Advances in Canine Esophageal Disorders – New Insights and Treatment Approaches

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The normal swallowing reflex is a four-stage process, characterized by the oral preparatory phase, oral phase, pharyngeal phase, and esophageal phase. Pharyngeal and esophageal dysphagias in dogs can be a diagnostic challenge and occur when the elaborate mechanism of bolus transit from the pharyngeal cavity into the esophagus or along the length of the esophagus becomes compromised. A history of repetitive swallowing, gagging, and retching associated with meals, nasal regurgitation with meals, swallow-related coughing, falling of food from the mouth during swallowing, and recurrent pneumonia should cause the clinician to suspect pharyngeal dysphagia. The assessment of dysphagia encompasses multiple dimensions that include (1) review of the signalment, (2) review of medication history and inquiry regarding recent anesthesia, (3) physical examination (prefeeding assessment), (4) neurologic examination, (5) clinical feeding and swallowing evaluation, and (6) laboratory and other testing to provide a basic data set for neurologic evaluation, including imaging studies and endoscopic evaluation of swallowing. Age and breed associations with dysphagia have been well documented in dogs. Breeds that have a hereditary predisposition or a high incidence of pharyngeal dysphagia include the golden retriever (pharyngeal weakness), cocker and springer spaniels (cricopharyngeal dysphagia), Bouvier des Flandres and cavalier King Charles spaniel (muscular dystrophy), and boxer (inflammatory myopathy).

Physical and Neurologic Examination

Physical examination of the dysphagic animal must include careful examination of the oropharynx using sedation or anesthesia if necessary to help rule out morphologic abnormalities such as dental disease, foreign bodies, cleft palate, glossal abnormalities, and oropharyngeal tumors. The pharynx and neck should be palpated carefully for masses, asymmetry, or pain. The chest should be auscultated carefully for evidence of aspiration pneumonia. Evaluation of cranial nerves should be performed, including assessment of tongue and jaw tone, and abduction of the arytenoid cartilages with inspiration. A complete physical and neurologic examination may identify clinical signs supporting a generalized neuromuscular disorder, including muscle atrophy, stiffness, or decreased or absent spinal reflexes. The gag reflex should be evaluated by placing a finger in the pharynx; however, the presence or absence of a gag reflex does not correlate with the efficacy of the pharyngeal swallow nor the adequacy of deglutitive airway protection.

Observation of Eating and Drinking

Careful observation of the dysphagic animal while it is eating (kibble and canned food) and drinking in the hospital cannot be overemphasized, and such observation helps to localize the problem to the oral cavity, pharynx, or esophagus. Dogs with an abnormal oral phase of swallowing typically have difficulty with prehension or aboral transport of a bolus to the tongue base, and these disorders often can be diagnosed by watching the animal eat. Dysphagias affecting the pharyngeal phase of swallowing can be more challenging to diagnose and often present with nonspecific signs such as gagging, retching, and the necessity for multiple swallowing attempts before a bolus is moved successfully into the proximal esophagus. These patients have abnormal transport of bolus from the oropharynx to the hypopharynx or from the hypopharynx to the proximal esophagus. Dogs with esophageal strictures or esophagitis can exhibit evidence of odynophagia and regurgitation seconds to minutes following ingestion of the bolus.

DIAGNOSTIC WORKUP

Routine Laboratory Screening

Routine laboratory screening including a CBC, serum chemistry profile, and urinalysis can aid in the identification of several common systemic diseases that may result in neuromuscular weakness.[1] Specific abnormalities that may be identified on routine screening include anemia, hypo- and hyperglycemia, hypo- and hyperkalemia, hypo- and hypernatremia, hypo- and hypercalcemia, hypophosphatemia and hypomagnesemia. Additional testing procedures that should be part of baseline testing in any dog with clinical neuromuscular disease includes measurement of serum creatine kinase (CK) activity, cardiac troponin I, plasma lactate concentration, and determination of thyroid status. Serum CK activity should be on every neuromuscular minimum database, and most importantly on pre-neuter blood evaluations in young dogs. Creatine kinase activity may be normal in the presence of muscle disease, and muscle disease should not be ruled out based on normal CK activity. Marked or persistent increases of CK may be indicative of a congenital or inherited muscle disease even though the animal may be clinically asymptomatic at the time. The most marked increases in serum CK activity (>20,000 IU/L) are associated with necrotizing myopathies or muscular dystrophies. Generalized inflammatory myopathies usually show moderate increases in CK activity (2,000-20,000 IU/L), while the CK activity in focal inflammatory myopathies such as masticatory muscle myositis (MMM), endocrine myopathies, neuropathies and other congenital muscle diseases are normal or only mildly increased (0-2000 IU/L).

Cervical and Thoracic Radiography

The pharynx of healthy animals is evident on radiographs because it is air filled. The size of the air-filled space can be decreased by local inflammation or neoplasia, laryngeal edema, or elongation of the soft palate. Pharyngeal size also can appear increased with dysfunction of the pharynx or upper esophageal sphincter, chronic respiratory (inspiratory) disease, and chronic severe megaesophagus. The normal esophagus is not visible on survey radiographs. An exception occurs following aerophagia due to excitement, nausea, dyspnea, or anesthesia.

Videofluoroscopic Swallow Study

Contrast videofluoroscopy involves real-time capture of images of the animal as it is swallowing liquid barium or barium-soaked kibble and is one of the most important procedures for assessing the functional integrity of the swallow reflex. Videofluoroscopy is used to determine the normal sequence of events that make up a swallow and to measure the timing of these events in relation to one another. Additionally, the movement of certain anatomic structures is measured in relation to a fixed point to assess function further. Swallowing events that occur out of sequence, at inappropriate times, or with reduced vigor can cause significant morbidity. One problem with videofluoroscopy is that animal positioning is not standardized in veterinary medicine. Alterations in body position (sternal versus lateral recumbency) do not appear to affect measurements of pharyngeal constriction ratio or the timing of swallowing in healthy dogs; however, cervical esophageal transit is significantly delayed when dogs are imaged in lateral recumbency.[2]

The fluoroscopic swallow study typically involves assessment of five swallows each of 5 to 10 ml of liquid barium (60% weight per volume) followed by five swallows of canned food mixed with barium and finally 5 swallows of kibble soaked in barium. The timing of the swallow can be determined easily when the swallow video is viewed frame by frame, with each frame representing 1/30th of a second in the National Television System Committee (NTSC) system, the analog television system used in the United States. The frame in which the epiglottis is observed to close over the larynx is considered as the starting point for all time measurements, and frames are counted until the observation of maximal contraction of the pharynx, opening of the PES, and closing of the PES. The swallow is considered completed when the epiglottis is observed to reopen, which usually takes five or six frames in healthy dogs. More recently, a contrast videofluoroscopy method for quantifying pharyngeal contractility in the dog has been described.[3] The pharyngeal constriction ratio is calculated by dividing the pharyngeal area at maximum contraction by the pharyngeal area at rest. As

pharyngeal contractility diminishes, the ratio approaches 1.0. This simple procedure provides important information regarding the strength of pharyngeal contraction in dysphagic dogs.

Laryngoscopy, Pharyngoscopy, and Esophagoscopy

Thorough laryngeal examination is important in all animals with pharyngeal and esophageal dysphagia to rule out laryngeal paralysis associated with a polyneuropathy.[4] Geriatric, large-breed dogs can experience a progressive generalized neuropathy, with associated pharyngeal weakness, pharyngeal dysphagia, and esophageal dysmotility.[5] Pharyngoscopy and esophagoscopy provide anatomic information about the structures involved in the oropharynx and esophagus, but both procedures are of limited diagnostic utility for evaluating functional disorders in anesthetized animals. This is an important limitation of these diagnostic procedures, particularly in animals that are dysphagic secondary to dynamic disorders such as cricopharyngeal dysphagia or esophageal dysmotility. Esophagoscopy is helpful for diagnosing esophagitis, esophageal strictures (that can be missed on barium swallow studies), and hiatal hernias.

Miscellaneous Laboratory Screening

The acetylcholine receptor antibody test should be performed in all cases of acquired dysphagia.[6] This test is not useful for congenital dysphagia as an immune basis is unlikely. The gold standard for the diagnosis of acquired MG remains the demonstration of serum AChR antibodies against native AChR by immunoprecipitation radioimmunoassay. This assay involves precipitation of serum IgG and IgM antibodies that bind to solubilized AChR complexed with a high-affinity peptide agonist, ^{125}I-labeled α-bungarotoxin. The precipitate's γ-emission reflects the amount of AChR bound to immunoglobulin. The assay is specific, sensitive and documents an autoimmune response against muscle AChRs. Although there is some cross-reactivity in AChR recognition of antibodies among species, the assay is relatively species specific, and a canine specific assay system should be used. Antibody titers in dogs are in general lower than in humans, and low-titer positives may be missed if human AChR is used as antigen. A positive AChR antibody titer, however, is not predictive of the degree of weakness. Within an individual, AChR antibody levels correlate with the disease severity, but antibody level between patients is highly variable and do not correlate well with severity. Although the current cut-off for a positive test result in dogs is > 0.6 nmol/L, dogs with acute disease and results between 0.4-0.6 nmol/L are highly supportive of early myasthenia gravis and will likely test positive (> 0.6 nmol/L) if retested 4-8 weeks later.

Electrodiagnostic Testing

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

Esophageal Manometry

Esophageal manometry measures pressure within the esophageal lumen and sphincters and proviU an assessment of the neuromuscular activity that dictates function in health and disease. Manometric techniques have improved in a stepwise fashion from a single pressure channel to the development of high-resolution manometry (HRM) with up to 36 pressure sensors. Advances in computer processing allow pressure data to be presented in real time as a compact, visually intuitive "spatiotemporal plot" of esophageal pressure activity. This spatiotemporal plot provides objective measurements of the forces that drive food and fluid from the pharynx to the stomach. This diagnostic modality has been shown to be feasible in fully awake dogs and provides a sensitive functional assessment of the UES, esophagus, and LES.[7]

Esophageal pH/Impedance Testing

Esophageal pH/impedance testing is a useful diagnostic tool that is used to diagnose acid and non-acid reflux in animals with suspected gastroesophageal reflux (GER), unexplained esophagitis, or hiatal hernias. The technology of esophageal pH testing has advanced tremendously in recent years, and clinicians have several choices when selecting esophageal pH probes. The catheter-free Bravo pH Monitoring System from Medtronic is the first catheter-free system used to measure esophageal pH in human patients and dogs that are suspected of having GER and is revolutionizing the way esophageal pH testing is done, because it is allows people and animals to maintain their regular diet and activities during pH testing. The Bravo system is an alternative to the traditional pH trans-nasal pH catheter that can cause patient discomfort and is easily dislodged by dogs and cats if the animal is not closely monitored. The main disadvantage of the Bravo system is that one can only record esophageal pH, and the system does not utilize impedance technology that allows one to measure both acid and non-acid reflux. Esophageal pH testing has been extensively utilized in awake[8] and anesthetized dogs to identify risk factors for GER and assess the effects of prokinetic agents on GER.[9]

Tissue Biopsies

Muscle, and in some cases peripheral nerve biopsies, should be collected early during diagnostic evaluation of a dog with dysphagia suspected to be caused by a neuromuscular disease.[10] A delay in collection of muscle biopsies can result in extensive muscle damage, fiber loss and fibrosis that may be irreversible diminishing the chances for a successful treatment. Muscle and nerve biopsies should be evaluated by laboratories with expertise in neuromuscular diseases. Muscle biopsies should be collected by an open-biopsy technique and evaluated in frozen sections, using a standard panel of histochemical stains and reactions including fiber typing. The usefulness of evaluating muscle and nerve in only paraffin sections is limited. Ultrastructural analysis is necessary for definition of structural abnormalities in selected congenital myopathies and is useful for peripheral nerve diseases. Results of tissue biopsies should guide further diagnostic testing focusing on laboratory tests that are relevant to the specific disease group or identify a specific disease and therapy if available. In addition to the diagnosis, results of muscle biopsies can also help determine a prognosis in many cases, as some neuromuscular diseases are treatable, and others are not.

TREATMENT

Disorders of the Proximal Esophageal Sphincter: Cricopharyngeus Muscle Dysfunction

Cricopharyngeus muscle dysfunction is a swallowing disorder of the UES characterized by either cricopharyngeus muscle asynchrony (functional) or cricopharyngeus muscle achalasia (structural). *Cricopharyngeus muscle asynchrony* is essentially a pump problem in which the weak pharyngeal muscles are unable to propel the bolus through the UES. Early evidence in the authors' laboratories points toward a neuropathy in these dogs. On videofluoroscopy, there is evidence of incoordination between the contraction of the dorsal cranial and middle pharyngeal contractor muscles (hyopharyngeus, pterygopharyngeus, and palatopharyngeus muscles) and opening of the UES (cricopharyngeus and thyropharyngeus muscles). A comprehensive workup should be completed to find a treatable cause of the suspected neuropathy (complete blood count and serum chemistry panel, AChR antibody titer, CK measurement, muscle and nerve biopsy). The prognosis for these dogs is similar compared to dogs with cricopharyngeus muscle achalasia. An effort should be made to identify the optimal consistency of food and water that these dogs will tolerate (by adding commercial food thickeners such as Thick-It), although these animals will ultimately succumb to repeated bouts of aspiration pneumonia and malnutrition unless they undergo surgical myectomy of the cricopharyngeus muscle. Enteral feeding via a percutaneous endoscopic gastrostomy tube is a viable alternative in these animals; however, silent aspiration and pneumonia can occur despite the use of enteral feeding devices. *Cricopharyngeus muscle achalasia* is the inability of the cricopharyngeus muscle to open during the cricopharyngeal phase of swallowing. The exact underlying causes have not been determined, although the disorder can be reproduced by transection of the pharyngeal branch of cranial nerve X.

Cricopharyngeus muscle asynchrony and achalasia are diagnosed via contrast videofluoroscopy. Cricopharyngeal achalasia has been well documented in miniature dachshunds and a variety of other toy breeds in the author's laboratory, and all dogs had marked hypertrophy of the cricopharyngeus muscle (cricopharyngeal bar) causing severe obstruction to propulsion of the bolus through the UES.

In dogs with cricopharyngeus muscle dysfunction a comprehensive workup must be undertaken before surgical intervention to ensure that systemic disorders (myopathies, polyneuropathies) are ruled out and aspiration pneumonia is managed properly. A fluoroscopic swallow study must be performed in dogs suspected of having cricopharyngeus muscle dysfunction to assess pharyngeal function before surgical intervention. Dogs that are diagnosed with underlying neuropathies or myopathies are managed conservatively with alterations of feeding practice or the use of low-profile gastrostomy devices if specific management of the underlying neuropathy or myopathy is not possible. Definitive treatment of cricopharyngeus muscle achalasia involves surgical myotomy or myectomy of the cricopharyngeus muscle. In veterinary medicine, the standard surgical approach for myotomy or myectomy has remained constant over the years, and the cricopharyngeus and thyropharyngeus muscles are approached either by a standard ventral midline approach with 180-degree rotation of the larynx on its longitudinal axis or by a lateral approach with 90-degree rotation of the larynx.

Megaesophagus

Idiopathic megaesophagus is the most common type of megaesophagus in the dog and is documented in approximately 50% of dogs with acquired megaesophagus at the authors institution. The syndrome may be manifested either in puppies at the time of weaning or in adulthood. The *etiology* of idiopathic megaesophagus is unknown. The congenital form of the disease may be due to a delay in maturation of the esophageal neuromuscular system; a theory that explains why young dogs may improve with careful feeding management. Idiopathic megaesophagus has been shown to be inherited in the wire-haired fox terrier and the miniature schnauzer. A breed predisposition also exists for the German Shepherd, Great Dane and Irish Setter. The site and pathogenesis of the lesion in idiopathic megaesophagus is unknown. Suggested hypotheses include abnormalities of the afferent limb of the reflex arc (receptors, neurons) or of the swallowing center in the CNS. Acquired megaesophagus may result from many systemic diseases including, autoimmune myasthenia gravis, SLE, polymyositis, polymyopathies, dermatomyositis, polyneuropathies, dysautonomia, botulism, distemper, neoplasia, brain stem disease, lead and thallium toxicity, Addison's disease, hypothyroidism, pituitary dwarfism, and thymoma. Many obstructive esophageal diseases can also lead to megaesophagus if they are of sufficiently chronic duration.

Repeat AChR antibody testing is important in dogs 3-4 weeks following a first negative AChR antibody test, particularly if the original titer is 0.4-0.6 nmol/l (borderline). Measurement of the CK activity is critical to help rule out a polymyopathy. Additional diagnostic procedures that can be performed based on the animal's signalment, history, and neurological examination include an EMG, nerve conduction velocities, and muscle biopsies. Medical management of idiopathic generalized megaesophagus involves modification of feeding practices. Treatment of the underlying cause (secondary megaesophagus) is of paramount importance. Dogs with megaesophagus generally tolerate a liquid or semi-liquid gruel better than solid food. Feeding from an elevated position allows gravity to help move the liquid into the stomach. If possible, the animal should be held in a vertical position for 5 - 10 minutes after eating. This can often be accomplished with the advent of a Bailey chair or similar device. Multiple feedings rather than one large single meal may also help minimize food accumulation in the esophagus. A subset of dogs with acquired idiopathic megaesophagus appear to develop a functional achalasia of the LES that markedly delays the passage of food from the esophagus into the stomach. The phosphodiesterase inhibitor, sildenafil, appears to be effective for reducing LES tone in puppies with congenital megaesophagus, and dogs given sildenafil (1mg/kg q8-12h) had a significant reduction in the frequency of regurgitation events and an increase in body weight compared to dogs given a placebo.[11] In

addition, the relative esophageal diameter of dogs administered sildenafil was also significantly reduced in compared to dogs receiving a placebo.[11] A second therapeutic consideration is the injection of botulinum toxin into the LES using a trans-bronchial needle and endoscope for injection. Insertion of low-profile-gastrostomy tubes for feeding can reduce the frequency of regurgitation events and subsequent aspiration pneumonia in many dogs with idiopathic megaesophagus. In addition, the placement of a fenestrated esophagostomy feeding tube for daily suctioning of esophageal contents (saliva, mucous, refluxate has also been shown to markedly reduce the frequency of aspiration events and prolong survival.[12] Pneumatic dilation of the LES is another viable therapeutic modality that has been performed on dogs successfully. The author recommends the use of a 30mm pneumatic balloon to minimize the risk of esophageal perforation. The use of a guidewire with the balloon is essential to maintain optimal positioning of the balloon. Surgical procedures including Heller myotomy and fundoplication (performed via laparoscopy or laparotomy) or the newest 3rd space procedure called POEM (per oral endoscopic myotomy) are viable considerations but require experience and expertise for the surgeon or endoscopist. The prognosis for dogs with megaesophagus is very variable depending upon the underlying etiology, the degree of dysfunction and the systemic status of the dog.

Esophageal Strictures

Esophageal strictures are a relatively common problem in dogs and can be caused by benign and malignant causes, although the latter are relatively uncommon in dogs. The most common cause of esophageal stricture formation is *gastroesophageal reflux in association with general anesthesia.* This phenomenon has been reported to occur in up to 65% of cases of esophageal stricture, with a median onset of clinical signs occurring 7.5 days post-anesthesia. The incidence of gastroesophageal reflux (GER) in dogs during anesthesia varies from 16-55% and occurs secondary to a decrease in LES pressure. Reduction of LES pressure occurs secondary to a variety of anesthetic agents, including atropine, morphine, acepromazine, thiopentol, xylazine, and isoflurane. The second most common cause of esophageal stricture formation is from *esophagitis induced by administration of doxycycline or clindamycin*. The proposed mechanism of tablet-induced esophagitis and stricture formation is from tablet retention in the esophagus due to poor esophageal clearance with a “dry” swallow. Other important causes of esophagitis and secondary stricture formation include chronic vomiting of acid contents from the stomach, foreign body ingestion, and swallowing of caustic substances. Esophagitis is associated with a weakening of the LES pressure that can result in further reflux of gastric contents and increased damage to the esophageal mucosa. Damage to the muscularis layer of the esophagus is often associated with fibroblastic proliferation and contraction leading to stricture formation. The clinical signs associated with severe esophagitis and/or esophageal stricture formation include odynophagia (painful swallowing), dysphagia, increased salivation, regurgitation, anorexia, coughing (secondary to aspiration pneumonia), and weight loss. These signs are often insidious at the onset and are often missed by owners but are progressive as the esophageal lumen gets progressively narrowed.

Mechanical dilation of the stricture is best accomplished using balloon dilation or bougienage. The theoretical advantage of balloon dilation is that the forces applied to the stricture are a radial stretch, in contrast to the longitudinal forces applied with the rigid bougienage instrument. However, a retrospective case series in 20 dogs and 8 cats with benign esophageal strictures that underwent bougienage treatment suggested that this procedure was safe and effective for most dogs and cats with benign esophageal strictures, with outcomes similar to balloon dilation.[13] The administration of triamcinolone into the stricture site using a four-quadrant approach before the balloon dilation procedure has been associated with a reduced rate of restructure formation[14] The author injects approximately 2.5 mg triamcinolone into each of the quadrants using a Wang needle (or similar transbronchial needle) that can be threaded down the biopsy channel of the endoscope. The steroid is generally used for the first 2-3 dilation procedures. Topical mitomycin C has also been shown to be beneficial for preventing restricture formation[15] Clinicians generally apply 5 mg of mitomycin using a soaked gauze sponge that is placed endoscopically at the stricture site for approximately 5 minutes. The site is then rinsed with 60 mL of water following the removal of the sponge.

Intraluminal stents are being used with increasing frequency in veterinary medicine for patients that have failed balloon dilation or for patients with recurrent stricture formation. Stents are available both covered (polypropylene) and uncovered. The covering helps prevent the ingrowth of tissue within the stent. Available stent materials include Nitinol (nickel plus titanium), Elgiloy (cobalt, nickel, plus chromium), stainless steel, polyester plastic/silicone, or a biodegradable material such as PDS. The selection of a particular stent is based upon the characteristics of the stricture such as its location and length, and the need for removal of the stent. Once the stent is deployed, it must be anchored in place, or it will rapidly migrate into the stomach. The stent can be secured in place using a suturing device (GI Stitch, Pare Surgical) that can be used through a double channel endoscope.

Esophagitis

Medical management of esophagitis involves a combination of proton pump inhibitors (PPIs) such as omeprazole, sucralfate suspension, and a potent prokinetic agent such as cisapride to minimize further gastric reflux and facilitate gastric emptying. Proton pump inhibitors should be administered q 12 hrs for 6-8 weeks before gradual tapering to once daily and then every other day before cessation of PPI therapy. H2-receptor antagonists can also be administered at night to help minimize nocturnal acid breakthrough, although H2-receptor antagonists are less potent compared to PPIs and are subject to a phenomenon called tachyphylaxis (tolerance) within 7-14 days following initiation of therapy.[16]

Gastroesophageal Reflux Disease (GERD)

DEFINITION OF GERD

The Montreal Consensus characterizes gastroesophageal reflux disease (GERD) as "a condition which develops when the reflux of stomach contents into the esophagus causes troublesome symptoms and/or complications."[1] GERD comprises a wide spectrum of disorders, ranging from GERD without significant clinical or pathological impact, through to the more severe complications of reflux disease, including erosive esophagitis, esophageal stricture, Barrett's esophagus, and esophageal adenocarcinoma. Extraesophageal manifestations of GERD are also common, including dysphonia, laryngitis, cough, aspiration, chronic bronchitis, and asthma. In addition, occult aerodigestive disorders in dogs presenting for cough without gastrointestinal signs have been increasingly recognized using thoracic radiographs and fluoroscopic swallow studies.[2]

FREQUENCY OF GERD IN PEOPLE AND DOGS

Gastroesophageal reflux disease (GERD) is a frequently encountered diagnosis in clinical practice, with an estimated prevalence in people ranging from 8-33% of the general population and associated economic impact in the United States totaling $12 billion on an annual basis.[3,4] Almost one-third of adults report typical GERD symptoms (i.e., heartburn, regurgitation, and esophageal chest pain) on a weekly basis. The mainstay of initial GERD management hinges on a proton pump inhibitor (PPI) trial to determine if symptoms improve with effective acid suppression. While approximately two-thirds of patients with erosive esophagitis (EE) and one-half with non-erosive reflux disease (NERD) will achieve symptomatic response with an empiric PPI trial, patients presenting with atypical symptoms, especially laryngeal symptoms such as hoarseness, cough, throat clearing, and sore throat, are much less likely to improve.[4] Although PPI response is utilized as a surrogate for diagnostic findings of GERD on objective testing, available literature suggests suboptimal sensitivity (ranging from 71-78%) and specificity (ranging from 44-54%) of a PPI trial when compared to GERD evidence on endoscopy and/or reflux monitoring studies.[4,5]

Gastroesophageal reflux during anesthesia in dogs is associated with 46-65% of cases of benign esophageal stricture and represents the most common cause of high-grade esophagitis and stricture formation.[6,7] Transient lower esophageal sphincter relaxations (TLESRs) and reduced lower esophageal sphincter (LES) tone secondary to administration of commonly utilized injectable preanesthetic and inhalant anesthetic agents are the most important causes for GERD under anesthesia.[8,9] The prevalence of hiatal hernia and GERD has increased with the rising popularity

of brachycephalic breeds, in particular the French bulldog.[10] Concurrent brachycephalic obstructive airway syndrome (BOAS) which increases negative intrathoracic pressure during inspiration can exacerbate the herniation and consequent GERD. A recent publication documented an improvement in esophageal acid exposure time and reduced swallowing impairment in French bulldogs following BOAS surgery, underscoring the role of upper airway obstruction in exacerbating hiatal hernia in affected dogs.[11]

ANATOMY OF THE ESOPHAGOGASTRIC JUNCTION (EGJ) AND ANTI-REFLUX BARRIER COMPONENTS

Several structures at the EGJ including the inner circular smooth muscle fibers at the lower end of the esophagus (clasp fibers), oblique smooth muscle fibers at the gastric cardia (sling fibers), esophageal hiatus (crural diaphragm), and phrenoesophageal ligaments tightly anchor the lower end of the esophagus to the crural diaphragm and serve as a functional complex maintaining a high-pressure zone in the area.[12] When the sling fibers contract, the closed part of the "C", or angle of His move toward the lesser curvature of the cardia, pulling the gastric fundus to the LES, resulting in a flap valve mechanism. The 5 main components of the anti-reflux barrier are summarized below:

1. **The lower esophageal sphincter (LES)**

The LES is the main component of the anti-reflux barrier and can maintain its function even when other components are absent, as in patients with hiatal hernia without GERD. Anatomical, myogenic, neurogenic, and humoral mechanisms all play a role in the maintenance of the anti-reflux barrier function and relaxation of the LES.

2. **Crural Diaphragm**

The diaphragmatic crus is considered an extrinsic component of the gastroesophageal barrier. It pinches the abdominal part of the esophagus at the level of the EGJ adding pressure to the LES. The presence of an intra-abdominal portion of the esophagus contributes to the valve mechanism because of the abdominal pressure collapsing the esophageal wall. Contraction of the crural diaphragm substantially enhances EGJ pressure during abdominal straining and abdominal compression.

3. **Phrenoesophageal ligaments**

The visceral peritoneum and phrenoesophageal ligaments help anchor the EGJ within the abdominal cavity.

4. **Angle of His**

The acute angle formed between the esophagus and the gastric fundus creates a longer distance between the gastric fundus (where food is stored) and the EGJ, providing a barrier to the rise of the refluxate.

5. **Gubaroff valves or plica cardiaca**

Create a cushion effect of the distal esophageal mucosa at the level of the EGJ.

PATHOGENESIS OF GERD

GERD occurs when there is an imbalance between the transdiaphragmatic pressure gradient (positive intra-abdominal pressure and negative intra-thoracic pressure) and the intricate valve mechanism at the level of the EGJ. Production of saliva in conjunction with esophageal peristalsis play an important role in esophageal clearance, whereas the LES, diaphragm, angle of His, the phrenoesophageal ligaments, and the Gubaroff valve act together to compose the valvular mechanism. Elevated transdiaphragmatic pressure can overcome this barrier, causing acid and bile to reflux into the esophagus. In hiatal hernia, dissociation between the LES (internal sphincter) and the crural diaphragm (external sphincter) occurs, and the widened hiatus makes the external sphincter action defective. About 30% of GERD patients have ineffective esophageal motility which results in defective mechanical clearance of refluxed gastric acid. Delayed gastric emptying can also worsen reflux disease by a direct back pressure to the esophagus and by enhanced triggering of TLESRs due to postprandial gastric distension. In addition, fundic distension (large meals) and delayed gastric emptying can precipitate reflux and esophagitis by pulling the LES distally and exposing the squamous epithelium to gastric juice. Repeated exposure of the epithelium can cause columnarization. Extension of inflammation into the muscularis propria causes progressive shortening of the esophagus and weakness of the LES, precipitating further reflux and subsequent esophagitis. The spectrum of disease ranging from NERD to EE to Barrett's esophagus to esophageal adenocarcinoma has been well documented in people and has been experimentally induced in canine models with surgically configured paraesophageal hiatal hernias, esophago-intestinal anastomoses, or biliary diversions that induce

reflux. There are sporadic cases of Barrett's esophagus and adenocarcinoma in dogs[13-16], but the progression may take longer than the median lifespan of a dog. It is also plausible that Barrett's esophagus is underrecognized because endoscopic esophageal biopsies are rarely obtained in dogs. Obesity is also associated with a higher risk of GERD due to increased intragastric pressure.[17]

CLINICAL FEATURES OF GERD IN DOGS

Clinical signs of GERD in dogs are wide-ranging as many dogs can experience subclinical reflux (asymptomatic) whereas others can exhibit signs associated with severe GERD and subsequent esophagitis (regurgitation, odynophagia, hypersalivation), esophago-oropharyngeal reflux (dysphonia), or aspiration (chronic cough) with subsequent pneumonia, chronic bronchitis, or bronchospasm. Nasal discharge, sneezing, and stertor can be associated with nasopharyngeal reflux and subsequent nasopharyngeal stenosis. Esophageal stricture and peptic ulceration are well-documented complications of GEDR in dogs, particularly following general anesthesia. The onset of odynophagia and regurgitation occurs relatively rapidly following anesthesia, with a median duration of 7 days following the procedure.[18] Recurrent aspiration pneumonia, Barrett's esophagus, and malnutrition are all possible sequalae in dogs with hiatal hernias or frequent bouts of GERD.

DIAGNOSIS OF GERD

There is no gold standard for the diagnosis of GERD. The diagnosis is thus based on a combination of assessment of history and clinical signs, endoscopic evaluation of the esophageal mucosa, fluoroscopic swallow study, reflux monitoring, and response to therapeutic interventions. People with GERD frequently complain of heartburn and regurgitation; however, these symptoms have variable sensitivity for erosive esophagitis (30-76%) with a specificity ranging from 62-96%.[19] The diagnosis of silent GERD is far more challenging in dogs compared to people, because the typical symptoms of globus, dysphagia, and heartburn commonly described in people cannot be conveyed by the animal. The author relies upon a careful assessment of the animals' signalment, history, physical examination, respiratory signs, and observation of the dog eating and drinking before pursuing thoracic radiographs and swallow fluoroscopy or esophagoscopy to confirm the diagnosis of GERD and evaluate for predisposing causes.

Swallow fluoroscopy should not be used solely as a diagnostic test for GERD because the presence of reflux on a barium esophagram has poor sensitivity and specificity for GERD when compared with pH testing. The prevalence of GER in healthy, free-feeding dogs was 41% as detected by fluoroscopic swallow study.[20] Swallow fluoroscopy can be performed to evaluate esophageal motility (dysmotility), sphincteric function, and hiatal herniation; however, the absence of a hiatal hernia during the procedure should not rule out this disorder considering the dynamic and intermittent nature of the herniation. A prospective study comparing barium radiology with esophageal pH monitoring for the diagnosis of GERD in people showed that only about 50% of patients with abnormal reflux on a barium study were found to have abnormal pH monitoring.[21] The finding of barium reflux above the thoracic inlet with or without provocative maneuvers somewhat increases the sensitivity for GER.

Upper endoscopy is the most widely used objective procedure for evaluating the esophageal mucosa and is warranted in dogs with a history of regurgitation, dysphagia, odynophagia, and weight loss. In people, the endoscopic findings of erosive esophagitis and Barrett's esophagus are specific for the diagnosis of GERD and the Los Angeles classification system is the most widely used and validated scoring system.[22] To maximize the yield of GERD diagnosis and assess for erosive esophagitis, esophagoscopy should ideally be performed after PPIs have been stopped for ≥ 2 weeks. Endoscopy is also important to determine the American Foregut Society (AFS) hiatus grade (from 1-4) during a retroversion maneuver. The grading of the EGJ integrity incorporates assessment of the hiatal axial length, hiatal aperture, and flap valve.[23]

Esophageal high-resolution manometry (HRM) can be used to assess motility abnormalities associated with GERD, but HRM should not be used alone as a diagnostic test for GERD. Weak LES pressure and ineffective esophageal motility often accompany severe GERD; however, no manometric abnormality is specific for GERD. HRM is invaluable for evaluating patients with esophageal achalasia and should be considered prior to performing anti-reflux procedures.

Unfortunately, HRM is not routinely available in veterinary hospitals and is currently only utilized in a few academic veterinary institutions.

Esophageal pH monitoring Ambulatory reflux monitoring (pH or impedance-pH) facilitates assessment of esophageal acid exposure to establish or refute a diagnosis of GERD and for correlating signs with reflux episodes. The main methods of reflux testing include a wireless telemetry capsule (Bravo Reflux Capsule; Medtronic, Minneapolis, MN) attached to the esophageal mucosa during endoscopy[11,24] and transnasal catheter-based testing.[25] The Bravo Reflux Capsule cannot obtain impedance data, limiting its use to detecting acid reflux (pH < 4) only. pH data can be collected for up to 96 hours, which minimizes variance and increases diagnostic sensitivity. The primary outcome measure assessed is distal esophageal acid exposure time (AET). Acid exposure time > 6% denotes pathologic GER, and < 4% is considered physiologic in humans.

Reflux scintigraphy has been used to detect reflux in people and dogs and pulmonary aspiration in human infants.[26] One of the benefits of scintigraphy is that the technique can detect small volume, nonacid reflux events that might occur intermittently and be missed by the owner or during swallow fluoroscopy. Reflux of variable magnitude was detected in 12/12 healthy dogs that were free-fed a meal containing colloidal ^{99}m-technetium phytate, although aspiration was not identified in any dogs.[27] Further studies are warranted in dogs with swallowing impairment to determine the utility of this adjunctive diagnostic procedure.

MANAGEMENT OF GERD

Management of GERD requires a multifaceted approach, considering the severity of the clinical signs, the signalment (brachycephalic breeds with severe BOAS will need multilevel BOAS surgery), endoscopy findings, and physiological abnormalities. Management decisions will be altered by the type and size of hiatal hernia, the presence of erosive esophagitis, peptic stricture, presence of obesity, and physiological abnormalities such as gastroparesis or ineffective esophageal motility.

Diet and Lifestyle Changes

The most important strategies for dogs involve weight loss for obese or overweight patients, the feeding of smaller meals more frequently (rather than larger meals fed once or twice daily), and the feeding of reduced fat diets.

Acid Suppressants

The backbone of pharmacologic therapy for GERD are acid suppressants (H2RAs and PPIs) that are directed at neutralization or reduction of gastric acid. PPIs demonstrate consistently superior heartburn control, improved esophageal mucosal healing, and relief of regurgitation compared with H2RAs in people. PPIs showed a significantly faster healing rate (12%/week) vs. H2RAs (6%/week), and faster, more complete heartburn relief (11.5%/week) vs. H2RAs (6.4%/week).[28] The healing rates of erosive esophagitis are not linear and people with EE experience far better symptom relief compared to those with NERD. Although all the PPIs are effective for healing reflux esophagitis when given in their standard dosages, there are wide variations in the acid-suppression potency of different PPI preparations.

If relative acid-suppression potencies of individual PPIs (based on their effects on mean 24-hour intragastric pH) are standardized to omeprazole to yield “omeprazole equivalents” (OEs, with omeprazole having an OE of 1.00), the relative potencies of standard dose pantoprazole, lansoprazole, omeprazole, esomeprazole, and rabeprazole have been estimated at 0.23, 0.90, 1.00, 1.60, and 1.82 OEs, respectively.[29,30] PPIs should be administered 30-60 min before meals to optimize effectiveness and the drug should be administered q12 hrs for 8-12 weeks for dogs with severe esophagitis to maximize effectiveness and ensure complete healing of esophageal erosions or ulcerations. The drug should be tapered gradually (administer once daily for 7-10 days followed by once every other day for 7-10 days) before complete cessation to reduce the likelihood of rebound acid hypersecretion.

Prokinetics

Cisapride is a serotonergic 5-HT4 receptor agonist that has been demonstrated to increase LES tone in dogs[31] and enhance gastrointestinal motility. The drug is vastly superior to metoclopramide that is limited by its relatively short half-life, CNS side effects, and lack of effectiveness in reducing GERD. A high dose of metoclopramide (bolus loading dose of 1.0 mg/kg IV), followed by a continuous infusion rate of 1.0 mg/kg/hr administered to 18 healthy dogs undergoing elective orthopedic surgery procedures was only associated with a 54% reduction in relative risk of developing GERD compared to a saline placebo.[32]

Baclofen

Baclofen is a $GABA^B$ agonist that reduces the TLERs that enable reflux episodes in ferrets, dogs, and humans. Administration of baclofen at 7μmol/kg to 4 dogs reduced the number of TLESRs in a dose-dependent fashion; however, repeated dosing of the drug was associated with development of mild tolerance, although this receptor desensitization effect was less pronounced than that observed in other animals.[33] It remains to be determined whether the reduction of TLESR incidence and reflux can be translated into a clinically useful effect in dogs.

Sucralfate

Sucralfate is a mucosal protective agent that is not routinely administered to people with GERD, unless during pregnancy. The ACVIM Consensus Statement on the rational administration of gastrointestinal protectants to dogs and cats mentioned that there was weak evidence in experimental animal models and humans to support the use of sucralfate for preventing or treating esophageal injury.[34] There is moderate evidence that sucralfate may have analgesic effects in people post-tonsillectomy, but no studies have evaluated the analgesic properties of sucralfate in people or animals with esophagitis. In addition, no evidence supports either a benefit or interaction when sucralfate is administered concurrently with H2RAs or PPIs.

ANTIREFLUX SURGICAL AND ENDOSCOPIC OPTIONS FOR GERD

Antireflux surgery performed by an experienced surgeon or endoscopic restoration of the normal antireflux valve mechanism performed by a skilled endoscopist is a consideration for long-term treatment of patients with objective evidence of GERD, especially those that have severe reflux esophagitis (LA grade C or D) or large hiatal hernias. The goals for antireflux surgery include reduction of hiatal hernia, re-establishment of the intraabdominal esophageal length, closure of concomitant crural separation, and application of a partial versus complete fundoplication. *Importantly, the presence of esophageal achalasia or absent esophageal contractility should be ruled out by performing swallow fluoroscopy, endoscopy and/or HRM before antireflux surgery is considered*. There is a plethora of surgical and endoscopic antireflux procedures that are performed in human patients; however, many of these procedures have not been performed in dogs with spontaneous GERD to date.

Magnetic Sphincter Augmentation (MSA)

Laparoscopic MSA or LINX® (Reflux Management System, St. Paul, MN) is an alternative to laparoscopic fundoplication for patients with regurgitation who fail medical management. The system is composed of a series of titanium beads with magnetic cores within each bead that encircles the distal esophagus to bolster the LES and prevent reflux. The beads are interlinked with titanium wires to form a flexible and expandable ring where each bead can move independently. This free-moving apparatus was designed to allow for a physiological mechanism to parallel the movements of the LES. Thus, the ring transiently opens to allow passage of a food bolus, permits belching and vomiting and approximates to its closed position at rest to prevent the upward migration of gastric contents. Both *ex vivo* and chronic *in vivo* studies were conducted in a pig model which confirmed the safety and competence of the implanted magnetic ring devices.[35] MSA seems to be a safe and effective alternative to laparoscopic fundoplication, with unequivocal superiority of MSA over twice-daily PPIs for the control of regurgitation.[36]

Transoral Incisionless Fundoplication (TIF)

TIF is an endoscopic procedure for the management of GERD that re-establishes and augments the gastroesophageal flap valve.[37] TIF is appropriate for patients that do not have a hiatal hernia > 2 cm, paraesophageal

hernia, or severe esophagitis (LA grade C or D). TIF and traditional fundoplication have functional and technical similarities; however, TIF creates a true flap valve generating the high-pressure zone around the distal esophagus. Patients with a hiatal hernia > 2 cm can undergo conventional laparoscopic hiatal hernia repair with complete or partial fundoplication, or a concomitant laparoscopic hiatal hernia repair with TIF, known as concomitant TIF (cTIF).

Fundoplication

Fundoplication is widely regarded as the "gold standard" among the antireflux procedures for its efficacy in improving the physiologic parameters of GERD such as LES pressure and esophageal acid exposure time; however, long-term follow-up (> 10 years post-op) studies have shown an increased failure rate with recurrence of GERD, and post-operative dysphagia, gas-bloat, and inability to belch or vomit, particularly following Nissen (complete) fundoplication.[38,39] Laparoscopic fundoplication is preferred over open antireflux surgery and has been associated with a > 80% possibility of long-term freedom from acid suppressants in people.

FUTURE CONSIDERATIONS

The future of GERD diagnosis and management looks bright with the advent of esophageal mucosal integrity assessment, esophageal function testing, and the implementation of artificial intelligence to optimize the interpretation of mucosal and histological lesions. Noninvasive, multiomic and multicompartmental biomarkers of reflux disease (pepsin, volatile sulfur compounds, and acetic acid) are being evaluated for the diagnosis of GERD. Newer potassium-competitive acid blockers (PCABs) are being developed that provide more rapid, potent, and sustained suppression of gastric acid with faster and more durable symptom relief in people. Endoscopic techniques such as MSA and TIF are being optimized to replace the need for indefinite PPI therapy in people with GERD, and these procedures hold promise for dogs with hiatal hernia and chronic reflux. Personalization of management to the individual patient's unique presentation and needs will further augment GERD diagnosis and management.

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