ANIMALS	
Helicobacter species	*Host species*
Helicobacter felis	Mainly cats, but also dogs
Helicobacter heilmannii	Pigs, cats, dogs and humans
Helicobacter pylori	Humans and cats
Helicobacter mustelae	Ferrets
Helicobacter acinonyx	Cheetahs
Helicobacter bizzozeronii	Dogs
Helicobacter salomonis	Dogs
Helicobacter bilis	Dogs
Helicobacter pametensis	Cats
Helicobacter cinaedi, Helicobacter colifelis, Helicobacter rappini	In the liver and faeces of dogs

J.Simpson In Practice 2005

However determining the type of organism is difficult, light or electron microscopy is rarely effective but PCR techniques are being developed. Most GHLOs are found within the stomach in the mucus overlying the mucosal surface as well as within the gastric pits and

Parietal cells. As GHLOs are urease producers they can alter the local pH of the environment and survive within the highly acidic stomach. In addition mucus buffers help to maintain the organism. In addition helicobacter have been found in both normal and diarrhoeic faeces.



Distribution of *Helicobacter*-like organisms in the stomach of dogs (red) and cats (green)

Fig 2 distribution of helicobacter

The distribution of GHLOs in the stomach varies in dogs and cats. In dogs the organisms are mostly found within the stomach fundus or body, in cats they are more concentrated within the antrum. In man *H. pylori* in the antrum is associated with increased acid production, infection of the fundus results in destruction of parietal cells and pH rises. The changes in acid production associated with GHLO infection man are not seen in dogs and cats. This may reflect the type of species found in dogs and cats in comparison to man.

Prevalence

Various studies have been carried out to investigate the prevalence of GHLO in dogs and cats (see table below). GHLO's have been isolated from between 41 and 91% of

Healthy cats and between 67 and 86% of healthy dogs. In sick animals GHLOs have been found in 57-76% of vomiting cats and 74 to80% of vomiting dogs.

Table 1. Prevalence of gastric *Helicobacter*-like organisms in Dogs.

State of Health	Infected (%)	# Of Dogs	Authors
Healthy	100	15	Weber 1958[12]
Healthy	100	30	Henry 1987[26]
Healthy	100	30	Hanninen 1996[17]
Healthy	100	10	Happonen 1996[8]
Healthy	67–100	54	Eaton 1996[16]
Healthy	93	68	Neiger 1998[22]
Healthy	86	21	Yamasaki 1998[27]
Healthy	96	25	Happonen 1998[28]
Sick	74	42	Geyer 1993[9]
Sick	82	122	Hermanns 1995[10]
Sick	61	56	Yamasaki 1998[27]
Sick	90	21	Happonen 1998[28]

Table 2. Prevalence of gastric *Helicobacter*-like organisms in Cats.

State of Health	Infected (%)	# Of Cats	Authors
Healthy	100	12	Weber 1958[12]
Healthy	41	29	Geyer 1993[9]
Healthy	97	32	Otto 1994[11]
Healthy	100	25	El-Zataari 1997[29]
Healthy	100	15	Papasouliotos 1997[14]
Healthy	90	10	Yamasaki 1998[27]
Healthy	94	32	De Majo 1998[30]
Healthy	91	58	Neiger 1998[13]
Healthy	100	15	Norris 1999[31]
Sick	57	60	Geyer 1993[9]
Sick	76	127	Hermanns 1995[10]
Sick	64	33	Yamasaki 1998[27]
Sick	100	24	Papasouliotos 1997[14]

K. Simpson *et al* JVIM 2000 p224

Many of these studies do not record the specific species of *Helicobacter* isolated. However it should be noted that *H. pylori* is primarily a human pathogen, but occasional cases of feline infection have been recorded. Potential routes of infection are direct contact between dogs, a faecal-oral route or an oral oral route especially in cats with *H. pylori* infection which is thought to be associated with owners kissing their cats.

Pathogenicity

Different species of *Helicobacter* vary in their pathogenicity and ability to colonise the gastric mucosa depending on adherence, urease production and level of motility. After adhesion various cytokines are produced which change the structure of gastrocytes and tight junctions. *H. pylori* is also thought to be

able to induce antibody production against the proton pump on the apical membrane of parietal cells causing an autoimmune disease which can lead to achlorhydria.

In man *H.pylori* infection results in gastritis which is reversible following antibiotic therapy and subsequent elimination of the organism. Disruption of the gastric mucosal barrier and gastritis occur through phospholipase activation and the production of cytotoxin and the induction of gastrocyte apoptosis. Interleukins, proinflammatory mediators are also induced contributing to the development of gastritis and ulceration. The presence of *H. pylori* predisposes to the development of gastric carcinoma via atrophic gastritis and to mucosal associated lymphoid tissue (MALT) lymphoma, the mechanism is not as yet understood.

The relationship between GHLOs and gastritis in dogs and cats remains unresolved, probably due to the various GHLO species and their likely varying pathogenicity. When considering a microrganism as a cause of disease it is important to establish whether it fulfils Koch's postulates. These were established in 1882 for anthrax but remain essential and relevant.

Koch's postulates.

1. **The organism must always be associated with clinical disease**
2. **Must be isolated from a case and grown in a series of pure cultures**
3. **A late pure culture reproduces the disease in a susceptible animal**
4. **The organism is subsequently re-isolated from the latter**

Naturally occurring GHLO infection in dogs and cats appears to induce a mild lymphocytic-plasmacytic gastritis with parietal cell degeneration. However GHLO have also been found in gastric biopsy samples with no inflammatory changes and gastritis occurs without GHLO infection. Cats but not dogs may harbour *H.* pylori directly associated with infection and can be demonstrated by experimental re-infection. *H. felis* given to specific pathogen free cats results in lymphoid hyperplasia and infiltration of the mucosa with lymphocytes plasma cells and eosinophils however acid secretory function remained intact. It is therefore likely that infection with some species of GHLO is clinically insignificant while others are pathogenic as yet Koch's postulates are unsatisfied. An improved ability to differentiate between species and asses immune responses to each should help to unravel the problem.

Clinical signs

Range from clinically silent to chronic vomiting. To date a case of gastric ulceration with GHLO has yet to be reported.

Diagnosis

The difficulty in routinely assessing which species or strains are pathogenic or non pathogenic complicates diagnosis. This in turn complicates the decision to treat and may in part the varying described responses to treatment.

Diagnostic tests for *Helicobacter* infection
Endoscopic biopsy samples
Urease test
Histopathology using silver stains
Culture
PCR
Electron microscopy
Non-invasive tests
Serology
Urea breath test

Table 2 diagnostic tests for helicobacter

Endoscopic biopsy samples

A biopsy is incubated in broth containing urea if GHLO are present the urea is broken down to ammonia and the media pH changes causing a change in media colour. All GHLOs can produce this change

Histopathology

Allows determination of the type and severity of gastritis to be determined together with the presence of GHLOs. Attention should be paid to the number and location of GHLOs ie within the mucus, gastric pits or parietal cells. This will help in deciding whether to treat the patient

Culture

Very difficult

Polymerase chain reaction

In development

Electron microscopy

Non invasive tests

Serology As yet unavailable in veterinary medicine, available human kits do not pick up affected individuals

Urea breath tests

Treatment yes or no?

All human patients with gastritis and associated helicobacter infection are treated, in canine and feline patients this decision is not so clear cut. Despite large numbers of studies this question remains unresolved, and until a readily available method of determining the stain present and its pathogenic significance this is likely to remain the case.

If a **cat** is found to harbour GHLOs and no other cause can be found for the associated gastritis the author would treat the patient, or if the cat was responding poorly to standard inflammatory bowel disease management. If an owner reports GHLO infection the cat should be treated.

In the **dog** *H. pylori* is very rare however *H. heilmannii* is more common and this has been implicated in human disease, if an owner reports GHLO infection the dog should be treated. Otherwise it should be treated on the following basis

- do not treat animals with GHLO but no evidence of gastritis
- if gastritis and GHLO infection present concurrently treat the patient only if other known causes of gastritis eg food hypersensitivity have already been treated

- where no other cause for the gastritis can be found and the numbers of GHLOs are high or they are invading the gastric pits the patient should be treated

Treatment Regimes

Various protocols exist all must be administered for 14 days after which the patient is re-assessed. Possible protocols include

- Clarithromycin 5-10mg/kg twice daily, with omeprazol 1mg/kg once daily. **NB these drugs are not licensed for veterinary use**
- Amoxicillin 10-20mg/kg twice daily with metronidazol 10mg/kg twice daily and omeprazol 1mg/kg/day

These protocols may not eliminate GHLOs and signs may reoccur once treatment stops, it is unknown whether the antibacterial or antacids are responsible for the clinical response. If treatment fails the cause of gastritis any well have been missed and not due to GHLOs.

Gastric Ulceration

Gastric ulcers are associated with a number of primary gastric and non gastric disorders. Clinical signs vary from chronic mild to acute and life threatening, the later often going unrecognised. The pathogenic mechanisms can broadly be divided into impairment of the gastric mucosal barrier through direct injury, interference with gastroprotective prostaglandins (PGE2), mucous or bicarbonate, decreased blood flow and hypersecreation of gastric acid. (fig 3).

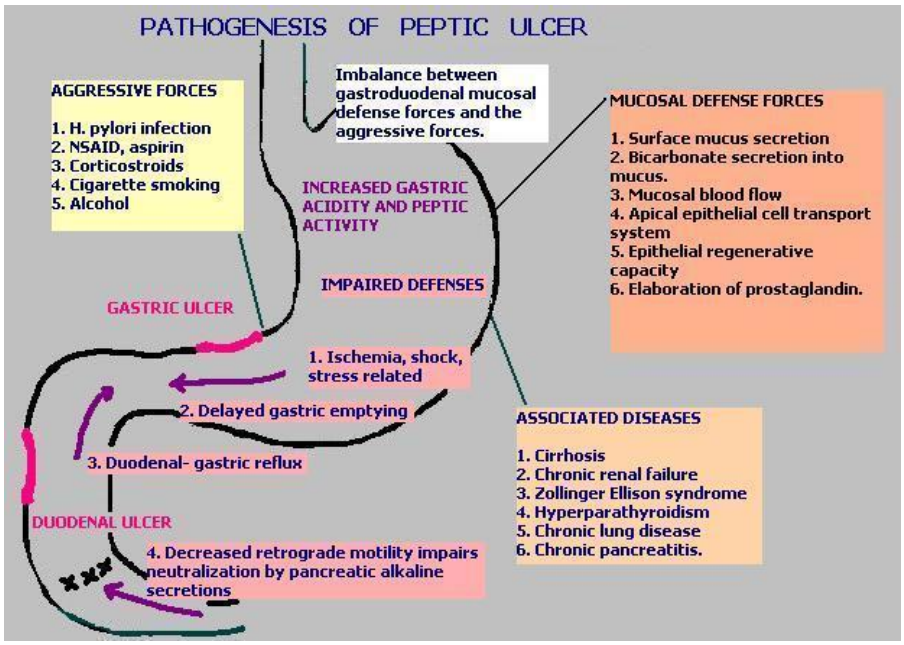


Fig 2 Pathogenesis of gastric ulceration

Diseases associated with gastric ulceration and erosion are shown in table 3. The most predictable of these is the administration of NSAIDs either alone or especially in combination with a glucocorticoid. NSAIDs cause direct mucosal damage and interfere with prostaglandin synthesis.

PROBLEM	**RELATED DISEASE**
Metabolic/Endocrine	Hypoadrenocorticism, uraemia, liver disease, mastocytosis, dic, Hypergastrinaemia and other APUdomas
Inflammatory	Gastritis
Neoplasia	Adenocarcinoma, lymphoma, leiomyoma etc
Drug Induced	NSAIDs and steroids
Hypotension	Shock, sepsis

Table 3 diseases associated with gastric ulceration

NSAIDs and gastric ulceration

The primary site of NSAIDs toxicity is in the GI tract in both man and animals. Effects have been linked to inhibition of the cytoprotective effects of COX-1 induced synthesis of prostaglandins on the mucosal border, local irritation and direct inhibition of platelet aggregation by inhibition of TXA2. The introduction of COX-1 sparing drugs has reduced the incidence of these effects but not eradicated them. Interestingly COX-1 knockout mice do not spontaneously develop mucosal ulcerations. COX-2 expression is increased on the edges of gastric ulcers where it accelerates ulcer healing by increasing angiogenesis via upregulation of PGE2. In a rat model COX-1 sparing NSAIDs have been shown to delay gastric ulcer healing. **Therefore the use of COX-1 sparing NSAIDs such can cause GI ulceration and caution should be exhibited in the use of these drugs in sick animals.**

Clinical findings

Clinical signs are variable from mild abdominal pain to weakness, inappetance, hypersalivation, haematemesis and melaena. If perforation occurs collapse and septic shock will follow.

Haematology anaemia is often evident this is initially regenerative but then will become microcytic hypochromic and minimally regenerative. When accompanied by thrombocytosis and decreased iron saturation these findings are consistent with chronic bleeding and iron deficiency. Lack of a stress leukogram and eosinophilea is supportive of hypoadrenocorticism. Eosinophilea could also be consistent with dietary allergy, gastritis or mastocytosis. Attention should be paid to a neutrophilic leucocytosis with a left shift as this may represent perforation.

Biochemistry and urinalysis. Findings consistent with renal, hepatic disease or dehydration may be evident. The presence of a metabolic alkalosis, hypochloraemia, hypokalaemia and acid urine is consistent with a high GI obstruction or a hypersecretory state such as hypergastrinaemia (Zollinger Ellison) and mastocytosis. Tests for primary and secondary haemostasis should be performed.

Diagnosis

Diagnostic imaging Plain radiographs will rule out other causes of vomiting, ultrasonography can be performed to evaluate the gastric wall thickness.

Endoscopy Allows direct visualisation. NSAID ulcers tend to be found in the pyloric antrum and are not associated with excessive thickening of the mucosa cf ulcerated tumours which have thickened edges and mucosa. Biopsies should be performed at the periphery to prevent perforation. Care not to over insufflate stomach and duodenum where an ulcer is suspected is recommended

NB The combination of mucosal erosion or ulceration, antral mucosal hypertrophy, copious gastric juice and oesophagitis is highly suggestive of a gastric hypersecretory state. If possible measurement of pH and gastrin should be considered.

Treatment

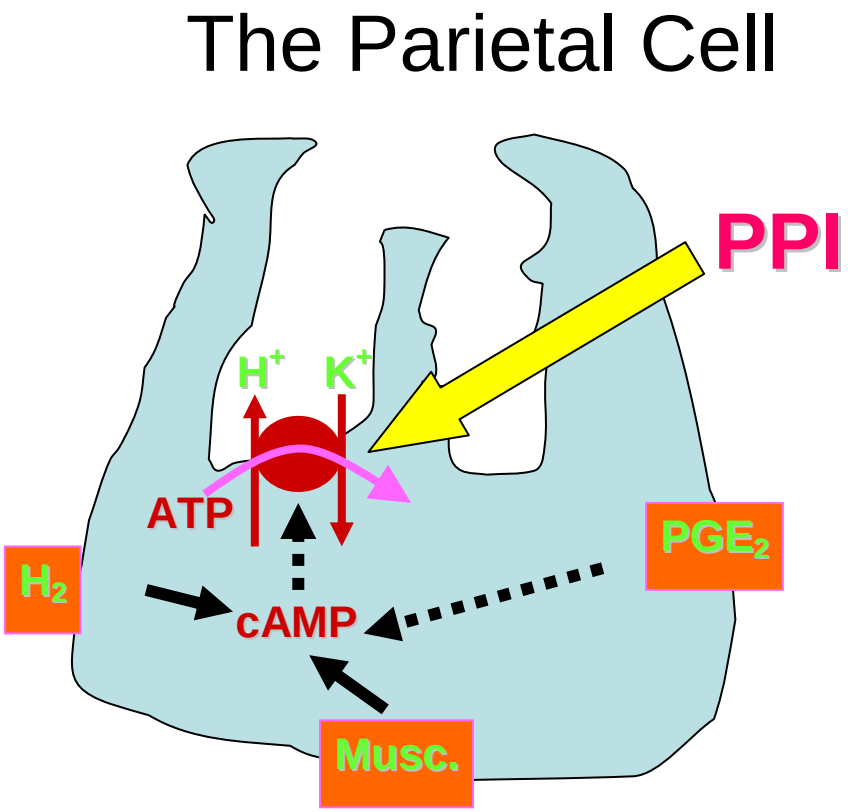
Ulcer management requires treating the underlying cause and ensuring that adequate hydration with fluid therapy and perfusion of the mucosa including blood transfusion if required. Restoration of electrolyte and acid base balance is essential, additional support is aimed at protecting the mucosa and decreasing gastric acid protection.

Gastric Ulceration
Case addisons -
Case neoplasia

Treating Oesophagitis, Gastric Ulceration and Gastritis - the use of antacids
Antacids form the corner stone of treatment of oesophagitis, gastritis and gastric ulceration. However much of current usage in veterinary patients is based on human medicine. This section explores rational use of antacids.

The Gastric Mucosa, Acid Secretion and Defences
The gastric mucosa is normally exposed to HCl, and Pepsin and at times NSAIDs however in the healthy individual it can maintain its integrity. Defences consist of a prepithelial mucus and bicarbonate barrier, an epithelial layer consisting of a continous layer of cell joined by tight junctions. The epithelial cells produce bicarbonate and anti-inflammatory proteins. There is continuous epithelial cell renewal and continuous flow of blood through the microvasculature.

Gastric acid secretion is both hormonally and neurologically controlled, in response to basolateral surface binding of parietal cells, of gastrin, acetyl choline, histamine and prostaglandins. See diagram below



Types of antacid therapy available

H2 Receptor Antagonists (H2RA)

These drugs are reversible competitive antagonists of the H2 receptor. This blocks histamine-induced gastric acid and pepsin secretion. These drugs have been used widely but many are not licensed for veterinary use.

Cimetidine, Has the longest history of veterinary use, it can be given both intravenously and orally. However its pharmacokinetics require it to be given four times daily. It is metabolised by the liver and has effects on hepatic cytocrome P450 activity means care with drug dose of drugs such as cyclosporine, ketokonazol, diltiazam, metronidazole are required to avoid toxicity. It would be wise to use an alternative H2 blocker where hepatic impairment is present.

Ranitidine has a longer duration of action than cimetidine and only has to given twice daily, although see discussion below. It does not have the hepatic side effects of cimetidine and has a mild prokinetic effects which can be of benefit where ileus or poor gastrointestinal motility is present.

Famotidine Is up to 20-50 times more potent than cimetidine. Its duration of action means once daily dosing only is required, although again see discussion below, this can be useful in cats or difficult to pill animals.

Proton pump inhibitors (PPIs)

Omeprazole

PPIs proton pump inhibitors irreversibly bind to the proton pump which forms the final step in acid secretion. There are no veterinary licensed products Omeprazole is approx 20-30 times more potent than H2 blockers; however it may take 48-72 hours to reach therapeutic levels in the blood stream and therefore where rapid decrease in acid secretion is required overlapping with H2 blockers should be considered. Omeprazole is available in capsules which if split should be reconstituted into other capsules as the drug is unstable in an acid environment It is the treatment of choice in severe ulceration hypersection syndromes such as Zollinger-Ellison or mastocytosis and is available in oral and injectable forms. As omeprazole is a very potent antacid it can cause reflex hypergastrinaemia and potentially hypertrophic gastritis.

Mucosal Protectants

Drugs used as mucosal protectants include

Prostaglandins, the PGE2 analogue misoprostol protects against NSAID damage without blocking acid secretion, this drug may cause diarrhoea and must not be given to pregnant animals. This drug is not effective at healing pre-existing ulcers, but may be of use in dogs which need to take long term NSAIDS

Sucralphate (polyaluminium sucrose) binds to areas denuded of mucosal epithelium forming a barrier against the penetration of gastric acid. Sucralphate also may stimulate endogenous prostaglandins, increase epidermal growth factor and mucosal blood flow and inactivate pepsin. It is available as both a liquid and a tablet form nether of which have a veterinary licence. It is probably best to separate sucralphate administration from that of other drugs as it may inhibit there absorption however evidence for and against this is unclear, however antibiotics must be given two hours before Sucralphate.

Clinical application of proton pump inhibitors and H2RA in Man

PPIs

PPI are effective in the treatment of gastric ulcers in man due eg tohypersecretory states such as Zolinger Ellison syndrome, inflammatory disease, NSAID administration. Where a neoplastic or underlying cause such as hypoadrenocorticism is present healing will be less effective unless this is addressed. In a landmark study in 1990 Burget et al demonstrated a significant correleation between

ulcer healing and duration of acid suppression and length of therapy. Healing rate increased as duration of suppression of PH is increased.

Dosing rate and effectiveness

Once daily dosing of PPI decreased acid secretion by 66% after 5 days in man, therefore emphasising a course of medication must be taken rather than dosing symptomatically as required. A study in the USA (Pezanoski 2005) shoed that only 23% of patients with ulcer disease take their PPI correctly. H2RA are more rapidly effective and therefore may be of use in the acute situation. (Wolfe et al 2005). A Cochrane report in 2002 showed H2RA to suppress gastric acid by 37-68% over 24 hours in man, there was a dose responsiverelationship to ulcer prevention and healing. Standard doses were preventative in duodenal but not gastric ulcer formation.

Clinical applications of PPIs and H2RA in dogs

Clinical assessment of antacids in experimental animals with spontaneous disease are sparse, most studies have been completed in healthy animals . In man it is known that optimum treatment of gastric ulceration and oesophageal relux disease occurs when an intragastric Ph of >3 is maintained for >75% of the time, or >4 for 67% of the time respectively. Bersenas et al (2005) determined the degree of acid suppression associated with 4 gastric acid suppresents, ranitidine 2mg/kg iv twice daily, famotidine 0.5mg/kg iv bid, pantoprazol 1mg/kg iv twice daily and omeprazol 1mg/kg po twice daily or once daily. Each was compared to administration of saline in 12 healthy beagles. Omeprazol, pantoprazol and famotidine all suppressed acid compared to placebo at the given doses but famotidine did not, increasing the dose of famotidine to three times daily from twice daily made no difference to suppression. Omeprazol twice daily was the only regime which approached the values suggested from work in man to be effective in ulcer and oesophagitis treatment from work in man.

A study by Tolbert et al 2011, studied gastric pH in 6 healthy dogs and compared omeprazol paste (equine gatroguard) and tablets 1.5-2.6mg/kg twice daily to famotidine 1-1.3mg/kg, PO, twice daily. Both forms of omeprazol performed better than famotidine in this study, and famotidine was no more effective than placebo. The time pH was >3 was 63% for tablet and 54% for paste form. Work has also been completed in working sled dogs, prone to gastric ulceration. (Williamson et al 2007, 2011). Omeprazol at 0.85mg/kg once daily was compared to famotidine 1mg/kg once daily and 2mg/kg twice daily. Famotidine at the standard dose was not as effective in preventing ulcers in dogs running for 330 hours compared to 100hours. High and low dose famotidine were similar, Omeprazol was superior to both.

The benefits of coadministration of PPI and H2PA have been investigated as this is common practice. Tolbert et al 2015, studied famotidine and pantoprezol vs pantoprezol alone in 12 healthy dogs. The study raised concerns that simultaneous use of the drugs may decrease the effectivity of PPI due to the requirements of PPIs for activation in the acidic canicula environment of the partietal cell. No significant difference in acid suppression was seen, caution is required in interpretation of this as there

is a body of evidence in man suggesting the benefits of combination therapy and this is a very small study.

The effect of oesophageal pH of PPIs and H2RA were investigated in dogs by Zacuto et al in 2012. The aim was management of reflux oesophagitis. Dogs undergoing routine orthopaedic surgery showed increased oesophageal pH but not reflux events with administration of PPIs. This is likely to decrease the propensity to stricture as a lowpH is required for activation of pepsin, and work in rabbits and dogs suggests that dripping acid onto the oesophagus for 60mins is associated with minimal damage without the addition of pepsin.

Adverse Effects

These have not been well documented in dogs and cats and are extrapolated from man. The most commonly described include B12 deficincy, diarohea and enteric infections especially c.diifficile. Garcia-Mazcomo et al 2012 studied the effect of omeprazol 1.1mg/kg bid on the gatric and duodenal microbiome, and showed no effect. However relative rather than absolute bacterial numbers were examined, and specialtion not attempted.

Inflammatory bowel disease

It is important that a full GI work up is performed before gut biopsies are considered and IBD can be diagnosed. This includes ruling out dietary indiscretion, parasitism, foreign body, and food allergy, EPI etc. The main differential by the time this diagnostic step is reached is intestinal lymphoma.

The mucosal immune system and its role in inflammatory bowel disease

The mucosal immune system is distinct from the systemic and contains more lymphoid elements than any other area of the body. The gut associated lymphoid tissue (GALT) is divided into distinct afferent and efferent sites. Afferent sites consist of Peyer's patches, which can be clearly seen within the small intestine and the lymphoid follicles found throughout the jejunum and large intestine. In these structures antigen both bacterial and food derived is sampled through specialised cells and presented via antigen presenting cells (APC's) in association with MHC II, to naïve B cells. Signals from associated CD4+ ab determine whether B cells develop into memory or antigen producing plasma cells. However all lymphoid cells re-circulate to the effecter site of the mucosal immune system the lamina propria, via lymphocyte homing using addresin molecules. Within the lamina propria plasma cell, T helper cells (CD4+) and cytotoxin CD8+ T cells are found in association with APCS which express MHCII. Intraepithelial lymphocytes are also found and epithelial cells express MHCI. The nature and association of expression molecules of antigen presentation will determine whether a tolerant or inflammatory response occurs. (Fig 1)

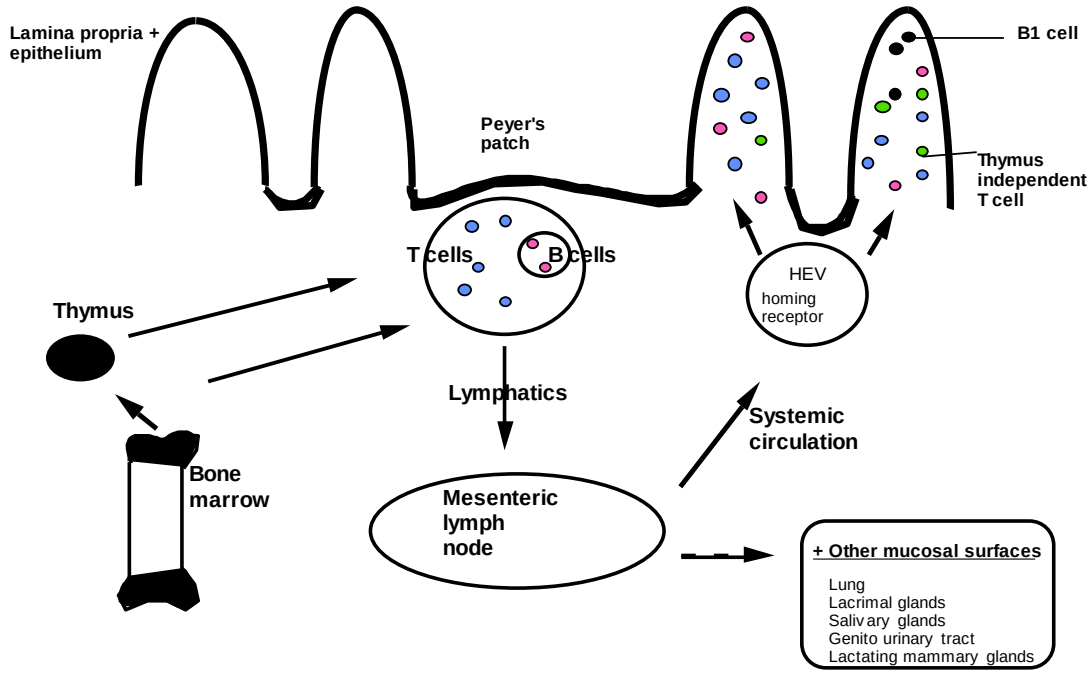


Fig 1 REcirulation of lymphocytes within the mucosal immune system

The mucosal immune system is exposed to a vast array of antigens, a delicate balance between response to pathogens and tolerance to harmless substances must be made. If this is disrupted a state of chronic uncontrolled inflammation may ensue. Experimental studies indicate that disruption in any of three critical areas can result in inflammation, the mucosal barrier ie the epithelium, the mucosal lymphoid tissue or the microbial flora. Regardless of the initial cause of inflammation the

presence of an endogenous flora causes exacerbation of this inflammation and specific pathogen free animals will not develop chronic inflammation

Canine and feline IBD

These disorders are characterised by persistent/recurrent clinical signs of undetermined cause associated with histological evidence of inflammation.

A range of disorders is probably characterised by these disorders. The most common causes are lymphocytic/plasmacytic and eosinophilic. Breed specific enteritises exist table 1

Enteropathy	**Breed Affected**
Immunoproliferative enteropathy	Basenji
Protein loosing enteropathy/nephropathy	Soft coated wheaten terrier
Gluten sensitive enteropathy	Irish setters
Histeocytic-ulcerative colitis	Boxers
Antibiotic responsive diarrhoea	German shepherd dogs

Table 1 A selection of breed related enteropathies

The pathogenesis is likely immune mediated with immunological, environmental and genetic factors contributing to the expression of disease. Environmental factors include microbial and dietary antigens, no specific microbial species have been shown to cause feline or canine IBD but it is likely that antigens derived from the endogenous microflora play a part in ongoing pathogenesis.

Dietary therapy provides clinical benefit in some cases of canine and feline IBD, implicating dietary factors, eg soft coated wheaten terriers with protein losing enteropathy develop immune responses to dietary antigens. A number of studies have implicated genetic factors in the pathogenesis of human IBD with associations to certain MHC histocompatability types also an increased proportion of human chrones patients have the NOD-2 gene.

Lymphocytic-Plasmacytic Enteritis

Most studies have concentrated on measurement of immunohistochemical markers to delineate the presence of different immune cell populations in inflammatory bowel disease. Increased lamina propria T cell numbers have been demonstrated especially CD4, in association with increased IgG plasma cells, macrophages and granulocytes indicating an important role for the T cell in association with ongoing inflammation. Acute phase proteins such as C reactive protein and nitrous oxide have also been implicated. In summary immune deregulation has been demonstrated in canine and feline

IBD but the underlying cause is rarely demonstrated genetics, food and microbial antigens are implicated as evidenced below.

a) Genetics and IBD immunoprolferative enteropathy in the Basenji

A strong genetic component is suggested and is probably autosomal recessive. Pathogenic changes include gastric mucosal hypertrophy, lymphoid cell infiltration and hyperplasia of the parietal cells and fundic glands, the whole of the small intestine can also be involved with villous blunting, crypt elongation and lamina propria infiltration... there is a marked polyclonal increase in serum IgA. Immunosuppressive doses of prednisalone are required for control; dietary factors are thought to be less important due to the poor response of these patients to dietary manipulation.

b) Dietary factors, familial protein losing enteropathy and nephropathy in soft coated wheaten terriers and gluten sensitive enteropathy in the Irish setter.

The breed distribution in the Wheaten Terrier suggests a genetic component however the mode of inheritance is not yet known. Histopathological changes consistent with IBD are seen, ie inflammatory cell infiltrates, villous blunting and epithelial erosions. Inflammatory cells usually consist of lymphocytes and plasma cells. In a study 6 soft coated Wheaten Terriers with protein loosing enteropathy were evaluated by gastroscopic food-sensitivity testing, provocative dietary trials and an assay of faecal IgE responses. Positive Reponses were elicited by gastroscopic food-sensitivity in 5 of 6 dogs and all 6 dogs showed adverse effects on provocative feeding ie vomiting, diarrhoea and weight loss. There were concurrent decreases in serum Albumin. No variations in IgE were found.

Gluten sensitive enteropathy has been documented in Irish Setters and is caused by exposure of affected individuals to Gluten. An autosomal mechanism of inheritance is suggested but unlike Celiac disease there is no relation to DQA or DQB histcompatability antigens. Histopathology reveals villous atrophy and variable inflammatory cell infiltration. Abnormal mucosal permeability is recognised. Changes resolve with withdrawal of gluten and re-challenge will increase the number of circulation CD4 cells and granulocytes.

c) The role of bacteria, histeocytic colitis in boxer dogs and feline IBD associations with bacteria

Intramucosal bacteria predominantly Gram-positive coccobaccili were present in 100% of ulcerative colitis Boxer large bowel biopsies but no control samples in a recent study (Simpson 2006). Invasive bacteria hybridised with FISH probes for *E.coli*. Ulcerative colitis in boxers has been shown to respond well to antibiotic therapy especially Baytril.

In a study of feline IBD samples by the same author the presence of mucosal atrophy, fusion of villi and epithelial changes were strongly correlated with clinical abnormalities, bacterial load, and Il-8. These changes were correlated by the presence bacterial antigens demonstrated by FISH studies.

Eosinophilic Enteritis

This is less common than lymphocytic plasmacytic enteritis, Rottweilers and GSDs appear predisposed. Dogs are often younger than with other forms of IBD. Parasitism and hypersensitivity should be considered as differentials and where peripheral eosinophilea is present hypoadrenocorticism.

Granulomatous enteritis

Occasionally demonstrated important rule outs in cats include FIP and mycobacterium and a Z/N stain should be requested

Treating IBD

Management of IBD

We have seen that feline ad canine IBD encompasses a range of diseases. The known factors involved in pathogenesis lead towards management strategies, ie dietary manipulation, immunomodulation and the use of antimicrobial agent. Approach to treatment varies with severity of clinical signs, histopathology etc

Feeding an exclusion diet,

Hydrolysed diets, omega 3 and IBD

Dietary therapy is of benefit in a number of cases of chronic canine and feline enteropathies, recent innovations include the use of hydrolysed protein diets and manipulation of the n-3:n-6 fatty acid ratio. Hydrolysed protein diets usually based on either chicken or soy protein are already marketed (HILLs Z/D). These diets contain protein derivatives of lower molecular mass than that proposed for food antigens (10-70KD) they would be expected to be hypoallergenic). However there is as yet little objective evidence to confirm this hypothesis in part because it is unclear what target molecular mass would guarantee a protein is rendered hypoallergenic. There is also concern that the chemical digestion process may expose hidden epitopes allowing the development of new adverse effects. A recent clinical trial has shown beneficial effects of a hydrolysed diet in chronic canine IBD (Hannah et al 2000). The author tends to recommend a home cooked diet or one of the less processed sensitivity diets as a first line of treatment (as described below in the fact sheet for owners) before the use of these diets, reserving hydrolysed diets for more severely or refractory individuals.

Manipulation of n-3:n-6 fatty acid ratio has been beneficial in human inflammatory disease including rheumatoid arthritis; results in IBD are more variable. There is little objective evidence for the use of these diets in dogs.

Feeding and exclusion diet advice given to owners and referring vets

Dietary allergy or intolerance can underlie a number of diseases. Feeding an exclusion diet is an important part of diagnosis and management. In moderately effected patients it is worth starting an exclusion diet before other therapy especially while waiting for biopsy results. (Clinical scoring system can be used to decide this).

Information provided to owners

What is an exclusion diet?

An exclusion diet is a diet designed to remove ingredients that a patient has previously encountered. Food can trigger clinical disease in a number of ways, including food allergy, toxicity and intolerance (e.g. lactose [milk sugar] intolerance). Clinical signs of dietary sensitivity include vomiting, diarrhoea, and itchy skin, ear disease, coughing and wheezing, amongst others.

Why feed an exclusion diet?

We recommend exclusion diet feeding for two reasons: diagnosis and treatment. The diagnosis of food sensitivity requires the demonstration of improvement of signs when the food is withdrawn and return of signs after feeding the food again. If a patient gets better when on an exclusion diet, long-term feeding of an appropriately balanced diet may be a very effective treatment

How long do we feed a diet for?

For the purpose of diagnosis, we typically recommend at least 4 weeks of exclusion diet feeding. Some authorities have suggested up to 12 weeks may be necessary to completely exclude a dietary sensitivity from possible causes of disease.

What foodstuffs can cause dietary sensitivity?

Theoretically, any foodstuff or ingredient (including additives) can trigger a reaction. In pets in the UK, however, we tend to avoid commonly encountered ingredients in exclusion diets, such as chicken, beef, lamb, soya and wheat.

What can we feed?

The are two options: home-cooked food and proprietary diets. Home-cooked food has the big advantage that we can be certain what is in it. Proprietary foods are formulated to be balanced for long-term feeding, but have the disadvantage that they inevitably are less ‘exclusive' than home-cooked diets. We generally recommend that the diagnostic phase of an exclusion diet (typically the first 4 weeks) be based on a home-cooked regime. We also recognize that this is not always easy, depending upon an owner's life-style>

For both home-cooked and proprietary diets, we try to choose a combination of a single novel carbohydrate and a single novel protein neither of which we believe the patient has previously eaten

.

Carbohydrate options	Protein options
Boiled potato	Turkey
Porridge oats (cooked in water)	Fish (e.g. salmon, cod, capelin)
Boiled rice	Pork
Polenta	Rabbit
Tapioca	Venison

How much should I feed?

It is impossible to give accurate amounts to feed an individual, because there are so many variables, not least the underlying disease. For home-cooked food we normally recommend 1/3 cooked protein: 2/3 cooked carbohydrate, fed to appetite in 2-3 meals daily. Amounts can be adjusted according to intake and body weight. Occasionally, we will add some vegetable oil to provide extra calories.

This regime is adequate for the diagnostic phase of the feeding trial. For longer term feeding a more nutritionally balanced diet must be designed; sometimes a proprietary diet is the best option at this stage.

What should I give to drink?

Plain water only should be offered. Milk etc. can be a culprit food.

But my dog is a scavenger!

Dogs, particularly, are scavengers by nature. They will hoover up everything that might be food. This behaviour must be prevented for an effective exclusion diet trial. Times of particular difficulty are when there are young children or visitors in the house, when there are multiple pets, during walks when off the lead and during social events, e.g. parties. Use of a short lead, constant supervision and, occasionally, a muzzle may be necessary.

What about his treats/vitamins/supplements?

Whilst a balanced diet is very important for long-term health the smallest amount of a triggering food can cause clinical signs, which may often be quite dramatic (think of peanut allergies in children). We therefore advise the strictest of exclusions, especially in the diagnostic phase of any exclusion diet trial. All treats, animal-based chews, vitamin supplements etc. should be withdrawn. Note that some medications may contain animal protein in the formulation: ask your clinician about this if you are concerned. Many pets consider any food given outside normal meal times a treat, so normal treats may be substituted with a small morsel of the exclusion diet itself

Immunomodulation in canine and feline IBD

Corticosteroids

a) **Prednisolone** Once lymphoma is ruled out this is the treatment of choice in marked canine and inflammatory bowel disease. The author always combines use of prednisalone with an exclusion diet. Prednisalone is started at a dose of 1mg/kg bid and then tapered a two weekly intervals depending on clinical response.
b) **Budesonide** a steroid preparation which shows extensive first pass in the liver and may therefore be useful in patients especially sensitive to steroids.

Between April 2001-2006 a retrospective review of patients was carried out at Davies Veterinary Specialists to determine dose and side effects of budesonide medication (Battersby 2007). Demonstrating that although side effects such as pu/pd, weight gain and lethargy are seen with budesonide these are less severe and common than with prednisalone. Elevations in ALP and ALT were observed and one dog was shown to have suppression of the hypothalamic pituitary axis. Doses of 0.05-0.49mg/kg were used and 0.1-0.15mg/kg is suggested as a starting point. The optimum duration of treatment is yet to be elicited, and it should be emphasised that this was a retrospective study.

Novel therapies and refractory cases

a) **Cyclosporine.** Specifically affects T-lymphocyte function by a variety of mechanisms, including interference with IL-2 expression and induction of T-lymphocytes that suppress cytotoxic responses. In human medicine failure to respond to medical treatment with steroids is observed in 20-30% of patients and a recent retrospective study of 80 dogs with IBD revealed 13% of cases had intractable disease. Cyclosporine A has been shown to be effective in steroid refractory bouts of human IBD and a recent study (Allenspach et al 2006) has demonstrated its clinical effectiveness in dogs. Cyclosporine is metabolised via the cytochrome p450 system and care should be employed if given along side drugs such as cimetidine or raniditine. The bioavailability is variable among individuals... An initial treatment of 5mg/kg sid for 10 weeks is suggested in refractory cases of IBD.
b) **Chlorambucil.** May be beneficial in steroid refractory cases of IBD in cats. The author has achieved success with the following regime in refractory cases 20mg/m^2 every other week, reassess at 4 weeks then space out doses
c) **Azathioprim** not in cats

Vitamin supplementation B12 and folate

Evidence from feline IBD suggests that B12 deficiency may hamper gut healing and recovery in IBD, it is therefore advisable to measure B12 in cases of IBD in both dogs and cats and supplement parentally appropriately. Folate may also be low in chronic GI disease and supplementation is recommended especially while feeding a strict exclusion diet the dose is 18mg/kg however since folic acid is rarely available in sizes less than 400mg the smallest most convenient dose should be used orally there are no known side effects of folic acid overdose.

Antibiotic treatment, antibiotics, prebiotics and probiotics

Although antibiotics treatment may lead to resolution of clinical signs the true effect of antibiotics on small intestinal bacteria is unknown. German shepherd dogs treated with oxytetracylin have demonstrated resolution of clinical signs and reduction in inflammatory cytokine RNA expression without decline in bacterial numbers. Antibiotics are unlikely to sterilise the canine gut and their effect is probably resultant from changes in the make up of the flora by providing selection pressure on less harmful bacteria and hence a change in the patients immune response.

The author will prescribe antibiotics where secondary SIBO or antibiotic responsive diarrhoea (see below) are thought to be present or as an adjunct to corticosteroids and dietary therapy. Where there is a neutrophilic component to the inflammation I will use antibiotics as a first treatment rather than corticosteroids

Drugs used a) Oxytertracyclin 20mg/kg tid

a. Metranidazol 10mg/kg bid

Case complicated IBD

Protein Losing Enteropathies

Protein loosing enteropathy (PLE) is encountered in several gastrointestinal (GI) diseases in both the dog and the cat. It is less common in the cat than the dog. The condition varies in severity from mild to severe with life threatening complications such as pulmonary thromboembolism. The syndrome results when loss of plasma protein through the diseased or damaged GI tract exceeds that of protein synthesis and hypoproteinaemia results with weight loss. Plasma proteins such as albumin and globulin are essential for maintenance of plasma oncotic pressure. Oncotic pressure is the force that draws extracellular fluid forced out of the vascular space by hydrostatic pressure at the arterial end of the capillary network back into the venous space. Alteration in oncotic or hydrostatic pressure therefore can result in alteration of fluid balance between vascular and extravascular compartments and if the derangement is large enough the development of ascites (see fig 1), oedema and pleural effusion. The extent of effect is due to the degree of protein loss. A careful, problem orientated approach to investigation allows accurate diagnosis and tailored management of treatment and prognosis.

Aetiology

Causes of PLE are shown in table one. These fall into broad diagnostic groups, of inflammation, lymphangectasia, neoplasia both focal and diffuse, infectious, and structural. Certain dog breeds appear predisposed to this condition, including the soft coated Wheaton terrier which has a well documented syndrome of PLE and protein loosing nephropathy (PLN), the Basenji, which has a unique enteropathy, the Yorkshire terrier and the Shar Pei although any breed of dog or cat may present. Most commonly encountered causes in canine practice are idiopathic inflammatory bowel, lymphangectasia; primary or secondary and lymphosarcoma. GI lymphosarcoma is the most common feline cause. In juveniles endoparasites should always be considered.

Causes	Examples
Inflammation	Ideopathic inflammatory bowel disease, lymphocytic-plasmacytic but also eosinophilic and granulomatous
Neoplasia	Lymphoma
Infectious	Parvovirus, salmonellosis
Lymphangectasia	Primary, lymphatic dissorder, Secondary to right sided heart failure, IBD
Endoparasites	Giardia, Ancylostoma, Uncinaria
Anatomic	Intersussception, chronic obstruction

Table 1 . Causes of PLE in the dog and cat

Clinical Presentation

A patient with PLE is likely to present with symptoms of chronic gastrointestinal disease the exception being acute presentation of GI intersusception or obstruction. Therefore diarrhoea, vomiting, melaena, haematemesis and weight loss associated with panhypoproteinaemia are the classical signs of the condition. These symptoms are sometimes associated with ascites. The development of ascites is far less common in the cat than the dog. Not all cases of PLE will present classically, eg lymphangectasia patients often present with asicites alone other patients present with weight loss alone. The loss of protein through the damaged gut causes ubiquitous loss of antithrombin III, therefore these patients are predisposed to the development of thromboembolism. Signs associated with thromboembolism depend upon the site of the clot, eg pulmonary thromboembolism and sudden onset of respiratory symptoms. A problem list for a dog or cat with PLE often therefore consists of ascites (dogs), panhypoproteinaemia and vomiting with or without diarrhoea.

Diagnosis PLE

Diagnosis of PLE requires that the clinician establish that protein loss is from the gut and then pinpoint the disease causing gut damage and protein loss.

Laboratory work; Haematology, Biochemistry and urinalysis

Blood samples should be collected for biochemical and haematological evaluation. Biochemistry often reveals a panhypoproteinaemia with decrease in both albumin and globulin. An exception is Basenji enteropathy, a proliferative disease which results in excessive production of immunoglobulin and hence a high or high normal globulin with low albumin. Globulin increase can be high enough to produce total protein within the normal range. Basenji enteropathy is uncommon and certain other conditions eg lymphoma may produce a rise in globulins. Other possible differentials of low plasma

protein include protein loosing nephropathy (PLN) and failure of hepatic protein production. Biochemistry screens should therefore include a full liver profile of ALT, ALP, GGT, AST and bilirubin if possible, and attention should be paid to glucose levels and cholesterol both of which may be low in chronic liver disease. Hypocholestrolaemia is often seen in PLE as opposed to PLN and nephrotic syndrome where it may be high. Any suggestion of liver disease as a cause of the low protein should be followed up with a bile acid stimulation test. PLE patients are often hypomagnesaemic and hypocalcaemic. The hypocalcaemia is resultant of not only hypoalbuminaemia and a decreased protein bound faction but also decreased ionised calcium. It is suggested that vitamin D and calcium metabolism may be affected in PLE especially where lymphangectasia is the underlying cause. Serum vitamin B12 and folate although not of direct relevance to protein loss may point to small intestinal disease and malabsorbtion if low.

Renal parameters of urea and createnine should be examined, and these combined with examination of a urine sample. Ideally this is collected by cystocentesis. If protein is noted in the urine careful observation of number of leucocytes, sediment, culture and a protein createnine ratio should be performed to assess the relevance of this to the patient's pan-hypoproteinaemia. An active sediment may indicate a urinary tract infection, but a significant increase in protein createnine ratio (normal this is below 0.5) would suggest that the observation of low total plasma protein is due to a glomerulonephropathy.

Abdominocentesis and fluid analysis

A sample of any ascitic or pleural fluid should be taken. Ideally this should be done under ultrasound guidance as it is both safer and increases the likelihood of achieving sufficient sample in smaller effusions. The site for single abdominocentesis is a point approx 1cm lateral and to the right of the ventral midline 1-2 cm caudal to the umbilicus. The area is prepared aseptically and an open 21G(dog) 1 to 1.5 inch and 23G(cat), ¾ inch, hypodermic needle used to collect fluid. Initially the fluid should be allowed to drain freely and only if it does not gentle pressure from a syringe is applied. If fluid is still not forthcoming the procedure is repeated in three other sites, right caudal, left cranial (NB risk of splenic perforation) and left caudal. Each site is prepared aseptically. Samples of fluid are collected into EDTA for cytology, a plain tube for protein and biochemical analysis and a sterile tube for bacteriological culture if necessary. In addition several air dried smears can be made. It should be noted that abdominocentesis can be a difficult procedure when performed blind, potential complications include organ perforation and bleeding. GI perforation, most small holes made by a hypodermic needle will seal quickly but if fluid suggestive of GI contents is aspirated the patient should be monitored for development of peritonitis and continued drainage through the abdomincentesis site, in which case a pressure dressing can be applied.

Pleural fluid should be collected if present, aseptic preparation is essential prior to this. The easiest position for drainage is with the animal in sternal recumbancy with manual restraint or minimal sedation. Thoracocentesis is usually performed at the 7 and 8 intercostal space unless radiography or ultrasound imaging suggest otherwise. If only pleural fluid is present the needle is placed in the dorsal

third of the thorax. Either a butterfly needle, or over the needle catheter can be used. A three way tap is attached and fluid sample collected. Potential complications include lung laceration, pneumothorax, pyothorax and haemorrhage.

Fluid should be submitted to the laboratory for analysis but a large amount of initial information can be gained with in house analysis ie by microscopy, measurement of protein content by refractometer and if appropriate in house biochemical analysis. The makeup

of the different types of abdominal fluids are listed in table 2

Characteristic	Transudate	Modified TRansudate	Exudate
SG	<1.015	1.015-1.025	>1.025
TP g/l	<25	>25	>25
Cells X 10(9)	<5	>5	>50
Cell type	Monocytes, mesothelial	Lymphocytes, neutrophils, moncytes, mesothelial	Neutrophils, monocytes, lymphocytes red blood cells

Table 2 abdominal effusions (adapted from BSAVA Manual of small animal Pathology)

The most common form of abdominal fluid obtained in PLE is a transudate, although a modified transudate may be present if the effusion has been present for a while resulting in reactive change in the peritoneum. If bacteria and characteristics of an exudate are seen this may indicate gut perforation in PLE. In this case changes would be expected in the blood work indicative to developing sepsis, such as leucocytosis with neutrophilia and potentially left shift. A highly fibrinous proteinaceous ascetic fluid in a cat would prompt consideration of FIP and coronavirus titres, in association with alpha 1 antiglobulins, albumin and globumin ratios should be persued.

Faecal analysis

Full faecal analysis with culture for *Salmonella, Campylobacter Spp* should be undertaken. This can be especially important in puppies where heavy worm burdens with *Uncinarea* can result in gut damage and protein loosing enteropathy. Isolation from *Campylobacter spp* is of uncertain diagnostic significance as similar numbers have been isolated from healthy and diarrhoeic dogs. Investigation of GI disease should not stop with the detection of *Campylobacter spp*, although due to the zoonotic potential it should be treated.

Virus testing

All cats with suspected PLE should be tested for FeLV and FIV before more invasive diagnostics are undertaken.

Radiography

Survey abdominal radiographs are of little help in animals with suspected PLE due to the loss of abdominal contrast when ascites are present of in thin animals. The exception being acute obstruction of the GI tract by a radio dense foreign body. Thoracic films may show the presence of a pleural effusion and or metastatic neoplasia

Ultrasonography

Ultrasonography is more useful than radiography in imaging the abdomen when investigating protein loosing enteropathy.

Endoscopy and Gastrointestinal biopsy

Definitive diagnosis of PLE in dogs and cats requires intestinal biopsy. Many of the diseases mentioned in table 1 are diffuse and multiple biopsies are required. Endoscopy is therefore the modality of choice for obtaining small intestinal and gastric biopsies.

Treatment and prognosis

Treatment is tailored to specific cause of PLE and prognosis varies with the severity of disease and presence of complications such as thromboembolism, highlighting the need for though diagnostic work up.

Prior to the collection of biopsies or general anaesthesia the provision of colloid support is often required. If albumin loss is excessive it is worth considering prophylaxis for thromboembolic disease. This may include the prescription of low molecular weight heparin (fragmin) at dose 100iu/kg three times daily. As yet no definitive study has been done into the use of low molecular weight heparins in this situation. Low dose aspirin can also be considered. Also important is preventing blood stasis and predisposition to clot formation in recumbent patients by good nursing care, turning the patient and encouragement or assistance to walk and move around. Ascites can be partially treated with diuretics and spironolactone is more effective than furosamide. Excessive drainage of large ascitic volume is not recommended as a treatment as it likely to cause excessive loss of protein and electrolyte imbalance. Effective treatment of PLE relies on accurate diagnosis so that treatment can be tailored to disease.

Acute causes of PLE such as obstruction or intersussception are treated surgically, with associated fluid and analgesic support. Uncinaria is treated by proper worming programs in puppies it is suggested that pyrantel preperations are used as they are rapidly acting and safe. Enteric infections such as *Campylobacter* or *Salmonella* are treated with appropriate antibiotics therapy.

In all cases of chronic GI disease with secondary PLE careful consideration to nutrition is essential. These patients may be profoundly malnourished and supportive feeding by oesophagostomy or nasogastric tube may be required while therapy is started. Oesophagostomy tube feeding is preferred

by the author in severely affected patients as it allows adequate concentration of calories to be administer more easily than via nasogastric tube, however a short GA is required for placement.

The treatment of idiopathic inflammatory bowel disease relies on the use of a combination of diet, immunomodulatory drugs and antibiotics. Once a definitive diagnosis of PLE secondary to IBD in a dog or cat is made the author's approach is to start a low fat limited antigen exclusion diet. Ideally this is home cooked consisting of one protein and one carbohydrate source eg turkey and potatoes or white fish and potatoes. Dependent on the severity of clinical signs prednisolone is also started at this time at dose 0.5-1mg/kg twice daily. This dose is tapered as the animal improves clinically. A percentage of patients with inflammatory bowel disease appear resistant to corticosteroid therapy in which case alternative immunomodulatory agents such as azathioprine (not in cats) or ciclosporin may be used. In cats the use of chlorambucil in addition or as an alternative to prednisalone in poorly responsive patients is advised. If there is any suggestion of secondary bacterial overgrowth or antibiotic responsive element to diarrhoea metronidazole at dose 10mg/kg can be introduced. Potential vestibular side effects of this drug should be bourne in mind especially in the cat. In addition it is always worth treating empirically with fenbendazole as occult endoparasitic disease such as giardia is likely to compromise management. Prognosis for canine and feline IBD patients is variable from fair for animals with minimal clinical signs and moderate protein loss, to very poor where severe hypoproteinaemia and clinical signs, thromboembolism and malnutrition are present.

Secondary lymphangectasia is treated by treating the primary underlying process if possible, eg pericardiocentesis or treatment of IBD. The aim of treatment of primary lymphangectasia is to reduce fat in the diet as much as possible while feeding a calorie dense ration. Weight control diets although low in fat are inappropriate, as insufficient nutrition is provided. High content of easily digestible protein is suggested, eg white meat, eggs. Fat absorption is poor in lymphangectasia and a fat soluble vitamin supplement (especially containing vit D and E) may be required. Corticosteroid therapy at similar doses to that used in IBD are beneficial in some patients especially if a lymphangitis is suspected. If the patient fails to respond to corticosteroids it is worth giving consideration to the use of ciclosporin as there is anecdotal reports of its use successfully. Unfortunately the majority of patients with primary lymphangectasia have a guarded prognosis

GI lymphoma is the most common cause of PLE in cats and commonly encountered in dogs. Unfortunately dogs with diffuse GI lymphoma respond poorly to chemotherapy protocols and there is a risk or GI perforation, in contrast to multicentric lymphoma. If the owner wishes to pursue treatment advice from a specialist oncologist is advised and nutritional support and careful monitoring for signs of perforation while the patient therapy is commenced. In contrast cats have a much more favourable prognosis to treatment of GI lymphoma. Histological grade is important in gauging prognosis the small cell low grade form being more amenable to treatment than the intermediate to high grade form. Positive response to combination chemotherapy and prednisolone and chlorambucil alone are seen. Again the advice of a specialist oncologist is invaluable.

Case PLE