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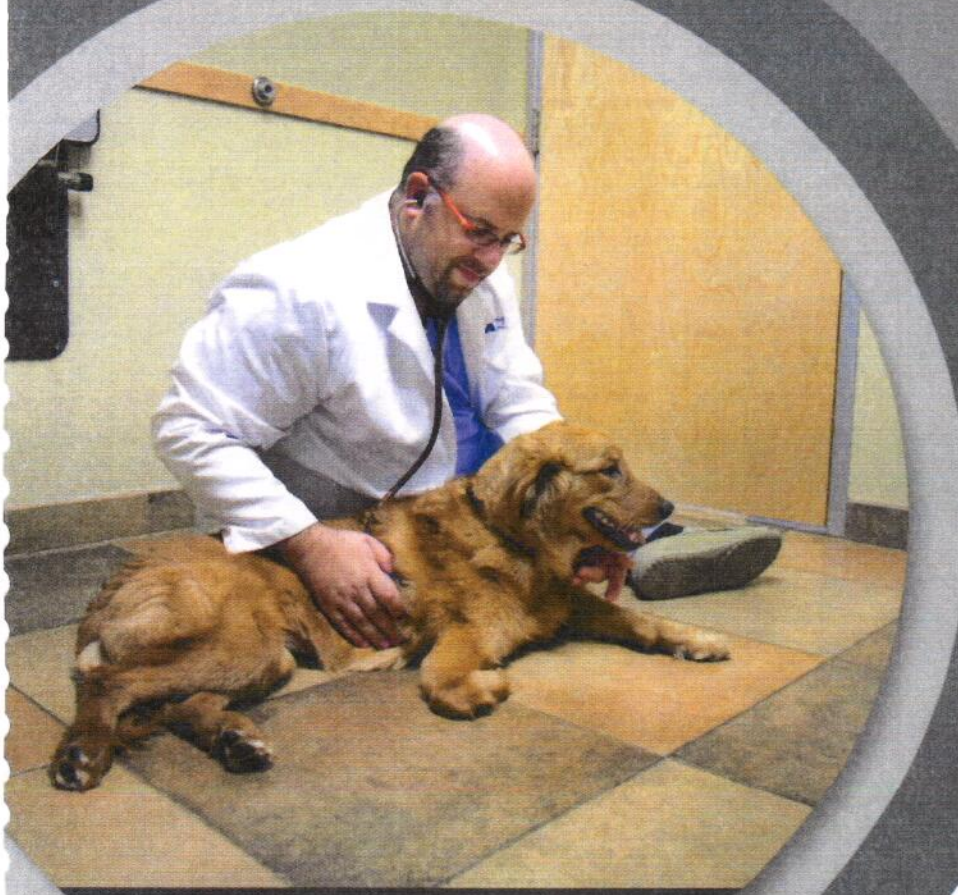

VCA Midwest Veterinary Referral & Emergency Center

HEPATIC ENCEPHALOPATHY

Christopher G. Byers, DVM, DACVECC, DACVIM (SAIM), CVJ
Omaha, Nebraska

Hepatic encephalopathy (HE) is a multifactorial neurologic syndrome that occurs when hepatic dysfunction (>70% function loss) causes systemic biochemical alterations that induce disruptions of cerebral metabolism. Clinical and biochemical abnormalities associated with this syndrome cannot be sufficiently explained by any single hepatic or cerebral metabolic defect. Hepatic encephalopathy is most frequently reported in dogs is portosystemic vascular anomalies.

Three types have been categorized:

- Type A – associated with acute hepatic failure
- Type B – associated with portosystemic vascular anomaly without intrinsic hepatic failure
- Type C – associated with marked hepatic parenchymal disease and portal hypertension

Several theories have been proposed to explain the clinical manifestation of HE:

- Hyperammonemia
  - Ammonia-rich blood bypasses hepatic parenchyma in the presence of an extra-hepatic portosystemic vascular anomaly.
  - Glutamate in astrocytes is converted to glutamine in the presence of ammonia; glutamine formation is increased, but secretion is impaired in hyperammonemic states, thus inducing cellular swelling and neuronal edema.
  - Glutamine in mitochondria is converted by glutaminase into glutamate and ammonia, inducing reactive oxygen and nitrogen species formation.
- Inflammation
  - Proinflammatory cytokines alter astrocyte glutamate uptake, expression of gamma aminobutyric (GABA) receptors, and blood-brain permeability.
- Glutamate transmission defect
  - Hyperammonemia reduces glutamate uptake by astrocytes secondary to down-regulation of glutamate transporter GLT-1.
- Gamma-aminobutyric (GABA) agonist elevations
  - Liver dysfunction is associated with reduced GABA clearance, and Type A hepatic encephalopathy is associated with a hyperpermeable blood-brain barrier. Subsequently cerebral GABA levels increase to inhibit neurotransmission through hyperpolarization of neuronal membranes.
- Benzodiazepine-like substances elevations
  - Benzodiazepine-like substances may come from vegetables, certain medications and may be produced by the intestinal microbiota.
  - The number of astrocyte-associated benzodiazepine receptors is increased in hepatic encephalopathy; these receptors are involved with the formation of tetrahydroprogesterone and tetrahydrodeoxycorticosterone (both potent GABA receptor agonists).
- Serotonergic system defect
  - Elevated levels of serotonin, its receptor, and monoamine oxidases have been documented in patients with hepatic encephalopathy.
- Amino acid metabolism alteration
  - Plasma concentrations of aromatic amino acids (AAA) increase due to reduced hepatic extraction, and elevated AAA levels overwhelm normal AAA metabolic pathways; use of alternative metabolic pathways results in the formation of octopamine and phenylethanolamine, both false neurotransmitters that block normal catecholamine activation.
- Manganese toxicity
  - Elevated cerebral manganese levels have been associated with altered cerebral metabolism, reduced glutamate uptake by astrocytes, and modified glutamatergic and dopaminergic neurotransmission.
- Neurotransmitter alterations
  - Taurine levels have been directly correlated with the severity of hepatic encephalopathy
  - Intestinal microbiota produce multiple neurotransmitters that have been implicated in hepatic encephalopathy.

CLINICAL FEATURES

The Clinical signs of HE can be readily divided into two groups: signs associated with hepatic failure and signs referable to the CNS. Hepatic failure signs are non-specific, and include anorexia/hyporexia, nausea, diarrhea, depression, weight loss, lethargy,

and/or polyuria/polydipsia. Common CNS signs are behavioral changes, aggression, compulsive behaviors, head pressing, tremors, vocalization, blindness, deafness, stupor, seizures and coma. Cumulatively, clinical signs are divided into four stages, and patients commonly fluctuate episodically between stages.

- Stage I: confusion, hyporexia, dull mentation or irritability, but may appear normal
- Stage II: dull mentation, cortical blindness, ptyalism, lethargy, ataxia, personality changes
- Stage III: stupor, confusion, marked ptyalism (cats), seizure activity, copper-colored irises (cats), occasional aggressive
- Stage IV: recumbency, coma that may rapidly lead to death

THERAPY

Three goals of the management are (1) to reduce the incidence of predisposing factors, (2) to alleviate neurologic signs, and (3) to determine the primary underlying hepatic disease. Acutely patients benefit from medications to reduce cerebral edema and possible anticonvulsants. Mannitol (0.5 – 1.5 gm/kg IV over 10-20 minutes) induces osmotic fluid shift, reduces cerebrospinal fluid production, decreases blood viscosity, and serves as a free radical scavenger. Levetiracetam (20 mg/kg IV q8 hr) and sodium bromide (600-1200 mg/kg IV over 8 hr, diluted in a 3% solution with 1L sterile water) are effective anti-convulsants. Administration of benzodiazepine antagonists (flumazenil @0.02 mg/kg IV; sarmazenil @ 3 mg/kg IV) may be beneficial in comatose patients.

Chronic therapy chiefly targets the intestinal microbiota to reduce plasma ammonia levels. Interventions may include administration of a non-absorbable disaccharide, antimicrobial(s), and probiotic(s). Lactulose (1-3 mL/kg PO q6-8 hr; dose adjusted so patient produces 2-3 soft bowel movements per day) is very effective, and can also be administered per rectum in those with incomplete swallowing reflex (5-10 mL/kg cleansing warm water enema followed by 5-10 mL lactulose diluted 1:3 q8 hr). Upon exposure to lactulose, the intestinal microbiota produce various acids (acetic, butyric, propionic and lactic) to form an acidic environment that promotes conversion of ammonia to ammonium, the latter of which is subsequently eliminated in feces. Lactuose also induces osmotic diarrhea that increases colonic motility and reduces ammonia-producing microbiota. Antibiotics (neomycin @ 20 mg/kg PO q6-12 hr; metronidazole @ 7.5 mg/kg PO q12 hr; Clavamox @ 13.75 mg/kg PO q12 hr) decrease bacterial deamination and reduce the production of aromatic amino acids, short chain fatty acids, mercaptans and false neurotransmitters. Probiotics may modify pathogenic bacterial substrates and decrease plasma ammonia levels. Novel interventions include administration of zinc (1-3 mg elemental zinc/kg PO q24 hr; target level is 200-500 ug/dL) to impair urea cycle enzymes / nitrogen detoxification and L-Dopa (dogs: 6.8 mg/kg PO once; then 1.4 mg/kg PO q6 hr) to increase renal ammonia excretion.

PROGNOSIS

Reported negative prognostic factors are hyperbilirubinemia, prothrombin time >100 seconds, idiosyncratic drug reaction, viral hepatopathy, and/or extreme ages. The prognosis for patients with acute hepatic failure is guarded. Common causes of death are cerebral edema, hemorrhage and/or sepsis. Prognosis is fair-to-good with surgical attenuation of EH-PSVA, and guarded-to-fair with coil embolization of IH-PSVA. Similarly, the prognosis is guarded to fair for those patients with chronic liver disease. If clinical signs do not resolve within 72 hours, investigation for a persistent precipitating factor is recommended.

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AN UPDATE ON GASTROESOPHAGEAL REFLUX DISEASE

Jessica M. Clemans, DVM DACVIM (SAIM)
Omaha, Nebraska

INTRODUCTION

Gastroesophageal reflux disease (GERD) is becoming progressively more recognized in canine and feline patients as a cause of discomfort and recurrent chronic illness. Clinical signs are most commonly referable to the esophagus, stomach, and proximal small intestines, and may include:

- Esophagus: regurgitation, dysphagia
- Stomach and Proximal Small Intestines: nausea, ptyalism, hyporexia, weight loss, discomfort

Clinical signs of GERD are not always obviously gastrointestinal in nature. Those patients with chronic coughing, sneezing, and/or intermittent nasal discharge should also be evaluated for GERD. Reflux may be aspirated and/or nasal tissues may be exposed to reflux resulting in upper and/or lower airway inflammation +/- infection.

DIAGNOSIS

Testing will initially be directed at evaluating the esophagus and any other the organ of interest (i.e.: don't forget the chronic coughers and snufflers!). Thoracic radiography may identify a dilated distal esophagus. Fluoroscopy may afford visualization of reflux. Esophagoscopy is uniquely beneficial, and common findings include:

- Fluid or foam
- Hyperemia
- Ulcers and erosions, particularly to the lower esophageal sphincter
- Dilation of the lower esophageal sphincter

Endoscopic evaluation of the oropharynx and lower airways may reveal erythema, edema, erosions/ulcers in those with chronic respiratory signs.

TREATMENT

Therapeutic goals include reducing the acidity of gastric fluid and promoting proper gastrointestinal motility. Interventions to achieve these goals include:

Dietary Manipulation

Feeding a diet with lower fat and moderate protein content may help reduce gastrin production to subsequently raise gastric pH. Some readily available prescription diets that may be appropriate to feed GERD patients include Royal Canin Gastrointestinal Low Fat, Hill's Prescription Diet i/d low fat, Purina OM, Hill's Prescription Diet w/d. Feeding frequent, small meals may also help control gastric acid production.

Antacids

Proton pump inhibitors/PPIs (e.g. omeprazole, pantoprazole) and H2 antagonists (e.g. cimetidine, famotidine, ranitidine) are used to treat patients with GERD. H2 antagonists are not as effective as PPIs for raising gastric pH, but oral PPIs do not exert their benefits immediately. Furthermore, long-term administration of PPIs to humans has been associated with bacterial overgrowth, calcium/phosphorus imbalance, and acute kidney injury. The effects of H2 antagonists are variable. Famotidine has been shown to be more effective than other medications in this class, and has a large margin of safety. Cimetidine has been associated with more side effects, and may affect the metabolism of other medications. Ranitidine is not consistently effective in veterinary patients. Serial monitoring is recommended for patients receiving chronic H2 antagonists and/or PPIs.

Pro-Kinetic / Esophageal Sphincter Tone Therapy

Pharmacologic intervention to improve the tone of the lower esophageal sphincter is often beneficial. Administration of metoclopramide may be helpful. Administration of ondansetron, a 5HT3 serotonin antagonist, may also exert benefits. Patients who are actively vomiting should be treated aggressively, and maropitant (NK1 antagonist) is frequently helpful. Administration of erythromycin that stimulates small intestinal motilin receptors can also promote appropriate peristalsis, subsequently reducing the incidence of reflux.

Mucosal Protection

Administration of sucralfate as a slurry to coat the esophageal and gastric mucosa provides mucosal protection and helps prevent progression of erosive/ulcerative disease.

Multimodal therapy should be provided for at least one month. At that time, medications may be gradually tapered and discontinued if clinical signs are appropriately controlled. Medications should be weaned/discontinued one at a time. Complete resolution of clinical signs is not always possible, and some patients require lifelong therapy.

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PROTEIN LOSING NEPHROPATHY

Jessica M. Clemans, DVM DACVIM (SAIM)
Omaha, Nebraska

INTRODUCTION

Protein loss at the level of the kidney is important to recognize. Protein is damaging to the kidney tissue and has been associated with increased mortality in cats and dogs no matter in what health state they are. Dogs with a UPC >1.0 have diseases associated with increased risk of uremic crisis, morbidity, and mortality.

URINE

Urine is the most overlooked, but easiest to obtain fluid sample. You do not need a sample collected by cystocentesis for a valid sample every time. However, to truly identify "renal" cause of proteinuria, sterile sample needed. A free catch or catheterization sample can be good if the urine is inactive and effective for monitoring.

TESTING

What do I mean by saying urine is inactive? An inactive urine is one whose sediment has no casts, bacteria, sperm, or too much blood (e.g. gross hematuria, TNTC RBCs, pyuria). Urine doesn't have to be isosthenuric to have significant proteinuria. When do you run a UPC? What type of patients are you evaluating? What triggers you to submit a UPC? Most often you are dealing with a chronic disease process.

Laboratory results that lead one to evaluate a UPC include azotemia, thrombocytopenia, anemia, elevated ALP, protein on dipstick (with inactive sediment), and PLI elevations. Urine dipsticks may be falsely positive for proteinuria when pH >7.5. A negative urine dipstick is a true negative. When in doubt, recheck a fresh sample two weeks later. If a patient has persistent renal proteinuria, s/he has kidney disease no matter the creatinine value. There are three basic kidney statuses that exist with renal proteinuria: progressive chronic kidney disease, temporarily stable/subclinical CKD, and indefinitely stable/subclinical CKD. An apparently stable or nonclinical CKD patient still needs therapy and monitoring to give a longer functional renal life.

PERSISTENCE, LOCALIZATION, MAGNITUDE

Persistence

To document persistence, one needs to document proteinuria in three samples collected at least two weeks apart with no concurrent evidence of post-renal proteinuria. Microalbuminuria may be the only evidence of a persistent kidney insult. A thorough diagnostic investigation and appropriate therapy should be recommended and initiated.

Localization

When you have documented persistent proteinuria, a thorough diagnostic investigation is warranted to screen for major possible underlying contributing etiologies, including:

- Primary renal disease: Documenting proteinuria is part of the IRIS staging system. Persistent proteinuria has been associated with complications and acute worsening of renal function. This finding provides justification for specific therapies to help prolong the effective life of the kidney.
- Cardiac patients: Proteinuria is a marker of more severe disease and of early kidney disease. As cardiac patients with kidney disease need more frequent monitoring and care, it is important to recognize.
- Immune-mediated disease: Proteinuria may be associated with certain diseases, including systemic lupus erythematosus that is associated with a glomerulonephritis.
- Infectious disease: either this recommends you look for protein or it is a signal to look for infections.
- Chronic inflammatory diseases: Many chronic diseases, including IBD, atopy, recurrent skin infections, chronic hepatitis, long standing osteoarthritis, may cause proteinuria.
- Hypertension: Elevated blood pressure will damage the glomerulus.
- Endocrinopathies: Hyperadrenocorticism (both typical and occult) and hyperthyroidism commonly induce proteinuria.
- Neoplasia: multiple myeloma, lymphoma, hemangiosarcoma
- Exogenous corticosteroid use/administration

Magnitude

The higher the UPC, the higher morbidity and severity.

- UPC < 0.2: non-proteinuric (dog and cat)
- 0.2-0.5 (dog) or 0.2-0.4 (cat): borderline, treat any underlying disease and reassess in 2 months
- >0.5 (dog) or >0.4 (cat): proteinuria

Furthermore, a persistent UPC >/= 2.0 is most frequently the result of significant glomerular. Some studies have shown cats with a UPC > 0.3 have less chance of surviving an illness. UPCs can vary up to 40%, especially when present in small amounts; thus one should pay particular attention to borderline UPC values.

THERAPIES

We need to treat any underlying disease process and reassess in 2-4 weeks after "control "or resolution of disease.

Dietary

An appropriate diet is moderately protein restricted, but contains a high quality protein source. Supplementation with omega-3 fatty acids is also beneficial. Elevated omega-6 fatty acids augment proteinuria, so if start an over the counter fish oil and the UPC elevates, double check the omega source. One should recheck renal values, BP, UA, UPC two weeks after starting supplementation to determine if a dose adjustment is needed.

Medications

- Angiotensin-converting enzyme inhibitor (ACE-I)
- Doxycycline: sometimes this is with or without documented HW, Tick, or leptospirosis.
- Amlodipine: This is when hypertension is not controlled by ace-inhibitor alone. Recheck in one week BP; if BP is approaching goals then recheck renal values, BP, UA, UPC.
- Angiotensin II Receptor Antagonists (e.g. losartan, telmisartan): This class of drug compliments an ACE-I and may be more helpful in reducing proteinuria than an ACE-I. It has been shown to work well for humans, but limited research has been done in veterinary medicine.
- Immunomodulatory therapy (e.g.: chlorambucil): Due to risks, it is best to rule out as many other diseases as possible and ideally have a kidney biopsy.
- Anti-platelet & anticoagulant medications (e.g.: aspirin, clopidogrel, enoxaparin): These interventions are beneficial for patients with either UPC >2.0, hypoalbuminemia, low antithrombin level, and/or suspicion of thromboembolism. There is an expense and injection concern with enoxaparin, but in patients that have recurrent or devastating clots, I recommend this.

RECHECKS

The therapeutic goal is at least a 50% reduction in UPC. One should make sure azotemia, if present, is not worsening and that other renal values, including albumin, remain unchanged. Recheck examinations should look for changes that would most commonly occur in patients with kidney disease (e.g.: hypertension). Chronic recheck examinations typically occur every 4-6 months, and include CBC, Chemistry, UA, UPC, BP, and urine culture (at least yearly urine culture). Any sign of illness warrants a patient reevaluation.

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UPDATE ON LARYNGEAL PARALYSIS

Marina Manashirova, DVM, DACVS
Omaha, Nebraska

ANATOMY OF THE LARYNX

The larynx is a semi-rigid organ composed mainly of hyaline cartilage and muscles. The cartilages of the larynx include epiglottic, paired arytenoid, sesamoid, inter-arytenoid, thyroid and cricoid cartilages. The arytenoid cartilages have the following processes: corniculate which form the dorsal margin of the laryngeal inlet, cuneiform which form the most of the lateral border of the laryngeal inlet and serves as an attachment of ventricular ligaments and ventricularis muscles, vocal processes serve as an attachment of vocal ligament, and muscular processes are the insertion of cricoarytenoideus dorsalis muscles. The larynx is innervated by cranial and caudal laryngeal nerves, branches of the vagus nerve which originates from the caudal nucleus ambiguus in the medulla. The cranial laryngeal n. supplies the cricothyroideus muscle and receives sensory fibers from mucosa cranial to the vocal folds and serves as afferent limb of cough reflex. The caudal laryngeal nerve is a terminal segment of recurrent laryngeal nerve (RLN) and supplies all intrinsic laryngeal muscles (except crycothyroideus muscle). The left RLN arches around the aorta and ascends on the left side of the trachea, whereas the right RLN arches around the right subclavian artery and ascends on the right side of the trachea. As the RLNs ascend, they give rise to the paralaryngeal recurrent nerves that run parallel to the RLN and supply sensory innervation to the esophagus and trachea.

LARYNGEAL PARALYSIS

As a dog pants in attempt to thermoregulate, the respiratory rate increases, as does the velocity of air passing through the larynx, leading to a turbulent airflow and negative intraglottic pressure. Excessive negative pressure can lead to secondary elongation of the soft palate and eversion of the laryngeal saccules. The constant rubbing of the arytenoid cartilages against each other can result in mucosal ulcerations and edema at the level of the corniculate processes (Monnet & Tobias 2012). Dysphonia is caused by the inability to tense the vocal cords, which results in the dog's voice changing to a weak, hoarse bark (Kitshoff et al. 2013). Paradoxical movement in dogs occurs when the increased negative airway pressure during inspiration results in adduction of the arytenoids and the positive pressure during expiration results in passive return of the arytenoids to their resting position (Monnet & Tobias 2012). Congenital laryngeal paralysis has been reported in Bouvier des Flandres, Siberian Huskies, Bull terriers, Dalmatians, white-coated German shepherd dogs, Pyrenean mountain dogs, Afghan hounds, cocker spaniels, dachshunds, miniature pinchers (Monnet & Tobias 2012; Ridyard et al. 2000; Gabriel et al. 2006) due to motor neuron loss in the nucleus ambiguus. Also, in Dalmations and Rottweilers due to axonal degeneration and loss of myelinated nerve fibers of the RLN and paralaryngeal nerves (Mahony et al. 1998; Braund et al. 1994). Acquired laryngeal paralysis etiologies reported include: idiopathic or geriatric onset laryngeal paralysis polyneuropathy, trauma/infection/mass in the cervical or thoracic region, caudal brainstem disease, endocrine diseases (hypothyroidism and hypoadrenocorticism), myasthenia gravis, paraneoplastic syndromes, idiopathic myositis, systemic lupus erythematosus, organophosphate toxicity, polyradiculoneuritis (Coonhound paralysis), and Rabies (Monnet & Tobias 2012). In the past decade, several studies have investigated the theory of the condition suspected as idiopathic laryngeal paralysis being a part of a generalized, progressive neuromuscular disorder recently referred to as "geriatric-onset LP polyneuropathy" syndrome (GOLPP) (Wilson et al. JAVMA 2016; Thieman et al. 2010; Bookbinder et al. 2016; Andrade et al. 2015; Jeffery et al. 2006; Stanley et al. 2010). Concurrent neurological exam abnormalities are noted in 22-50% of dogs presenting with acquired laryngeal paralysis. Several studies have documented abnormalities on electromyography, nerve conduction studies and muscle/nerve histopathology in dogs with acquired laryngeal paralysis (Thieman et al. 2010; Andrade et al. 2015; Jeffery et al. 2006). Preoperative esophageal dysfunction appears to increase the odds of postoperative complications and is thought of as an another sign of GOLPP (Bookbinder et al. 2016; Wilson et al. 2016). The common presentation for acquired laryngeal paralysis is a Labrador Retriever, male castrated, median age of 9 years olds with clinical signs stridor and exercise intolerance. Treatments may include conservative or surgical. Surgical treatments include unilateral arytenoid lateralization (most commonly performed), partial laryngectomy, bilateral ventriculocordectomy, castellated laryngofissure, or permanent tracheostomy. Postoperative complications encountered in 10-58% of patients. Most common complications include: aspiration pneumonia (10-32%), recurrence of clinical signs (4-20%), persistent stridor (13%), persistent coughing/gagging after eating (30%) (Monnet & Tobias 2012; Wilson et al. 2016). Improvement of clinical signs and quality of life after surgery is reported in 88-90% of patients (Snelling et al. 2003; Monnet & Tobias 2012). Survival times for dogs with acquired laryngeal paralysis undergoing unilateral arytenoid lateralization are 94% at 1 year and 75% at 4 year follow up (Wilson et al. 2016).

CONCLUSION

Although there is evidence that dogs presenting with acquired laryngeal paralysis may eventually develop clinical signs of a generalized neuromuscular disorder, this should not discourage recommendation for treatment (conservative or surgical as indicated). Laryngeal paralysis can be a life-threatening condition, thus treatment is warranted and has been shown to improve quality of life and survival times.

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DIAGNOSIS AND TREATMENT OF FELINE ASTHMA INCLUDING USE OF INHALED MEDICATIONS

Philip Padrid, DVM
Albuquerque, New Mexico

INTRODUCTION

Chronic bronchial disease in cats occurs most commonly in two forms, including chronic bronchitis and asthma. *Chronic bronchitis* is defined as an inflammatory disorder of the lower airways that causes a daily cough, for which other causes of cough (including heart failure, pneumonia, neoplasia etc) have been excluded. *Asthma* is more loosely defined as that disorder of the lower airways that causes airflow limitation, "that may resolve spontaneously or in response to medical treatment". The symptoms of asthma can be dramatic, including acute wheeze and respiratory distress. Sometimes however, the only symptom of asthma is a daily cough, and in human patients this is referred to as "cough-variant" asthma.

Chronic bronchitis is diagnosed by excluding other disorders that cause daily cough. Definitive diagnosis of asthma is usually based on specific pulmonary function studies that require patient cooperation. Because both disorders, bronchitis and asthma, can cause a daily cough as the only clinical sign, there are many times when it is not possible to distinguish one from the other in an individual feline patient. Nevertheless, the diagnosis, prognosis and treatment options for both diseases overlap with great frequency.

DIAGNOSIS

There are no specific tests in general practice that can be used to definitively diagnose asthma or bronchitis in cats. Therefore, we rely upon clinical criteria, including:

1. A history of (some or all of these clinical signs) cough, acute wheeze, tachypnea and respiratory distress including labored, open mouth breathing. This is usually quickly relieved with some combination of oxygen, bronchodilators, and corticosteroids.
2. Radiographic evidence of bronchial wall thickening, which is usually described as "doughnuts" and "tramlines." Radiographs may also demonstrate atelectasis, most commonly of the right middle lung lobe. It is usually easier to see this pattern on a DV or VD exposure because the right middle lung lobe silhouettes with the base of the heart on the lateral view. Atelectasis most commonly occurs in the right middle lung lobe because of mucus accumulation within the bronchus, and this airway is most commonly involved because it is the only airway that has a dorsal/ventral orientation within the bronchial tree, and therefore subject to the effects of gravity. Air trapping may also be demonstrated by hyperinflated airways. This is seen most prominently on the lateral view and can be appreciated by recognizing the position of the diaphragmatic crus at approximately the level of L1-L2.
3. Response to therapy is an important diagnostic measure. Cats with asthma may stop coughing or wheezing within 10 minutes after administration of a bronchodilator. The great majority of cats with bronchitis or asthma respond to high dose corticosteroid therapy within 5-7 days (see below under treatment). If your patient with bronchitis or asthma does not respond in this manner it is time to reevaluate the diagnosis.

PATHOPHYSIOLOGY

In the simplest terms, airways are tubes. They may be thought of as the plumbing system of the lung, and the primary purpose of the airway tree is to bring air from the environment into the lung for gas exchange. Although the potential causes of bronchitis and asthma are numerous, the airways are capable of responding to noxious stimuli in only a limited number of ways. Airway epithelium may hypertrophy, undergo metaplastic change, erode, or ulcerate. Airway goblet cells and submucosal glands may hypertrophy and produce excessive amounts of viscid mucus. Bronchial mucosa and submucosa are usually infiltrated with variable numbers and types of inflammatory cells and may become edematous. Bronchial smooth muscle may remain unaffected, become hypertrophied, or spasm. In almost all cases, the unifying and underlying problem is chronic inflammation, whereas the exact cause remains unproved.

The resulting clinical signs of cough, wheeze, and lethargy are due to limitation of air flow from excessive mucus secretions, airway edema and airway narrowing from cellular infiltrates. Cats with asthma may additionally suffer acute airway narrowing from airway smooth muscle constriction. A 50% reduction in the luminal size of an airway results in a 16-fold reduction in the amount of air that flows through that airway. Clearly then, small changes in the size of the airway result in dramatic changes in air flow. The clinical implications of this finding are twofold. First, relatively small amounts of mucus, edema, or bronchoconstriction can partially occlude airways and cause a dramatic fall in air flow. Conversely, therapy that results in relatively small increases in airway size may cause a dramatic improvement in clinical signs.

CLINICAL FINDINGS

Clinical Signs

Clinical signs are variable. Bronchitic cats have a daily cough, and may be absolutely symptom free in between episodes of cough. Alternatively, cats with bronchitis may be tachypneic at rest. Asthmatic cats may cough, wheeze, and struggle to breath on a

daily basis. In mild cases, symptoms may be limited to occasional and brief coughing. Some cats with asthma may be asymptomatic between occasional episodes of acute airway obstruction. Severely affected cats may have a persistent daily cough and experience many episodes of life-threatening acute bronchoconstriction.

As previously outlined, a common problem for the practitioner is to distinguish between chronic bronchitis and asthma as the cause of a chronic cough in cats. Although these two disorders are frequently lumped together under the title of *chronic bronchial disease* or *lower airway disease*, the two disorders may require different therapeutic approaches and often have different prognoses. All cats with chronic bronchitis, by definition, have daily cough. Some cats with asthma may be asymptomatic between occasional episodes of acute airway obstruction. Other asthmatic cats may cough occasionally and demonstrate frequent tachypnea. Importantly, asthmatic cats, but not bronchitic cats, may benefit from bronchodilator treatment (see the section on therapy).

DIAGNOSTIC TEST FINDINGS

Physical Examination

There are no physical examination findings that can be relied on to make the diagnosis of asthma. In fact, cats with bronchitis or asthma may have a normal physical examination at rest. Conversely, respiratory distress primarily during the expiratory phase of breathing is the hallmark of these disorders in cats. Adventitious sounds, including crackles are often heard. Wheezes are more characteristic of feline asthma.

Thoracic Radiographs

Routine survey chest radiographs may be normal and should not cause the practitioner to abandon the diagnosis of asthma. Frequently, however, radiographs may demonstrate diffuse prominent bronchial markings consistent with inflammatory airways. Radiographic signs of increased lung lucency and flattening and caudal displacement of the diaphragm represent hyperinflation and suggest air trapping. In the author's experience, approximately 10% of chest radiographs of cats with bronchial disease have increased density within the right middle lung lobe associated with a mediastinal shift to the right. This is evidence of atelectasis. In more extreme cases, you may appreciate fluffy ill-defined heavy interstitial infiltrates in multiple lung lobes. The cause of these changes in cats with lower airway disease may be multiple small areas of atelectasis in multiple lung lobes resulting from multiple diffuse small mucus plugs. This presents a diagnostic challenge because this radiographic change is consistent with a number of disorders including neoplasia and diffuse interstitial pneumonitis.

THERAPY

Treatment of bronchial disease in cats is multifactorial, and includes environmental changes as well as drug therapy. Because there are limitations on the length of this manuscript, we will limit our discussion to newer inhaled medications. A thorough review of treatment options will be presented in lecture.

INHALED MEDICATIONS

Aerosol delivery

Aerosol administration relies upon the delivery of drug to distal airways, which in turn depends on the size of the aerosol particles and various respiratory parameters such as tidal volume and inspiratory flow rate. Even in such co-operative patients as humans, only approximately 10-30% of the inhaled dose enters the lungs. Recent studies in cats have demonstrated that passive inhalation thru a mask and spacer combination (aerokat) is an effective method of delivering sufficient medication to be clinically effective.

Delivery Technique

Drugs for inhalation typically come in a rectangular metered dose inhaler (MDI) or a round "diskus" form. At the present time, only the MDI form is practical for use in animals. The most effective means of using an MDI requires that inhalation be purposefully coordinated with actuation of the device. This coordination cannot be reliably done in most infants, small children, or animals. An alternative method was developed to allow children and animals to use MDIs without the need to coordinate their breathing patterns. In dogs and cats, this method involves the use of a spacer device and a mask specifically designed for them. Small, aerosol-holding chambers are attached to an MDI and a mask. The spacer is approximately the size of the inner cardboard roll used with toilet paper. The MDI fits on one end of the spacer, and the other end of the spacer has an attachment for the face mask. The MDI supplies precise doses of the aerosol drug, and the holding chamber contains the aerosol so it can be inhaled when the patients breathes. The mask is designed to cover the nose of the cat.

The MDI is first shaken to open an internal valve within the canister, and then it is attached to the spacer. The mask attached to the other end of the spacer is placed snuggly on the animal's nose.

Inhaled Corticosteroids

Fluticasone propionate (Flovent®)

The most commonly used inhaled corticosteroid is fluticasone propionate. Fluticasone propionate is a synthetic corticosteroid that has 18-fold greater affinity for the corticosteroid receptor compared with dexamethasone, the reference standard for corticosteroid potency. Flovent® is a large molecule and acts topically within the airway mucosa. As there is poor absorption across gut epithelium there is minimal oral systemic bioavailability; thus plasma levels do not predict therapeutic effects. This explains the lack of systemic side effects. However, it also suggests that clinically effective absorption into the airway mucosa is delayed. Optimal clinical effects therefore may not occur for 1-2 weeks. Flovent® comes in three strengths: 44 ug, 110 ug, and 220 ug per actuation. For cats with mild/moderate disease, 110 ug given twice daily frequently results in clinical responses equivalent to that achieved by administration of oral doses of prednisone 5 mg PO BID. Cats with more serious disease may require twice this dose (220 ug inhaled BID). Administration of Flovent® in excess of twice daily has not resulted in greater clinical efficacy in the author's experience.

Albuterol Sulfate

Albuterol is a selective beta2-adrenergic bronchodilator. This drug is available through different manufacturers and is commonly prescribed as Ventolin or Proventil. Albuterol only comes in a single uniform strength (i.e., 90 µg per inhalation). Albuterol usually results in relaxation of airway smooth muscles within 1 to 5 minutes, so the effect is almost immediate. This drug should be used in animals with documented or assumed bronchoconstriction. Symptoms that may indicate bronchoconstriction are wheeze, noisy lower airway breathing, and coughing. Albuterol can be used once daily prior to administering fluticasone or as needed for acute coughing and wheezing. In emergency cases, albuterol can often be used q30 minutes for up to 4 to 6 hours without serious side effects.

CONCLUSION

Chronic bronchitis and asthma cause a constellation of symptoms in the feline patient, including cough, wheeze and variable amounts of disability at rest. Other non-airway disorders can cause similar signs in these patients, and there are only a small number of diagnostic tests available to distinguish one disorder from another. Therefore, the clinician in general practice must rely on careful history taking, physical exam skills and accurate interpretation of thoracic radiographs to insure that a proper diagnosis is made. The use of inhaled medications to treat asthma and bronchitis is considered the standard of care in humans and is now widely recommended for cats with chronic bronchial disease. This approach avoids many of the side effects previously seen in patients treated with systemic medications.

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CANINE ATOPY – TREATMENT UPDATES

Katherine E. Irwin, DVM, DACVD
Omaha, Nebraska

INTRODUCTION

Canine atopic dermatitis (AD), aka environmental allergies, is a chronic pruritic and inflammatory skin condition usually associated with IgE antibodies against environmental allergens. It can be frustrating to manage, with no single treatment effective or appropriate for all dogs. Quality of life can be significantly impacted for both the affected dogs as well as their owners. Until recently, the major therapeutic options have included glucocorticoids, modified cyclosporine, and injectable immunotherapy. These "bigger gun" therapies are often combined with topical therapy, antihistamines, and essential fatty acids for additional relief. Antimicrobials are used as needed to treat secondary infections.

Recently several additional therapies have become available for relief of AD in dogs. These include sublingual immunotherapy (SLIT), oral oclacitinib (Apoquel®), and the recently released Canine Atopic Dermatitis Immunotherapeutic (aka CADI injections). As with previous treatments, these newer therapies are not effective or indicated for every dog with AD, but provide additional options for management of this chronic condition.

SUBLINGUAL IMMUNOTHERAPY (SLIT)

Subcutaneous allergen specific immunotherapy (SQ-ASIT) has been long used as a tool to control canine AD. It consists of administering gradually increasing quantities of allergen extract(s) via SQ injection to an allergic patient to reduce the symptoms associated with re-exposure to those allergen(s). Basically, we are trying to make the dog's immune system more tolerant and thus less reactive to the allergens. Instead of merely suppressing clinical signs, ASIT is the only treatment that directly addresses the underlying immunopathogenesis giving rise to the disease, and not only reduces reactivity to current problematic allergens, but also has the potential to prevent development of sensitivity to additional allergens and subsequent disease progression. The exact mechanism of ASIT is unknown, but it is generally accepted that it induces the formation of regulatory T-cells leading to production of anti-inflammatory cytokines, reduction in allergen-specific IgE, and production of allergen-specific blocking IgG.[1,2] Depending on the study, response rates, manifested as reduced itch and/or decreased use of other symptomatic therapies, have been reported as good to excellent in 50-80% of dogs treated for 6-12 months.[1] A range of 60-70% is often used by veterinary dermatologists when discussing response rates of SQ-ASIT. There are many benefits to SQ-ASIT including: safety – incidence of serious adverse events are less than 1-1.25%[1], no contraindications for use with other medications, compatible with many other diseases, reduced reliance on medications for symptomatic relief and/or treatment of infections, improved response to medications for symptomatic relief, and reduced frequency and severity of disease flares.

Sublingual immunotherapy (SLIT), also known as "allergy drops", has been introduced in the last several years, and is increasing in popularity. With SLIT, glycerin-stabilized allergen extracts are placed in the oral cavity, preferably under the tongue, and thus exposed to the dog's immune system in that way. It is important the allergen not be ingested, but that it sits as long as possible in the mouth and thus be absorbed via the oral mucosa (so no administration in food, or eating or drinking for at least 10 minutes after administration). SLIT has been used for human immunotherapy for over 50 years, predominately in Europe, although is gaining some traction in the U.S. It has been endorsed both by the World Health Organization, as well as the World Allergy Organization.[2,3] The proposed mechanism of action of SLIT is similar to SQ-ASIT, but due to the unique nature of the oral environment and the necessity it be able to tolerate a broad range of food antigens, the oral immune system may be better primed to encourage desensitization. There are some other differences between SLIT and SQ-ASIT. Unlike injectable immunotherapy, where it is typically administered on a weekly to be-weekly basis, SLIT must be administered daily and in most protocols overall dose of allergen administered is greater.

Some studies have evaluated the efficacy and safety of SLIT in dogs. In a small, open pilot trial of 10 predominately mite-sensitive atopic dogs over a 6-month period the mean glucocorticoid use reduced significantly over the study period, including 4 dogs that were completely weaned off glucocorticoids at the 6 month mark.[2] Eight of the ten dogs were rated as improved by their owners with an average degree of improvement of 72.5% (range: 65-100). There was also a significant reduction in mite specific IgE and increase in IgG with those dogs exhibiting the greatest increase in IgG showing the best clinical response. In another study assessing 124 atopic dogs with multiple sensitivities 68 (55%) exhibited a good to excellent response and 23% a fair response.[4] Of those dogs, 47 were "injection failures" of which 23 (49%) showed good to excellent response. In both studies SLIT was well-tolerated. Adverse reactions to SLIT appear limited, even in dogs with prior reactions to SQ-ASIT. Most common are oral/muzzle itch and vomiting (both usually self-limiting) and worsening of allergic symptoms.

APOQUEL® (OCLACITINIB)

The factors contributing to itch in dogs with AD are complex. It appears the cytokine interleukin-31 (IL-31) can contribute significantly in mediating itch in many dogs with this disease. So far researchers have been unable to identify any additional significant activities to which this molecule contributes. Thus, selectively blocking the activity of IL-31 has become attractive as a means to provide a more targeted approach to controlling itch with reduced impact systemically from what can be seen with more broad acting immune-modulators such as glucocorticoids and cyclosporine.

Apoquel® is a selective janus-kinase (JAK) inhibitor with preferential inhibition of JAK1 and to an extent JAK3 and minimal inhibition at label doses of JAK2, which is involved with hematopoiesis and innate immunity. JAK1 is an enzyme attached to the intracellular portion of the receptor that IL-31 binds to on a cell surface. Once the receptor is bound, this enzyme then activates itch pathways. JAK1 also interacts with additional pro-inflammatory/pro-allergic/pro-itch cytokines such as IL-2,4,6, and 13. Blocking the activity of these cytokine may potentially provide additional means for relief of allergic itch and inflammation. The label dose of Apoquel® is 0.4-0.6mg/kg twice daily for up to 2 weeks, then once daily thereafter. So far, all long-term safety and tolerability data is based off this dose. It has minimal inhibition of cytochrome P450 enzymes thus low risk of drug-to-drug interactions. However, with regards to risk of cumulative immune suppression, there is limited data on tolerability when used with other immunomodulators. In efficacy studies, Apoquel® provides quick speed of on-set (within 24 hours) and comparable itch relief as prednisolone and cyclosporine. And, when compared to cyclosporine provides faster on-set of action.[5-8]

Overall, Apoquel® appears to be well-tolerated. It is not labeled for use in dogs less than 12 months of age. In a pre-clinical margin of safety study using 6 month old beagles given 3 and 5x's the label dose, notable immune suppression occurred (demodicosis, bacterial pneumonia).[9] In another pre-clinical margin of safety study using adult dogs dosed at 1, 3, and 5x's the label dose for 26 weeks, there were no deaths or serious adverse events.[9] In that study some dogs (in all treatment groups) developed viral papillomas with most resorbing spontaneously. I have seen viral papillomas occur in only 1 patient so far. In the pre-clinical and clinical trials, the most common side effects were GI in nature, usually self-limiting, and comparable to the control groups (aside from the study with cyclosporine where GI side effects were significantly more frequent in the cyclosporine treated dogs).[5-7,9] There is a warning on the label that Apoquel may exacerbate neoplastic conditions. This is not to say Apoquel® will truly predispose to or exacerbate neoplastic conditions; we simply cannot at this time prove that it doesn't. No neoplasms were observed in the laboratory safety studies.[9] In the field studies, low numbers of tumors were noted. In a 112-day study, 2 of 283 dogs (0.7%) on Apoquel® were diagnosed with neoplasms (1 mast cell tumor, and 1 heart base mass) while 1 placebo-treated dog was diagnosed with a mast cell tumor.[6] In a continuation, compassionate use study dogs were monitored for up to 630 days. In these patients, 16 of 247 dogs (6.4%) were diagnosed with a neoplasm.[10] Mean age of on-set was 9.3 years. Three mast cell tumors and 3 adenocarcinomas were diagnosed; the remaining tumors each had only 1 occurrence. Thus far these rates seem comparable to what can be seen in similarly aged dogs.[10]

CANINE ATOPIC DERMATITIS IMMUNOTHERAPEUTIC (CADI)

Last fall CADI was released under a conditional license with the USDA. Thus far its use is largely restricted to veterinary dermatologists. After the conditional license program is complete, Zoetis plans for a full product launch. It contains caninized monoclonal antibodies against IL-31 and is administered via SQ injection.[11] It works in a similar fashion as Apoquel® - by blocking the activity of IL-31 - but at an earlier step by binding and neutralizing the molecule while still in circulation. On-set occurs within 1-2 days of injection and itch relief can last up to 56 days.[11] The injection can be given as often as once monthly. In a study of 50 client-owned dogs, >80% showed a reduction of 2cm or greater in their visual analog itch scores by day 3, with 70% maintaining treatment success by day 28, and 50% by day 56. Side effects were minimal and comparable to placebo. A 7-month laboratory study at 1.6 and 5x's the label dose revealed no significant adverse events. There are no restrictions with regards to age or concurrent drug use. Due to the conditional license, no off-label use is allowed.

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