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Inflammatory Bowel Disease. Diagnostic Path and Treatment

Differential Diagnosis and Therapeutical Management of Vomiting Patients
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3.1 INFLAMMATORY BOWEL DISEASE. DIAGNOSTIC PATH AND TREATMENT

INTRODUCTION

Inflammatory bowel disease (IBD) is the most common cause of vomiting and diarrhea in dogs and cats. This term comprises a group of pathologies characterized from the clinical viewpoint by partial anorexia, vomiting, diarrhea and persistent weight loss (> 3 weeks duration). From the viewpoint of histopathology, the gastrointestinal mucous is infiltrated by inflammatory cells (lymphocytes, plasmatic cells, neutrophils, eosinophils, histiocytes, etc.) with unknown etiology.

INCIDENCE

This type of pathology can be evidenced in dogs, and less frequently in cats. Certain breeds, such as Shar Pei, German Sheep Dogs and Siamese cats, are more susceptible, although it is also evidenced in other breeds and in mongrels. The large intestine is the portion of the digestive tract most frequently affected in dogs. In cats it is the small intestine. In most cases, lymphocytes and plasmatic cells are the predominant type of inflammatory cell.

PHYSIOPATHOLOGY

The physiopathology of the inflammatory bowel disease remains a poorly understood issue. It has been determined that the start and spread of this type of pathology is attributed to an inappropriate immune response to antigens that are normally tolerated (bacteria and food).

The origin of the inflammatory bowel disease is attributed to multiple factors. There are different hypotheses which propose the presence of one or more factors that trigger this inflammatory process, such as an alteration of the permeability of the intestinal mucous, an abnormal introduction of antigens to lymphocytes, and a loss or inhibition of the antigenic tolerance mechanism.

The alteration of the permeability of the intestinal mucous causes an excessive entry of antigens and, consequently, of their mediums. This context triggers an inflammatory response, with the release of prostaglandins, leukotrienes, Interleukin 1, Interleukin 6, Interleukin 8, and Alpha tumor necrosis factor (antigenic exclusion mechanism).

The persistence of altered permeability, or the existence of an abnormal immune response, establishes chronic inflammation. This alteration probably leads to a loss of the tolerance mechanism,
generating an immune response in the presence of food or bacterial antigens which are normally tolerated.

**CLINICAL SIGNS**

Clinical signs vary according to the portion or portions of the digestive tract affected. When the small intestine is infiltrated, the signs are partial anorexia or normal appetite, aqueous or steatorrheic fecal matter, increased volume of defecation, progressive weight loss, and may include sporadic vomiting, although the stomach is not directly compromised. If the colon is infiltrated, the signs will involve tenesmus, presence of mucous and fresh blood in fecal matter, increased number of daily defecations, partial anorexia or normal appetite and intermittent vomiting. In this case, weight loss is less frequent.

In cats, when the pathology is severe, in addition to the signs described, lethargy and depression are observed.

**DIAGNOSIS**

In order to diagnose IBD, a group of pathologies that induce vomiting and/or chronic diarrhea must be excluded. To this end, a coproparasitological analysis must be carried out to discard the presence of nematodes, Cestoda, Giardias, Cryptosporidium, etc. Blood tests must include a complete hemogram and blood biochemistry. This enables an assessment of the liver (ALT-AST-FAS), kidney (Urea- Creatinin), thyroid (T4), and adrenal (ACTH stimulation test) functions. In cats, it is additionally necessary to run FIV and FeLV tests.

The trypsin-like immune-reactive (TLI) test is useful for differential diagnosis of exocrine pancreatic deficiency. The serum values of B12 (cobalamin) and folate are useful for assessing ileum and jejunum absorption, respectively, and additionally for determining the presence of antibiotic-responsive diarrhea (ARD), also known as small intestine bacterial overgrowth (SIBO).

It is important to consider total protein and albumin counts to determine whether the condition is indicative of protein-loss enteropathy. Urine analyses are also necessary to determine whether loss of protein occurs via the urinary or intestinal tract.

Radiology is of little use for diagnosing IBD. Echography, on the other hand, enables determination of increased thickness of gastric or intestinal mucous, alterations to the stratification, and presence of reactive lymph nodes.

As part of the differential diagnosis, patients must be administered an antigen-free diet to discard food allergy.

Once these pathologies have been discarded, and a sure diagnosis has not yet been reached, an endoscopic biopsy must be carried out.
Macroscopic viewing is useful to determine the general condition of intestinal mucous, diagnose tumors, identify strictures, ulcerations, polyps, etc. Insufflation is more difficult in the presence of a process of stomach or intestinal mucous infiltration (due to greater resistance). Biopsies must be taken from several portions of stomach, small intestine or colon. Histopathological samples must be used to determine the predominant type of inflammatory cell, presence of pathological alterations (atrophy or fusion of intestinal villi, crypt collapse, fibrosis, etc), severity (slight, moderate or severe) and location of lesions (fundus or gastric antrum, jejunum, ileum, descending colon, etc). The histopathological analysis is highly significant. The pathologist must have perfect knowledge of the normal structure of the different portions of the digestive tract (for example, the lymphocyte population in the duodenum mucous is greater than in the jejunum), and consider the variations that may appear between different species.

TREATMENT

Pet owners must be informed that treatment of patients with IBD is NON-SPECIFIC due to lack of knowledge of the etiology or etiologies involved. At present, treatment involves the use of immunosuppressants, antibiotics and dietary changes. Treatment must be followed strictly in order to be successful. Additionally, the adverse effects of the use of glucocorticoids (at immunosuppressant doses) or immunosuppressant drugs must be known and accepted as part of the treatment.

Diet. In slight cases, often a mere diet modification will solve the problem. In other cases, this must be combined with medication. Diets must be highly digestible, hypoallergenic, balanced, palatable and low in fats. They must include an initial (novel) protein to which the patient has never been exposed before (lamb, soy, fish, rabbit, etc). A diet should not be hastily discarded when changes are not observed rapidly. In most cases, changes will only appear as from the fourth week or later. Commerially available hypoallergenic diets and diets with hydrolyzed proteins are generally useful. It is also advisable to supplement patients with Omega 3 fatty acids, which contribute to reduce the inflammation of the digestive tract. Whatever diet is selected (commercial or home-made), patients should be given 3 to 4 daily meals to improve digestion and nutrient assimilation.
Immunosuppressants

**Glucocorticoids:** in general, prednisone or prednisolone is used as the chosen drug for treating this group of pathologies. The dose generally ranges between 1-2 mg/kg at 12-hour intervals by the oral route. The dose is later reduced to half (for 4 weeks), and subsequently to the minimum effective dose administered every second day or discontinuation of treatment.

Cats affected by eosinophilic infiltrates can be given doses above 2-4 mg/kg at 12-hour intervals by the oral route, followed by a gradual dose reduction.

Dexametason can also be given via the oral route when patients display excessive side effects from the use of prednisolone (polyphage, polyuria, panting, etc).

Parenteral corticoids are an alternative for patients that display vomiting or when it is considered that digestive absorption may be altered by the infiltrating process.

Budesonide is a steroid that is two hundred times more powerful than hydrocortisone. Since it is largely destroyed (90%) when passing through the liver, it minimizes the risk of causing Cushing´s disease. The dose is 1 - 3 mg/day.

**Sulfasalazine:** This drug is a combination of 5-aminosalicylic acid and sulfapyridine, linked by an azo union. Once approximately 70 % of the dose administered reaches the colon, bacteria break up the azo union, splitting the two parts of the molecule. The half that is useful in this treatment for its anti-inflammatory properties is the 5-aminosalicylic acid portion. This is used to treat patients with colitis, generally obtaining a very good response. The dose used is 12.5 mg/kg at 6-hour intervals for 2 weeks in canines, followed by a similar dose at 12-hour intervals for 28 days.

Because cats are more susceptible to this drug, the dose used is 10-20 mg/kg daily for 14 days.

Side effects in both cats and dogs include anorexia and vomiting. Patients must be monitored closely, with a monthly hepatogram to prevent possible liver damage. Other possible side effects include dry keratitis or allergic dermatitis.

**Olsalazine:** this drug is made up by two 5-aminosalicylic acid molecules. It has been used in humans to replace sulfasalazize. The dose used in canines is 25 mg/kg/8 hours.

**Mesalamine:** this drug is also used for colon inflammatory pathologies. The dose used is 10-20 mg/kg/12 hs using the oral route.
**Azathioprine**: this immunosuppressant may be used when the response to conventional drugs is not good, or when a dose reduction is required due to the adverse effects of glucocorticoids. In canines, it can be used at a rate of 50 mg/m² or 1-1.5 mg/kg/day for 2 weeks, followed by administration every second day. In cats it is administered at a rate of 0.3-0.5 mg/kg at 48–72 hour intervals. Dogs must be checked periodically, running hemograms and hepatograms. In cats, it should be noted that this drug has a heightened myelosuppression effect, which requires weekly or fortnightly hemograms. Another side effect reported in cats is anorexia.

**Cyclophosphamide**: this drug is used infrequently for treating IBD in canines and felines, and is restricted to patients that are refractory to the treatments described above. The recommended dose is 50 mg/m² 4 days a week. Monthly hematology controls are required. Dog owners must be warned of possible hemorrhagic cystitis.

Some authors prefer to use **chloranbucyl** in stead of Azathioprine, especially in cats. The recommended dose is 2 – 4 mg/m² at 2 – 7 day intervals, or 10 mg/m² via the oral route at 14-day intervals.

**Cyclosporin**: this drug is a potent immunosuppressant that is frequently used in human medicine as part of the treatment in transplant patients. The dose used is 5 mg/kg/day. The greatest problem is its high cost.

**Antibiotics**: Metronidazole. This drug has antimicrobial (anaerobic) and antiprotozoan effects, and additionally inhibits the cell-induced immune response. It is generally not used alone, but combined with glucocorticoids. This allows a dose reduction. It can be used at a rate of 10-20 mg/kg/12 hours.

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3.2 DIFFERENTIAL DIAGNOSIS AND THERAPEUTICAL MANAGEMENT OF VOMITING PATIENTS

INTRODUCTION

The vomiting patient is among the regular daily clinical consultations. When an individual is compromised by acute gastroenteritis (infectious, toxic, parasitic disease, foreign body, etc.), it is usually easy to make a diagnosis and administrate successful treatment. However, when the symptoms persist for more time (weeks, months or years) the formulation of differential diagnoses and indication of complementary diagnostic methods may generate doubts, as may the implementation of effective treatment.

Vomiting may be triggered by stimuli reaching the vomit center (VC) either directly or indirectly. Patients with kidney or liver diseases or decompensated diabetic patients, present a high quantity of circulating toxins which stimulate emesis by acting on the VC or on the chemoreceptor trigger zone (CTZ). This stimulus may also originate in the central nervous system (tumor, hemorrhage or edema -related increased intracranial pressure), or from the peripheral or vagal route. The latter carries information from the digestive tract, as well as from the biliary ducts, urinary tract, internal genitals, mesentery, etc.

The vestibular apparatus can also induce vomiting in the presence of inflammation or infection of the middle or inner ear.

DIFFERENTIAL DIAGNOSIS

The first step in diagnosing a vomiting patient consists in performing a proper anamnesis and clinical examination. Initial differentiation must be based on regurgitation and productive coughing.

Regurgitation is caused by a passive mechanism that produces the expulsion of food or saliva from the pharynx or the esophagus through the mouth. It should be noted that this does not always occur immediately post ingestion. Unlike vomiting, regurgitation does not include a prodromic period, with a display of ptyalism, unrest, etc., or evident abdominal contractions.

When a vomiting condition has been established, emphasis must be made on the type of vomiting (food-related or otherwise), frequency, time at which it appears, relation to food intake, etc., as well as considering other symptoms.

Significant anamnesis data to be considered includes vaccination status, de-worming treatment administered, excessive intake of food, dietary changes, administration of drugs (AINES, digitalis, antibiotic, etc.), roaming habits, etc.
When this initial stage has concluded without leading to a sure diagnosis, a series of complementary methods must be requested to arrive at a conclusive diagnosis.

**BLOOD TEST**

**Hematology and blood biochemistry:** The following must be included: urea, creatinine (kidney assessment), total protein, albumin, ALT, AST and FAS (liver assessment). Clinical doctors usually include amylase, lipase, sodium/potassium ratio, glycemia, etc. according to the suspected diagnosis.

**IMAGE DIAGNOSIS**

**Simple X-Ray:** this method often contributes a definitive diagnosis (foreign bodies, tumors, intussusception, etc). However, some cases require the use of a contrast medium (barium) to improve visualization of the digestive tract.

**Contrast radiography:** this is useful for the assessment of partial obstruction of the digestive tract, gastric movement disorder (pyloric syndrome), or digestive mass not clearly visualized with a simple x-ray.

**Radioscopy:** this method allows the detection of pathologies that compromise the function and/or motility of the pharynx, esophagus, and stomach.

**Echography:** unfortunately, this method is only partially useful for exploring the digestive tract. It is however useful in the presence of a mass, or especially in the case of intussusceptions, and can even provide a definitive or certain diagnosis.

**Endoscopy:** this method is often used in the face of chronic pathologies for taking biopsy samples. Performing an endoscopy without taking a biopsy sample is completely inadequate and often useless, as certain pathologies are characterized for infiltrating the mucous membrane and are therefore invisible to the naked eye. The presence of masses, ulcerations, or anomalies requires a biopsy for histopathological analysis.

**TREATMENT**

**Causal Fluid therapy**

Patients with acute vomiting usually need fluid replacement. This is carried out conventionally by replacing pathological and contemporary losses with Ringer’s lactate, Ringer’s solution or
isotonic solution made up of sodium chloride with the addition of 20 meq/l Cl\textsubscript{K}. Maintenance is carried out with 5\% Dextrose and Ringer lactate in equal parts.

**Antiemetics**

D2 Dopaminergic Antagonists

Metoclopramide  This acts at the level of the chemoreceptor trigger zone (CTZ) and of the myoneural plate (peripheral effect). Metoclopramide increases the pressure of the lower esophageal sphincter (LES), stimulates stomach evacuation and coordinates motility between the stomach, pilorus and duodenum. It can cause side-effects such as hyperactivity or restlessness. Cats may display aggressiveness, confusion and a tendency to hide. These signs appear 20 to 30 minutes after administration of the drug and may last from 4 to 5 hours, but can be reverted with the use of Diphenhydramine. Metoclopramide must be used with caution in patients with kidney failure due to its anti-dopaminergic effect. It is contraindicated in patients with epilepsy or those that display a mechanical obstruction or bleeding of the digestive tract. The recommended dose is 0.2 - 0.5 mg/kg, \(6\) HS SC IM \(0\) for canines and felines \(C \& F\) or \(1 - 2\) mg/kg via continual IV infusion. Domperidone has a purely peripheral effect since it slowly and scarcely penetrates the hematoencephalic barrier. This drug stimulates stomach evacuation and improves coordination between the stomach, pilorus and duodenum. The recommended dose is \(0.1 - 0.3\) mg/kg. at 12 hr intervals via the oral or parenteral route.

\(\alpha\) 2 Adrenergic antagonists

Chlorpromazine  This phenothiazine by-product acts on the vomit center and on the chemoreceptor trigger zone. It also acts on other receptors, such as the dopaminergics, cholinergics and M1muscarinics. The recommended dose is 0.2 - 0.4 mg/kg/ 8HS SC/IM for canines and felines \(C \& F\) or \(1\) mg/kg./8 HS RECTAL \(C\). At this dose, the onset of sedative effects is highly unlikely. It can cause hypertension due to its alpha adrenergic blocking effect which causes arterial vasodilatation. This effect can be avoided by maintaining the patient under proper fluid therapy. Prochlorperazine acts at the central level (chemoreceptor trigger zone and vomit center), and is used at a rate of 0.5 mg/kg at 8 hr intervals via the parenteral route. It has the same side-effects as chlorpromazine.
**H 1 Histaminergic Antagonists**

The two drugs act on the CTZ and on the vestibular tract. Their most significant adverse effect is that they induce sleep. The dose used for Diphenhydramine is 2 - 4 mg/kg./ 8 hs orally or IM (C & F), and for dimenhydrinate 4 - 8 mg/kg. /8 hs orally (C & F).

**5-HT4 Serotonergic agonist**

**Cisapride** This drug has a peripheral effect, bonding with gastrointestinal cholinergic neuron 5-HT4 receptors and causing the contraction of the smooth muscle. It is a much more potent gastrokinetic drug than metochlopramide. Its effect on small intestine motility makes it useful for ileum treatment. It also has an effect on the colon, and can therefore be used in constipated patients. The recommended dose is 0.1 - 0.5 mg/kg/ 8 hs orally.

**5-HT3 Serotonergic Antagonist**

These drugs act on the chemoreceptor trigger zone and on the afferent vagal ducts. They can cause slight neurological signs such as head shaking, lip licking, etc. which usually disappear when treatment is discontinued. The dose used for ondancetron is 0.5 - 1 mg/kg/12 hs orally or parenterally; for Granicetron 0.5 - 1 mg/kg/12 hs orally or parenterally. Dolacetron may be used at a dose of 0.6 mg/kg/12 hs slow IV.

**Motillin Agonist**

**Erythromycin.** This macrolide which is used at lower doses than antibiotics, acts in a similar way to motillin (occupying its receptors), and is therefore used as a gastrokinetic. It is characterized for increasing pressure in the LES (cardia), accelerating stomach evacuation by stimulation of antrum contraction, and inducing small intestine contractions. The dose used is 0.5 - 1 mg/kg/8 hs orally (C & F).

Adverse effects are dose-dependent. They include anorexia, diarrhea, abdominal pain and skin allergies.

**Antacids**

In patients with persistent vomiting or chronic gastritis, it is common to evidence gastric and esophagus mucous erosion or ulceration. Consequently, the patient must be treated to reduce the secretion of acid by the stomach.

Antacids are classified according to the level at which they act.

**H2 Antagonists** These drugs block type 2 histaminergic receptors in parietal cells, reducing acid secretion. The antacids most widely used
in Veterinary Medicine are cimetidine, at a rate of 5 - 10 mg/kg/ 6-8 hs orally or SC (C & F), or 10/mg/kg EV (slow infusion for 30 minutes); ranitidine, at a rate of 1- 4 mg/kg/12 hs SC or IV (C & F); and famotidine, at a rate of 0.3 - 0.6 mg/kg/ 8-12 hs orally (C). Nizatidine is a new antacid for which the dose in Veterinary Medicine has not been established yet.

**Cell membrane ATPase mechanism**

**Inhibitors**

**Omeprazole.** This benzimidazole by-product is a potent inhibitor of acid secretion. The recommended dose is 0.7 - 2 mg/kg/ 24 hs. Orally.

**INTRACELLULAR AND MEMBRANE INHIBITORS**

Mysoprostol is a synthetic prostaglandin that increases the blood flow in the gastric mucous, and increases the production of bicarbonate in the gastric mucus layer. The dose used is 1-3 mg/kg/ 8-12 hs orally (C).

Due to its effect on intestinal motility (diarrhea), it must be used with precaution in patients with gastroenteritis.

**Oral antacids**

Aluminium hydroxide, calcium carbonate and magnesium hydroxide have been used for a long time as gastric mucus protectors. Their use in Veterinary Medicine is reduced due to the difficulty in administering them, the possible rebound and their short activity.

On the other hand, **sucralfate** (octo sucrose sulfate combined with aluminium hydroxide) is a gel that sticks to the surface of ulcers (precipitation on proteins), protecting them from acid and pepsin activity. It also stimulates the local secretion of prostaglandins, generating a cytoprotective effect that helps in the treatment of erosive or ulcerating processes. The recommended dose is 125 - 250 mg 8-12 hs orally (F) and 250 - 1000 mg 8-12 hs orally (C).

**Diet:** If a patient displays acute vomiting, it must be kept from ingesting liquids or solids for 24 hours. Once vomiting has been controlled, a liquid (water) diet is commenced with small volumes taken at frequent intervals. If liquids are well tolerated, a semi-soft liquid diet is given (small portions several times a day), consisting basically of a source of carbohydrate (rice, potato, pasta, etc), a highly-digestible hypoallergenic protein (dairy products, soy), and little or no fats, since these delay stomach evacuation. There are commercial diets available that are suitable for patients with digestive pathologies.

Once the patient has recovered, it may return gradually to its regular diet.
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