The clinical importance of vomiting stems from its association with a large and varied group of diseases and the potentially life threatening consequences of vomiting per se (e.g. aspiration pneumonia and fluid and electrolyte depletion). Patient management is directed at detecting and treating the cause and consequences of vomiting. Where the cause is undetermined it is necessary to adopt a rational approach to controlling emesis.

**Initiation of vomiting**

Vomiting is a reflex act initiated by stimulating the vomiting center in the medulla. The vomiting center can be stimulated directly, or indirectly via the chemoreceptor trigger zone (CRTZ) situated in the area postrema where the blood brain barrier is accessible to blood borne substances such as toxins or drugs. Neurological input from the vestibular nucleus can also stimulate the CRTZ or the vomiting center. Disease or irritation of the gastrointestinal tract, abdominal organs or peritoneum and cerebral diseases can directly stimulate the vomiting center via visceral receptors and vagal afferents. Once the vomiting center is adequately stimulated a set of visceral events is initiated - these include the sequential inhibition of proximal gastrointestinal motility, a retrograde power contraction in the small intestine and antral relaxation that enables transfer of intestinal contents to the stomach. These events are followed by moderate amplitude contractions in antrum and intestine and shortening of the intra abdominal esophagus. Dilatation of the cardia and lower esophageal sphincter enables transfer of gastric contents to the esophagus during retching and vomiting. Retching often precedes vomiting and is characterized by rhythmic inspiratory movements against a closed glottis. Negative intrathoracic pressure during retching prevents expulsion of esophageal contents. During vomiting the abdominal muscles contract and the intrathoracic and intrabdominal pressures are positive which results in the forceful expulsion of gastric contents from the mouth.

**Causes of vomiting**

There are so many potential causes of vomiting that it is often easiest to think in broad terms initially i.e. gastric, intestinal, intra-abdominal non-GIT, metabolic-endocrine, drugs, toxins, dietary, neurologic, infectious diseases and consider more specific causes when vomiting is localized to one of these groups (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Causes of vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
</tr>
<tr>
<td>Gastritis, Ulceration, Neoplasia, Outflow obstruction, Foreign bodies, Motility / functional disorders</td>
</tr>
<tr>
<td>Intestinal</td>
</tr>
<tr>
<td>Inflammatory Bowel Disease, Neoplasia, Foreign bodies, Intussusception, Enteritis / enteropathy, Functional disorders</td>
</tr>
<tr>
<td>Intra-abdominal non-GIT</td>
</tr>
<tr>
<td>Pancreas</td>
</tr>
<tr>
<td>Pancreatitis, Pancreatic Neoplasia</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>Hepatitis, Cholangitis, Biliary Obstruction, neoplasia, cysts</td>
</tr>
<tr>
<td>Spleen</td>
</tr>
<tr>
<td>Mast cell tumor</td>
</tr>
<tr>
<td>Genitourinary</td>
</tr>
<tr>
<td>Nephritis, Pyelonephritis, Nephrolithiasis, Urinary obstruction, Pyomertra,neoplasia</td>
</tr>
<tr>
<td>Peritonitis</td>
</tr>
<tr>
<td>Metabolic / Endocrine</td>
</tr>
<tr>
<td>Uremia, Diabetic Ketoacidosis, Hyperthyroidism, Hepatic Encephalopathy, Hypercalcaemia, Septicaemia</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Intravenous medications, Digoxin, Chemo therapy, Xylazine, NSAID</td>
</tr>
<tr>
<td>Toxins</td>
</tr>
<tr>
<td>Lilies, Ethylene Glycol, Lead</td>
</tr>
<tr>
<td>Dietary</td>
</tr>
<tr>
<td>Sudden change. Indiscretion, Intolerance, Allergy</td>
</tr>
<tr>
<td>Neurologic</td>
</tr>
<tr>
<td>Vestibular disease, Encephalitis, Neoplasia, Raised intra-cranial pressure</td>
</tr>
<tr>
<td>Infectious</td>
</tr>
<tr>
<td>feline panleucopoeina, virulent calici, FIP, FeLV, FIV, salmonellosis, heartworm</td>
</tr>
</tbody>
</table>

**Patient evaluation and diagnostic approach**

The initial plan for vomiting animals is to separate those whose problems are acute and self-limiting from those in need of more thorough investigation and treatment. If vomiting is acute and the animal is systemically well, in-depth diagnostic testing is usually not warranted as vomiting frequently resolves on its own or after short-term symptomatic therapy.

If the animal is systemically unwell, has been vomiting for more than a week, or has vomiting associated with hematemesis, bloody diarrhea or abdominal pain a more aggressive work-up is necessary to define the nature of the problem.
Most non-gastrointestinal causes of vomiting, and gastrointestinal causes such as a foreign body or intussusception, are usually detected, or ruled out, by taking a detailed history, performing a thorough physical examination, routine laboratory tests (e.g. CBC, profile, UA, fecal, with evaluation of cobalamin, folate, lipase/PLI, T4, FeLV, FIV where indicated) and abdominal radiographs. Abdominal ultrasound is useful for detecting pancreatic, hepatic and splenic lesions, GI thickening (focal or diffuse) and sampling masses and parenchymal abnormalities. If these tests are negative or show abnormalities compatible with primary gastric or diffuse intestinal disease, endoscopic examination of the stomach and upper duodenum or contrast radiography are the principal diagnostic options. Endoscopy enables detailed examination and sampling of the gastric and duodenal mucosa with minimal patient discomfort and is generally accepted as the best method of evaluating mucosal abnormalities. Radiographic contrast studies (± fluoroscopy) are generally restricted to examining functional (emptying) disorders of the stomach and the anatomy and patency of the intestinal tract distal to the duodenum. Patients with evidence of focal intestinal disease or concurrent involvement of multiple organs (e.g. liver, pancreas, intestine in cats with triaditis) are often best evaluated surgically.

Overview of therapy for vomiting

Patient management should be aimed at detecting, and treating the cause and consequences of vomiting. Parenteral fluid therapy (usually IV) should be tailored to correct volume depletion, and electrolyte and acid base abnormalities. Dietary alteration in patients with acute vomiting is traditionally NPO for 24-48hrs followed by a transition to a bland, carbohydrate rich diet (to facilitate gastric emptying) when vomiting decreases. However, this notion has been challenged by the results of early enteral nutrition in dogs with parovirus enteropathy, where feeding was associated with decreased duration of hospitalization and reduced intestinal permeability. Modified diets may be useful in patients with delayed gastric emptying, or chronic gastroenteropathies associated with food intolerance. Gastric protectants (e.g. sucralfate) can be used to bind toxins and protect the GI mucosa where vomiting is associated with gastritis or gastric ulceration. Inhibitors of gastric acid secretion (usually H2 antagonists) are used to limit gastric erosion/ulceration in patients with gastritis / ulceration and those considered at risk of developing GI ulceration (e.g. shock) or esophagitis. Inhibition of gastric acid may also limit the hypochloremia and alkalosis associated with gastric outflow obstruction. Analgesics may decrease vomiting associated with acute abdominal conditions e.g. buprenorphine for pancreatitis. Antiemetics are indicated in patients with vomiting that is compromising hydration status, affecting electrolyte and acid base balance, and those at high risk for esophagitis or aspiration pneumonia, and those distressed by repeated vomiting. Antibiotics are usually limited to suspected infections, acute abdominal conditions or gastritis associated with Helicobacter infection. Prokinetic agents are used to promote gastric and intestinal motility in patients with a patent GI tract. Surgery is indicated to remove large foreign bodies, treat some causes of pyloric outflow obstruction, and to obtain biopsies of the GI tract and concurrently diseased organs.

Pharmacological control of vomiting

The pharmacological control of vomiting involves antagonizing central and peripheral receptors that regulate emesis and stimulating receptors promoting ordered gastrointestinal motility. The receptor subtypes involved in vomiting and examples of drugs that are commonly used in the management of vomiting are summarised in Figure 1.

Some antiemetics have more than one mechanism of action e.g. Phenothiazines (e.g. chlorpromazine) are antagonists of α1 and α2 adrenergic, H1- and H2-histaminergic and D2-dopaminergic receptors; Metoclopramide antagonizes D2-dopaminergic and 5HT3-serotonergic receptors and has cholinergic effects on smooth muscle.

Antiemetics are generally contraindicated in patients with gastrointestinal toxicity where they may limit expulsion of the toxic agent. Antiemetics can effectively mask signs of serious underlying disease hence a clinical response to antiemetics should not preclude a search for the underlying cause of vomiting. Non-selective cholinergic receptor antagonists (other than the M1 specific antagonist-pirenzpine) e.g. atropine, scopolamine, aminopentamidine, isopropamide, may cause ileus, delayed gastric emptying and dry mouth. It is recommended that phenothiazines and the NK1 antagonist maropitant are not given to hypotensive patients. Phenothiazines may
also cause unwanted sedation and decrease the seizure threshold in animals with epilepsy. Maropitant is metabolized by the liver and is heavily protein bound, hence careful monitoring is suggested in patients with liver disease and hypoproteinemia, and maropitant should not be used for more than 5 consecutive days. Maropitant can prolong the Q-T interval and is contraindicated in bradycardia. Antiemetics with prokinetic activity, such as metoclopramide, are contraindicated where there is a suspicion of intestinal obstruction.

The animal species, and age may also impact selection of antiemetic. Certain antiemetics are not recommended / require caution / are ineffective when used in the cat e.g. the cat is resistant to apomorphine induced vomiting suggesting the D2-dopaminergic metoclopramide may have less activity than a2 adrenergic antagonists. Maropitant is currently not licensed for use in dogs <12 wks of age due to dose dependent bone marrow hypoplasia.

Despite the high frequency of antiemetic use in veterinary practice there is a paucity of controlled studies of their efficacy.

The comparative efficacy of commonly used antiemetics against vomiting induced by apomorphine (central stimulus) and ipecac (peripheral stimulus) in laboratory dogs indicates that maropitant, chlorpromazine, and metoclopramide have similar activity against apomorphine induced emesis (all had greater activity than ondansetron), and that ondansetron and maropitant have equal activity against ipecac (both had greater activity than metoclopramide and chlorpromazine). Maropitant has been shown to reduce vomiting induced by xylazine in cats and has an analgesic effect in cats undergoing ovariohysterectomy. 5HT3 antagonists have been shown to reduce cisplatin and dexmedetomidine-induced emesis in cat, but do not block the effect of xylazine.

Clinical trial are lacking in cats. Two recent clinical trials in dogs, one in Europe, the other in the USA have focused on maropitant.

In the US study of 275 dogs, 50% of dogs treated with placebo (32/64) versus 22% (41/188) treated with maropitant vomited at some point after treatment. In the European study vomiting was controlled in 97% of dogs receiving maropitant vs. 71% of those receiving intermittent metoclopramide (0.5-1mg/kg /day over 3 doses).

Strategies for managing persistent vomiting

Uremia

Vomiting in uremia is mediated via the effects of uremic toxins on the CRTZ and afferent inputs from the inflamed stomach. Control of vomiting is focused on ameliorating uremia with fluid therapy, antagonizing the effects of uremic toxins on the CRTZ and limiting potential afferent input from the GI tract e.g. uremic / hypergastrinemic gastritis. Recenty studies in cats and dogs have shown that gastric ulceration is rarely associated with uremia. In cats maropitant (1mg/kg SC/24hrs for no more than 5d) or ondansetron (0.5mg/kg BID) are typical first line antiemetics for uremia associated vomiting. H2 antagonists (e.g. famotidine 0.5-1.0mg/kg SID-BID) and mucosal protectants (sucralfate 0.25-1g PO TID) are frequently prescribed to address concurrent gastritis, though recent studies have questioned the association of uremia with gastric ulcers in dogs and cats. Metoclopramide may not be an effective centrally acting antiemetic in the cat and its potential impact on renal dopamine receptors should be considered in cats with primary renal disease. Mirtazapine (1.88mg EOD) appears to be an effective appetite stimulant and anti-emetic for cats with CKD and could be a useful adjunct to the nutritional management of these cases.

Gastric ulceration

Vomiting in patients with suspected acute gastritis or gastric ulceration is managed by providing adequate fluid therapy and limiting afferent input from the inflamed gut by decreasing gastric acid secretion (e.g. H2 antagonists) and providing mucosal protection (e.g. sucralfate). Where ulceration is severe and vomiting is not adequately controlled antiemetics such as maropitant, ondansetron and phenothiazines may be used.

In patients with severe or persistent ulceration more complete inhibition of gastric acid secretion can be achieved with the H/K ATPase inhibitor - omeprazole (0.7 mg/kg SID PO). This drug may be particularly effective in patients with excessive secretion of gastric acid e.g. gastrinoma. The combination of omeprazole and the long acting somatostatin analog Octreotide (which decreases gastrin release and inhibits gastric acid secretion) effectively reduced vomiting in a dog with gastrinoma (but has not been evaluated in cats to date.

Mast cell tumors may cause vomiting via the central effects of histamine on the CRTZ and the peripheral effects of histamine on gastric acid secretion (with resultant hyperacidity and ulceration). Treatment of mastocytosis with H1 and H2 histamine antagonists (e.g. diphenhydramine and famotidine) may reduce the central and peripheral effects of histamine. Corticosteroids are used to decrease tumor size and release of histamine.

Gastritis

The treatment of gastritis is guided by the presence or absence of gastric Helicobacter. In cats with chronic vomiting, lymphoid follicular / lymphocytic gastritis, and gastric Helicobacter spp., antibiotics directed against Helicobacter have produced positive clinical responses. In an uncontrolled trial of antibiotics in dogs and cats with gastritis and Helicobacter spp. infection clinical signs in 90% of 63 dogs and cats responded to treatment with a combination of metronidazole, amoxicillin, and famotidine. 74% of 19 animals re-endoscoped had no evidence of Helicobacter spp. in gastric biopsies. A recent controlled trial of amoxicillin (15mg/kg PO BID x 14d), metronidazole (10mg/kg PO BID 14d) and bismuth + famotidine in 24 dogs found a similar decrease in vomiting (86.4%) and reduced gastritis scores in dogs that were Helicobacter negative at 6mo. The use of famotidine did not improve resolution of clinical
results of controlled studies in asymptomatic Helicobacter-infected dogs and cats. Another recent study gave metronidazole (11-15mg/kg PO BID), amoxicillin (22mg/kg PO BID) and bismuth subsalicylate (0.22ml/kg PO Q-TID) to 5 Helicobacter infected animals (3 dogs and 2 cats) for 21d, and documented resolution of vomiting and long term eradication of Helicobacter (9-38months) in all animals (15). The author has employed the combination of amoxicillin (20 mg/kg PO BID), clarithromycin (7.5 mg/kg PO BID) and metronidazole (10 mg/kg PO BID) for 14 days to successfully eradicate Helicobacter pylori infection in cats. Taken as a whole, these studies suggest that a longer duration of treatment (21d) or the use of antibiotics that can eradicate intracellular Helicobacter (clarithromycin) improve eradication, but further studies are required before clear guidelines regarding the treatment of gastric Helicobacter spp. in dogs and cats can be made. The author recommends treating only symptomatic patients that have biopsy-confirmed Helicobacter spp. infection and gastritis.

**Chronic gastritis of unknown cause**

Helicobacter negative lymphocytic plasmacytic gastritis is relatively common in dogs and cats (@ 25to 40% of cases, unpublished observations). The cellular infiltrate varies widely in severity and it may be accompanied by mucosal atrophy or fibrosis, and less commonly hyperplasia. Gastritis may also be accompanied by similar infiltrates in the intestines, particularly in cats (who should also be evaluated for the presence of pancreatic and biliary disease).

Patients with lymphoplasmacytic, Helicobacter-negative, gastritis are initially treated with diet. The diet is often restricted in antigens to which the patient has been previously exposed, such as a lamb-based diet if the patient has previously been fed chicken and beef, or contains hydrolyzed proteins (usually chicken or soy) that may be less allergenic than intact proteins. Many of these diets are also high in carbohydrate and restricted in fat, which facilitates gastric emptying, and may contain other substances such as menhaden fish oil or antioxidants that may alter inflammation. The test diet is fed exclusively for a period of about 2 weeks while vomiting episodes are recorded. If vomiting is improved it is a challenge with the original diet is required to confirm a diagnosis of food intolerance. The introduction of a specific dietary component to the test diet, such as beef, is required to confirm sensitivity to that component. If vomiting is unresponsive the patient is usually placed on a different diet for 2 more weeks (usually the limit of client tolerance). If there is no response to dietary manipulation the next step is immuno-modulation with prednisolone (1 to 2 mg/kg/day PO, tapered to every other day at the lowest dose that maintains remission over 8 to 12 weeks). Antacids and mucosal protectants are added to the therapeutic regimen if ulcers or erosion are detected at endoscopy or if hematemesis or melena is noted.

If gastritis is unresponsive to antibiotics, diet, prednisolone, and antacids, additional immunosuppression may be indicated. However, it is important to carefully re-evaluate the patient record and histopathology (e.g. is lymphoma a possibility?) before ramping up immunosuppression. Chlorambucil is a safer alternative to azathioprine in cats and has been successfully employed in the management of inflammatory bowel disease and small cell lymphoma (PO 5mg per cat every other day). Prokinetic agents such as cisapride and ranitidine can be used as an adjunct where delayed gastric emptying is present (see below).

**Delayed gastric emptying**

Delayed gastric emptying is caused by outflow obstruction or defective propulsion and is usually suspected by the vomiting of food 8-12hrs after ingestion. Other signs include abdominal discomfort, distention, bloating and intermittent anorexia. Outflow obstruction can be caused by polyps, foreign bodies, tumors, pyloric hypertrophy or stenosis, granulomata and extraluminal masses such as pancreatic tumors. Defective propulsion may result from primary gastric diseases such as gastritis, ulceration, neoplasia, and parasitism or non-gastric disorders such as stress, trauma, peritonitis, pancreatitis, infectious enteritis, electrolyte and metabolic derangements, drugs and surgery. Disordered motility may be involved in the initiation of gastric dilatation volvulus. The finding of hypochloremia, hypokalemia, and metabolic alkalosis, ± aciduria, should raise the suspicion of an upper GI obstruction or less commonly a hypersecretory state such as gastrinoma or mastocytosis.

Radiography is used to investigate vomiting and to confirm delayed gastric emptying (retention of food or fluid >15hrs after a meal, or delayed gastric emptying of liquid barium (30%w/v, 12-16ml/kg via stomach tube : the stomach should empty within 15-60 min in cats and 1-2hrs in dogs), barium meal ( normal < 10-15hrs) or barium polypspheres (normal dogs, ten 5mm and thirty 1.5mm spheres: 50% empty by 7.5hrs, 75% by 13.1, 90% by 22.5hrs)). Endoscopy is useful for confirming gastric outflow obstruction and gastric and duodenal causes of decreased propulsion (e.g. ulcers, gastritis). Measurement of gastric pH and serum gastrin may help to determine the cause of gastric ulceration or mucosal abnormalities.

Treatment of gastric emptying disorders is directed at the underlying cause- e.g. surgery for pyloric stenosis or, antacids, mucosal protectants and/or antibiotics for gastritis. In non-obstructive situations gastric emptying can be enhanced by dietary modification to facilitate gastric emptying (small amounts of semi-liquid, protein and fat restricted diets fed at frequent intervals e.g. intestinal diets blended with water and mixed with an equal volume of boiled rice may also be of benefit) and prokinetic agents such as metoclopramide (0.2-0.5mg/kg PO SC TID), cisapride (0.1-0.5mg/kg PO TID) or ranitidine (1-2mg/ kg PO BID) and nizatidine (2.5-5mg/kg PO SID) may be effective. I am not aware of studies evaluating erythromycin as a prokinetic in cats.
**Pancreatitis**
Vomiting is likely due to direct afferent input to the vomiting center from the inflamed pancreas and adjacent intestines and ileus secondary to inflammation. Analgesia (e.g. buprenorphine 0.01mg/kg SC BID) is used to decrease afferent stimulation of the vomiting center, and may also have direct central effects on emesis. 5HT3 receptor antagonists such as ondansetron, and the NK1 antagonist maropitant are increasingly used, and may offer the additional benefit of decreasing pancreatic or visceral stimulation of emesis.

**Motion sickness**
Maropitant (1.0 mg/kg) was effective in preventing motion-induced emesis in cats.

**Cancer chemotherapy**
Granisetron (1 mg/kg, i.m TID) day reduced the retching+vomiting response induced by cisplatin on days 1 and 2; dexamethasone (0.01-1 mg/kg, i.m, TID) reduced significantly the retching+vomiting response by 68.8-100.0% (P<0.05) and 33.3-100.0% (P<0.05) on days 1 and 2, respectively (Rudd et al 2000).

**Persistent vomiting of undetermined etiology**
Symptomatic fluid support, diet restriction or modification, analgesia and antiemetic therapy to control vomiting are considered where vomiting is frequent or severe enough to cause derangements of fluid, electrolyte and acid base balance. Antiemetic use and selection in patients with unknown causes of vomiting is based on a best guess, least harmful approach taking into consideration the potential contraindications to antiemetic use in general e.g. ingestion of toxic substances, and contraindications for specific agents e.g. age, hypotension, bradycardia.

References and further reading
Lucot JB Blockade of 5-hydroxytryptamine 3 receptors prevents cisplatin-induced but not motion- or xylazine-induced emesis in the cat Pharmacochem Behav 1989,32,207.
Quimby JM1, Lunn KF. Mirtazapine as an appetite stimulant and anti-emetic in cats with chronic kidney disease: a masked placebo-controlled crossover clinical trial. Vet J. 2013 Sep;197(3):651-5.


