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FELINE EMESIS

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"Vomiting is the most common sign associated with inflammatory bowel disease (IBD) in cats."

Is this statement, often repeated in the veterinary literature, actually correct? Is vomiting truly more common than diarrhoea in IBD, or do cats simply tend to vomit 'publicly' in view of their owner, whilst burying any evidence of diarrhoea in the neighbour's garden? More importantly, does this largely unsubstantiated statement potentially lead to an incorrect, presumptive diagnosis of IBD in any chronically vomiting cat and, consequently, inappropriate treatment.

Figure 1. 'Mabel' - the subject of our case study.

An understanding of what vomiting is and how it is coordinated is necessary not only to understand why vomiting may or may not be the most common sign associated with IBD, but also to appreciate the many differential diagnoses and to provide rational therapy. The evidence concerning feline emesis has recently been reviewed in detail (*Batchelor et al, 2013*).

Vomiting is a reflex action that allows gastroduodenal contents to be evacuated safely without inhalation of the vomitus and is inevitably a complex process. The co-ordination of the many actions involved (i.e. changes of posture, retching, intestinal retroperistalsis, gastric relaxation with diaphragmatic and abdominal wall compression at the same time as protection of the airways by closure of the glottis and nasopharynx) requires integration of several neural pathways associated with the area postrema (AP) in the brainstem.

This area receives inputs not only from the periphery, but also mid- and fore-brain structures, the vestibular apparatus, and an area outside the blood-brain barrier called the chemoreceptor trigger zone. Neurons involved in coordinating vomiting are distributed in an area extending from the AP and dorsal vagal motor nucleus through the nucleus tractus solitarius and lateral tegmental field of the reticular formation to the retrofacial nucleus in the ventrolateral medulla *(Batchelor et al, 2013).* So for simplicity the area is often termed the "vomiting centre", but in reality is an area of overlapping nuclei, where summation of stimuli may reach a threshold that elicits the vomiting reflex.

The various inputs that can stimulate vomiting are summarised in fig. 2. Peripheral inputs are largely from the GI tract via the vagus nerve, but peritonitis, pancreatitis and hepatic disease can all elicit vomiting. Within the GI tract there are gastric chemoreceptors, and this may be one mechanisms by which anti-thyroid medication can cause vomiting in cats. Nociceptors responding to inflammation and intestinal distension occur throughout the intestine, although the highest concentration of receptors is found in the duodenum. This helps explain why vomiting may indeed be the most common sign of IBD, even in cats that have no primary gastric disease.

Cardiac disease is associated with vomiting in people but coronary receptors and/or coronary disease are not seen in cats. However an association between feline heartworm (dirofilariasis – not recorded in UK) and

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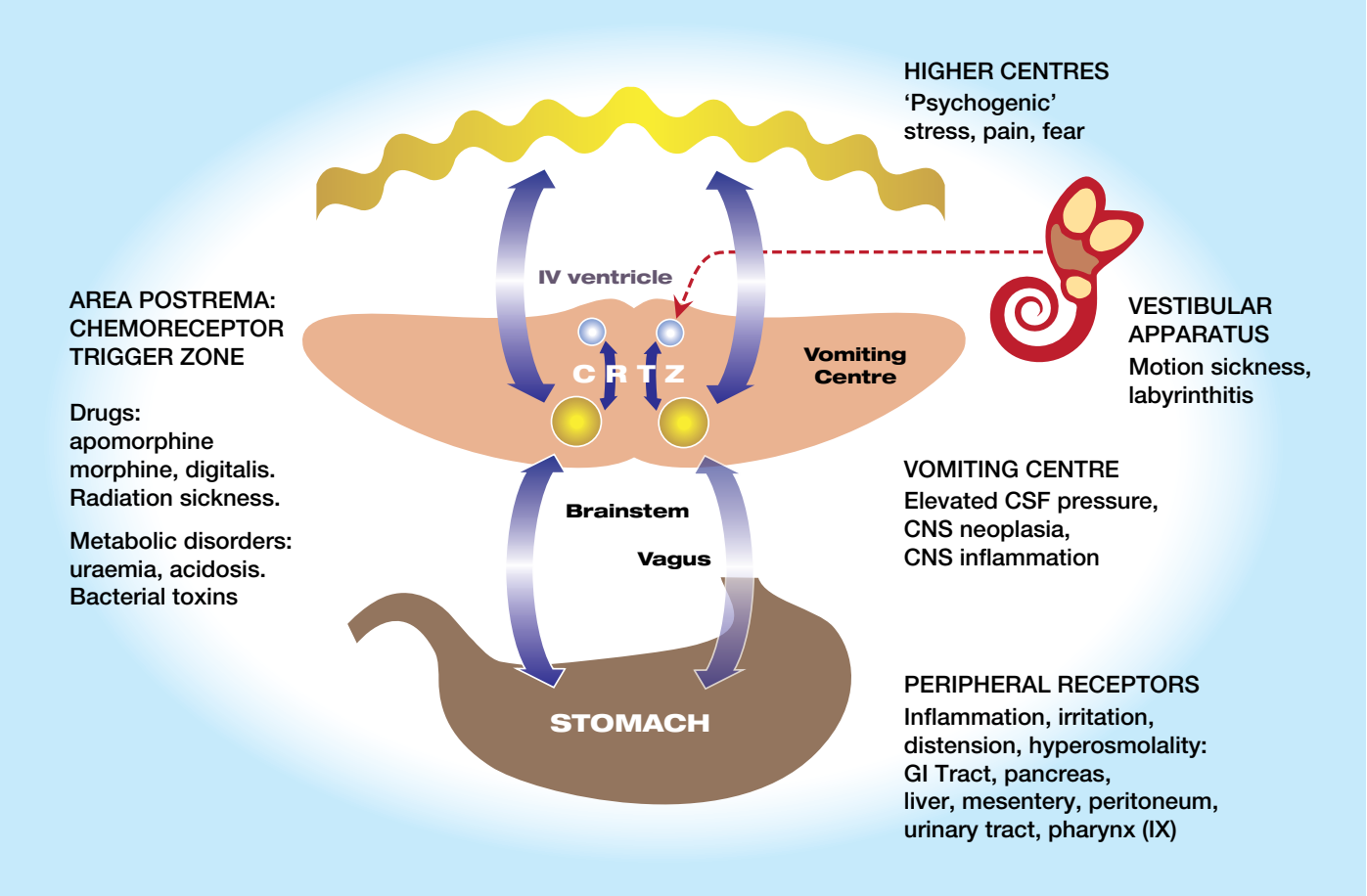

Figure 2. Inputs to the vomiting centre.

vomiting has been noted, although the presence of concurrent GI disease is not often evaluated in these reports. Salivary and pharyngeal disease, through glossopharyngeal innervation, can also trigger vomiting but this is unusual in cats.

More commonly, systemic diseases stimulate vomiting through blood borne endogenous toxins acting on the chemoreceptor trigger zone (CRTZ); for example, uraemia causes vomiting because of stimulation of the CRTZ as well as causing uraemic gastritis. Drugs, such as opioids and chemotherapy agents, also elicit vomiting by stimulating the CRTZ. The vestibular apparatus inputs to the vomiting centre, hence the vomiting seen in vestibular disease and motion sickness. Raised intracranial pressure, from space-occupying lesions, and intracranial inflammation cause vomiting and potentially higher centre activity can lead to vomiting through 'stress', although this is a diagnosis of exclusion.

Nausea is a subjective sensation that typically precedes and/or accompanies vomiting, and is often either a common clinical sign of disease or an adverse effect of a drug therapy or surgical procedure. Signs of inappetence, restlessness, drooling and unproductive retching in cats are subjectively interpreted as reflecting nausea, but reliable objective assessment measures are lacking. The neural pathways involved in nausea are poorly understood but anthropomorphically it is believed that it involves the conscious perception of an adverse feeling, and that anti-emetics inhibit the vomiting reflex at lower doses than are needed to abolish nausea.

Symptomatic treatment

The management of vomiting in cats is of course aimed at treating any primary underlying cause but symptomatic treatment of vomiting is also important as emesis is distressing, both for the patient and the owner.

A number of anti-emetics appear suitable for cats. Some of these do not have Marketing Authorisations for cats and must be used off-label according to the Cascade with informed owner consent. The publisher and author cannot take responsibility for information provided on dosages in this article; details of this kind must be verified by individual users from appropriate sources.

Maropitant

There are no published clinical trials of anti-emetics in cats, but maropitant citrate *(Cerenia®, Zoetis)* does have a marketing authorisation (is licensed) for the prevention and treatment of vomiting and reduction of nausea in both dogs and cats, although for motion sickness it is licensed only for use in dogs.

Cerenia® is administered to cats as a subcutaneous injection at 1 mg/kg (1 ml per 10 kg) once daily. It is known to cause a local stinging reaction in about one third of feline patients, especially if the solution is at room temperature when administered. Therefore the bottle should be stored in the refrigerator, not for microbiological safety reasons, but so the solution can be drawn up and injected cold. Only the subcutaneous route is licensed and onset of action is rapid, so there is never any indication to give maropitant intravenously, although it has been given by that route experimentally without reported problems.

Its safety has not been tested in cats less than 16 weeks of age *(Krautmann et al, 2012)*, nor in pregnant or lactating queens and, therefore, it should be used in such patients according to a benefit/risk assessment. However, there may be an age-related effect on metabolism, with juvenile cats showing more rapid clearance, and hence it is likely to be safe *(Boucher et al, 2007)*. Indeed, it was shown to be well tolerated in young cats injected daily with up to 5 mg/kg (i.e., 5 times the recommended dose) for 15 consecutive days, i.e. 3 times the recommended duration of administration *(Hickman et al, 2008)*. A steady state seems to be reached in cats after three days *(Boucher et al, 2007)* but because of high protein binding the drug may accumulate and a washout period of 48 hours is recommended after 5 doses before repeating treatment if needed.

The hepatic metabolism of maropitant in cats involves two cytochrome P450 isoenzymes (CYP1A and CYP3A related) and appears to differ from dogs *(Boucher et al, 2007)*. Nevertheless it should be used with caution in cats with liver disease. It should also be used with caution in cats suffering from or with a predisposition for heart diseases, and should not be used concomitantly with calcium channel antagonists as it has an affinity for calcium channels.

Maropitant antagonises neurokinin (NK1) receptors, the receptor for substance P. Thus, as well as its central activity mediating emesis in the vomiting centre, this neurotransmitter mediates nociception in visceral organs and is involved in neurogenic inflammation. Consequently there is some interest in the efficacy of maropitant as an analgesic. Intravenous maropitant has been shown to reduce the minimum alveolar concentration (MAC) of sevoflurane needed to be given to maintain anaesthesia in cats during stimulation by traction on the ovarian ligament *(Niyom et al, 2013)*. Whether this observed effect translates into any clinical benefit by reducing the amount of volatile inhalant anaesthetic agent needed during ovariohysterectomy, or providing any post-operative analgesia or pain relief in naturally occurring conditions such as pancreatitis is not known.

Metoclopramide

Metoclopramide has been used as an anti-emetic in cats for many years and it currently has a marketing authorisation (is licensed) for dogs and cats in oral solution *(Emeprid®, Ceva)* and injectable *(Emeprid®* and *Vomend®, Dechra)* formulations. Historically it was often associated with side-effects in cats, with motor and behavioural abnormalities (e.g. abnormal movements, tremors, agitation, ataxia and vocalisation) reported. However, this perhaps reflects inadvertent overdosing as the dosage originally reported in some formularies (i.e. 0.5 to 1.0 mg/kg q6-8h) appears to have been incorrect. The correct oral and injectable dose is 0.5 to 1.0 mg/kg/day administered in divided doses repeated at 6 to 8 hour intervals. The injectable formulation *(Emeprid®)* can be given intravenously or by the intramuscular or subcutaneous routes *(Emeprid®, Vomend®)*. Because of its short half-life it is given as frequent divided doses or, preferably, as a continuous rate IV infusion (1.0 mg/kg day). The dose should be reduced by 50% in cats with renal impairment as metoclopramide is excreted via the urine.

Although an effective anti-emetic in dogs, the rationale for metoclopramide being an effective central anti-emetic in cats seems lacking. Indeed, there is likely to be minimal central activity, because metoclopramide is a central dopamine receptor (D_2) antagonist, yet α_2-adrenergic receptors are much more important in controlling vomiting in the feline vomiting centre. This explains why xylazine is an effective emetic in cats. Nevertheless, clinical experience suggests metoclopramide does have some anti-emetic effect in cats with gastric disease. This may reflect its peripheral action of stimulating gastric motility in cats with gastritis and gastric atony. The prokinetic effect on gastro-duodenal transit is mediated by muscarinic activity, D_2 receptor antagonist activity and 5-HT_4 receptor agonist activity in the GI tract.

Ondansetron

Ondansetron *(Zofran®)* is an effective anti-emetic, acting as a 5-HT_3 antagonist, both centrally and locally in the GI tract. It was developed for the prophylactic management of vomiting associated with chemotherapy. Not licensed for cats, it is useful in refractory vomiting due to pancreatitis, hepatic lipidosis, severe IBD, GI neoplasia and cholangitis if licensed products alone are ineffective. The empirical dosage in cats is 0.5 mg/kg q12h. Dolasetron is an alternative, but more expensive 5- HT_3 antagonist supplied as an injectable and as tablets which must be reformulated for use in cats. The empirical dosage is 0.6–1.0 mg/kg IV or PO q24h.

Phenothiazines

As α_2-agonists, such as xylazine, are potent emetics in cats it might be predicted that $\alpha\alpha_2$-antagonists such as phenothiazines would be good anti-emetics in cats. Indeed chlorpromazine at 0.1–0.5 mg/kg SC q8h can be effective in cats; prochlorperazine is typically used in cats in countries other than the UK. Phenothiazines are

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central anti-emetics which actually act via antagonism of dopamine, histamine (H_1) and muscarinic receptors as well as α_2- adrenergic receptors, and inhibit vomiting at the CRTZ and directly at the vomiting centre. Ultimately the use of phenothiazines in cats is limited, firstly because they are not licensed, secondly they require frequent dosing, and thirdly they can cause hypotension due to α_2- adrenergic blockade.

They are mostly used as adjunctive treatment in cats with refractory vomiting caused by pancreatitis, GI neoplasia, chemotherapy, and the fact that they can cause mild sedation through their antihistamine effects may be beneficial if the cat is being maintained on IV fluids.

Acid blockers

H_2 antagonists and proton pump inhibitors have no direct anti-emetic effects, although are likely to be helpful in vomiting cats if they have gastritis or gastric ulceration. Famotidine is often the preferred H_2) antagonist in cats because of its formulation, because its taste is not aversive to cats, and because it only needs to be given once daily. Similarly omeprazole, and other proton pump inhibitors, are given once daily, although formulation size makes it less suitable for cats.

CASE EXAMPLE

Whilst it is likely that many cats with IBD vomit, there are many other causes of vomiting that should be ruled out before empirical steroid therapy is prescribed, as the following case illustrates:

Mabel was a 9 year old FN farm cat which hunted rodents avidly. She had been observed to vomit food intermittently for several months. Her owner was not concerned until she noticed Mabel was eating less and had lost a little weight. Closer inspection found evidence of blood in the vomit, and veterinary advice was sought. Physical examination was unhelpful but confirmed a body condition score of 3/9. There was no diarrhoea nor melaena noted on the rectal thermometer. A serum T4 was at the lower limit of the reference range suggesting euthyroid sick syndrome due to an underlying illness. So having had hyperthyroidism, a common cause of vomiting and weight loss, ruled out Mabel was prescribed omeprazole for gastric ulceration, and prednisolone for presumed IBD. The vomiting was virtually abolished, but Mabel's appetite did not improve and she continued to lose weight. She was therefore referred for further investigations, which showed a mild regenerative anaemia, consistent with ongoing blood loss, and normal serum biochemistry. Abdominal ultrasound identified focal thickening of the lesser curvature of the stomach with loss of layering, consistent with a gastric neoplasm. Gastroscopy was performed. The oesophagus and duodenum were unremarkable except for an incidental finding of two live roundworms in the duodenum that were removed endoscopically *(fig 1)*. The majority of the stomach was grossly normal but an irregular, ulcerated mass was seen arising in the lesser curvature *(fig 2)* and was biopsied.

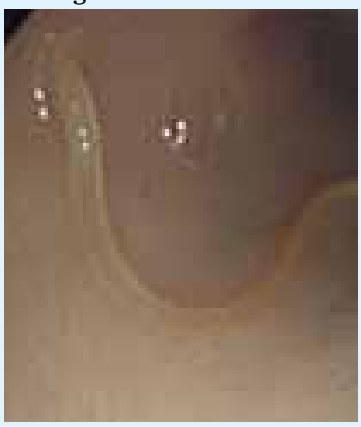

Figure 3.

The gross appearance was most typical of a gastric carcinoma, and the initial biopsy report was suggestive of an anaplastic carcinoma. However, the presence of a lymphocytes, and the apparent steroid-responsiveness led to a recommendation that immunohistochemistry be performed. This revealed a definitive diagnosis of gastric lymphoma Despite the guarded prognosis, Mabel was treated with a standard cyclophosphamidevincristine-prednisolone (COP) protocol, and went into remission. She remains well two years later, the only problem being that the owner struggles to catch her when her treatment is due because she is always out hunting!

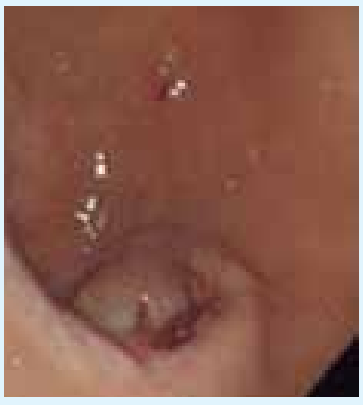

Figure 4.

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Approach

When presented with any vomiting patient there are three key questions that need to be answered first:

1. **Is the patient dehydrated and in need of fluid therapy?**

With chronic vomiting significant dehydration is unlikely unless there is underlying renal disease or the cat stops drinking, but loss of skin elasticity in cats that have significant weight loss may mislead, and other signs such as dry mucous membranes, tachycardia with weak pulses and increased PCV/TS should be looked for.

2. **Is the patient vomiting or regurgitating?**

Vomiting is confirmed if prodromal signs followed by active abdominal contractions are observed. This distinction is important as the differential diagnosis and potential treatment is very different if the cat actually has oesophageal disease.

3. **If the patient is vomiting, is this because of primary gastrointestinal (GI) disease, or underlying systemic disease?**

Many systemic causes of vomiting can be ruled in or out by the history, physical examination and/or by serum biochemical findings. It is better to diagnose renal disease by blood tests rather than identify uraemia as the cause of gastritis by gastroscopy!

Investigations

Non-GI and GI causes of vomiting are listed in Tables 1 to 3. Hyperthyroidism is an important differential diagnosis for vomiting in older cats and should be ruled out early in any investigation.

Haematology may give indications of GI bleeding, but an inflammatory leukogram is a non-specific finding, although more typically associated with non-GI disease or pancreatitis. Measurement of serum pancreatic lipase *(Spec fPL®)* is the most sensitive test for pancreatitis, but finding suggestive ultrasonographic changes (e.g. irregular pancreatic shape and heterogeneity, free abdominal fluid, pain, hyperechoic fat) strengthens the validity of the laboratory result. However, pancreatitis may also be associated with concurrent IBD and cholangitis.

Imaging (i.e. radiography, computed tomography, ultrasonography) of the GI tract to look for primary or concurrent GI and/or biliary disease is important.

In cats where primary GI is suspected and no focal lesions beyond the reach of the endoscope (i.e. beyond the proximal jejunum) have been identified, endoscopy and biopsy are indicated. Alternatively exploratory surgery may be preferred if there is a need to examine and biopsy the pancreas and liver concurrently.

Gastroscopy in cats can be challenging because of their small size, and a gastroscope with a tip diameter < 8 mm is preferred. With a gastroscope this size, pyloric intubation is not usually difficult assuming the endoscope can be steered successfully around the tight angle of the lesser curvature. Intestinal inflammation may be the cause of the vomiting, so intestinal as well as gastric biopsies should always be collected, even if there are no gross abnormalities, as there may be microscopic evidence of inflammation.

The most common histological diagnosis in vomiting cats is lymphoplasmacytic gastroenteritis, although the recognition of GI inflammation is sometimes problematic despite the use of the WSAVA guidelines *(Day et al, 2008, Washabau et al, 2010).*

- **CNS Disease**
  - Space-occupying lesion
  - Meningitis/encephalitis
  - Hydrocephalus
  - Stress?
- **Stimulation of chemoreceptor trigger zone**
  - Uraemia
  - Hepatic encephalopathy
  - Drugs
- **Motion sickness**
- **Vestibular disease**
- **Hyperthyroidism**
- **Severe pharyngeal/salivary disease**
- **Sepsis**
- **Dirofilariasis? (not in UK)**

Table 1: Non-gastrointestinal diseases that can cause vomiting in cats.

- **Adrenal gland tumour**
- **Hepatobiliary disease**
- **Mesothelioma**
- **Pancreatic disease**
- **Peritonitis**
- **Renal disease**
- **Splenic disease**
- **Steatitis**
- **Urogenital disease**

Table 2: Non-gastrointestinal, intra-abdominal disease associated with vomiting in cats. (adapted from Batchelor *et al,* 2013).

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- **Self-limiting (haemorrhagic) gastroenteritis**
- **Infection:**
  - Coronavirus ◆ FIP
  - Feline parvovirus (panleukopenia)
  - Bacterial ◆ Yeasts
  - Ollulanus tricuspis
- **Dietary:**
  - Food sensitivity ◆ Dietary indiscretion
- **Gastric foreign body:**
  - Linear foreign body ◆ Trichobezoar
- **Gastric entrapment:**
  - Diaphragmatic rupture
  - Gastro-oesophageal intussusception
  - Dilatation-volvulus ◆ Hiatal hernia
- **Gastritis**
  - Acute
  - IBD : Food sensitivity
    : Eosinophilic
  - Parasitic ◆ Associated with spiral bacteria
  - Associated with foreign body
- **Gastroduodenal (peptic) ulcer:**
  - Mast cell tumour ◆ NSAIDs
  - Associated with spiral bacteria
- **Delayed gastric emptying:**
  - Outflow obstruction
    : Hypertrophic gastropathy
    : Pyloric stenosis
    : Neoplasia
  - Dysmotility
    : Dysautonomia

Table 3: Gastrointestinal disease associated with vomiting in cats (adapted from Batchelor *et al,* 2013).

Treatment

The management of all the diseases that can cause vomiting is beyond the scope of this article, and the symptomatic treatment of vomiting has already been discussed.

Gastric ulceration should be treated with an acid blocker (H_2 antagonist or proton pump inhibitor) and sucralfate as well as trying to remove any underlying cause. Gastric outflow obstructions and tumours are managed surgically, whilst gastric lymphoma may respond to combination chemotherapy.

Dysmotility is addressed by correcting any electrolyte abnormality and then giving prokinetic drugs. Metoclopramide combines anti-emetic and prokinetic activity although cisapride (if available) is a more effective prokinetic. Neither should be used before an obstruction has been ruled out. Maropitant appears to have no prokinetic activity, but GI obstruction should still be ruled out first, as masking of signs by controlling vomiting could delay diagnosis and definitive surgical treatment.

Acute gastritis is likely to be self-limiting, but chronic gastritis will require treatment. Again if there is a known cause (e.g. NSAIDs, Ollulanus) it should be eliminated. Non-specific treatment with an acid blocker may allow restoration of the gastric mucosal barrier and resolve the problem, but idiopathic gastritis is likely to relapse. Chronic gastritis may be part of IBD and require treatment with immunosuppressive agents, but dietary manipulation is usually indicated first. A low-fat, highly digestible diet speeds up gastric emptying, although may not be palatable to cats, and more likely to be successful is an exclusion diet; this may be a novel single protein diet or a hydrolysed preparation.

Ollulanus is an unusual gastric parasite that is a rare cause of feline gastritis. Easily treated with fenbendazole, it is most noted for its mode of transmission: the ingestion of vomitus from an infected cat permits spread. The vexed question of whether gastritis is caused by the spiral bacteria (Helicobacter) commonly found in the feline stomach has yet to be answered, but it seems logical to attempt therapy if the acid blockers and exclusion diet fail, before giving immunosuppressive treatment. A triple therapy combination of amoxicillin, metronidazole and an acid blocker is usually recommended, although possible metronidazole resistance (as seen in human Helicobacter infections) has led to the recommendation to substitute metronidazole with clarithromycin.

And finally, if the vomiting is truly a sign of idiopathic IBD, management with an exclusion diet, prednisolone with or without chlorambucil, and supplementation of cobalamin as necessary is indicated.

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