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Sarcopenia and weight management in older dogs – How I approach... The old coughing dog – Dermatology and the aging dog – How I approach... Gingival enlargement in the dog – Nutrition of aging cats – Canine cognitive dysfunction – Pathologic hypercalcemia in the dog

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Editor-in-chief: Ewan McNeill, BVMS, Cert VR, MRCVS
Editorial secretary

- Laurent Cathalan (laurent.cathalan@1health.fr)

Artwork

- Pierre Ménard

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THAT AGE-OLD QUESTION

"Education is the best provision for old age" – **Aristotle**

The question as to how we cope with aging has been with us for...well, since civilization began. For many societies today, "youth" is seen to epitomize all that is ideal – health, strength and enthusiasm for life, whilst the term "old age" will often conjure up images of illness, frailty and exhaustion. And this negative view of aging is not a new concept; for example, amongst the pantheon of ancient Greek gods, Geras was the personified and malevolent spirit of old age, usually portrayed as a decrepit, shriveled-up little man. His opposite number was Hebe, the goddess of youth, who was depicted as radiating health and beauty, and was regarded as having the ability to rejuvenate mortals.

Now whilst Geras is not one of the well-known ancient deities, his name is still reflected in the word *geriatric*. Although this is a modern neologism, coined only around a hundred years ago, it would appear the idea that geriatric medicine is a recent notion is a fallacy. The ancient cultures were very aware of the problems that could accumulate as the years rolled past; the debate surrounding aging and disease began with Hippocrates and focused on the crucial questions of whether old age is a natural or a pathological condition. Indeed, at least one medical work from this period not only included comments such as "fevers are not so acute in old people" but offered a (fanciful) suggestion as to the cause of aging (namely, that it resulted from a progressive loss of heat from the body, which gradually became colder and drier).

However, no specialization in training, research or clinical practice in human geriatric medicine appeared until the nineteenth century, and the veterinary approach to our older patients has lagged behind that – it is only recently that there has been a real focus on senior pets, whether that be with regard to their specific nutritional needs, age-related diseases or physiological alterations. Thus it is that this issue of *Veterinary Focus* seeks to underscore the quote from Aristotle that headlines this piece – but whilst the Greek philosopher probably meant that education would prepare an individual for old age, there is surely another interpretation; namely, educating the clinician will help ensure the best care for our patients as they get older.

Ewan McNEILL
Editor-in-chief, *Veterinary Focus*

In this issue of *Veterinary Focus*

SARCOPENIA AND WEIGHT MANAGEMENT IN OLDER DOGS

Muscle loss, or sarcopenia, in old dogs is a real and frequent problem; this article discusses how best to recognize and treat it.

KEY POINTS

1. Sarcopenia is defined as a reduction in skeletal muscle mass associated with aging. The causes are multifactorial, but it is not associated with an underlying disease process (as is cachexia).
2. When evaluating muscle condition and screening for sarcopenia, body condition scoring should be taken into consideration, as this influences the overall assessment.
3. Treatment of sarcopenia entails a combination of exercise and nutritional interventions, with the former being the more effective therapy, but pharmacotherapy options are also continually evolving.
4. Nutritional strategies for treating sarcopenia often include a combination of increased protein intake and supplementation of leucine, omega-3 fatty acids, vitamin D, and probiotics.

Introduction

Given that expected lifespan differs considerably across dog breeds, particularly when contrasting between small and large breeds, there is no exact cut-off for "aging", and distinguishing between the various (arbitrary) age categories or life stages differs for each animal (1). According to the 2019 AAHA Canine Life Stage Guidelines, a dog is classified as *senior* **(Figure 1)** after entering into the last 25% of its estimated lifespan and through to the end of its life (2). The term *geriatric* has also been frequently used when referring to some of our more aged patients in veterinary medicine, and is often used interchangeably with *senior*, but an exact definition for this geriatric subcategory in animals remains to be defined. In human medicine, the term denotes a subpopulation of patients in the senior life stage category, often with multiple medical conditions, and is usually inclusive of senility or dementia (3). While such differentiation still requires a bit of fine-tuning regarding an exact definition, it does seem logical to differentiate or recognize geriatric animals as being separate from the broader category of senior animals. This is because their requirements (from nutrition to exercise) and general management are different (1).

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Figure 1. Dogs such as this one are classified as senior when they enter the last 25% of their estimated lifespan through to the end of their life.

So if such a classification is essential, how do we work towards better defining this subpopulation? In human gerontology, it has been proposed that a patient needs to exhibit at least three of the following criteria to be classified as geriatric (3):

- Weakness
- Weight loss
- Slowed mobility
- Fatigue
- Low levels of activities

While such criteria help distinguish geriatric patients from senior ones, there are other terms often used to describe this subpopulation further, whether it be in relation to monitoring and

Matthew A. Kopke

BSc, BVSc (Hons), Dip. ACVIM (SAIM), Veterinary Nutrition Group, Sydney, Australia

Dr. Kopke obtained his undergraduate, veterinary, and honors degrees from the University of Pretoria, South Africa before undertaking a small animal internal medicine residency at Massey University, New Zealand. After completing his residency he joined Veterinary Nutrition Group to offer remote consultancy in internal medicine and nutrition, and became a Diplomate of the American College of Veterinary Internal Medicine in Small Animal Internal Medicine. He also works part-time as a clinical internal medicine specialist.

treatment strategies, or perhaps when discussing prognosis. Such terms include *frailty*, *sarcopenia*, and *anorexia of aging*, to mention a few.

How do we assess frailty?

Firstly, what is frailty? A widely accepted definition is a decline in an organism's physiological reserves, leading to an increased vulnerability to stressors (4,5). When it comes to assessing frailty in elderly people, more than 20 methods have either been used or proposed, and either quantitative or qualitative methods can be utilized. The index of frailty is an example of a quantitative method, whereas using the phenotype of frailty adopts a qualitative approach. Given their different methodology, they are considered complementary rather than alternatives to one another.

In people, when using the phenotype of frailty, five components are employed for the assessment (4):

- Chronic undernutrition (assessed by unintentional weight loss)
- Exhaustion (self-reported)
- Low physical activity level (measured through a weighted score of the number of kilocalories expended per week)
- Poor mobility (assessed as time to walk a distance of 15 feet)
- Weakness (grip strength)

A recent study evaluated a clinical definition (using the above five components) of a frailty phenotype in aged guide dogs (5). They found that dogs with two or more components were more likely to die during the follow-up period than those with one or no components, and thus concluded that signs of frailty appeared to be a risk factor for death.

What is sarcopenia?

Sarcopenia is defined as a reduction in skeletal muscle mass associated with aging, albeit the underlying mechanisms are multifactorial in nature (6,7). It is essential to distinguish between sarcopenia and cachexia, with the latter also involving a reduction in skeletal mass but associated with disease processes such as congestive heart failure (CHF), chronic kidney disease (CKD), various types of cancer, and several other chronic diseases (7). Various contributory factors have been identified in humans with sarcopenia, and such mechanisms are believed to play a similar role in sarcopenia in dogs. These include physical inactivity, increased cytokine production, decreased concentrations of hormones (growth hormone, testosterone, IGF-1), changes in type II muscle fibers (motor-unit remodeling), insulin resistance, and reduced protein synthesis (7). Enhanced autophagy has also been identified as one of the factors potentially contributing to muscle atrophy associated with aging in dogs (8).

In humans, the loss of lean body mass associated with sarcopenia has been shown to have significant consequences, such as increased mortality and a negative impact on strength, immune function, and quality of life. This has prompted extensive research into its identification, prevention and treatment strategies (7). And while sarcopenia is defined as a loss of lean muscle mass associated with aging (in the absence of disease), such loss in humans begins early in life, around 30 years of age, and, likely, a similar earlier onset of loss is also the case in our canine companions (7).

How do we assess for sarcopenia in dogs?

Because sarcopenia is a gradual process, it can often go unnoticed until it becomes significantly pronounced; in addition, a concurrent increase in body fat can mask the presence of sarcopenia, making it difficult to evaluate in such dogs (6). In other words, maintenance of body weight is possible despite considerable loss of lean body mass. While challenging and compounded by other variables, early recognition is crucial to slow further progression by instituting appropriate treatment strategies.

In human medicine, various techniques have been employed to screen for loss of lean body mass, including regional computed tomography (CT), dual-energy x-ray absorptiometry (DEXA), urinary creatinine excretion testing, and whole-body potassium and total body water determination (6). In particular, CT has been widely utilized to measure the cross-sectional area of thigh muscle in elderly humans to assess for muscle loss (9). This technique has shown both high precision and accuracy.

In veterinary patients, DEXA has been used to assess changes in body composition associated with aging in dogs (10,11). While studies have

shown that it is a feasible means of measuring body composition, there are also several limitations when it comes to measuring lean body mass (12). It is also not widely available, and is especially rare in clinical practices. However, a more recent study assessed several methods of evaluating sarcopenia in old dogs and found that both ultrasonography and CT were realistic options of measuring epaxial muscle area and diagnosing reduced muscle area consistent with sarcopenia (6).

Fasting urinary creatinine to urea nitrogen ratio has been shown to be an indicator of protein catabolism in healthy Beagle dogs fed low-protein diets. This technique might have applications in the early detection of protein catabolism before muscle breakdown occurs, but further studies are required to determine its applicability in sarcopenic patients (13).

How do we treat sarcopenia in dogs?

As the underlying mechanisms for sarcopenia are multifactorial, it is reasonable to assume that treating such a syndrome will rely on a multimodal strategy. Treatment of sarcopenia has historically relied upon a two-fold approach, incorporating nutritional intervention and exercise, with the latter being by far the more effective in facilitating muscle protein synthesis. However, nutritional strategies are both complementary and a necessity (14,15), and important goals to consider, based on findings in other species (humans, rodents), include those listed in **Box 1**.

In people with sarcopenia, 25-30 grams of high-quality protein per meal is recommended as part of their management. A 3-year study on elderly men and women demonstrated that high protein intake was associated with 40% less muscle mass loss (16). Not only is the quality and quantity of the protein essential, but also the distribution of the intake during the day. Recent research has identified further benefits associated with an even distribution of protein intake over the day (17). In senior dogs, providing at least the AAFCO minimum for protein (5.1 g/100 kcal) for adults is recommended, but higher dietary protein levels may be more beneficial (7). Due to increased protein turnover and reduced synthesis, protein requirements increase with age, and senior dogs likely require approximately 50% more dietary protein than younger adults. This can be achieved by either feeding a commercially available senior diet or having a home-prepared diet formulated by a board-certified veterinary nutritionist **(Figure 2)**.

Box 1. Nutritional goals for patients with sarcopenia (7,16-20).

- Adequate energy
- Increased protein intake
- Protein quality
- Leucine (or beta-hydroxy-beta-methylbutyrate) supplementation
- Omega-3 fatty acid supplementation
- Adequate vitamin D

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Figure 2. Increased protein intake is one of several strategies used to treat sarcopenia in dogs. The protein should be high quality and evenly distributed throughout the day for optimal effect.

Leucine is an essential amino acid that stimulates and initiates muscle protein synthesis, and its supplementation has been shown to restore or normalize muscle protein synthesis in other species (humans, rodents) (18,19). It has also been proposed that one of the metabolites of leucine, beta-hydroxy-beta-methylbutyrate, may also be utilized in protecting or even rebuilding muscle mass in older people with reduced lean body mass (20). It remains to be clarified whether supplementation with either is effective in sarcopenic dogs.

Diets enriched with omega-3 fatty acids and antioxidants may prove helpful in patients with sarcopenia and also benefit common comorbidities such as cognitive decline and osteoarthritis in this subpopulation (17). Omega-3 fatty acids result in less potent inflammatory mediators (eicosanoids) than omega-6 fatty acids, and also decrease TNF and IL-1 production, although the optimal dosage has yet to be determined. It has been recommended that animals with any degree of cachexia be provided with 40 mg/kg/day of eicosapentaenoic acid and 25 mg/kg/day of docosahexaenoic acid (7). Fish oil supplements from a reliable supplier are recommended, and they should always contain vitamin E as an antioxidant, but other nutrients should be excluded to avoid toxicities **(Figure 3)**.

Activity and exercise have been associated with various benefits in elderly people, and such effects can likely be transcribed to senior dogs (14). Potential benefits that have been reported include:

- A higher level of cardiorespiratory and muscular fitness
- Healthier body mass and composition
- Better cognitive function
- Decrease in all-cause mortality

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Figure 3. Including fish oil supplements in the diet for senior dogs can help manage sarcopenia and treat common comorbidities in this subpopulation, namely osteoarthritis and cognitive dysfunction.

"Because sarcopenia is a gradual process, it can often go unnoticed until it becomes significantly pronounced; in addition, a concurrent increase in body fat can mask the presence of sarcopenia, making it difficult to evaluate in such dogs."

Matthew A. Kopke

Resistance training is the most effective for improving sarcopenia (14,15). This anabolic stimulus has been demonstrated to increase myofibrillar muscle protein synthesis. While such exercise has the most significant potential benefit for patients with sarcopenia, the positive effects are negated without appropriate supportive nutrition. Protein intake is crucial to provide the building blocks for muscle protein synthesis, particularly branched-chain amino acids (15). In humans, the literature suggests that commencing with resistance training earlier in life may provide superior effectiveness (14), but the optimal age to start with such intervention in our veterinary patients remains to be determined.

For dogs, gentle, controlled exercise in the form of daily leash walking and therapeutic activities for flexibility and strength (*i.e.*, resistance training) are recommended, using, for example, an underwater treadmill or physical training and rehabilitation tools **(Figure 4)**.

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Figure 4. Exercise, particularly resistance training, is the most effective method to facilitate muscle protein synthesis in patients with sarcopenia. An example of such activity in dogs is using a balance disc, as depicted here.

In addition to exercise and nutrition, pharmacotherapy is a continually evolving sphere of treatment for sarcopenia in other species **(Table 1)**. Drugs that target proteostasis and mitochondrial signaling through myostatin (MSTN), renin-angiotensin-aldosterone system (RAAS), and AMP-activated protein kinase (AMPK) pathways have reached various stages of clinical trials in humans (21). Repurposed hormonal drugs have also emerged as promising therapies for sarcopenia, including those with either growth-promoting or anti-inflammatory effects, such as testosterone, insulin, and ghrelin (21). Treatment strategies in general aim to reduce energy requirements, enhance energy intake, improve nutrient absorption, and modify metabolic alterations to prevent and even reverse muscle loss (7). Such pharmacotherapy has yet to make its way into the field of veterinary science, although further research might shed more light and offer potential applications for these purported therapeutic options.

Table 1. Examples of pharmacotherapy agents used in the management of sarcopenia in other species (7,21).

Pathway/ mechanism	Drug class/example
Myostatin (MSTN) pathway	MSTN inhibitors, activin receptor antagonists, follistatin fusion proteins and gene therapy
Renin-angiotensin-aldosterone system (RAAS)	Angiotensin-converting enzyme inhibitors, angiotensin II type I receptor antagonists, mineralocorticoid antagonism, mitochondrial assembly receptor agonists
AMP-activated protein kinase (AMPK) pathway	Metformin
Repurposed hormonal drugs	Testosterone, selective androgen receptor modulators, ghrelin and its mimetics
Other/miscellaneous	Nonsteroidal anti-inflammatory drugs, appetite stimulants

Finally, appetite stimulants (*e.g.*, mirtazapine, cyproheptadine, capromorelin) may benefit some animals. However, if the above measures fail, it is essential to consider feeding tube placement earlier rather than later to avoid end-stage disease with severe debilitation, which would inevitably have a poorer outcome.

What is anorexia of aging?

This is defined as a decreased appetite and food (or energy) intake in old age, and is highly prevalent in humans; it is also considered a predictor of morbidity and mortality (22). Its prevalence in senior dogs remains to be determined. In humans, consequences associated with anorexia of aging include (22):

- Malnutrition leading to immune dysfunction, delayed wound healing, and decreased cognitive function
- Frailty and sarcopenia
- Disability and injury, resulting in loss of functionality
- Increased mortality

Client communication regarding anorexia of aging in senior dogs is critical. Owners must be educated on what (subtle) signs to monitor for and report these to their veterinarian. These can range from reduced food intake to changes in food preferences or even a cyclical appetite.

Strategies that can be employed to limit anorexia of aging in senior dogs include (7):

- Smaller, more frequent meals to increase food intake
- Using flavor enhancers to increase palatability (but this must be tailored to any comorbidities present in the patient)
- Warming food, as temperature can significantly impact food intake
- Changing to a dinner plate (instead of a food bowl) or trial feeding in a different place in the house

Examining the senior dog

When it comes to the assessment of our senior patients, consistency is key. In addition to a thorough physical examination, we should incorporate some of the components of the phenotype of frailty into our monitoring protocol (5). Further screening tools vary on a case-by-case basis and might include hematology, serum biochemistry, urinalysis, etc.:

- Dental disease; a thorough oral examination (+/- dental radiographs) for dental disease that can impair food intake is important and should not be overlooked.

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Figure 5. Unintentional weight loss (greater than 5% of body weight in less than 12 months) can provide a valuable clue for chronic undernutrition, and senior dogs should have regular weigh-ins performed.

- Chronic undernutrition; this is a critical problem and must be identified as soon as possible. It can manifest as unintentional weight loss (*i.e.*, loss of greater than 5% of body weight) in less than 12 months **(Figure 5)**. Low body condition scores, specifically less than 4/9, may provide another clue. Poor or low body condition scores have been associated with a worse prognosis in dogs with CKD (23); dogs classified as underweight at diagnosis have a shorter survival time than moderate (BCS 4/9-6/9) and overweight (BCS 7/9-9/9) individuals. Although this relates to cachexia, it may also apply to sarcopenic patients. Dogs with poor appetite or decreased food intake should also raise suspicion for chronic undernutrition. Dietary assessment is also essential, and the clinician should inquire whether clients are feeding deficient diets such as chicken and rice, a diet consisting primarily of treats, or an unbalanced raw diet.

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Figure 6. Assessment for the loss of lean muscle mass (severe in this dog) should be done using the WSAVA muscle condition score chart for dogs, palpating over the spine, scapulae, skull, and wings of the ilia.

- Low physical activity and poor mobility; things to assess here include identifying an abnormal gait or joint pain, which requires cursory neurological and orthopedic examinations, with further investigation as needed.

- Loss of muscle mass; assessing lean muscle mass in senior dogs is important by using the WSAVA muscle condition score (MCS) chart. This entails palpating over the spine, scapulae, skull and wings of the ilia **(Figure 6)**. Patients should be graded based on their lean muscle mass; this can be categorized as normal, or as mild/moderate/severe muscle loss. The use of MCS has been shown to have substantial repeatability and moderate reproducibility for assessing muscle mass in dogs (24). MCS should always be interpreted in conjunction with BCS to (hopefully) avoid missing either considerable muscle loss in dogs that are overweight (BCS 6 or 7/9) or obese (BCS 8 or 9/9), or underweight dogs (*i.e.*, BCS < 4/9) without muscle loss (25).

CONCLUSION

When managing senior animals, a multimodal approach is required to minimize the consequences of aging and to treat common comorbidities identified in this population. Nutritional support entails feeding small, more frequent meals to meet an animal's requirements. Often a dietary change is needed (unless contraindicated because of a comorbidity) but the diet must be complete and balanced. In addition, feeding energy-dense, high protein, highly palatable diets, and often ones with a strong aroma, are recommended. If the reduced appetite persists, it is worth considering use of appetite stimulants. In patients where there is a more significant concern for reduced intake, and pharmacotherapy has failed to improve appetite, placement of a feeding tube can be beneficial. Other facets of managing senior animals include increasing controlled activity and exercise. Careful monitoring of body weight, BCS, MCS, and caloric intake is just as important as any of the above changes or therapies.

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HOW I APPROACH... THE OLD COUGHING DOG

The old dog that presents with a chronic cough can offer a number of diagnostic possibilities, as Lynelle Johnson describes here.

KEY POINTS

1. Coughing in the older dog is often related to airway inflammation, airway collapse or bronchiectasis.
2. Definitive diagnosis can require blood tests, radiography and airway sampling under anesthesia.
3. Chronic diseases typically need long-term management and can be variably controlled, but rarely cured.
4. Cough suppressants are necessary in some cases, but can occasionally result in trapping of secretions and worsened disease.

Introduction to the dog with a chronic cough

The chronically coughing elderly dog is a frequent presentation to the first-opinion veterinarian, with common causes being airway collapse (tracheobronchomalacia) and inflammatory airway disease (chronic bronchitis or lymphocytic airway inflammation). Additional disorders associated with chronic cough include repeated airway insult due to aspiration injury and bronchiectasis. While acute onset is often expected in dogs with an infectious disease, organisms such as *Bordetella* and *Mycoplasma* can also cause chronic clinical signs similar to those seen with these other causes. Unfortunately, there are few distinguishing features that make these conditions easy to diagnose definitively, and many of these disorders are found concurrently (1,2) or sequentially in the individual dog, thus the clinician may require expanded diagnostic testing – and must maintain vigilance – when managing a coughing dog.

Tracheal collapse is one of the most common causes of cough and airway obstruction in the otherwise healthy dog. It is characterized by dorsoventral flattening of the cartilaginous rings with elongation of the dorsal tracheal membrane into the airway lumen. The etiology is unknown, but some affected dogs have been shown to have a reduced number of chondrocytes in their tracheal rings, which decreases the rigidity of the cartilage. The condition can affect the cervical and/or intrathoracic trachea, and bronchial collapse (bronchomalacia) can be present alone or in combination with tracheal collapse. The cervical trachea collapses during inspiration, while the intrathoracic portion collapses on expiration. Bronchial collapse can be static or dynamic on expiration. Collapse leads to mechanical irritation of the opposing mucosa, which enhances mucosal edema and inflammation and perpetuates further coughing.

Canine chronic bronchitis is an inflammatory condition defined by the presence of cough for more than 2 months of the year for which no specific etiology can be identified. Inflammatory damage to the airways results in epithelial cell hypertrophy and squamous metaplasia, goblet cell hypertrophy, submucosal gland hyperplasia, and mucosal/submucosal inflammation, edema and fibrosis. These result in an increase in the amount and viscosity of mucus and chronic irritation within the airway. Typically, airway inflammation is neutrophilic in nature, although in some affected dogs lymphocytic inflammation can be seen (3).

Bronchiectasis is characterized by irreversible dilatation of the bronchi, and it is often accompanied by suppurative airway secretions. It can result from poorly controlled inflammatory or infectious lung disease, aspiration injury, or smoke inhalation. Loss of normal airway tapering leads to mucus stasis and recurrent pneumonia.

Aspiration of gastrointestinal contents or micro-aspiration injury may play a role in development of all the diseases described above, and could also exacerbate causes of cough (4).

Lynelle R. Johnson

DVM, MS, PhD, Dip. ACVIM (Small Animal Internal Medicine), Dept. of Medicine and Epidemiology, University of California Davis (UCD), USA

Dr. Johnson graduated from The Ohio State University College of Veterinary Medicine in 1987 and pursued a Residency in Small Animal Medicine and Master of Science at the University of Illinois before doing a post-doctoral Fellowship in Radiation Oncology at Colorado State University. She is currently Professor in the department of medicine and epidemiology at UCD, with a special interest in canine and feline respiratory conditions, having authored two textbooks on the subject.

Incidence and prevalence

When presented with a coughing dog, patient signalment assists in prioritizing the list of differential diagnoses. Cervical tracheal collapse is common in smaller dogs (Pomeranians, Poodles, Chihuahuas, Yorkshire Terriers) while bronchomalacia occurs in both large and small breeds. Similarly, large or small breed dogs can cough due to bronchitis or bronchiectasis. Bronchiectasis is more common in certain breeds, particularly the Cocker Spaniel, but also the Malamute and Standard Poodle, while micro-aspiration or aspiration injury is more likely in animals affected by laryngeal dysfunction, such as older, large breed dogs (5).

History

Most older dogs with coughing related to airway disease (collapse or inflammation) are healthy except for the presence of unrelenting cough. In fact, dogs with tracheal collapse are often young at the onset of signs and then display waxing and waning clinical signs throughout life. The condition can be exacerbated by endotracheal intubation, weight gain, infection or inflammation. Other dogs with tracheal or airway collapse can present in middle age with either intermittent or severe clinical signs. The cough is typically described as being paroxysmal, dry, and "honking", particularly after drinking, eating or exercise, with excitement, or in hot or humid conditions. Dogs that have bronchomalacia are more likely to have exercise intolerance and expiratory effort in conjunction with the cough.

Chronic bronchitis can result in a cough that is harsh or moist, depending on the type of secretions in the lower airways and the severity of disease. Exercise intolerance or expiratory effort can develop late in the disease course, and pulmonary hypertension can lead to syncope in severely affected animals. However, there are usually few other clinical complaints or historical findings.

Dogs with bronchiectasis can have a moist, productive cough related to accumulation of suppurative secretions. The disease syndrome most closely resembles pneumonia, is of variable severity, and is partially responsive to antibiotics.

Appetite is not usually affected in dogs with airway disease, and many dogs are overweight, which creates added stress on the respiratory system.

Dogs with aspiration-related disease can have a history of vomiting, regurgitation or difficulty swallowing, along with lower respiratory tract signs, but those with micro-aspiration or aspiration pneumonitis can have more subtle signs, such as lip-smacking, or a cough after drinking or lying down. They might also display a retch, gag or cough due to laryngeal accumulation of secretions. Other dogs might have laryngeal signs and display voice change, although this is not always the case either. In one study, almost 20% of dogs with chronic cough demonstrated laryngeal paresis or paralysis in the absence of any history or clinical signs of laryngeal disease (5).

Physical examination

The physical exam should focus initially on respiratory rate and effort. Distinguishing inspiratory from expiratory effort is helpful, because inspiratory effort reflects disease outside the thorax while expiratory effort indicates intrathoracic disease. Dogs with severe cervical tracheal collapse can display inspiratory effort and stridorous respiration. This must be distinguished from laryngeal dysfunction, which occasionally can be found concurrently in individuals with tracheal collapse. More importantly, laryngeal paralysis can result as a consequence of tracheal ring surgery, so it is important to establish normal laryngeal function if this surgery is planned.

Expiratory effort or an expiratory push is classic for intrathoracic airway collapse, bronchomalacia or bronchitis. An expiratory honk is consistent with intrathoracic collapse of a large airway. Some dogs with dramatic expiratory effort will herniate the cranial lung lobes through the thoracic inlet during breathing or coughing, and this can be visualized or palpated at the base of the neck (6). Crackles (inspiratory and/or expiratory) on thoracic auscultation can indicate opening and closing of airways with airway collapse, or can be heard with mobilization of secretions in dogs with bronchitis or pneumonia associated with bronchiectasis. Expiratory wheezes are considered typical for bronchitis, but are heard in a minority of patients. Induction of a cough during the physical examination can be helpful to confirm the nature of the cough observed at home, but increased tracheal sensitivity is only a reflection of airway inflammation and does not indicate a specific disease process.

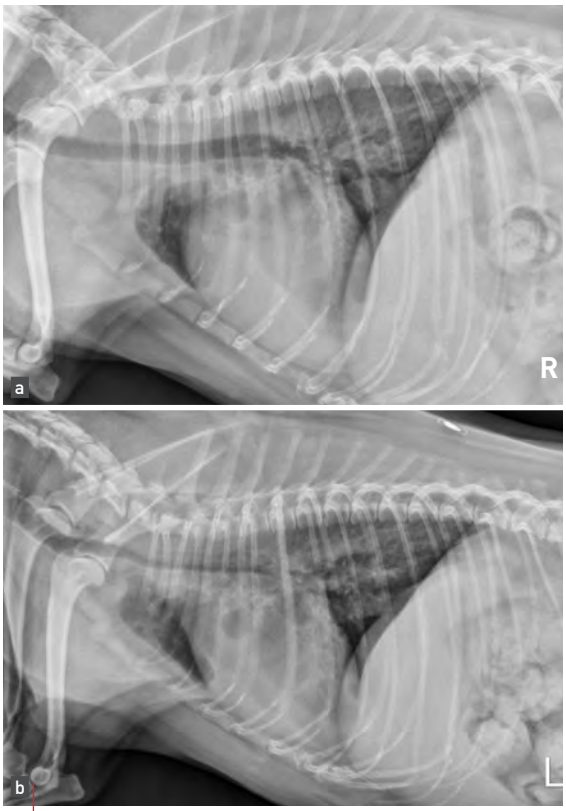

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Figure 1. The right lateral thoracic radiograph **(a)** is an inspiratory view that shows an open intrathoracic trachea. The left lateral thoracic radiograph **(b)** of the same dog is an expiratory view with the intrathoracic trachea collapsed. In both images, marked hepatomegaly is apparent as well as a moderate bronchial pattern.

Accurate assessment of body condition score (BCS) is very important to determine the contribution of obesity to respiratory signs and in devising a therapeutic plan. Most dogs with airway disease are overweight or obese, which worsens respiratory effort and augments airway collapse. On a scale from 1-9, 5/9 is usually considered ideal, although most respiratory patients would benefit from achieving a BCS of 4/9.

Careful cardiac auscultation is indicated in all respiratory patients due to the commonality of concurrent cardiac murmur in many small breed dogs. Additionally, respiratory disorders can lead to pulmonary hypertension, and detection of a new heart murmur could signal the development of a secondary cardiac condition that would complicate management of the existing respiratory condition.

Diagnostics

Blood tests are indicated during the work-up of a coughing dog, both to help prioritize differential diagnoses and to assess the safety of anesthesia. In addition, although the diagnosis of tracheal collapse can be strongly presumed based on the signalment, history, and physical examination findings, a diagnostic work-up should be performed to define concurrent disorders and to provide appropriate therapy. Routine blood tests are typically normal, although a stress leukogram (neutrophilia, lymphopenia, and monocytosis) is not uncommon. Bronchiectasis with pneumonia or aspiration pneumonia would be anticipated to result in neutrophilia, perhaps with a left shift. Peripheral eosinophilia should raise concern for possible eosinophilic lung disease, more common with the severe forms of pulmonary eosinophilia. Liver enzyme elevation and even mildly increased bile acids are common in dogs with airway collapse for reasons that remain obscure (7), although theories include hypoxemia and fatty infiltration of the liver.

Cervical and thoracic radiographs are not reliable in diagnosing airway collapse (8) but can help elucidate concurrent pulmonary diseases – such as pneumonia or bronchiectasis – and cardiac disorders. When both inspiratory and expiratory lateral views are obtained, it can improve visualization of variations in luminal dimensions: on full inspiration, it is anticipated that the cervical trachea will collapse, while on expiration radiographs can reveal attenuation of luminal dimension in the intrathoracic region or at the large bronchi **(Figure 1)**. Overall, radiographs suffer from a high number of false positives, yet they underestimate the degree of collapse, do not always identify the appropriate site of collapse, and are unreliable in documenting intrathoracic airway or lobar bronchial collapse. Fluoroscopy is more helpful in evaluating dynamic airway obstruction, and also allows correlation of airway collapse with cardiac and respiratory cycles. Cranial herniation of the lung through the thoracic inlet due to disruption of the fascial connections in the area has been reported in 70% of fluoroscopic studies in dogs with cough (6). Inspiratory and expiratory computer tomography (CT) can also document airway collapse (9), although it can be challenging to obtain a cross-sectional image for all bronchi.

Thoracic radiography in dogs with bronchitis can show a bronchial pattern **(Figure 2)** or increased number and thickness of airway walls, but in some cases radiographs can also be relatively unremarkable. Bronchiectasis is characterized by

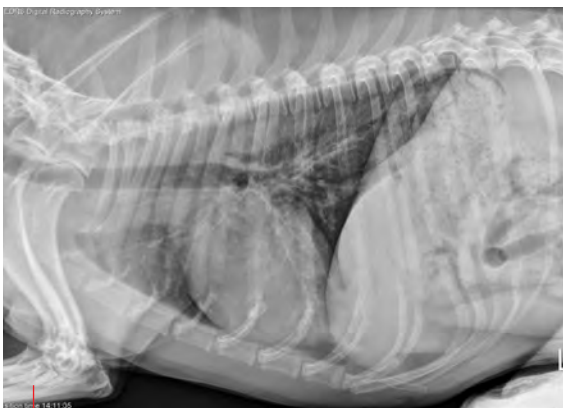

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Figure 2. This left lateral thoracic radiograph demonstrates a mild bronchial pattern.

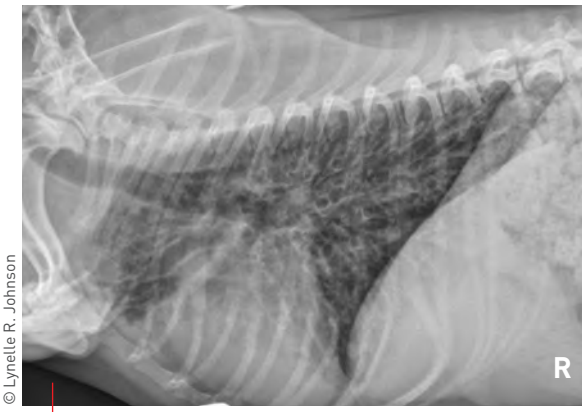

Figure 3. This right lateral thoracic radiograph is remarkable for severe bronchiectasis, with dilatation of multiple airway walls and failure of airways to taper at the periphery.

dilatation of airway walls and lack of normal tapering towards the periphery **(Figure 3)**, however radiographs are relatively insensitive for confirming this condition. Use of CT to assess airway diameter is more sensitive and documents the extent of disease.

Bronchoscopy can be used to confirm tracheal and airway collapse and to grade the severity of disease **(Figure 4)**. It is likely the best method available for diagnosing bronchomalacia involving multiple lobar segments **(Figure 5)** and can also confirm the dynamic nature of disease in smaller airway segments. Bronchoscopy can also identify bronchiectasis **(Figure 6)** or other irreversible changes such as bronchitis nodules or inflammatory proliferations into the airways **(Figure 7)**. Finally, it allows collection of an airway sample for documentation of infectious or inflammatory airway disease **(Figure 8)**. However, bronchoscopy in dogs with airway collapse can be risky, especially in obese or anxious individuals with severe tracheal sensitivity or marked expiratory effort. Anesthesia can result in loss of active respiratory maneuvers that keep airways open, resulting in failure to recover properly from anesthesia. Additionally, excitement during recovery can result in excessive abdominal effort that potentiates lower airway collapse.

If bronchoscopy is not available and an airway sample is desired, a tracheal wash sample can be collected for cytology and culture; this might be performed if the animal is anesthetized for an elective procedure such as dental prophylaxis or mass removal. Slow recovery from anesthesia is advisable, with oxygen supplementation and adequate sedation as well as cough suppression.

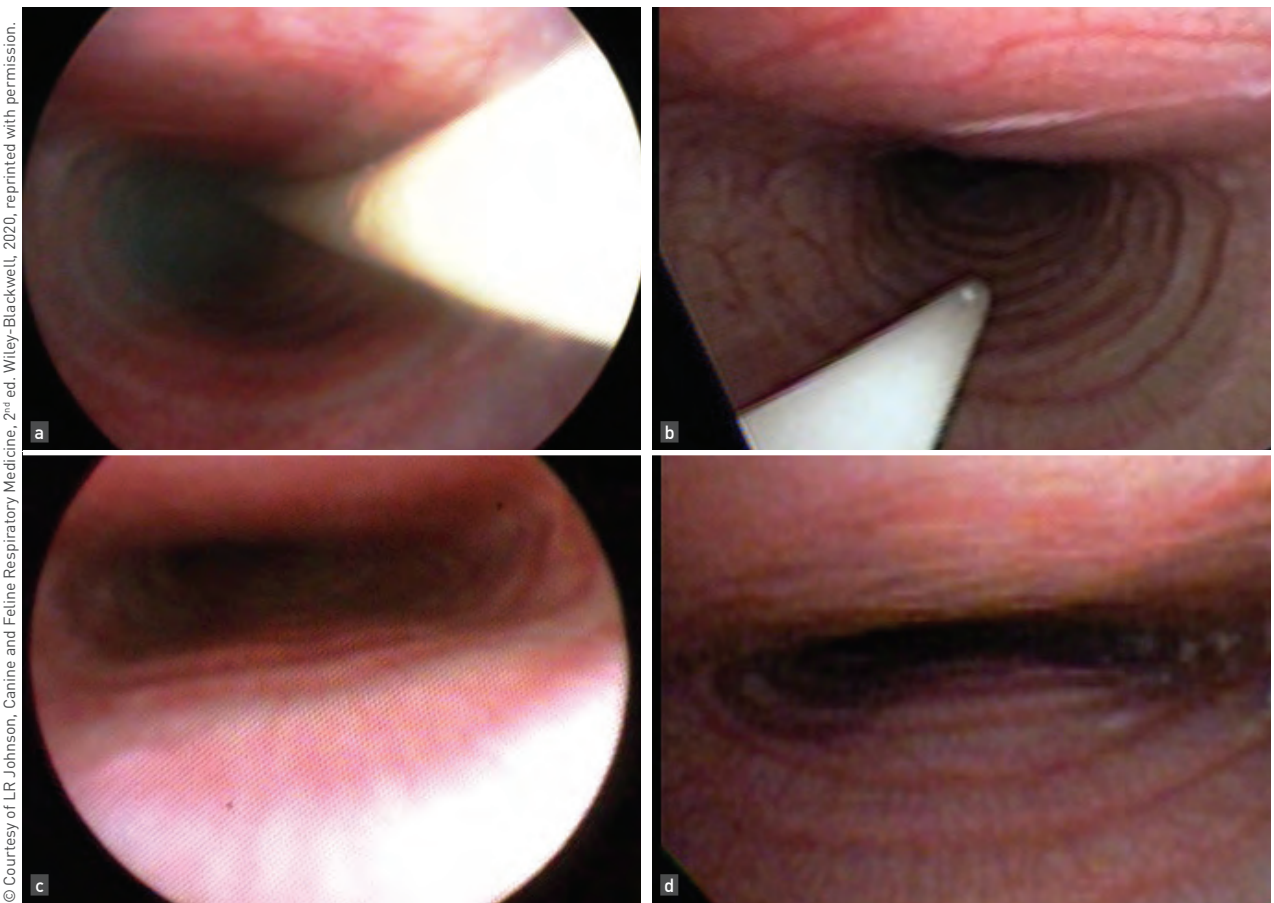

Figure 4. This compilation of bronchoscopic images illustrates the grades of tracheal collapse from I (25% collapse) **(a)** to II (50% collapse) **(b)** to III (75% collapse) **(c)** to the most severe form of collapse (IV) **(d)**.

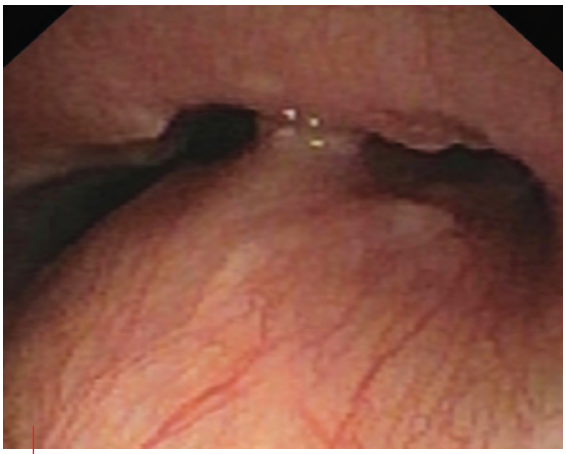

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Figure 5. This bronchoscopic image shows ~50% collapse of the left cranial lobar bronchus (at the 15:00 position of the clock face) and of the left caudal lobar bronchus (at the 09:00 position of the clock face).

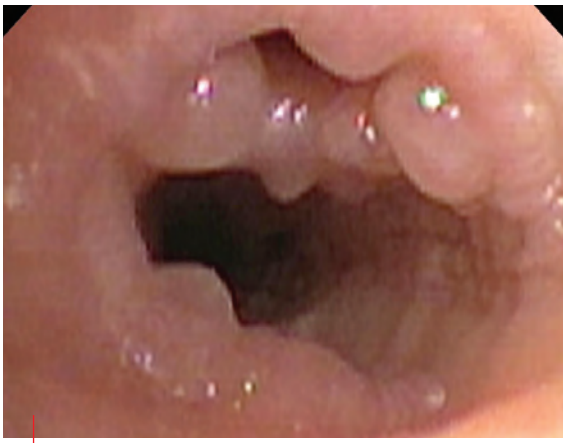

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Figure 7. This bronchoscopic image shows marked epithelial irregularity, and multiple smooth, polypoid bronchitic nodules comprised of neutrophilic infiltrates.

Treatment

Initial therapy

In the emergency situation where a dog with chronic cough has developed acute respiratory distress due to development of infection, stress, or aspiration-related disease, calming measures are indicated. Supplementation with oxygen and a cool environment are essential. Judicious use of acepromazine (0.01-0.04 mg/kg SC, IM or IV) can be used in combination with butorphanol (0.1-0.4 mg/kg SC, IM or IV), with one or both drugs repeated as needed. Thoracic radiographs can be helpful in determining whether or not administration of antibiotics, anti-inflammatory agents, or mucolytic therapy is required, although repeat airway sampling is needed in some instances.

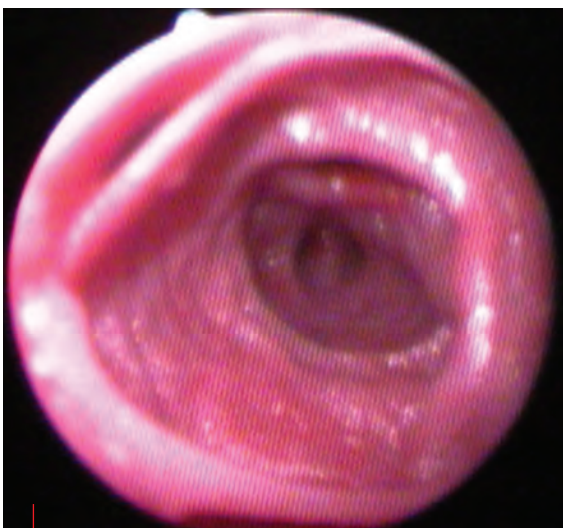

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Figure 6. This bronchoscopic image illustrates marked bronchiectasis with hyperemia, thinning of bronchial bifurcations, and increased space within the airways.

Chronic management

Owners should be aware that dogs with a chronic cough due to inflammatory or degenerative airway disease virtually always continue to cough. The goal of therapy is to control clinical signs by at least 50% with an acceptable level of intervention, although hopefully even better control can be achieved, and this relatively conservative goal will help manage owner expectations.

When a complete diagnostic work-up has been performed, treatment is tailored to the results obtained. For infection with *Mycoplasma*, doxycycline is recommended, while *Bordetella* infection can require nebulization with gentamicin (10). Owners can be instructed to purchase an ultrasonic or compressed air nebulizer which creates particles 2-5 µm in size that will reach the lower airways. The antibiotic can be placed in the nebulizer cup and administered for 10-20 minutes daily for up to 6 weeks. Aspiration injury does not always require management with antibiotics (11), and in some cases use of acid suppression, in conjunction with physical changes to feeding (*e.g.*, an elevated feeding bowl) to manage laryngeal dysfunction or gastroesophageal reflux disease, can be helpful in alleviating the cough. For suspected bilious vomiting syndrome, consider feeding a small meal before bedtime so that the stomach is not empty for a long period of time. Where a gastrointestinal problem is suspected, a full work-up should also be recommended, including assessment of vitamin B_{12}/folate and abdominal ultrasound.

In dogs with chronic bronchitis, anti-inflammatory therapy with corticosteroids can be used to break the cycle of mucosal damage and to reduce excessive production of secretions. Oral prednisone or prednisolone can be used at relatively high doses initially (0.5-1.0 mg/kg PO q12h for 5-7 days) and then tapered as rapidly as possible while maintaining control of the cough. Some dogs require alternate day therapy for prolonged periods of time. Exacerbations of disease are treated with

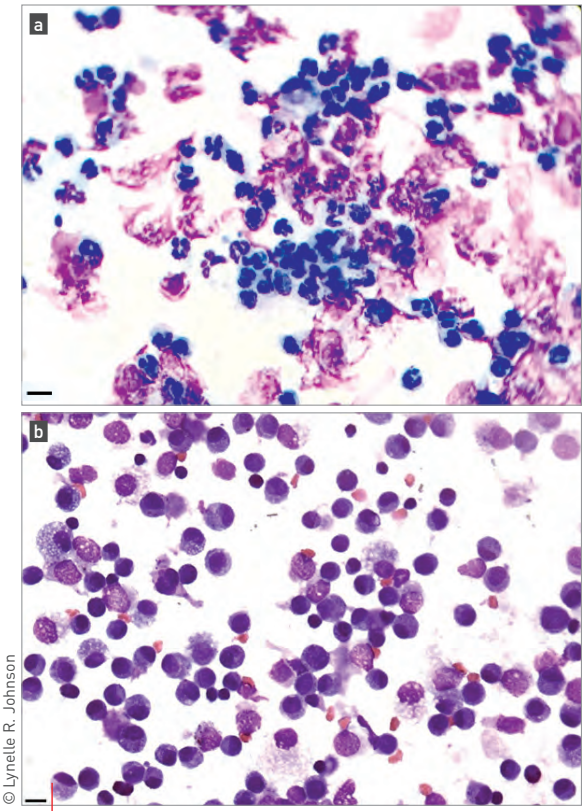

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Figure 8. **(a)** Bronchoalveolar lavage fluid cytology shows a preponderance of neutrophils, characteristic of chronic bronchitis. Bar denotes 15 µm. **(b)** Bronchoalveolar lavage fluid cytology demonstrates primarily lymphocytic inflammation, a variant of inflammatory airway disease common in dogs with airway collapse. Bar denotes 10 µm.

an increase in prednisone dosage to the point that effectively controls clinical signs. Animals that cannot be controlled on oral glucocorticoids, or those that suffer excessively from side effects associated with corticosteroid use, can be treated with inhaled steroids by using a facemask and spacing chamber for delivery. In general, inhaled corticosteroids are preferred to oral treatment in order to facilitate weight loss and to lessen other side effects of glucocorticoids, such as panting that can worsen upper respiratory inflammation. In one study, dogs with ACVIM class B2 or C heart disease diagnosed with bronchomalacia based on clinical examination and imaging findings were treated with steroids (fluticasone propionate via a metered dose inhaler with spacing chamber, at 110 mcg/puff, 1 puff BID) without having bronchoscopy performed. All demonstrated at least 50% reduction in cough, as well as improved quality of life, and the owners expressed satisfaction with the ease of treatment (12). This study might suggest that inhaled steroids could be considered appropriate care for some dogs suspected of bronchomalacia even in the absence of a definitive diagnosis.

Dogs that fail to respond to anti-inflammatory therapy may benefit from the addition of extended-release theophylline (10 mg/kg PO BID) to reduce the effort of breathing and potentiate the effect of corticosteroids. This drug is classified as a bronchodilator, but because dogs with bronchitis and bronchomalacia do not actively bronchoconstrict, this mechanism of action is not pertinent here. Instead, the drug might work through effects on intracellular calcium or adenosine antagonism. Side effects of theophylline include anxiety, anorexia, and diarrhea, but with gradual introduction it is generally well tolerated. Alternately, some dogs with bronchitis or bronchiectasis suffer from excessive accumulation of secretions, and these animals can benefit from saline nebulization to aid in evacuation of mucus. As above, owners can be instructed to purchase a suitable nebulizer and use sterile saline vials once or twice daily to help hydrate secretions.

In dogs with tracheal collapse and bronchomalacia, a narcotic cough suppressant can be required if coughing persists after inflammation has been controlled. Butorphanol (0.55 to 1.1 mg/kg PO BID-QID) and hydrocodone (0.22 mg/kg PO BID-QID) are most useful; they generally have to be given frequently in the initial stages of disease, then tapered downwards after 24-48 hours. The animal has to be kept very sedate initially to break the cough cycle, but if the dose of narcotic remains high the drug will lose its effectiveness. Similarly, if the drug is started at a low dose and titrated upwards, the animal will become addicted, and the medication will not be effective in controlling the cough. Other drugs, such as tramadol (2-5 mg/kg PO BID-TID) or gabapentin (5-10 mg/kg PO BID-TID), can be considered for use, but they are not as effective.

Finally, obesity is a common problem in the canine population in general and it seems to be over-represented in animals with chronic respiratory disease. Obesity results in poor lung expansion, reduced thoracic volume, and increased work of breathing, and this can lead to worsened cough and respiratory effort. A weight loss program should be recommended, because this alone can result in improvements in gas exchange and reduction in cough.

"Induction of a cough during the physical examination can be helpful to confirm the nature of the cough observed at home, but increased tracheal sensitivity is only a reflection of airway inflammation and does not indicate a specific disease process."

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The first step in such a program is an accurate assessment of BCS. In a dog with an ideal score (5/9), the ribs and hip bones can be palpated readily and may be visible in smooth-coated breeds; the waist is obvious from above and from the side. For each point above the ideal, a dog would be considered 10% overweight. The second step is to calculate the calories currently being consumed by the dog, with the goal of achieving weight loss through a reduction in calories using its usual diet. Animals can be started on 80% of their current caloric intake. Alternately, the resting energy requirement (RER), (as calculated by 70 x (body weight in kg)$^{0.75}$) can be used to determine the daily calories necessary. Use of a low fat, restricted calorie content diet can improve participation in a weight loss program by enhancing satiety and thus reducing food-seeking behavior (13). The high-fiber content reduces the tendency to overeat and improves stool character. However, with a weight loss goal of 1-2% per week, it can easily take months for an appropriate and sustainable weight to be achieved; a 20% weight loss from a 6/9 to a 4/9 will take 20 weeks, or 5 months. Therefore, it is important to give owners specific guidelines, and frequent follow-up with clients improves compliance (14). Providing owners with the opportunity to offer low calorie treats to their pets can also be useful, enhancing the overall success rate. When possible, the animal should be encouraged to participate in gradually increasing amounts of exercise, but collars should be avoided and exposure to excessive heat and humidity minimized.

Finally, it is worth noting that dogs with cervical tracheal collapse that fail aggressive medical and dietary management can require placement of external prosthetic rings for stabilization of the trachea, or insertion of an internal stent for intrathoracic tracheal collapse. Research is currently being conducted to establish possible methods for stabilization of individual bronchi.

CONCLUSION

The clinical presentation of the dog with tracheal or airway collapse is generally relatively characteristic, although ruling out concurrent infectious or inflammatory airway disease and confirming the site and degree of airway collapse requires fluoroscopy and airway sampling. Control of cough is best achieved when a definitive diagnosis has been established, but there are multiple reasons why this is not always achieved. Owners may not understand the value of performing specific diagnostic tests or may be unable to afford them. They may also fear placing their dog under anesthesia for advanced imaging or airway sampling, and in some cases the veterinarian shares these fears; here it is necessary to choose the most rational therapy that can benefit the patient without causing harm. Obesity must be aggressively managed with dietary and behavioral modification.

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DERMATOLOGY AND THE AGING DOG

As dogs age, their skin also ages; this paper offers an overview of what these changes are and the most common dermatologic conditions seen in older dogs.

KEY POINTS

1. As dogs age, various skin changes occur; these include callus formation, loss of elasticity and wrinkling, as well as alterations in hair color and texture.
2. Common endocrinopathies such as hypothyroidism and hyperadrenocorticism have significant effects on the skin and hair coat.
3. Any patient suspected of having demodicosis should be skin scraped, regardless of their preventative status.
4. Epitheliotropic lymphoma has a varied clinical presentation, and can be easily mistaken for other inflammatory or infectious skin diseases.

Geriatric dermatology – An introduction

Skin is an amazing organ, continuously battling the elements and protecting vital structures, but as dogs age, their skin and hair coat age as well. Callus formation, loss of elasticity, skin wrinkling, and changes in hair color and texture can be seen. The immune system ages with the dog, and older animals are more susceptible to skin infections and may have difficulty keeping their resident *Demodex* mite populations in check. Additionally, some systemic diseases are more common in the geriatric dog, many of which have cutaneous manifestations – for example, hypothyroidism and hyperadrenocorticism can be most evident at times through their skin changes. Metabolic conditions, such as superficial necrolytic dermatitis, also occur more often in the aging population. Finally, geriatric canines are more likely to develop cutaneous masses – both benign and malignant tumors – than their younger counterparts. This paper offers an overview of dermatology in the geriatric dog.

General changes to the skin and hair coat

Senile changes occur at various ages in our pet population – typically later in life for small breed dogs, and earlier for larger ones. Genetic factors, breed differences, nutritional support and many environmental factors can all influence the onset of aging changes. Senescence is a normal process that cannot be avoided; as dogs get older, their ability to rejuvenate their cellular population wanes, there is increased cellular atrophy in most structures, and a variety of changes at the microscopic and ultrastructural levels can be observed.

The epidermis may thin, especially with extreme age, poor nutrition, and certain endocrinopathies that are more common in older animals. Some dogs develop skin hyperpigmentation with age, which cannot be attributed to more common causes (sun exposure, trauma, endocrinopathies) (1). Epidermal collagen fibers show increased cross-linkage, and their bundles appear more fragmented. Elastin fibers lose elasticity and show increased calcium and pseudoelastin in their fibers; fragmentation may also be seen (2). Arrector pili muscles can appear fragmented, vacuolated, and sometimes hard to find. Some older literature describes cystic dilation of epitrichial sweat glands, and even atrophy of sebaceous glands (1). Blood vessels and lymphatics do not typically change in appearance with age. Perifollicular mineralization in the dermis is a reported change in older poodles (3,4).

Commonly visible changes to aging skin and hair coat, along with potential causes, include (2,5,6):

- Graying of the hairs **(Figure 1)**: atrophy of pigment cells and reduced tyrosinase activity
- Dull coat appearance: changes in sebum production

Mitzi D. Clark

DVM, Dip. ACVD, College of Veterinary Medicine, Cornell University, Ithaca, NY, USA

Dr. Clark received her DVM from Louisiana State University and went on to complete a small animal rotating internship at the MSPCA Angell Animal Medical Center in Boston and a residency in Veterinary Dermatology at Cornell University. She then worked in private practice in Austin, Texas as a Board-Certified Veterinary Dermatologist for several years before returning to Cornell in 2019, where she is currently an Assistant Clinical Professor of Dermatology and Dermatology Section Chief.

- Thinner hair coat: decreased follicular activity
- Skin wrinkling: tissue dehydration, loss of skin elasticity, possible epidermal atrophy
- Callus formation: prolonged pressure exposure and hyperkeratosis
- Paw pad hyperkeratosis **(Figure 2)**: aging hyperkeratosis as well as hyperkeratosis secondary to abnormal wear of the paw pads, and also gait changes secondary to osteoarthritis

In terms of intervention, there is no prevention for aging changes to the skin. However, as exposure to the sun can hasten these changes, reducing exposure and utilizing sunscreens and physical sun barriers, especially in sparsely haired and lightly pigmented dogs, may be of benefit. Moisturizing the coat, nasal planum and paw pads can combat dryness, whilst padded bedding can minimize pressure on bony prominences and may decrease callus formation.

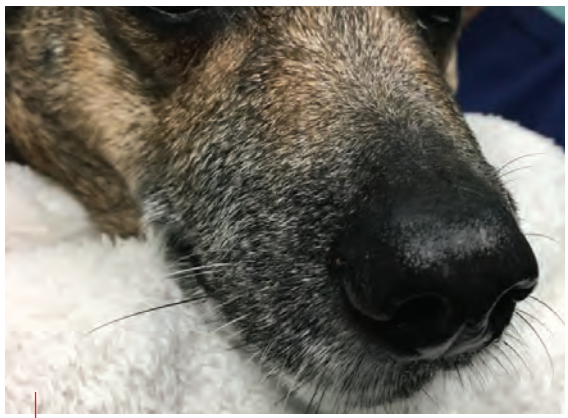

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Figure 1. Graying of the muzzle of an older dog.

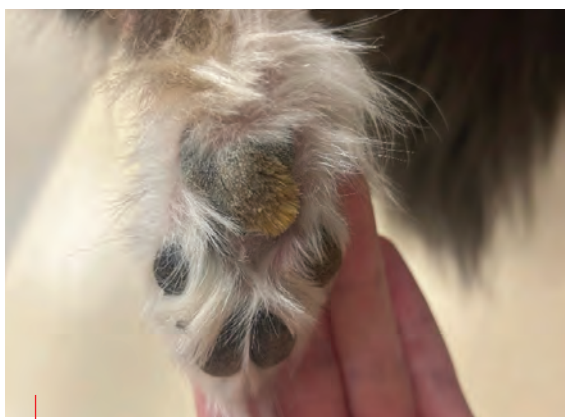

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Figure 2. Paw pad hyperkeratosis due to abnormal wear in an adult Shetland Sheepdog.

Endocrine and metabolic conditions

Common endocrinopathies, such as hypothyroidism and hyperadrenocorticism, significantly affect the skin and hair coat and tend to occur in middle-aged and older animals. Owners often notice the cutaneous changes, which may be the only reason the animal presents to the veterinarian, although systemic signs are also likely to develop. Another metabolic condition, hepatocutaneous syndrome (HCS) or superficial necrolytic dermatitis (SND), also occurs more commonly in older animals.

In canine hypothyroidism, common cutaneous manifestations include a thinning hair coat, especially at frictional areas, but also including the tail **(Figure 3)** and bridge of the nose; a predisposition to bacterial folliculitis; hyperpigmentation; scale; and myxedema in more advanced cases. Hairs need thyroxine (T_4) to enter into anagen. Hypothyroid animals have more telogenized hairs that may bleach and lighten in color with repeated sun or chemical exposure as new hairs are no longer cycling in. Additionally, telogen hairs can epilate with time, and hypotrichosis and alopecia may be observed without new hairs cycling. Receptors for thyroid hormones are also found on sebocytes, so a lack of hormone could lead to sebaceous gland atrophy. Changes in T_4 levels can affect fatty acid concentrations in the skin, which in turn can lead to a keratinization defect, resulting in widespread

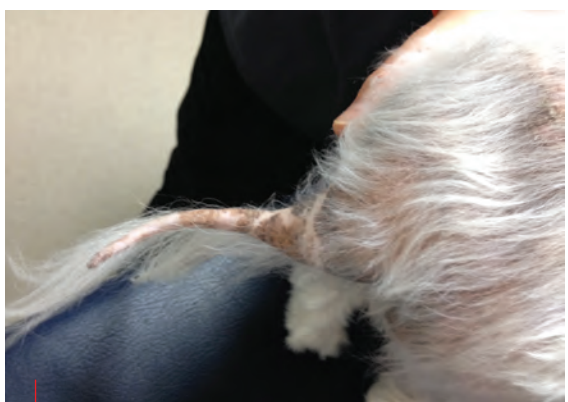

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Figure 3. Tail hypotrichosis in a dog with hypothyroidism.

scale and a dull and dry coat appearance. These changes also make the animal more susceptible to bacterial and *Malassezia* infections as the skin loses some protective barrier function. Hyperpigmentation is a non-specific sign resulting from chronicity and can be seen in various hormonal and inflammatory conditions. Hypothyroid dogs can accumulate hyaluronic acid in the skin, causing a thickness of the skin and the classic "tragic face" appearance of myxedema (7).

Non-cutaneous signs of hypothyroidism include weight gain, lethargy, mental dullness, and heat-seeking behavior (8). Diagnosis is confirmed via blood testing, but remember that many things can interfere with the total T_4 levels, so care should be taken in interpreting this test result in patients with other illnesses or those taking certain medications such as glucocorticoids, sulfonamide antibiotics, phenobarbital, clomipramine, and non-steroidal anti-inflammatory drugs (NSAIDs). Interpreting a complete thyroid panel, including total T_4, free T_4, and thyroid stimulating hormone (TSH) +/- antithyroid antibodies, may provide a more accurate diagnosis. Treatment of canine hypothyroidism is with oral levothyroxine and is generally well-tolerated.

Hyperadrenocorticism in the dog can lead to hair loss, especially symmetrically on the flank. The skin may be thinned and hypotonic. Comedones and milia are common, and phlebectasias may be present (9). Secondary skin infections are more common in animals with hyperadrenocorticism. Calcinosis cutis is an occasional sequela **(Figure 4)**. In this condition, adrenal glands overproduce cortisol, either due to a primary adrenal tumor or, more commonly, as the result of adrenal hyperplasia influenced by a pituitary tumor. This excessive cortisol significantly affects the hair follicles and sebaceous glands, leading to atrophy – the consequence of which is hyperkeratosis (excessive scale) and hypotrichosis-to-alopecia. Hair follicles are also filled with hyperkeratosis, leading to the comedone and milia formation. Easy bruising occurs due to weakened blood vessels from the cortisol influence, and phlebectasias result from vessel dilatation. Striae or stretch marks can be seen secondary to the thinned skin and poor healing, which results in this scarred pattern (9,10).

Non-cutaneous signs of hyperadrenocorticism include polydipsia and polyuria, as well as polyphagia, excess panting, and exercise intolerance. Affected animals may have a classic "pot-bellied" appearance. Diagnosis is not always straightforward, and a combination of results from abdominal ultrasound, ACTH stimulation test, and low-dose dexamethasone suppression test (LDDS) may be needed. Treatment may involve surgical removal of the adrenal gland in some adrenal-dependent cases, although oral trilostane or mitotane (the most common option to treat pituitary-dependent cases) is also occasionally used.

Hepatocutaneous syndrome (HCS) or superficial necrolytic dermatitis (SND) is a metabolic condition that occurs in the dog, whereby a hepatopathy causes hypoaminoacidemia and aminoaciduria. As a result, affected dogs develop skin lesions, such as

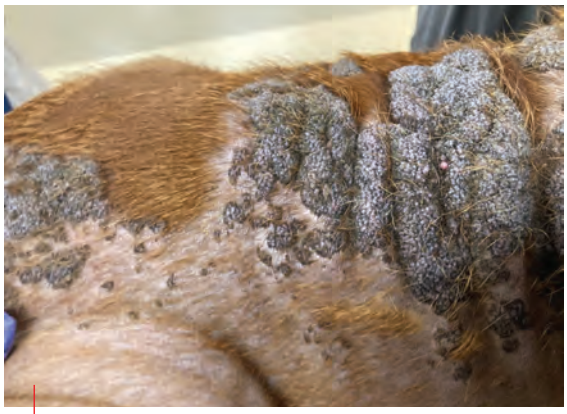

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Figure 4. Calcinosis cutis in a bulldog after exogenous steroid use.

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Figure 5. Paw changes (crusting, erythema, hyperkeratosis) in a dog with superficial necrolytic dermatitis.

crusting, erosion and ulceration, and occasional vesicle formation. These skin changes most commonly affect areas exposed to wear or trauma, such as paw pads **(Figure 5)**, elbows, hocks, genitalia, muzzle and the periocular area. Skin biopsy and abdominal ultrasound, along with blood and urine amino acid levels, can confirm the diagnosis. SND previously resulted in relatively short survival times (as low as 3-6 months after diagnosis) despite supplemental nutritional therapy. Recently, longer survival rates have been reported with this condition (and in dogs with aminoaciduric canine hypoaminoacidemic hepatopathy syndrome (ACHES) without skin lesions) through a combination of therapies (11,12). In terms of intervention, a mix of intravenous amino acid +/- lipid infusions, balanced diets, and enteral supplements may provide the best outcome (13).

Skin and aging immunity

The skin's immune system is complicated. Innate components include the physical barrier of the epidermis, which can recruit phagocytic cells, activate complement, and produce cytokines. Adaptive responses include antigen recognition and subsequent responses by lymphocytes (14). Aging may not be a disease, but an aged immune system

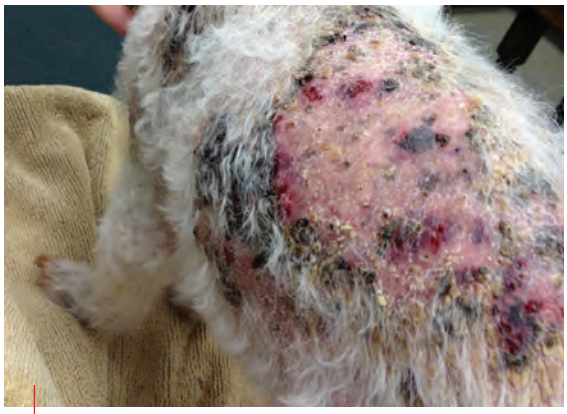

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Figure 6. Adult-onset demodicosis and secondary bacterial folliculitis.

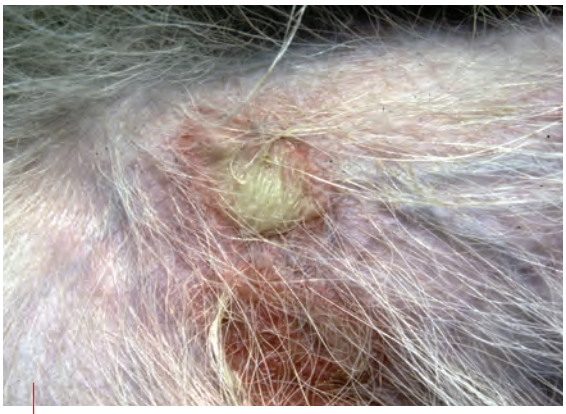

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Figure 7. Bullous impetigo in an immunosuppressed dog.

makes fighting infection more challenging. Additionally, our older pet population will be more likely to have other underlying conditions (such as endocrine disease, chronic allergies, immune-mediated skin disease, and cutaneous neoplasia) which can predispose them to secondary skin and ear infections.

Like their younger counterparts, senior dogs are susceptible to ectoparasites such as fleas or scabies mites. Demodicosis in the older dog **(Figure 6)** is often a warning sign of internal disease or immunosuppression, although adult-onset demodicosis can also be idiopathic. Only hyperadrenocorticism, hypothyroidism, and leishmaniasis were associated with adult-onset demodicosis in one study (15), but interestingly underlying neoplasia was not. The clinician should remember to look for causes of immunosuppression in older animals with all cases of demodicosis. Many parasiticides have been used to treat the condition, including avermectins, milbemycins, amitraz and others, but it has recently become much easier to manage with the advent of newer parasiticide therapies, such as the isoxazolines.

Bullous impetigo **(Figure 7)** is a superficial pustular-to-bullous condition most commonly reported secondarily to staphylococcal infections in aged animals with endocrinopathies, such as hypothyroidism, diabetes mellitus, or hyperadrenocorticism (16). Superficial and deep bacterial folliculitis/furunculosis cases, often caused by *Staphylococcus* spp., are also seen in older dogs with endocrinopathies, allergic dermatitis, or any barrier-disrupting condition. Occasionally, these bacterial infections occur more frequently in geriatric animals with no apparent underlying condition; this could be due to the fact that as the skin's immune system ages, it is slower to respond to infection. Antimicrobials (topical and systemic) may be required for extended periods to clear the infection properly. *Malassezia* dermatitis typically occurs secondarily to allergic dermatitis, conformational issues in the skin and ears, in areas with increased cutaneous humidity, and secondary to excessive moisture as seen in swimmers. The skin may show extreme lichenification and hyperpigmentation in older animals with chronic *Malassezia* issues.

Topical therapy is ideal for superficial skin infections when possible; 3% or greater concentrations of chlorhexidine should be effective against *Staphylococcus spp.* and *Malassezia spp.* infections. Systemic antibiotics should be chosen based on bacterial culture when possible.

Cutaneous tumors

Skin tumors can occur throughout a dog's life, but they are seen more frequently as animals age. Skin masses can arise from epithelial or mesenchymal origins; neural, vascular, adipocytic and fibroblastic tumors can all occur. Various aspects, such as genetic predisposition and immunologic factors, can generally affect the growth of skin tumors, whilst other contributors, such as environmental factors (including ionizing radiation and ultraviolet light) can have cumulative influences. More exposure to these factors comes with prolonged age, which may play a role in certain tumor development.

Melanomas and mast cell tumors are common in older dogs (17), but since abundant information about these tumors and their treatment is already available to the practitioner, these will not be reviewed in detail here, and this discussion will focus on tumors seen frequently in the specialty dermatology and general practice. Briefly however, melanomas are most commonly seen as solitary lesions on the head, limbs or digits, and can appear gray or black. They may be well- or ill-defined and are often raised. Dogs are usually older than nine years of age at onset (18). Mast cell tumors can have a varied clinical presentation, often appearing as solitary masses, ranging from dermal-to-subcutaneous, soft-to-firm, and haired-to-alopecic. Masses may ulcerate or be pruritic, and the average age of onset is eight years (19).

Many benign growths in dogs, such as lipomas, occur with increased frequency in senior dogs. Lipomas arise from mature adipocytes, with obesity and age being risk factors. These tumors are most often present in the subcutis, but can present in a more dermal aspect, or alternatively infiltrate deeper structures. Nodular sebaceous gland hyperplasia, sebaceous epithelioma, and

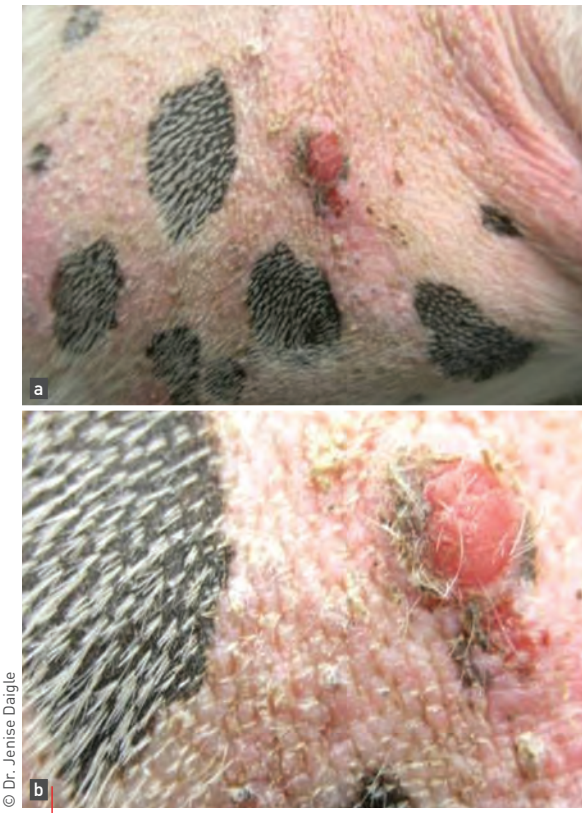

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Figure 8. Actinic changes, comedones **(a)**, and a squamous cell carcinoma lesion **(b)** in a lightly pigmented dog following chronic sun exposure.

sebaceous adenomas are benign growths seen on the trunk, limbs, and face in older animals. Less often, sebaceous gland adenocarcinoma can occur. Lesions are wart-like or cauliflower-like in appearance, with affected regions including the trunk and limbs, as well as around the eyes (20). While oral papillomas are more common in young animals, older dogs can get papillomas in non-oral areas, such as the paws, head, and eyelids, and lesions can be single or multiple. In the older pet, there is more concern for malignant transformation to squamous cell carcinoma (20). In terms of intervention, observation is allowed for most benign growths in the geriatric dog, but if the lesion bothers the pet or the owner, surgical removal via traditional methods, cryotherapy or CO_2 laser is appropriate.

Chronic sun exposure can predispose dogs to develop actinic keratosis, and sun exposure is believed to be a trigger in some dogs that develop skin cancer. Squamous cell carcinomas (SCC) and hemangiomas/hemangiosarcomas are occasional sequelae. SCC in the dog has also been associated with papillomaviruses and other infectious and inflammatory dermatoses. It can occur in various locations, but is commonly seen on the digits (21). When UV light is implicated, lesions are more likely in non-haired or glabrous areas **(Figure 8)** such as the ventrum. Hemangiomas also occur on the ventrum of dogs secondary to prolonged sun exposure; these are usually blue or red in appearance and dermal-to-subcutaneous. Dermal hemangiosarcomas can also develop in this area, although they are usually less well-circumscribed

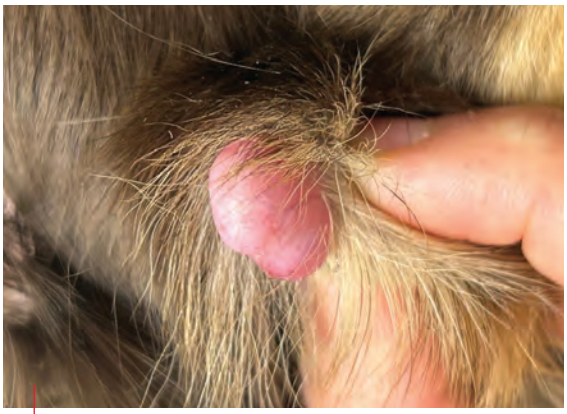

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Figure 9. Trichoblastoma on the face of a dog.

than their benign counterparts. Multiple masses are often present on the ventrum (22). Actinic-induced lesions such as SCC, cutaneous hemangiomas, and hemangiosarcomas can be treated with surgical resection, cryosurgery, and CO_2 laser ablation. Topical imiquimod may also help to improve lesions.

Numerous follicular masses are seen in older dogs, including various follicular cysts, trichoepitheliomas and trichoblastomas, and can be solitary or multifocal. Trichoepitheliomas favor the trunk and limbs, while trichoblastomas **(Figure 9)** have a predilection for the neck and head. Follicular cysts are named after the area of the hair follicle that is affected and the type of keratin produced. They commonly present as solitary nodules, and can become inflamed and infected if traumatized. Complete surgical excision is the treatment of choice when follicular lesions are problematic, although observation is another option if lesions are few, inconspicuous, and not prone to trauma and secondary infection.

Epitheliotropic lymphoma **(Figures 10-12)** involves infiltrative T-lymphocytes that favor the epidermis and adnexal epithelium. It has a varied clinical presentation, with early lesions commonly mistaken for allergic dermatitis and bacterial or yeast infections. Previous inflammatory skin disease may predispose animals. The skin may

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Figure 10. Periocular ulceration/erythema and rostral muzzle depigmentation, erosion, and erythema in a dog with epitheliotropic lymphoma.

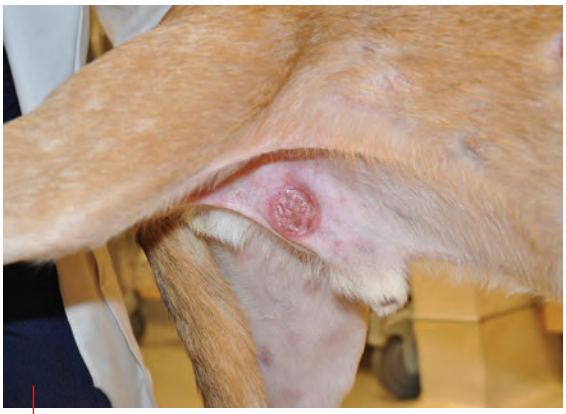

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Figure 11. Ulcerative nodule/plaque in a dog with epitheliotropic lymphoma.

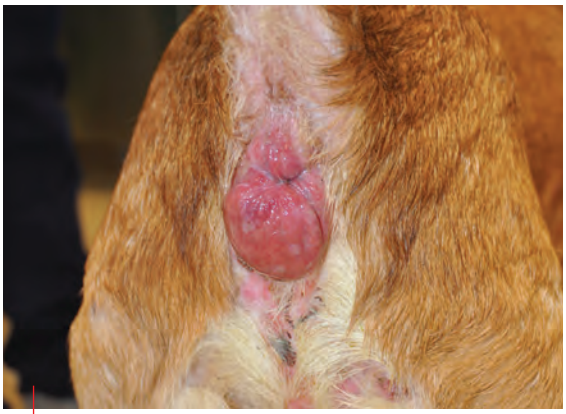

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Figure 12. Perianal erythema and swelling in a dog with epitheliotropic lymphoma.

appear erythematous with or without scale and exfoliation. Depigmentation around mucocutaneous junctions can occur, and these areas may develop a "puffy" or thickened appearance. Paw pads can show hyperkeratosis, erosion and ulceration, and may depigment. With time, erythematous plaques and nodules may develop, and ulceration can be seen (23-25). Pruritus can be variable. Diagnosis is via skin biopsy, with immunohistochemistry performed as needed. There is no one effective treatment for epitheliotropic lymphoma; various chemotherapeutics have been used with varying success. In some cases, especially with mucocutaneous disease, radiotherapy has been beneficial. Glucocorticoids, safflower oil, and retinoids have utility (23), and it is important to manage secondary infections and control pruritus in those animals with pruritus; lokivetmab may help with this in some patients.

CONCLUSION

In summary, a variety of changes to the skin and hair coat occur in geriatric dogs. A basic understanding of typical aging manifestations can help the clinician understand when abnormalities are present in an older canine. Aging immune system changes may predispose the skin to secondary infections. Geriatric animals have the propensity to develop endocrine and metabolic diseases as well as cutaneous neoplasia, and prompt recognition and intervention can help ensure a favorable outcome in some, but not all, cases.

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HOW I APPROACH.... GINGIVAL ENLARGEMENT IN THE DOG

Christopher Sauvé

DVM, Dip. AVDC, Pulse Veterinary Specialists, Edmonton, Canada

Dr. Sauvé graduated from Canada's Western College of Veterinary Medicine in 2012 and discovered a passion for dentistry while working in both primary care and emergency medicine clinics in Edmonton. He then completed a three-year veterinary dentistry and oral surgery residency in Kansas City and is now board-certified, practicing at a Canadian Specialist and Emergency Hospital. He sees his job as enabling him to have a positive impact on his patients' quality of life that comes with optimizing their oral health. He is especially interested in endodontics, diagnostic imaging and maxillofacial reconstruction following traumatic injuries.

Gingival enlargement in a dog's mouth is a common presentation in the exam room; this paper covers the common pathologies encountered and discusses the preferred approach to treatment.

KEY POINTS

1. The clinical appearance of a gingival enlargement (GE) in most patients is not pathognomonic, and a diagnosis should be obtained prior to creating a definitive treatment plan.
2. When evaluating a GE, a complete oral health examination should be performed; this includes a visual assessment, orodental charting, diagnostic imaging, and a full description of the lesion.
3. In some cases, it may be rational to perform both diagnostics (an incisional biopsy in the form of a gingivectomy and gingivoplasty) and treatment during the same procedure.
4. Gingival hyperplasia is a non-neoplastic reactive inflammatory lesion most commonly caused by plaque-induced gingivitis/periodontitis, occlusal trauma, and certain medications.

Introduction – What is gingival enlargement?

The descriptive term "epulis" is regularly used in primary care practice to describe a focal enlargement of the gingiva, but it is also ambiguous. In the Greek language "epulis" means "on the gum" and although this descriptive terminology seems logical, there is a lack of clarity and consistency between practitioners on what exactly an "epulis" describes and implies, which can result in medical errors, inappropriate treatment, and confusion for clients and colleagues. In a contemporary dentistry service, I recommend that we collectively avoid using the word, and instead the term "gingival enlargement" (GE) should be encouraged to describe a focal enlargement of the gingiva in the absence of a histopathological diagnosis and absence of an inferred prognosis. A GE may therefore subsequently be identified as a benign or malignant neoplastic lesion, or a non-neoplastic, reactive tumor-like lesion of the gingiva (1).

This short article aims to demonstrate the diversity of pathology that can present as a gingival enlargement in a dog's mouth. It will reveal the importance of obtaining a diagnosis of a GE through histopathology, and provide superficial information on treatment and prognosis for various conditions (including, where appropriate, to perform treatment and obtain a diagnosis during the same procedure). It will also offer a guide on how to perform gingivectomy and gingivoplasty in a clinical scenario where focal fibrous hyperplasia, a type of gingival hyperplasia, is suspected.

How to evaluate a GE

When evaluating a GE, it is imperative that the fundamentals of a COHAT (Complete Oral Health Assessment and Treatment) are followed. This encompasses a visual assessment; orodental charting that includes periodontal probing; diagnostic imaging [either intraoral radiographs or computed tomography (CT)]; and measurement of the GE along with a description, including the location, shape, size, texture, color, etc.

To achieve a diagnosis, an incisional biopsy is obtained from the abnormal tissue and submitted for histopathology. Obtaining large and deep incisional biopsies is important to provide the pathologist with adequate tissue to properly diagnose the lesion. A common error in primary care practice is taking superficial biopsies that do not reflect the pathology present, or have regions of necrosis, leading to misdiagnosis and inappropriate treatment. I use either a scalpel blade to take an elliptical incisional sample, or a punch biopsy of appropriate size. If indicated, the biopsy site edges should then be apposed with resorbable suture. For a pedunculated GE, I often incise the pedunculated stalk at the interface between pathology and normal gingiva. Fine-needle aspiration is commonly non-diagnostic and is not recommended.

For most patients, the clinical appearance of a GE is not pathognomonic, and a diagnosis should be obtained prior to creating a definitive treatment plan and discussion with the owner. It is important to explain the rationale of this approach to the client to ensure that the correct treatment modality is elected, an appropriate extent of surgery is performed, and proper systemic evaluation is performed (such as staging, sentinel lymph node assessment, etc.).

In some cases, there may be a recognizable pattern of GE, and it may be rational to perform both diagnostics (incisional biopsy in the form of a gingivectomy and gingivoplasty) and treatment during the same procedure. The most common example of this would be when generalized GE is identified in a mature Boxer, a breed notorious for developing gingival hyperplasia (most commonly a type known as "focal fibrous hyperplasia"). Following discussion with the owner, it may be reasonable to perform gingivectomy and gingivoplasty to both recontour the gingiva to "as close as possible to the physiologic gingiva" and to simultaneously obtain representative samples for histopathology in order to confirm the clinical suspected pathology.

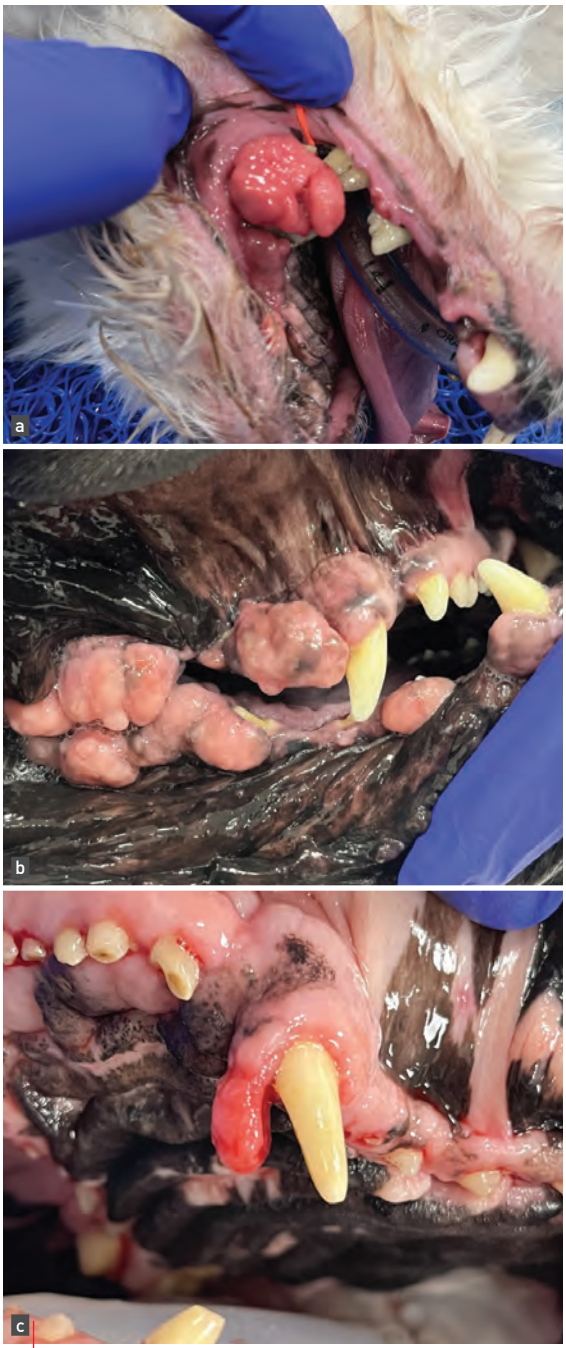


Figure 1. All three images are representative of gingival hyperplasia; all were confirmed by histopathology.

Gingival hyperplasia

Gingival hyperplasia is a non-neoplastic, reactive inflammatory lesion that can vary in its appearance **(Figure 1)**. The most common causes are plaque-induced gingivitis/periodontitis, occlusal trauma, and certain medications (most commonly cyclosporine and amlodipine) (2). The term "focal fibrous hyperplasia" is used to describe a form of gingival hyperplasia that is characterized by negligible hyperplasia of the epithelium, but rather is defined by its dense fibrous connective tissue (2).

Treatment of gingival hyperplasia includes resection (by gingivectomy and gingivoplasty) of the excess tissue and recontouring of the attached gingiva for both diagnosis and therapeutic purposes (see the following page). If occlusal trauma is stimulating gingival hyperplasia to form,

HOW TO PERFORM A GINGIVECTOMY AND GINGIVOPLASTY

by Christopher Sauvé

STEP 1

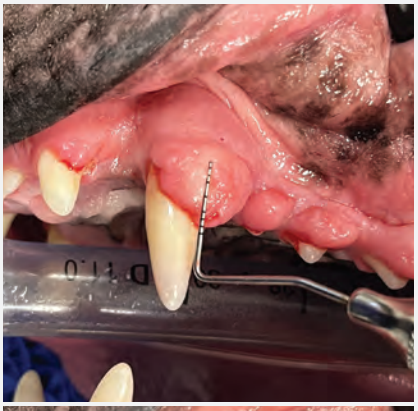
Obtain appropriate diagnostic imaging under general anesthesia (intraoral radiographs or CT).

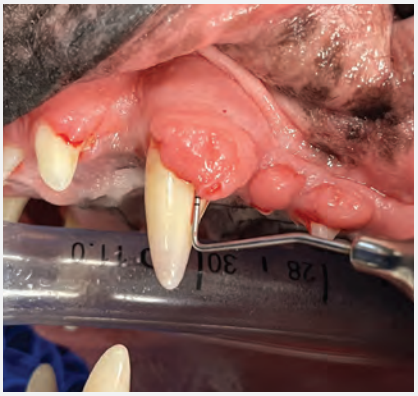
STEP 2

Ensure appropriate analgesia is performed; my typical protocol includes a preoperative opioid such as methadone and a local nerve block of the infraorbital and/or the inferior alveolar nerves using bupivacaine prior to surgery. If systemically tolerated, a non-steroidal anti-inflammatory is also administered postoperatively; I most commonly use meloxicam, as the liquid suspension formation is easily administered to patients that are recovering from oral surgery.

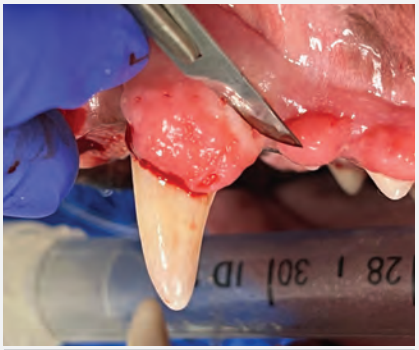
STEP 3

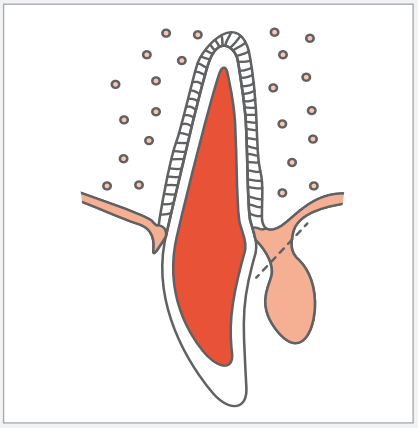
Determine the mm of gingival enlargement to be resected using a periodontal probe or pocket marker.





STEP 4

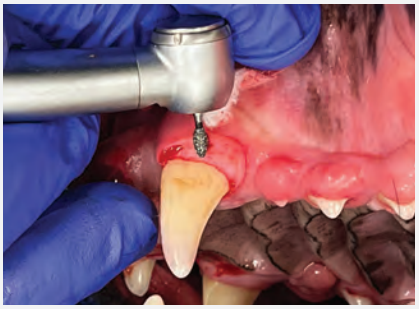




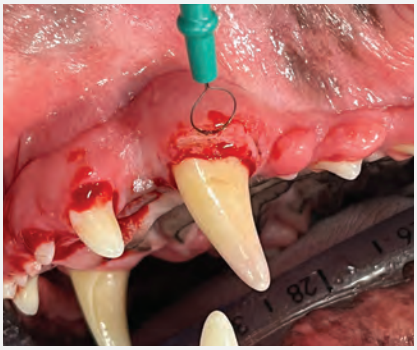
Using an external bevel approach, incise the gingival enlargement in an apicocoronal direction. The goal of this incision is to remove the bulk of the gingival enlargement for therapeutic and diagnostic purposes, aiming to grossly recreate the physiologic contour of the gingival margin.

STEP 5

Using a football diamond bur, abrade the gingiva to create a smooth physiologic contour of the gingival margin.



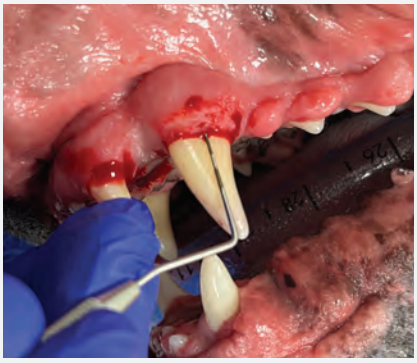
STEP 6



Hemostasis can be controlled with a focal radiosurgery unit.

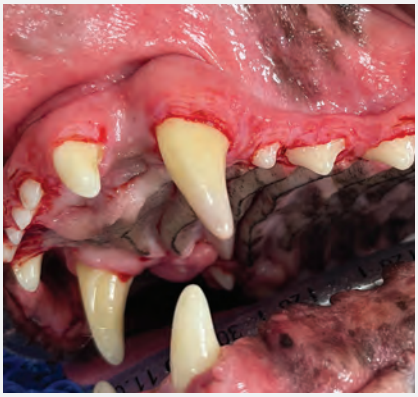
STEP 7

Assess sulcus depth to ensure that it resembles the physiologic sulcus depth (1-3 mm depending on patient size).



STEP 8

On completion, any gingival hemorrhage should be negligible.



resolution of the malocclusion is recommended. If the patient is being treated with a medication that induces gingival hyperplasia, alternatives to the drug should be explored in addition to recontouring of the gingiva.

These lesions often create a local environment between the GE and tooth surface that allows for rapid plaque and calculus accumulation; this space is referred to as a pseudopocket. Due to this phenomenon, it is common to encounter various stages of periodontal disease associated with the GE. In addition to resolving the GE, the course of treatment would depend on the stage of periodontal disease and the owner's wishes, but could include surgical extraction or more conservative treatment options.

Gingival hyperplasia is typically recurrent, but the rate of recurrence can be reduced with effective plaque control. This is accomplished through daily home care and scheduled professional dental cleaning; the latter includes regular proactive resolution of pseudopockets through gingivoplasty from emerging gingival hyperplastic lesions, and is commonly performed annually.

Peripheral odontogenic fibroma

Peripheral odontogenic fibroma (POF) is also sometimes referred to as fibromatous epulis of periodontal ligament origin (FEPLO). There continues to be debate regarding the appropriate naming for this type of lesion (2), so to avoid contributing to the controversy the combined FEPLO/POF acronym will be used here. Clinically, these are typically exophytic, broad based, smooth in texture with an intact epithelium, but can have a cauliflower-like appearance **(Figure 2)**. It is thought that the FEPLO/POF originates from the periodontal ligament-gingival attachment site, with a pathogenesis that includes some contribution of reactive hyperplasia (2). These lesions are differentiated from gingival hyperplasia/focal fibrous hyperplasia as they retain some features of periodontal ligament-derived fibroblasts in addition to the proliferative mesenchymal cells (2). Varying degrees of mineralization can be seen in FEPLO/POF lesions, which may represent cementum, bone or a combination of both. Although not a rule, displacement of dentition is more common in benign neoplasms such as FEPLO/POF. On diagnostic imaging (computed tomography or intraoral radiography), the lesion should not be seen to induce bone lysis **(Figure 3)**, although periodontal bone loss due to the presence of the pseudopocket created by the FEPLO/POF may be present.

Recommendations regarding treatment of FEPLO/POF vary. Marginal excision may be adequate to resolve these lesions; however, tumor persistence is common and definitive therapy may include surgical extraction of the involved dentition with alveoloplasty and gingivoplasty of the FEPLO/POF origin, or *en bloc* resection (3).

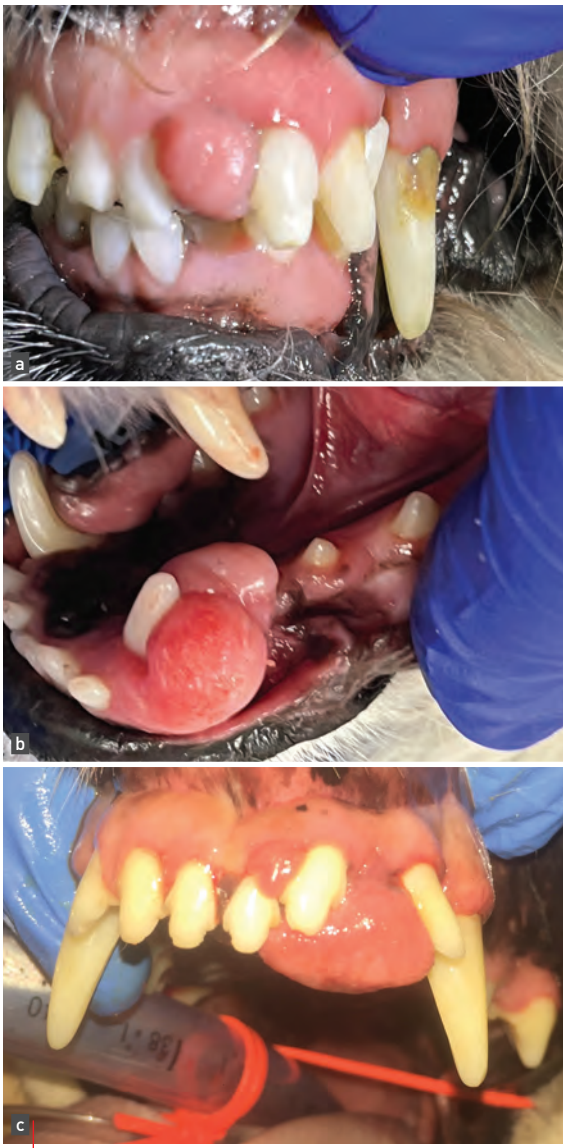
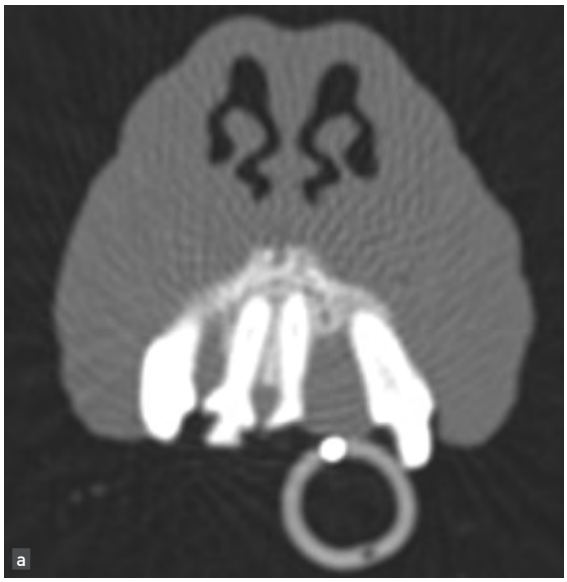
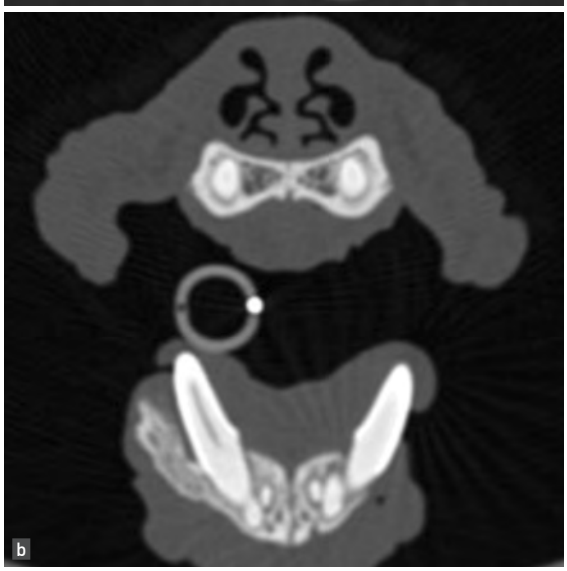


Figure 2. The photographs illustrate various presentations of FEPLO/POF; all were confirmed by histopathology.

Osteomyelitis

Treatment of osteomyelitis in the dentate maxilla or mandible **(Figure 4)** typically includes extraction of the associated dentition with harvesting of tissue samples for culture, debridement of the compromised tissues and administration of systemic antibiotics. I typically obtain a piece of compromise bone and submit it with instructions for maceration of the tissues, then aerobic and anaerobic culture and sensitivity to guide antibiotic therapy. Occasionally, resective surgery and an extended course of antimicrobials are required to resolve osteomyelitis, as some lesions will progress to osteonecrosis (4).





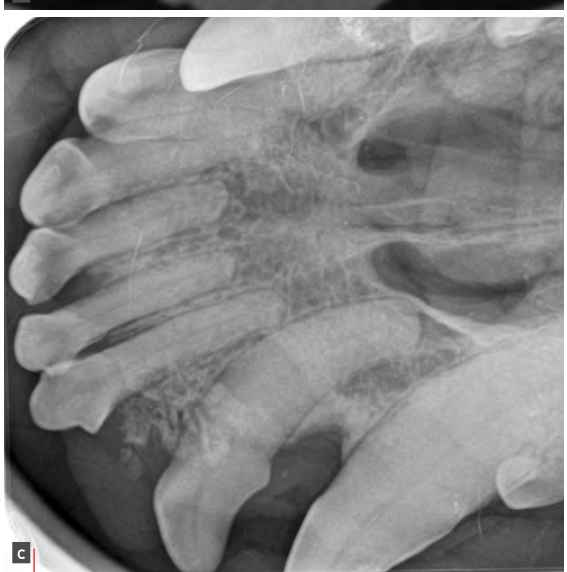


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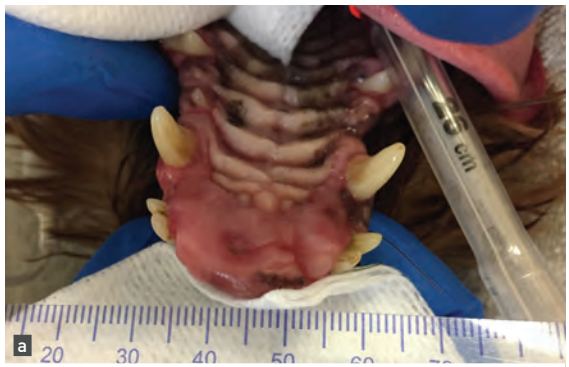
Figure 3. **(a)** and **(b)** are CT images obtained during the diagnostic work-up for the lesions seen in **Figures 2a and b** respectively. **Figure 3c** is an intra-oral radiograph of the lesion in **Figure 2c**; in each case note the periodontal bone loss due to the pseudopocket created by the FEPLO/POF.



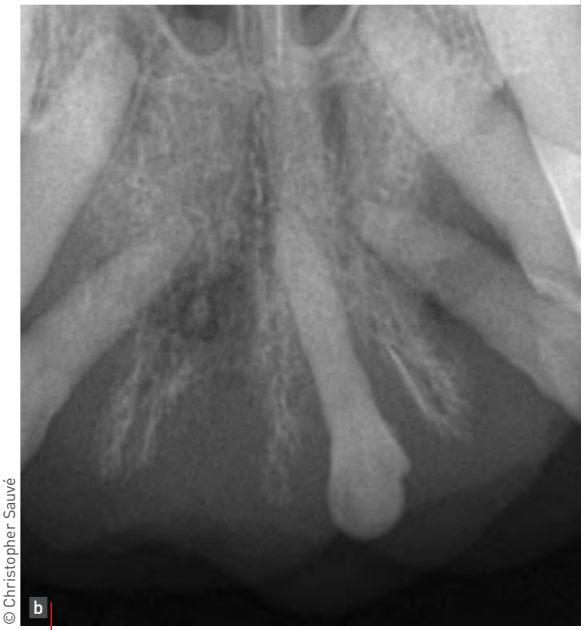


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Figure 4. Osteomyelitis; **(a)** demonstrates a generalized enlargement of the attached gingiva and palatal mucosa associated with the maxillary incisors, including loss of the normal tissue texture; **(b)** is an intraoral radiograph that demonstrates vertical bone loss of the maxillary incisors which have > 50% attachment loss. Incisional biopsy of the soft tissues and alveolar bone identified osteomyelitis.

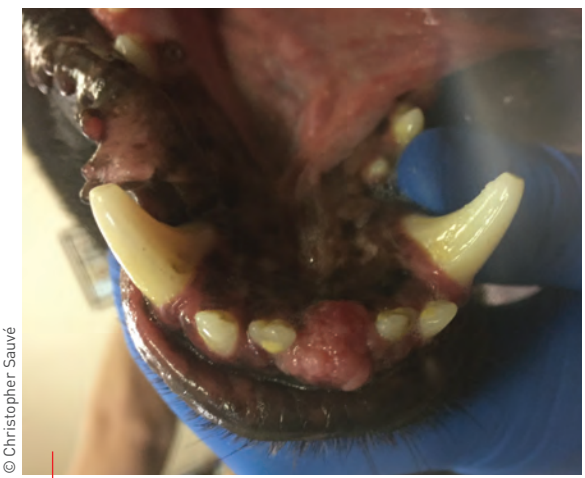

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Figure 5. A round but irregularly textured gingival enlargement in the region of 301 and 401 (teeth not present). .

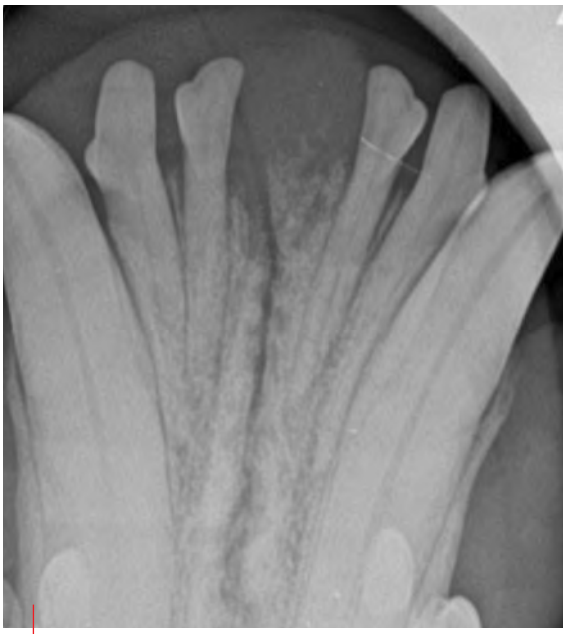

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Figure 6. An intraoral radiograph of the dog in **Figure 5**, demonstrating local destruction of the bone caused by the lesion. Incisional biopsy diagnosed an acanthomatous ameloblastoma (formerly acanthomatous epulis).

Alveolar bone expansion

Alveolar bone expansion (the clinical description) or chronic alveolar osteomyelitis (the histopathological diagnosis) is a bulging or thickening of the alveolar bone under the attached gingiva. It represents a chronic inflammatory state associated with periodontal disease and potentially tooth resorption (5), and is perhaps more common in cats than dogs. Typically, intraoral radiographs of the affected area will show vertical bone loss on the mesial and distal surfaces of the tooth, which can be confirmed with a periodontal probe; attachment loss is usually > 50%. This pattern of vertical bone loss is very commonly associated with alveolar bone expansion (6), but histopathology of the bone is required to confirm the suspected diagnosis. Treatment includes surgical extraction of the involved tooth, alveoloplasty and primary closure of the mucogingival flap. The attached gingiva is often thin and more firmly attached to the alveolar bone, and periosteal elevation should be performed with care to avoid perforation and formation of an oro-nasal fistula.

Acanthomatous ameloblastoma

Acanthomatous ameloblastomas (AA) are odontogenic tumors which have a basic structure that resembles the enamel organ **(Figure 5)**. These tumors are considered locally destructive as they commonly cause regional bone invasion and are non-metastatic **(Figure 6)**. Treatment most typically includes *en bloc* surgical resection. Historically, AA were described to have a high rate of tumor

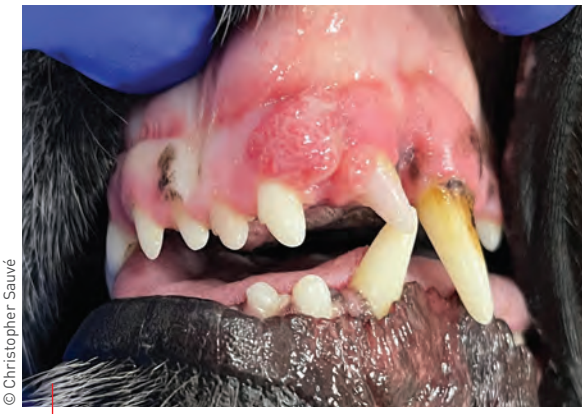

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Figure 7. A round and irregularly textured gingival enlargement associated with the attached gingiva of 202 and 203. Incisional biopsy confirmed a papillary squamous cell carcinoma.

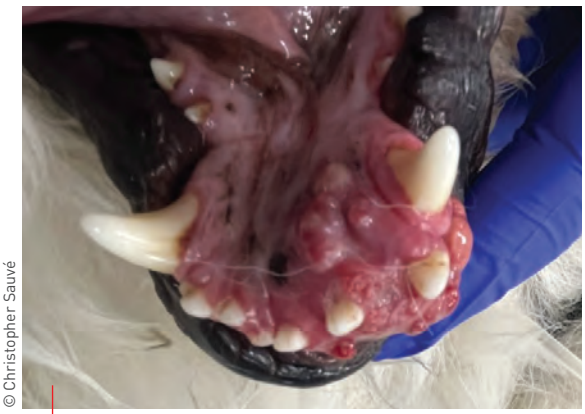

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Figure 8. The image shows regional enlargement of the attached gingiva and mucosa in the left rostral mandible involving 301-304. This is a good example of a lesion that may be best described as an oral mass, and exemplifies the importance of obtaining a proper diagnosis before pursuing definitive treatment, as histopathology diagnosed this lesion as a squamous cell carcinoma (SCC).

"Obtaining large and deep incisional biopsies is important to provide the pathologist with adequate tissue to properly diagnose the lesion. A common error in primary care practice is taking superficial biopsies that do not reflect the pathology present."

Christopher Sauvé

recurrence following resection, but a recent study has challenged this perspective; in a review of 263 patients with AA there was no evidence of tumor recurrence in any patients, even with 65.2% of patients having incomplete margins (7).

Papillary squamous cell carcinoma

Oral papillary squamous cell carcinoma (SCC) was historically considered a tumor of young dogs, but is now recognised to occur in dogs of all ages. This is a distinct type of SCC that is locally aggressive, as it often invades bone, but it does not appear to metastasize **(Figure 7)**. It is generally considered less aggressive overall, and carries a relatively more favorable prognosis, than other forms of oral SCC. Treatment typically includes surgical resection with 10 mm margins to completely remove the gross and microscopic tumor cells. Radiation therapy is also considered a reliable treatment for this tumor type (8).

Squamous cell carcinoma

Treatment for mandibular and maxillary SCC **(Figure 8)** (specifically noting that this is non-tonsillar and non-papillary) typically consists of surgical resection with 10 mm margins. This tumor does have metastatic potential, and local tumor persistence risk is higher than with papillary SCC. In a study where 21 dogs received surgical treatment, 94% were alive at one year follow-up (8). Radiation therapy is considered the treatment of choice for non-resectable SCC (8).

CONCLUSION

The goal of this illustrated guide is to convey that there is a wide variety of possible diagnoses when an animal presents with a gingival enlargement. Although a practitioner can use patterns to guide their clinical impression, a diagnosis and prognosis should not be implied based on the physical appearance, and a full investigatory work-up is to be recommended for each case in order to best guide optimal treatment.

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NUTRITION OF AGING CATS

Want to know how older cats differ in their nutritional needs from younger individuals? This article tells you what you need to know.

KEY POINTS

1. Although life stages were recently defined for cats, there are as yet no specific nutritional guidelines for senior pets.
2. Senior cats often have reduced digestive abilities which can affect their body and muscle condition scores.
3. Recent research has shown the importance of dietary phosphorus content and the calcium:phosphorus ratio.
4. More research is needed on supplements that may help address cognitive decline in older cats.

Introduction

It is only relatively recently that life stages have been defined for cats, although these vary slightly between different organizations **(Table 1)**. According to the American Animal Hospital Association (AAHA) and the American Association of Feline Practitioners (AAFP) 2021 guidelines, feline life stages are divided into five categories: kitten (from birth up to one year of age), young adult (1-6 years), mature adult (7-10 years), and senior (>10 years), with an additional "end-of-life" stage that can be at any age (1). The International Society of Feline Medicine (ISFM) designates the stages slightly differently, as follows: kitten (birth–6 months), junior (7 months-2 years), adult (3-6 years), mature (7-10 years), senior (11-14 years), and super senior (15+ years) (2). These differences aside, the increasing understanding about different life stages in our companion animals means that there is now more interest in appreciating the nutritional differences between these stages, including during aging. While organizations such as the American Association of Feed Control Officials (AAFCO) and the European Pet Food Industry Federation (FEDIAF) have nutritional recommendations and guidelines for growth (which FEDIAF further divides into early and late-stage growth phases), reproduction, and adult, there are no guidelines for senior pets. This proves to be a challenge, as understanding how to care for pets in their older age is an issue that is becoming more important as the population ages; approximately 20-40% of cats in the United States could be classified as "senior" and "super senior" (3) **(Figure 1)**.

Table 1. Life stage descriptions by pre-eminent veterinary feline health organizations.

Life stage	AAHA & AAFP	ISFM
Kitten	Birth to < 1 year	Birth to 6 months
Junior	–	7 months-2 years
Young adult	1-6 years	–
Adult	–	3-6 years
Mature adult	7-10 years	7-10 years
Senior	> 10 years	11-14 years
Super senior	–	15+ years

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Figure 1. Our population of pet cats is aging; approximately 20-40% of cats in the United States are now estimated to be classed as "senior" and "super senior".

While there are some studies on nutrition for older cats, there is also a dearth of studies that look at specific nutrients, both for essential nutrients and for those that we think may be of benefit outside of these key requirements. This article will review

Lori Prantil

MPS, DVM, Dip. ACVIM (Nutrition), Royal Canin, Aimargues, France

Dr. Prantil is a board-certified veterinary nutritionist who graduated from Tufts University Cummings School of Veterinary Medicine in the United States. Following graduation, she completed an internship in small animal medicine and surgery at an emergency and referral hospital and then returned to the Cummings School for a residency in clinical nutrition. After completing this she joined the team at VCA South Shore (Weymouth) Animal Hospital in Boston, Massachusetts where she managed their Nutrition Service, before joining Royal Canin in Aimargues, France as a member of the R&D Develop Pet & Product Science team.

Y. Becca Leung

BVSc, PhD, Dip. ACVIM (Nutrition), Veterinary Nutrition Group, Sydney, Australia

Dr. Leung was born in Hong Kong and raised in the United States of America. She received her bachelor's degree in animal science from the University of Florida, and then traveled across the world to Massey University in New Zealand for her veterinary studies. Following the completion of her veterinary degree she remained at Massey University to pursue a combined PhD and ACVN nutrition residency program. She completed her specialist board certification in 2021 and joined Royal Canin's Global Headquarters four years ago, until recently working in R&D as a Research Veterinary Nutritionist. She currently is the COO at Veterinary Nutrition Group (VNG) based in Sydney, Australia.

nutrition-by-nutrient and discuss what we do know, as well as what we believe based on current evidence, to be important considerations for our senior feline companions.

Overall diet digestibility/calories

When it comes to digestibility, we have long known that mature and senior cats have decreased digestibility, with up to 33% of cats having reduced fat digestibility, and approximately 20% having reduced protein capabilities (4). In addition, more recent information has shown that a decline in the weight of older cats, both in those considered "healthy" and those which are "non-healthy", may at least in part be attributable to a decreased digestibility of nutrients. It is also common to see loss of lean body mass and a drop in muscle condition score in older cats, and this may be partly attributed to decreased protein digestibility resulting in a negative nitrogen balance (5). Furthermore, questions have been raised about whether protein amounts currently recommended for maintaining nitrogen balance in cats are enough to also maintain lean body mass, and if higher requirements should be considered (6).

There are other reasons besides a reduced diet digestibility which can lead to weight and lean body mass loss in older animals. In elderly humans, the senses of smell and taste diminish, and it is likely that this is also the case with other animals (7). Strategies to help with this include offering diets with varying aromas and flavors, and also providing food at the optimal temperature of 37°C/98.6°F (8) **(Figure 2)**. Disease can also lead to reduced appetite and interest in food due to pain (such as with dental disease), metabolic derangement (such as uremic toxins in chronic kidney disease (CKD), or increased cytokine production in inflammatory diseases), and/or medications (such as chemotherapeutic agents that can directly affect the taste of foods). Diseases that occur commonly in older cats also can directly impact weight and muscle loss, such as seen with hyperthyroidism, chronic enteropathy, lymphoma, and diabetes mellitus. Finally, sarcopenia, or the loss of lean body mass associated with aging and unrelated to disease, has been described in both dogs and cats (9).

Therefore, senior, even healthy, cats may require a higher caloric intake to maintain weight, and a diet that has higher digestibility might result in improved nutrient absorption. Feeding guidelines are provided by manufacturers to give an average estimate of requirements, but individuals may vary up to ± 50% from average (10). Assessment of body weight, body condition score and muscle condition score, and appropriate caloric, and

Figure 2. It has been suggested that the senses of smell and taste diminish as cats age, which may lessen their food intake. Strategies to help with this include providing diets with varying aromas and flavors, and by providing food at the optimal temperature of 37°C/98.6°F.

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Figure 3. All cats that are considered senior or super senior should be regularly assessed for their body weight, body condition score and muscle condition score, and their dietary requirements revised as necessary.

potentially diet, adjustments should be done regularly for all cats that are considered senior or super senior **(Figure 3)**.

Dietary moisture

Dehydration can occur in aging animals due to a decreased thirst drive, decreased mobility and/or a disease process (11), but it can be difficult to assess the hydration status of a patient, as clinical signs of dehydration are not consistent despite significant water loss (12). Therefore, it is important to encourage water intake in senior cats, even if they do not appear overtly dehydrated **(Figure 4)**. Ensuring clean, fresh water is a central tenet in this endeavor, but providing dietary moisture by feeding a wet diet can also improve intake. Dental disease is common, with one study reporting it to be present in over 50% of senior cats (13), so if there is evidence of oral discomfort or a reduced ability to chew kibble, feeding a wet diet may be of some benefit (alongside other appropriate measures for the underlying problem) **(Figure 5)**. Other conditions where dietary moisture is important for management include CKD and all forms of urolithiasis. However, it is essential to remember that increasing dietary moisture also decreases the caloric density of a diet. Therefore, it is important to ensure feeding amounts are appropriate for the cat's daily needs and that intake levels remain sufficient. If the cat has difficulty consuming the daily volumes required, mixed feeding or a dry diet may help to meet energy needs.

Protein

While we know that some senior cats have reduced protein digestibility, it is less clear what level of protein should be recommended for older individuals that are otherwise considered healthy. Given that CKD is a fairly common diagnosis in older cats, with one estimate suggesting 30-40% of animals over 10 years of age being affected (14), and because decreased dietary protein is generally recommended for cats in the later stages of the disease, it is

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Figure 4. Dehydration can occur in aging animals due to various factors, but it can be difficult to assess the hydration status of a patient, and it is therefore important to encourage water intake in senior cats even if they do not appear overtly dehydrated.

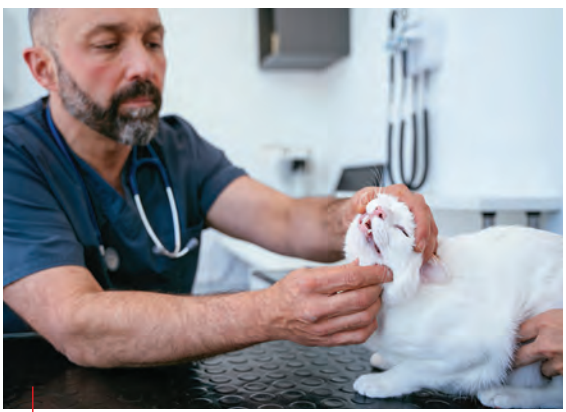

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Figure 5. Senior and super senior cats will often suffer with dental problems, which can in turn affect their food intake. Cats in this these categories should undergo a full dental examination regularly.

sometimes believed that an early reduction in dietary protein for all older cats might be of benefit. However, there is insufficient evidence to confirm that reducing dietary protein as cats age will reduce the occurrence of CKD. In addition, as mentioned above, sarcopenia is documented in cats as early as 7 years of age, so given the compromised protein digestive capacity in older cats, a reduced protein diet may increase the risk of developing sarcopenia. Therefore, as cats are obligate carnivores and have a high dietary protein requirement, these factors suggest that feeding lower levels of protein should be reserved for cats with active renal disease and is not recommended prophylactically for healthy older cats.

Fat

As previously noted, senior cats can have reduced fat digestibility which can contribute directly to decreased caloric absorption, as fat has more calories than either carbohydrate or protein per gram. Feeding foods with a higher fat content, particularly diets which also have higher protein and carbohydrate digestibility, can be good options for cats that might be otherwise healthy but that are losing weight and body condition over time. Conversely, if a cat is overweight, using a diet that is lower in fat and thus lower in calories would be preferred. The Association for Pet Obesity Prevention in the United States estimated in 2022 that 61% of pet cats are overweight or obese (15), and with many cats living longer, it is likely that this statistic includes those in the senior category. Cats with obesity are more likely to have respiratory, dermatological, musculoskeletal and/or dental problems, as well as urinary tract disease and diabetes, therefore while higher levels of fat might be recommended for cats that are unintentionally losing weight, there may be situations where weight loss is the goal, requiring lower levels of fat intake.

Carbohydrates

While carbohydrates are not a required nutrient, they are important in that they help provide energy needs and balance protein and fat content to the desired proportions in the overall diet. Keeping in mind that for healthy aging cats (rather than where digestible carbohydrates might need to be evaluated more closely, such as with a cat with diabetes mellitus – **Figure 6**), consideration of carbohydrates on their own is often only done after protein and fat content have been addressed. However, cooked carbohydrates, which are readily digested and absorbed by cats, can have a protein-sparing effect by providing a source of glucose instead of relying on glucogenesis using protein. There is no evidence that digestible carbohydrates induce either obesity or diabetes in cats, and thus there is no reason to avoid this nutrient. In fact, higher fat diets are more likely to lead to obesity, and the amount of fat in a given diet can be decreased by increasing the percentage of protein and/or carbohydrate content.

Undigestible carbohydrates are a form of dietary fiber which can promote a healthy intestinal tract. Fermentable fibers (beet pulp, chicory pulp, fructo-oligosaccharides) are utilized by the intestinal microbiota, and fermentation end-products such as short-chain fatty acids may directly benefit animals during aging. In senior dogs, feeding a diet with a higher concentration of total dietary fiber has been shown to decrease intestinal ammonia (16), an important factor in cases of CKD and hepatic encephalopathy. However, dietary fiber does decrease the caloric density of a diet, and can affect palatability, so the right balance for the individual is key.

"Assessment of body weight, body condition score and muscle condition score, and appropriate caloric, and potentially diet, adjustments should be done regularly for all cats that are considered senior or super senior."

Lori Prantil

Vitamins and minerals

Phosphorus and calcium:phosphorus

While there is insufficient evidence that higher protein diets can cause CKD in senior cats, there is evidence that diets with higher amounts of phosphorus may do so. In two recent studies, diets with differing phosphorus content and calcium:phosphorus ratios were tested in a cohort of healthy cats. The diets with the highest phosphorus level (the majority of which was from inorganic sources) and lowest calcium:phosphorus ratio induced renal changes in the cats (17). Further testing of different diets with varying levels

Figure 6. Older cats may have special dietary needs, such as the cat with diabetes mellitus; in this situation the digestible carbohydrate component of their diet may need to be carefully evaluated.

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Figure 7. One study has shown that cats with osteoarthritis which receive supplemental fish oils are likely to have higher activity levels and are more able to cope with climbing and jumping.

of total phosphorus, inorganic phosphorus sources and calcium:phosphorus ratios indicated that a high level of inorganic phosphorus leads to a dose-dependent peak in plasma phosphorus concentrations which is higher than what occurs with organic phosphorus (18). However, not all forms of inorganic phosphorus cause the same postprandial rise in plasma phosphorus concentrations. While more work in this area is needed, avoiding diets that have high levels of soluble, inorganic phosphates and those with a calcium:phophorus ratio of less than 1:1 is advised (19).

However, it must be acknowledged that in the manufacturing of pet food, the levels of protein and organic phosphorus tend to run together; that is, the higher the level of one of these nutrients is, the higher the likelihood that the other one will be as well. We are seeing newer diets on the market (particularly therapeutic diets targeted for early kidney disease) where this is less likely, due to careful ingredient selection, but for many maintenance diets it may not. Thus, maintaining high dietary protein levels whilst avoiding the highest phosphorus levels might be challenging when evaluating regular, maintenance-type diets for older cats.

"It is common to see loss of lean body mass and a drop in muscle condition score in older cats, and this may be partly attributed to decreased protein digestibility resulting in a negative nitrogen balance".

Y. Becca Leung

Other minerals and vitamins

While it is a given that cats of all ages require complete and balanced diets with appropriate vitamin and mineral content, there may be some further considerations for aging cats. Because of the decreased fat digestibility capacities of these animals, vitamins that are fat-soluble may have compromised absorption. To date, we have no data on deficiencies of these vitamins in older cats due to poor absorptive capacity. However, should a cat be eating a diet that is not being properly absorbed, or is not complete and balanced, and is losing body and muscle condition, deficiencies of these key nutrients may be a consideration.

Antioxidants in vitamin form, such as vitamins C, E, and the provitamin beta-carotene, may be of benefit in older animals. While vitamin C is not an essential nutrient for cats (as they can synthesize it endogenously), there is some evidence that higher levels of vitamin E and beta-carotene in feline diets can contribute to increased longevity (20). While not necessarily an issue for healthy older cats, water-soluble vitamins such as vitamin B_{12} can be lost if there is increased water loss through polyuria or through malabsorption, and supplementation may be considered for those animals.

EPA & DHA

One of the most common conditions in senior cats is degenerative joint disease (DJD), or osteoarthritis; one study found that 92% of cats over the age of 14 had radiographic evidence of DJD (21). While there are numerous types of dietary supplements suggested for individuals with this condition, the studies using eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the strongest in reporting a benefit from these additives. One study showed that cats with osteoarthritis receiving supplemental fish oil had higher activity levels, less stiffness, could jump higher, and showed more owner interaction (22) **(Figure 7)**.

Nutrients for cognitive decline

As there are increasing numbers of cats falling into the "senior" and "super senior" categories, cognitive decline and cognitive dysfunction are becoming more common and easily recognized, even in cats that are otherwise deemed healthy. In fact, this is often considered part of the normal aging process. One study showed 36% of owners of cats aged 7-10 years (mature adult and senior categories), and 88% of owners with cats between 16-19 years (super senior category) reported that their pets had developed age-related behavioral problems (23).

These changes can lead to a decreased quality of life for the cat and the owner, and as such there is a great deal of interest in finding diets and/or supplements that can slow this process.

A number of additives have been studied, with mixed results. Some evidence has been seen for supplementary S-adenosyl-l-methionine (SAMe), and there are anecdotal reports on other additives such as melatonin, L-theanine, milk protein hydrolysates, and pheromones. However, most of these supplements have been used to address general anxiety issues in cats and not cognitive decline specifically. Further clinical trials examining the effects of additives on cognitive decline are warranted. Medium chain triglycerides (MCTs) are another nutrient that has been used in dogs to address cognitive dysfunction, but further work needs to be done in cats. Previous studies using MCTs in this species had indicated there may be palatability challenges, although newer reports suggest this may not be the case (24,25). Recent research is targeting the gut-brain axis with the idea of improving brain function during aging. In addition to studies involving MCTs (which focus on the action of ketones and direct effects of the medium-chain fatty acids), prebiotics and probiotics are other considerations for future work that may address the cognitive needs of aging animals.

CONCLUSION

Many companies now offer diets or supplements labeled for senior cats based on their own considerations and beliefs without having the research or understanding about what is needed. While we are beginning to understand the nuances of some nutrients, the nutritional requirements for aging cats is still largely undefined. It is a broad category that encompasses consideration of several nutritional needs, even for seemingly healthy, older cats, so it is difficult to standardize recommendations for all; instead, dietary advice should be done on an individual basis. As our population of cats gets older, we continually look to better understand their needs and provide evidence-based recommendations to support them into their senior and super senior years.

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CANINE COGNITIVE DYSFUNCTION

Canine "dementia" is becoming more common as our pet population ages; this article reviews the signs, differential diagnoses and treatment for such cases.

KEY POINTS

1. Canine Cognitive Dysfunction (CCD) is a common problem in elderly dogs, but it can be managed to improve the welfare of both patients and owners.
2. Early recognition and intervention is key to an improved prognosis for CCD.
3. Many conditions can mimic CCD, so it is important to consider a range of medical differentials and comorbidities when assessing possible cases.
4. Combining several management options (such as environmental or diet changes and nutraceuticals) have been shown to be the most effective treatment for CCD.

Introduction to CCD

Canine cognitive dysfunction (CCD) is a form of dementia affecting geriatric dogs (1) and although it cannot be cured, the clinical signs can be managed and the prognosis improved with early detection and intervention (2,3). The condition is probably more common than is generally recognized (4) as dog owners often attribute the signs to part of the normal aging process and/or believe they are untreatable (5), and so do not discuss their concerns with their veterinarian (1). Indeed, it has been estimated that somewhere between 22.5-68% of elderly dogs express at least one sign of cognitive dysfunction (1,3,6), although this does not mean they necessarily have CCD, as the signs may be associated with other issues such as chronic pain. Accordingly, CCD is an important disease for veterinary professionals to be aware of, and it should be proactively discussed with owners in order to improve the health and welfare of elderly pet dogs **(Figure 1)**. This article will consider the key signs, diagnosis and differentials of CCD, and discuss treatment options and the outlook for the condition.

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Figure 1. Owners may think that their dog is simply showing a normal aging process, so the clinician should be proactive in discussing possible signs of CCD during any consultation.

Presentation and etiology

CCD is a condition of older age, and therefore occurs in geriatric patients; it is commonly reported from 11 years of age, although this varies with the size of the dog and the typical life expectancy of the breed. In some studies females are reported to be more likely to be diagnosed with CCD (1). However, castrated male dogs and smaller dogs are believed to be more prone to demonstrating signs of CCD, and castrated dogs may deteriorate more rapidly (6).

The behavioral signs of CCD are frequently described using the acronym DISHA **(Table 1)**, but the acronyms DISHAA and DISHAAL may also be used, with the additional A standing for anxiety or apathy, and the L for learning (7,8). Regardless of the preferred acronym, it is important to appreciate that

Beverley M. Wilson

BVMedSci, BVM, BVS (Hons), PgC(SAM), GPCert(SAM), MSc, CCAB, MRCVS. Animal Behaviour, Cognition and Welfare Group, Dept of Life Sciences, University of Lincoln, UK

Dr. Wilson graduated from the University of Nottingham in 2012 and spent time in general practice (both private and charity clinics) whilst also undertaking a post-graduate certificate in small animal medicine. She subsequently obtained her Masters in Clinical Animal Behaviour from the University of Lincoln and is currently undertaking a residency in Veterinary Behavior with the European College of Animal Welfare and Behavioral Medicine. She is also a Certified Clinical Animal Behaviorist for dogs.

Daniel S. Mills

BVSc, PhD, CBiol, FRSB, FHEA, CCAB, Dip. ECAWBM(BM), FRCVS. Animal Behaviour, Cognition and Welfare Group, Dept of Life Sciences, University of Lincoln, UK

Professor Mills graduated from the University of Bristol in 1990 and spent several years in UK charity practice, where he was responsible for setting up behavior clinics. He then worked in private mixed practice before moving into academia. He was the first person within the UK to be recognized as a specialist in veterinary behavioral medicine by the Royal College of Veterinary Surgeons (RCVS) and the EBVS European Veterinary Specialist. He was awarded RCVS Fellowship in 2016 in recognition of his contribution to the field.

there are wider emotional issues in many cases relating to temperament, mood and immediate emotional responses, such as depressive states, poor frustration tolerance or increased attention seeking, in addition to the more classic avoidance responses associated with anxiety. **Table 1** reviews the classic signs relating to DISHA and important differentials to consider. Dogs vary enormously in the reported signs in the initial stages, with no consistent pattern evident (9), so early detection can be challenging. However, CCD is a progressive disease and so further signs are commonly reported over time, which means it is important to monitor these cases from the first time a sign is noticed, even if a diagnosis is not made at that time. Indeed, many owners may only seek support from the veterinarian when particular signs are causing a problem for either the dog or themselves. For example, a sudden loss of a previously known behavior (*e.g.*, recall when off lead), house soiling **(Figure 2)**, significantly reduced activity/interaction with the owners, or

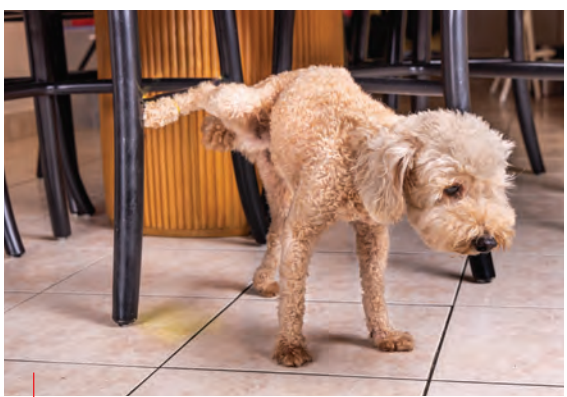

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Figure 2. A sudden loss of a previously known behavior, such as house soiling, may potentially be a sign of the underlying neurodegenerative changes associated with CCD.

Table 1. Cardinal signs of CCD with examples and common differentials to consider.

Cardinal sign (DISHA)	Examples	Possible differentials
Disorientation	• Appearing lost in familiar locations	• Loss of hearing/vision
	• Struggling with obstacles – *e.g.*, going to wrong side of door or unable to navigate around furniture	• Mobility issues – *e.g.*, osteoarthritis • Loss of vision
Interactions altered in relation to social stimuli	• Increased contact with owner	• Discomfort (*e.g.*, osteoarthritis) • Endocrinopathy (*e.g.*, hypothyroidism) • Liver disease • Neurological issue (*e.g.*, space-occupying lesion) • Hypertension
	• Social withdrawal	
	• Conflicts or reduced interactions with household animals	
Sleep/wake changes	• Night-time waking	• Discomfort • Endocrinopathy • Causes of polyuria/polydipsia (PUPD) • Liver disease • Anemia
	• Lethargy during the day	
House soiling	• Toileting overnight • Change in toileting location	• Discomfort (*e.g.*, cannot access areas previously used) • Liver disease • Renal disease • Endocrinopathy/other causes of PUPD
Activity levels alterations	• Pacing • Stereotypic behaviors • Increased/decreased activity	• Neurological issue (*e.g.*, space-occupying lesion) • Discomfort • Liver disease • Hypertension

night-time waking. In these cases, the owner's focus is on the behavior problem, but it is essential to appreciate that the issue may be more complex due to the potential role of underlying neurodegenerative changes associated with CCD. The importance of thorough history taking during consultations cannot be overstated, as many owners may be unaware of important signs or may not appreciate that they can be addressed, often assuming the changes seen are part of an inevitable aging process. Senior pet health checks and routine appointments (such as for vaccinations) provide an opportunity to actively ask an owner about signs of CCD.

CCD is used as a model for Alzheimer's disease in people, so it is not surprising that the pathology has been studied extensively (10). Changes noted within the brains of dogs affected by CCD include reduced brain mass, reduced frontal lobe volume, cortical atrophy, reduced neuronal density, increased ventricular size and increased beta-amyloid plaques (7). In humans tau protein fibrils are also noted in Alzheimer's, but this pathology is more typically found in cats (who coincidentally do not typically show the amyloid plaques found in humans and dogs). Given that the lesions are irreversible and their causal significance not well established, the pathology will not be discussed further here.

Diagnosis of CCD

CCD is a diagnosis of exclusion, and there are no definitive antemortem diagnostic tests available. A presumptive diagnosis is reached through the information provided by the owner and by ruling out other conditions which could be responsible for the clinical signs (4). Given the presenting signs there are many possible differential diagnoses which need to be excluded **(Table 1)** and information obtained from the owners is central to the clinical presumptive diagnosis of CCD; to aid this process in terms of speed, consistency and completeness, various screening questionnaires are available (11). Some of these can be completed independently by the owner, such as the canine cognitive dysfunction rating scale (CCDR) (12), which can be given to the owner to complete prior to the appointment and then discussed within the consultation (see **Box 1**). Others can be completed during the consultation, such as the age-related cognitive and affective disorders score (ARCAD) (13).

In the authors' experience the CCDR scale is easy to use and can be given to owners to be completed at home if the veterinarian has suspicions of CCD based on the initial information obtained during a consultation (for example, from the history-taking process at a routine booster vaccination). This allows the owner to reflect on their pet's aging and creates a pathway for engagement in proactive geriatric care.

Given the concerns regarding the under-reporting of CCD, and the potential for subtle but progressive clinical signs, it is recommended owners complete a suitable questionnaire every 6 months for their geriatric dog. This allows early detection of possible CCD and intervention to improve treatment outcomes (12) as it helps distinguish between normal cognitive decline associated with aging and dysfunction.

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Figure 3. A dog which has become more withdrawn and spends long periods lying down may have CCD, but in reality it may be experiencing osteoarthritic pain.

In addition to the owner history and reported information, the other essential is to check for possible differential diagnoses. The diagnostic tests will depend on the presenting signs for each individual case, and it should be noted that co-morbidity is common. If other differentials have been excluded, a presumptive diagnosis of CCD can be made, but where the picture is obscured by co-occurring conditions with similar signs, clinical judgement must be used, and the uncertainties carefully explained to the client. It is always prudent to review the potential for a diagnosis of CCD whenever a case with related clinical signs does not improve or stabilize as expected, or if there is a sudden deterioration or progression of signs. Likewise, the involvement of unrelated pathologies should be considered in cases of CCD which show a similar pattern of change. For example, if a dog with a diagnosis of CCD fails to improve as expected, this should suggest other factors could be involved, and the case should be re-evaluated for underlying problems such as chronic discomfort which may mimic or contribute to the CCD signs identified.

Common differentials for CCD

There are numerous conditions which have a similar presentation to CCD, and it is important to consider each of these for every suspected CCD case.

Discomfort

Chronic discomfort can mimic many of the signs of CCD, including altered social interactions, sleep/wake cycles, house soiling and activity levels. For example, a dog which has become more withdrawn and less inclined to interact with the owner or other animals in the household may be experiencing osteoarthritic pain and so be reluctant or slow to rise **(Figure 3)**; it may spend more time lying down,

Box 1. Canine Cognitive Dysfunction Rating (CCDR) Scale (adapted from 12).

• WHAT IS CANINE COGNITIVE DYSFUNCTION?

Canine cognitive dysfunction (CCD) or doggy dementia is an age-related syndrome which presents with changes in behavior. It usually affects dogs over 8 years of age although it is more common in later years, with over 30% of dogs over 14 years estimated to have the disease. Behaviors that may be affected include:

- Sleeping and/or activity patterns
- Eating and drinking
- Spatial awareness and orientation
- Learning and memory

• HOW TO TELL IF YOUR DOG HAS CCD

The CCDR is an assessment tool designed to identify possible symptoms of CCD. The presence of enough symptoms in sufficient severity may be indicative of your dog having CCD. Despite this, it is important to remember that diseases of other body systems may also cause similar symptoms and your dog should be thoroughly examined by a veterinarian before a final diagnosis is made.

• THE CCDR

To complete the CCDR, select the most appropriate response for each question by marking it in the boxes provided. Only mark ONE response per question/line. Try to answer each question to the best of your knowledge based on your dog's current behavior or changes in its behavior in the last 6 months.

IMPORTANT: If your dog never displays a behavior now and it never displayed this behavior 6 months ago, select THE SAME in the appropriate change related questions. To determine your dog's CCDR score put the number for the response column you selected in the score box to the right of each question. For example: If your dog stares blankly at the walls or floor "once a week" it scores a 3 for that question. If there is a x 2 or x 3 next to the score you will need to multiply the number for the response column you selected by either two or three to give a final score. For example: If your dog fails to recognize familiar people or pets "slightly more" than 6 months ago it scores a 4 for that column and then is multiplied by 3 to give a final score of 12 for that question.

• THE RESULT

Finally, add up all of the scores to give the total. If your dog scored 50 or above there is a risk that it may have CCD and you should follow this up with your veterinarian. If your dog scored between 40 and 50 you should reassess your dog in 6 months' time to determine if there has been any change.

COLUMN SCORE	1	2	3	4	5		TOTALS
	Never	Once a month	Once a week	Once a day	> Once a day		
How often does your dog pace up and down, walk in circles and/or wander with no direction or purpose?							
How often does your dog stare blankly at the walls or floor?							
How often does your dog get stuck behind objects and is unable to get around?							
How often does your dog fail to recognize familiar people or pets?							
How often does your dog walk into walls or doors?							
How often does your dog walk away while, or to avoid, being patted?							
	Never	1-30% of times	31-60% of times	61-99% of times	Always		
How often does your dog have difficulty finding food dropped on the floor?							
	Much less	Slightly less	The same	Slightly more	Much more		
Compared with 6 months ago, does your dog now pace up and down, walk in circles and/or wander with no direction or purpose?							
Compared with 6 months ago, does your dog now stare blankly at the walls or floor?							
Compared with 6 months ago, does your dog urinate or defecate in an area it has previously kept clean (if your dog has never house-soiled, tick "the same")?							
Compared with 6 months ago, does your dog have difficulty finding food dropped on the floor?						x2	
Compared with 6 months ago, does your dog fail to recognize familiar people or pets?						x3	
	Much more	Slightly more	The same	Slightly less	Much less		
Compared with 6 months ago, what are your dog's activity levels like?							
					TOTAL		

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Figure 4. It is important to check if a dog that has possible signs of CCD has other problems that could be partially or totally responsible; for example, a dog with compromised vision may start to stay closer to the owners on walks.

or be less willing to interact and play with other dogs in the household, as this may exacerbate the discomfort. In some cases, there may be a sudden onset of aggressive behaviors between the dogs, as the individual experiencing discomfort aims to prevent and repel such interactions. Chronic discomfort can be difficult to recognize, especially if the dog is still able to participate in some normal activities (such as daily exercise, because the immediate motivation to go for a walk overrides any discomfort experienced, at least in the short term). Often these cases may not show overt signs during clinical examination, posing a further diagnostic challenge. In general, if there are suspicions of discomfort, a pain relief trial for a minimum of 4-6 weeks should be used to help evaluate the role of chronic discomfort. It is important to coach the owners that the typical response to the trial will be slow and possibly subtle, and so a behavioral diary can be invaluable to capture these changes. Equally, a gradual deterioration following cessation of the pain relief may be the only reported sign, which would support the suspicion of discomfort.

Changes in hearing, vision and smell

Loss of hearing, vision and smell can resemble some of the DISHA signs (14). For example, a dog with compromised vision can be reluctant to exercise, or may stay closer to the owners on walks or appear disorientated **(Figure 4)**. A thorough physical examination and history taking specifically related to these areas can be beneficial to assess the role of altered senses.

Systemic disease

Pathologies affecting many of the major organs can also lead to signs that mimic CCD. For example, reduced activity levels can be caused by dysfunction in the cardiovascular, respiratory, renal or endocrine systems, and the veterinarian must be careful not to approach a case with a preconceived idea as to the cause. If the dog is of the right age, the potential role of CCD alongside these conditions must be considered. Diagnostic tests should be undertaken to rule in or out medical factors which could contribute to the observed signs.

Normal cognitive decline

As part of the normal aging process dogs, like people, will experience a decline in cognition. The questionnaires described above help differentiate cognitive *decline* from cognitive *dysfunction* (12). Some dogs will remain in cognitive decline, whereas others will experience signs of dysfunction, hence it is important for the questionnaires to be completed every 6 months, or more often if needed, to help identify signs of dysfunction.

"Canine Cognitive Disorder is a progressive disease and it can be difficult to predict response to treatment or rate of progression for the condition."

Daniel S. Mills

Management and treatment options

Although CCD cannot be cured, early intervention can help slow the progression and improve the quality of life for both the dog and owner (15,16). Management options include medications, nutraceuticals, diet, environmental and behavioral modification. Studies show the most effective combination to be a combination of environmental measures and diet/nutraceuticals (17).

Table 2 summarizes common treatments commercially available where there is published evidence of efficacy.

In addition, it is also possible to use symptomatic treatment for specific clinical signs as required. For example, if an animal is struggling with night-time waking despite all other reported signs being well managed with dietary and environmental intervention (and checks have been made to rule out comorbidities) then the following could be considered:

- Setting a nighttime routine to promote a restful state, *e.g.*, walking and feeding in the evenings and closing the curtains to reduce light/noise.

Table 2. Common treatments commercially available for CCD.

Treatment category		Treatment aim/purpose and expected outcome
Medication	Selegiline	Demonstrated improvement in reported clinical signs and improved learning and memory; (15,18)
	Propentofylline	Improvement in mental dullness, lethargy and demeanor; improvement in some CCD signs, but some literature suggests no effect seen (19)
Diet (antioxidants, mitochondrial enzymatic cofactors)		Shown to reduce cognitive decline; reduced speed of deterioration at learning tasks; Improvement in clinical signs of CCD (2,20)
Nutraceuticals	SAMe	Improvement in CCD signs; improvement reported in activity and awareness (21)
	Antioxidant supplements	Improvement in reported clinical signs, particularly disorientation, interactions and house soiling (9,22)
Environmental modification (novel toys, exercise)		Demonstrated to reduce cognitive decline and reduce speed of progression of clinical signs (2,23)
Behavioral modification (games, training, exercise)		Demonstrated to slow cognitive decline and reduce speed of progression of clinical signs (2)
Pheromones		Reduction in observed signs of anxiety (8)

Box 2. Case study example 1.

A dog who used to walk perfectly at exercise has begun pulling on the lead and no longer walks on a loose lead, due to altered learning and cognition with CCD. The dog is started on dietary modification and environmental enrichment, but the owner declines support for reschooling in loose-lead walking, as the dog's concurrent arthritis means that long walks are no longer an option. The owner accepts that the dog will pull for its 10-minute walk around the village, and enjoys setting up scent games in the garden as enrichment for the dog to investigate.

The veterinarian's role here is to:

- Assess the risk of the problem behavior: a different approach may need to be adopted if the dog was a giant breed who risked injuring their elderly owner by pulling on the lead.
- Assess the health of the patient: is pulling on the lead likely to worsen signs related to any concurrent conditions such as osteoarthritis (as in this case)? In older medium to large breed dogs conditions such as laryngeal paralysis, osteoarthritis of the neck and forelimbs or intervertebral disc disease may also need to be considered.
- Help the owner appreciate what management options are available: these may be simple changes (*e.g.*, changing from a collar to a harness if there are neck issues) or more complex behavior modification options (*e.g.*, fun loose-lead walking/training in the garden, perhaps in place of some of the scent games).
- Potentially advocate for the patient: *e.g.*, the owner may not be concerned with the dog pulling, but the veterinarian may notice potential signs of discomfort on clinical examination, such as reluctance when assessing range of motion of the neck. This might be supported by the dog's behavior in the consultation room which the owner may not appreciate, such as a reluctance to pick a treat off the floor compared to treats eagerly and readily accepted from the veterinarian's hand. Here good communication skills are needed to highlight to the owner that pulling on the lead may be exacerbating discomfort, so it would be beneficial to address this. The most appropriate behavior modification plan can then be collaboratively designed by the client and veterinarian.
- Keeping an overview of multiple comorbidities and concurrent treatments; remember there is little published information regarding concurrent use of many medications, nutraceuticals and diets when comorbidities are present. As such the veterinarian will need to be conscious of possible interactions with items which the owner may be giving for conditions such as osteoarthritis, and since many supplements are freely available over the counter it is vital to specifically ask the owner about these. Caution should also be exercised in relation to products and diets which contain the same, or similarly acting, ingredients, as there is a risk of "over supplementation" and potentially overdosing.
- Offering dietary advice. Advise the owner that a recommended diet may be beneficial when it is fed exclusively, rather than when mixed with other foods. A pragmatic approach may be needed if palatability is an issue to ease transition from the previous diet.

Box 3. Case study example 2.

A dog has already been diagnosed with CCD and osteoarthritis, and management is in place for both conditions, but the owners report a new complaint of sudden onset house soiling. The following approach would be appropriate:

- Collect a thorough history regarding both the dog's general health and behavioral history, including signs suggestive of PUPD, pollakiuria, location, frequency and onset of house soiling, how the owners are cleaning the soiled areas and interacting with the dog at these times. Further clinical diagnostic tests are then run as appropriate. Here there is no history of PUPD or pollakiuria, so a free catch urine sample is obtained. The urine specific gravity (USG), dipstick and sediment examination are within normal limits. The dog's recent previous blood sample also did not give any cause for concern. It may be that the house soiling is most likely due to CCD, however discomfort due to OA cannot be excluded, although there may be no other compatible signs from the history. As a precautionary measure analgesia might be increased on a trial basis for 4 weeks while the owner maintains a diary to monitor progress (including measures of comfort, house soiling and activity levels).
- Advise on managing the house soiling while the role of discomfort is further investigated. Provide a cleaning regimen (*e.g.*, using an enzymatic cleaner), and advise taking the dog out regularly to the toilet, praising and rewarding whenever urine and feces are voided in appropriate areas, and possibly placing puppy pads in appropriate areas for when the dog is unsupervised. The owner may also be coached on how to set the dog up for success, *e.g.*, by structuring the day with regular toilet breaks (such as after eating or waking) and avoiding the use of punishment (which can lead to the dog toileting in the owner's absence and increase fear/anxiety) and creating a non-slip environment to allow easier access to the garden (*e.g.*, non-slip mats on any laminate or tiled floors which the dog has to walk across).

- Medications which may promote sleep, either directly or as a beneficial "side effect" (*e.g.*, chlorphenamine or melatonin).

It is important in such cases for the veterinarian to work closely with the client to discuss the behaviors of concern. As with any chronic condition, owners can find the management and lack of resolution of clinical signs frustrating and upsetting, so an empathetic approach will help. Effective communication regarding treatment options is also key, as the owner needs to be aware the clinical signs are unlikely to completely resolve, but the aim is to reduce the speed of progression and manage specific signs as needed. It is also vital to discuss the potential risks and benefits of each treatment option, especially in light of concurrent health issues which may be present in senior patients.

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Figure 5. Geriatric dogs should be routinely evaluated for signs of CCD, and records of their questionnaire score should form part of their routine clinical notes.

Pragmatic considerations

Given the reported prevalence of CCD, first-opinion veterinarians are likely to see patients frequently, and the wealth of treatment options can at first appear overwhelming. However, it is important to remember that a combination of treatments will be necessary in order to maximize benefits for the individual patient. An individualistic approach is recommended, tailoring treatment based on the dog's reported problem(s), as well as wider animal (such as concurrent conditions) and owner factors (such as lifestyle, time and ability to train). The primary aim is to improve the quality of life for patient and client by stabilizing or managing reported signs.

The owner's autonomy and wishes with regards to assessment and treatment costs must always be respected and accommodated, but that does not mean that owner-related behavior change cannot be encouraged. A pragmatic approach is often necessary, as it may not be appropriate to perform as many diagnostic tests as desired. There may also be reported behaviors which the owner does not feel it is necessary to address, as they do not

"Canine Cognitive Dysfunction is a diagnosis of exclusion and there are no definitive antemortem diagnostic tests available."

Beverley M. Wilson

view them as problematic, or they accept them provided their dog is enjoying a reasonable quality of life. The case studies **in Boxes 2 and 3** illustrate some of the challenges that might be involved and appropriate courses of action, and highlight the importance of clinical skills, communication and professional judgement in order to create a bespoke plan, which can be highly rewarding for the veterinarian as well as significantly improving the quality of life for both dog and owner.

Geriatric dogs should be routinely evaluated for signs of CCD (12) and records of their questionnaire score should form part of their routine clinical notes **(Figure 5)**. For dogs showing signs of CCD which are well managed, check-ups every 3 to 6 months may be all that is required, whereas more frequent contact will be required if the signs are progressive or not yet stabilized. For dogs that show persistent signs or a sudden deterioration, it is important to screen for any concurrent health issues which may have developed or progressed since the diagnosis of CCD. For example, if a dog previously showing mild signs of disorientation has suddenly begun to house soil then it is important to check for conditions such as osteoarthritis affecting their ability to toilet outside (*e.g.*, steps to get outside, a considerable distance from resting place to garden, or a slippery floor), renal, liver or endocrine disease (leading to polyuria/polydipsia (PUPD) and possibly a contributing urinary tract infection).

CONCLUSION

CCD is a progressive disease, and it can be difficult to predict response to treatment or rate of progression for the condition. Clearly patients with comorbidities have a more guarded prognosis. Owners should be encouraged to monitor the key signs (not just those of initial concern) and be made aware of the level and type of assistance available to help support their pet in order to improve quality of life. Even though outcome can be hard to predict, such an approach ensures the most is being made of the opportunity and many cases will respond favorably, which can be a source of great satisfaction for all involved.

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PATHOLOGIC HYPERCALCEMIA IN THE DOG

This paper looks at differential diagnoses and therapeutic management options when a dog is found to have elevated calcium levels.

KEY POINTS

1. Calcium homeostasis is tightly regulated by parathyroid hormone, calcitonin, and vitamin D, which primarily affect calcium mobilization, excretion, and absorption at skeletal, renal and intestinal tissues, respectively.
2. The most common causes of hypercalcemia in dogs are cancer, primary hyperparathyroidism and hypoadrenocorticism; idiopathic hypercalcemia – commonly seen in cats – is less common in dogs.
3. Clinical signs of hypercalcemia include primary polyuria with secondary polydipsia, generalized weakness, lethargy, gastrointestinal disturbances and weight loss.
4. Prompt medical intervention to enhance calciuresis with identification and treatment of the underlying cause for the hypercalcemia are critical for optimal patient management and a favorable outcome.

Introduction

Calcium is the fifth most abundant element in the body, existing as an essential cation found within bodily fluids and also stored within cellular organelles. It is responsible for many vital intracellular and extracellular functions, including neuromuscular transmission, enzymatic reactions, blood coagulation, vasomotor tone, hormone secretion and bone metabolism. While calcium is broadly distributed throughout cellular tissues, rapid fluctuations in intracellular calcium serve as a primary regulator of cellular responses following plasma membrane receptor activation, and it also serves as a secondary messenger responsible for perpetuating external signals into cells to orchestrate downstream biologic functions (1).

While intracellular calcium is critical for normal cellular activities, the clinical measurement of calcium is restricted to its presence in body fluids where it exists in three different forms, namely ionized, protein-bound, and complexed with anions or organic acids. Ionized calcium (iCa) is the biologically active form that can pass through plasma membranes by virtue of permeable ion channels, active transporters and cation exchangers (2), and comprises 50% of total serum calcium. The remaining fraction is approximately distributed as 40% protein-bound and 10% complexed. Given its importance in cellular functions, iCa concentrations must be tightly regulated to ensure proper physiologic activities of a myriad of cellular, tissue, and organ systems; this is done through the concerted actions of parathyroid hormone (PTH), 1,25-dihydroxycholecalciferol (active vitamin D_3 or calcitriol) and calcitonin (3). Similar to its importance for intracellular signaling, calcium within extracellular fluid also regulates cellular functions of many vital glandular and epithelial tissues, including the parathyroid gland, thyroid C cells, and kidney.

Calcium homeostasis

The three principal mediators, PTH, calcitonin, and calcitriol, are responsible for balancing whole-body calcium concentrations through the exertion of complementary and/or synergistic biologic activities on three target organs, namely the kidneys, small intestines, and inorganic bone matrix (hydroxyapatite) (3) **(Figure 1)**.

PTH serves as the master regulator, governing minute-to-minute fluctuations of calcium levels within the body. If calcium levels are increased, PTH secretion is downregulated, leading to a net calcium loss through the distal tubules in the kidneys, a reduction in intestinal absorption of calcium, and diminished osteoclastic bone resorption (4). Conversely, if serum calcium levels are decreased,

Jordan M. Hampel

DVM, Department of Veterinary Clinical Medicine, University of Illinois at Urbana-Champaign (UIUC), Illinois, USA

Dr. Hampel received her Doctorate of Veterinary Medicine from the University of Illinois in 2020 and then went on to complete a rotating small animal internship at Michigan State University. She returned to the UIUC to further advance her training as an oncology-dedicated clinical trial intern, and is currently a resident in Medical Oncology and pursuing a Master of Science degree that focuses on targeted strategies to amplify the cytotoxic activities of ionizing radiation therapy.

Timothy M. Fan

DVM, PhD, Dip. ACVIM (Oncology, Internal Medicine), Department of Veterinary Clinical Medicine, University of Illinois at Urbana-Champaign, Illinois, USA

Dr. Fan received his DVM from the Virginia-Maryland Regional College of Veterinary Medicine in 1995 and continued training to become board-certified in Small Animal Internal Medicine and Oncology at Cornell University and UIUC, respectively. He then completed a PhD focusing on tumor immunology at Illinois, and joined the faculty where he is professor, a core member in the Anticancer Discovery from Pets to People theme, and a program leader for the Cancer Center at Illinois that includes companion animals as sophisticated models to study cancer.

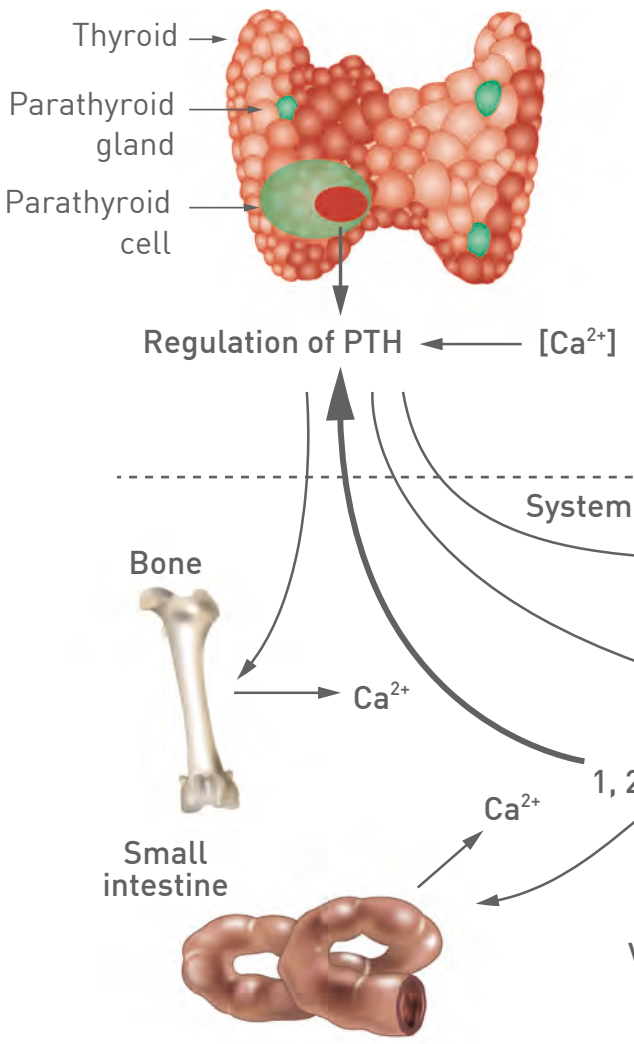

Figure 1. Mechanism of calcium homeostasis. The three principal mediators that balance whole-body calcium concentrations (PTH, calcitonin and calcitriol) can exert complementary and/or synergistic biologic activities on three target organs, namely the kidneys, small intestines, and inorganic bone matrix (hydroxyapatite). On the parathyroid cell surface, the calcium receptor senses fluctuations of extracellular calcium. In situations of hypocalcemia, PTH increases serum calcium levels through enhanced bone resorption and renal calcium reabsorption. PTH indirectly contributes to calcium absorption within the small intestine through the conversion of vitamin D to highly active vitamin D_3 (calcitriol) in the proximal renal tubules through the upregulation of 1-alpha-hydroxylase activity.

the parathyroid glands secrete PTH that acts on the distal renal tubules to cause calcium reabsorption and phosphorus excretion from the kidney. PTH also indirectly contributes to calcium absorption within the small intestine via the conversion of vitamin D to highly active vitamin D_3 (calcitriol) in the proximal renal tubules through the upregulation of 1-alpha-hydroxylase activity (4). Additionally, PTH will act on skeletal tissue to stimulate the proliferation of existing bone-forming cells (osteoblasts), which is an early effect and enhances bone mineral density (5). However, chronic PTH signaling can upregulate osteoblast RANKL expression, which results in osteoclast activation and survival, with subsequent augmented bone resorptive activities (6).

Calcitriol participates in calcium regulation principally through increased synthesis of calbindin-D proteins, which increase small intestinal absorption of dietary calcium with subsequent release into the bloodstream (7). Calcitriol can also operate as a negative feedback regulator of itself by conversion into 24,25-dihydroxycholecalciferiol, which is less active, as well as negatively regulating calcium by decreasing PTH mRNA transcription.

Calcitonin is not a major factor in the minute-to-minute regulation of calcium, but serves as an emergency hormone to reduce serum levels when there is a rapid increase in calcium. Calcitonin is released by C cells of the thyroid gland when stimulated by hypercalcemia and ingestion of high calcium meals, resulting in secretion of enteric hormones (*i.e.*, gastrin and cholecystokinin), and its biologic activities are principally mediated through inhibition of osteoclastic bone resorption (8).

Differential diagnosis

Hypercalcemia has been associated with a variety of physiologic and pathologic conditions in both dogs and cats, and these can be broadly categorized as parathyroid-dependent and parathyroid-independent. Parathyroid-dependent causes include primary hyperparathyroidism and (uncommonly) secondary nutritional or renal hyperparathyroidism. All other causes of hypercalcemia are considered parathyroid-independent and include diverse pathologies such as cancer-associated **(Figures 2 and 3)**, toxic, idiopathic, metabolic, skeletal, and granulomatous diseases (9). In recent studies evaluating large numbers of companion animals, the most common pathologic causes of ionized hypercalcemia in dogs were neoplasia, primary hyperparathyroidism, and hypoadrenocorticism (in comparison, the most common causes in cats are neoplasia (*e.g.*, oral squamous cell carcinoma), chronic kidney disease, idiopathic hypercalcemia (secondary to derangements in calcium-sensing apparatus) and (less commonly) hypervitaminosis D (10-14). Overall, the most common cause in companion animals is cancer, with approximately 60% of dogs (and 30% of cats) diagnosed with cancer-related hypercalcemia (11-13) **(Figures 4 and 5)**. There are various mnemonics or acronyms for

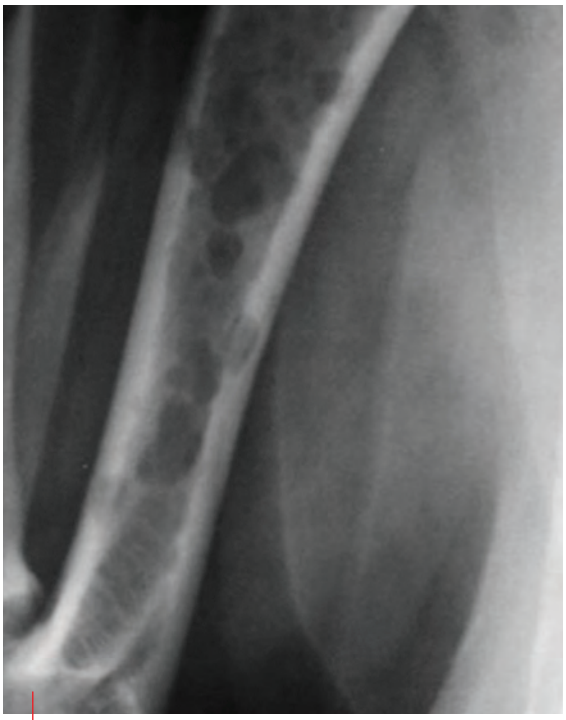

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Figure 2. Causes of hypercalcemia can be broadly categorized as parathyroid-dependent and parathyroid-independent. Parathyroid-independent causes vary but are often cancer-associated. Here a middle-aged Irish Setter that presented for generalized lameness, diffuse skeletal pain, and PU/PD was found to have a raised total calcium and marked elevations in serum globulins on a blood screen. Radiography identified discrete punctate osteolytic lesions in various bones, including the right humerus.

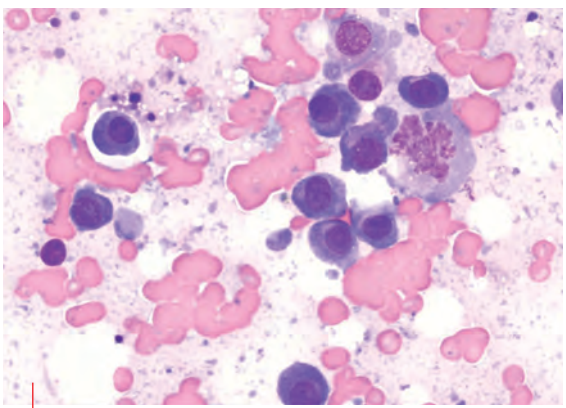

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Figure 3. A bone marrow aspirate identified an elevated percentage of plasma cells with features of malignancy, confirming the diagnosis of multiple myeloma.

recalling different clinical scenarios associated with hypercalcemia. Given that it can often foreshadow the identification of significant underlying disease pathologies, one very appropriate mnemonic is "GOSH DARN IT" **(Table 1)**.

Although elevations in calcium secondary to cancer are common, several discrete mechanisms can be responsible (15,16). The first and most common

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Figure 4. The most common cause of hypercalcemia in companion animals is cancer, as typified by this case, a geriatric whippet presenting for generalized peripheral lymph node enlargement (note enlarged mandibular node) and elevated ionized calcium.

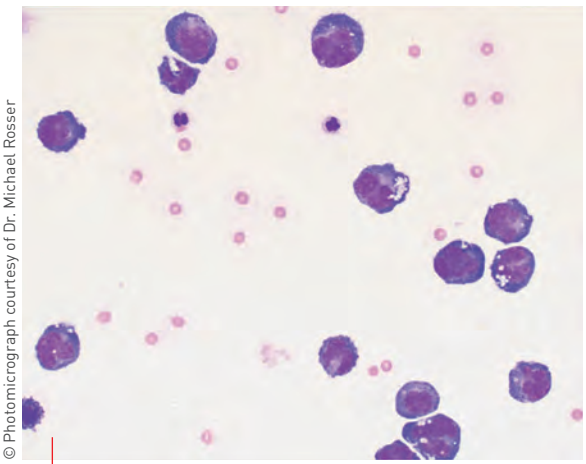

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Figure 5. Fine-needle aspirate cytology of a mass in the cranial mediastinum confirmed it to be large lymphoblastic lymphoma.

Table 1. GOSH DARN IT – A useful mnemonic and acronym for causes of hypercalcemia.

- **G**ranulomatous diseases (systemic mycoses, mycobacterial)
- **O**steolytic diseases (metastatic carcinomas (prostate, mammary, squamous cell), multiple myeloma)
- **S**purious or lab error
- primary **H**yperparathyroidism (parathyroid adenoma)
- vitamin **D** toxicity (rodenticide, psoriasis medicine)
- **A**ddison's disease (hypoadrenocorticism)
- **R**enal failure (acute or chronic)
- **N**eoplasia (humoral, production of PTHrp: lymphoma, apocrine gland anal sac adenocarcinoma, thymoma, and (rarely) others)
- **I**diopathic (seen in cats)
- **T**emperature (high fever – rare and transient cause)

cause for hypercalcemia is the production of soluble factors by tumor cells, which results in bone resorption, known as humoral hypercalcemia of malignancy (HHM). A second mechanism is direct invasion of tumor cells into bone, leading to osteolysis, commonly seen with carcinomas or hematopoietic bone marrow malignancies such as leukemias, lymphoma, and multiple myeloma. Lastly, and least commonly, production of the active form of vitamin D by 1-α-hydroxylase-expressing cells will enhance intestinal absorption of calcium.

Humoral hypercalcemia of malignancy (HHM)

Humoral hypercalcemia of malignancy may involve malignant secretion of parathyroid hormone-related peptide (PTHrp), which is structurally similar to PTH (17), and cytokines such as IL-1, IL-6, or tumor necrosis factor (15). These humoral factors lead to generalized and diffuse osteoclastic resorption without visible radiographic bone lesions. Because PTHrp is a secreted protein, any cell type which is secretory in nature and undergoing malignant transformation can potentially liberate excessive amounts of the hormone.

Lymphoma (LSA) is the most common cause of HHM, particularly mediastinal lymphoma, however, other tumors responsible for hypercalcemia in dogs (and cats) include apocrine gland anal sac adenocarcinoma (AGASACA), thyroid carcinoma, multiple myeloma, multiosseous bone tumors, thymoma, squamous cell carcinoma, mammary gland carcinoma/adenocarcinoma, melanoma, primary lung tumor, chronic lymphocytic leukemia, renal angiomyxoma, and parathyroid gland tumors. As a general rule of thumb, hypercalcemia can be seen in 10-35% of dogs with LSA, ≥ 25% of dogs with AGASACA, and approximately 20% of dogs with multiple myeloma.

Clinical signs

Given the wide range of physiological functions of calcium ions, both hypercalcemia and hypocalcemia will cause multisystemic effects (10,11). Increased serum calcium concentration causes decreased cellular function by altering the cell membrane permeability and the cell membrane pump activities. An increase in intracellular iCa can cause deranged cellular function and reduced energy production, which can result in cell death and lead to dystrophic and/or metastatic mineralization. While many tissues can be affected by hypercalcemia, the effects on the central nervous system, gastrointestinal tract, heart and kidneys are of greatest clinical importance. Regardless of the inciting cause, compromised renal function is a significant clinical feature of hypercalcemia, especially in the setting of neoplasia (18). Clinical signs associated with hypercalcemia can be nonspecific, insidious in nature, and vary in severity, but common signs might include primary polyuria

with compensatory polydipsia (PU/PD), anorexia, lethargy, weakness, vomiting, depression, muscle twitching, cardiac arrhythmias and seizures (9). This compares to hypercalcemia in cats, where gastrointestinal signs, particularly anorexia and vomiting, are among the most frequent signs (19).

Diagnostic approach to the hypercalcemic patient

Measurement of iCa is more accurate than total calcium in companion animals. Interestingly, the magnitude of calcium concentration elevation tends to be higher in cases of hypercalcemia of malignancy than other causes (12,13). When hypercalcemia is suspected in a patient, obtaining a thorough history and physical examination, which includes careful assessment of peripheral lymph nodes and rectal palpation (to check for AGASACA) **(Figures 6-8)**, should be the first clinical step. Guided by these findings, additional diagnostics (including a complete blood count, chemistry panel, urinalysis, thoracic radiographs, and abdominal ultrasound) can be performed to identify potential findings that might further corroborate clinical suspicions or conversely uncover pathologies not overtly identified during physical examination.

If an underlying cause for hypercalcemia cannot be identified following these diagnostics, further tests can be performed, including measuring the circulating concentrations of serum PTH, PTHrp and calcitriol. In patients with hypercalcemia of malignancy, serum PTH concentrations should be low or undetectable, while serum PTHrp levels can be measurable and/or elevated. Serum calcitriol is usually normal, but can be increased or decreased. Beyond these conventional diagnostics, additional tests such as bone survey radiographs, bone scans (nuclear scintigraphy), bone marrow aspiration and computer tomography (CT), can be considered if an underlying cause remains elusive **(Figures 9-11)**.

Calcium disturbances can be encountered in serious and life-threatening conditions and regardless of the underlying cause, hypercalcemia can lead to life-limiting complications if left untreated (20). Measuring iCa requires specialized analyzers, which are not always readily available to veterinary healthcare professionals. In attempts to mitigate this limitation, the clinician must often rely on deciphering nuances in the total calcium (tCa), which includes all three serum calcium fractions. Unfortunately, accurate interpretation can be difficult because total calcium is not a true

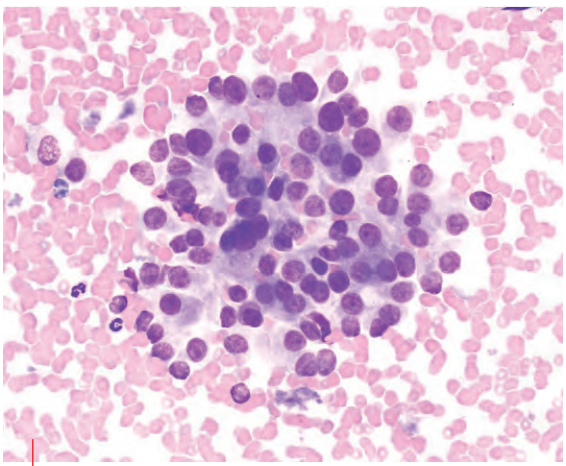

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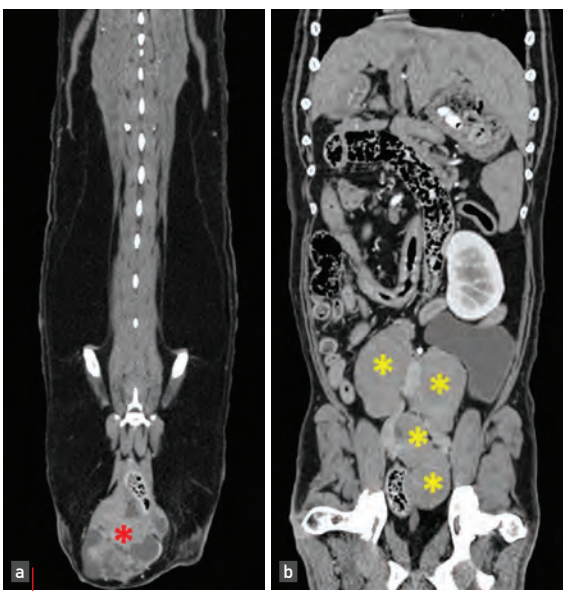
Figure 7. Cytology from the rectal mass revealed features consistent with apocrine gland anal sac adenocarcinoma (AGASACA).



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Figures 8. CT scans of the dog identified a large primary tumor (red asterisk) **(a)** and severely enlarged draining lymph nodes (yellow asterisks) **(b)**, confirming regional metastases.

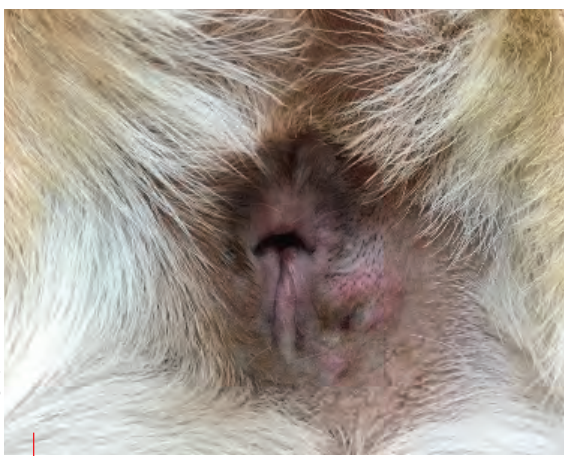

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Figure 6. Rectal examination of an elderly female mixed breed dog presented for rectal scooting, difficulty in defecation, and PU/PD. Identification of a soft tissue mass involving the right anal sac with corresponding elevations in iCa.

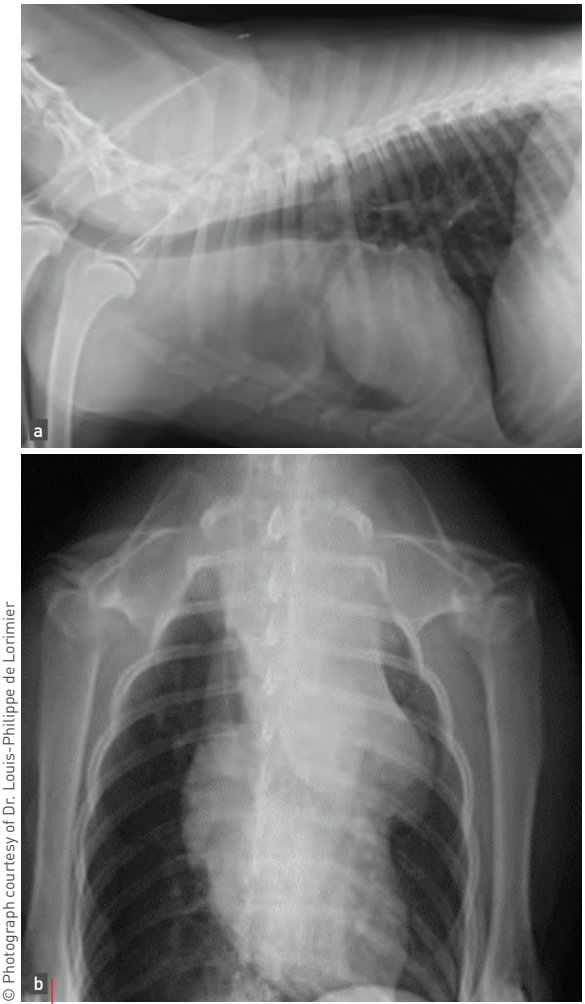

Figure 9. Radiography can be of value when investigating possible causes of hypercalcemia. Here a mixed breed dog presented for gradual onset tachypnea, coughing, and intermittent regurgitation, but was otherwise relatively asymptomatic. A chemistry panel identified a mild increase in total calcium with confirmed elevation of iCa. Lateral **(a)** and D-V **(b)** thoracic radiographs identified a well-defined mediastinal mass effect causing deviation of the trachea dorsally and laterally.

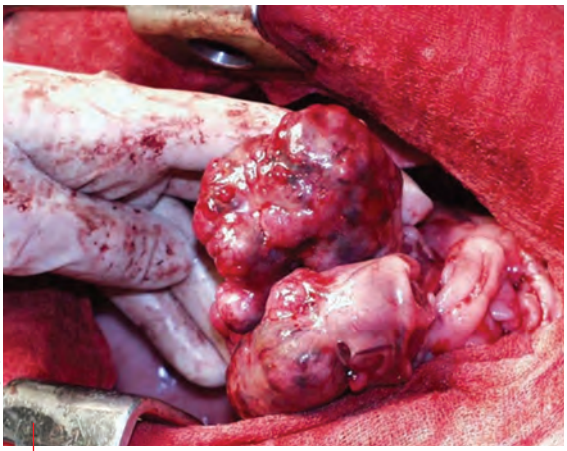

Figure 10. A surgical approach via a right-sided lateral intercostal thoracotomy revealed a multilobulated mediastinal mass.

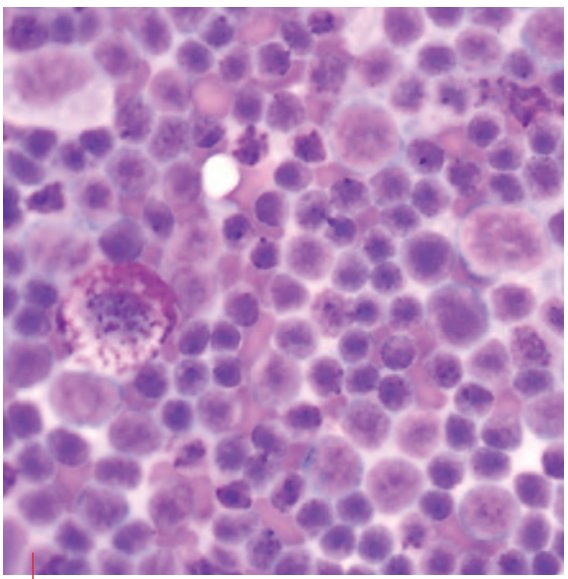

Figure 11. Cytology of the mass was consistent with a thymoma based upon the predominance of small mature lymphocytes, mast cells, macrophages, and plasma cells.

reflection of the iCa status in any particular patient. While correction formulas for total calcium using albumin and total protein have been proposed, these should not be considered reliable, and have failed to validate and improve upon the observed diagnostic discordance between total calcium and iCa (20,21). Because of this, it is recommended that any abnormality in the total calcium measurement should be further investigated with additional diagnostics to directly quantify true iCa concentrations.

Treatment

Given that hypercalcemia can arise from a wide range of disease processes, the proper treatment, severity of clinical signs, and the overall prognosis are based on the underlying etiopathogenesis. There is no single treatment protocol that is consistently effective for all causes, but induction of calciuresis can provide immediate clinical benefit in most patients. Definitive and optimal management of hypercalcemia is achieved by identifying and treating the underlying cause, although precise identification of some disease processes can be more complex and elusive. The clinical status of the patient will ultimately dictate how aggressive the treatment needs to be.

The most effective treatment for hypercalcemia of malignancy is removal of the underlying neoplasm by surgery if anatomically feasible, induction of clinical remission with chemotherapy (most applicable for hypercalcemia associated with LSA), or radiation therapy. Empirically, serum calcium concentration of 16 mg/dL (4 mmol/L) or greater has been recommended as the basis for initiating aggressive therapy; however, the intensity of patient management should be individualized and

guided by real-time assessment and diagnostic findings. Unfavorable prognosis should be anticipated in particularly compromised patients with any of the following characteristics:

- clinically ill patients from a hypercalcemia in excess of 16 mg/dL (4 mmol/L),
- patients with severe renal azotemia,
- patients where the calcium and phosphorous product is greater than 60 with resultant metastatic mineralization,
- patients suffering from hypercalcemia of malignancy associated with solid tumors that are not amenable to surgical removal.

Initial intervention for treatment should consist of aggressive fluid therapy with isotonic (0.9%) sodium chloride to correct existing dehydration, a common sequalae to hypercalcemia-induced primary polyuria (termed secondary nephrogenic diabetes insipidus). Hemoconcentration through decreased glomerular filtration leads to additional calcium retention as the kidneys attempt to conserve sodium, which decreases urinary calcium excretion (9). Judicious administration of IV saline will not only restore hydration, but also has the added benefit of promoting volume expansion with increased glomerular filtration rate and consequent enhanced calciuresis. Saline does not contain supplemental calcium, and the high sodium content competes with calcium for renal tubular absorption, which further helps promote calcium excretion (22). Once adequate rehydration has been achieved, the use of loop diuretics (*e.g.*, furosemide at 2-4 mg/kg BID or TID IV/SC/PO), in conjunction with continued saline fluid therapy, is recommended to further promote urinary calcium excretion and lessen the likelihood of iatrogenic hypervolemia. However, care is required to avert dehydration in these patients, as hemoconcentration can negate desired calciuresis.

Glucocorticoids can quickly provide benefit in the treatment of certain causes of hypercalcemia. However, ideally the underlying cause should be identified prior to its administration, as indiscriminate institution of glucocorticoids has the potential to confound definitive diagnosis (*i.e.*, covert underlying hematopoietic neoplasia) or could even be medically contraindicated (*i.e.*, infectious granulomatous disease). Glucocorticoids help lower serum calcium levels by decreasing bone resorption, impede intestinal calcium absorption, and increase renal calcium excretion (22). They are particularly beneficial when treating hypercalcemia associated with malignancy such as lymphoma, AGASACA, multiple myeloma, thymoma, hypoadrenocorticism, or hypervitaminosis D. Most commonly used options are prednisone (1-2.2 mg/kg BID IV/SC/PO), and/or dexamethasone (0.1-0.22 mg/kg BID), both being inexpensive and widely available. These doses should be tapered appropriately, and patients are not meant to be maintained at these high doses long term.

Bisphosphonates are another treatment option for hypercalcemia; these are drugs that were developed to inhibit pathologic bone

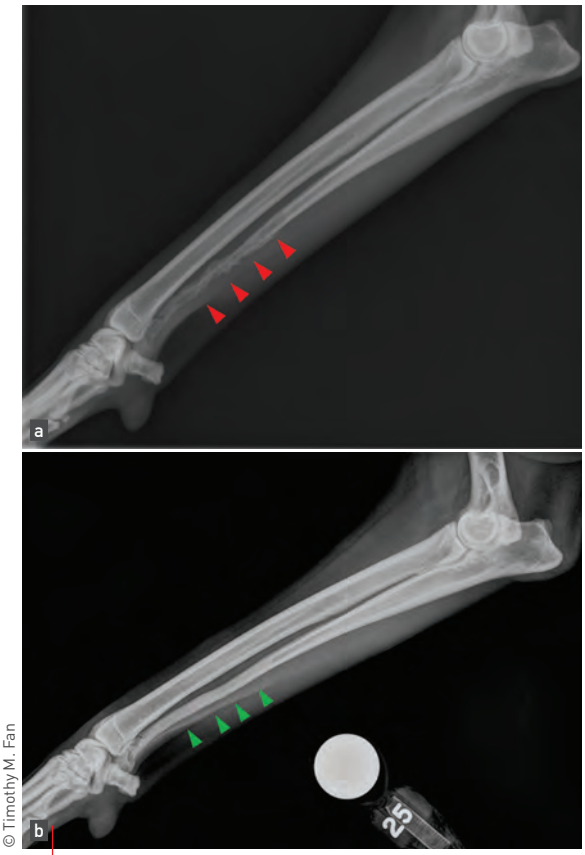

Figure 12. Border Collie with severe pathologic resorption of ulnar bone (red arrowheads) secondary to malignant plasma cell tumor invasion **(a)**. Treatment with ionizing radiation and monthly zoledronate completely reverses osteolytic damage **(b)** and restores healthy bone quality and quantity (green arrowheads).

resorption associated with osteoporosis and skeletal metastases in humans. Zoledronate and pamidronate are the most frequently used in human medicine and can normalize calcium levels in 4-10 days, with the effects lasting for about 1-4 weeks (23). While there is currently more data regarding the use of pamidronate, zoledronate has been shown to be efficacious in the control of acute hypercalcemia in dogs (24). Dosages of individual bisphosphonate drugs vary due to differences in antiresorptive potency and potential side effects **(Figure 12)**. The recommended dosing for zoledronate is 0.1-0.25 mg/kg diluted in saline and given IV as a constant-rate infusion over 15-20 minutes, while pamidronate dosage is 1.0-2.0 mg/kg diluted in saline given over 2-4 hours. An important consideration with the administration of these drugs is that bolus infusion of large dosages in preclinical toxicity studies had the potential to cause acute kidney injury. While the above recommended dosing practices in veterinary patients employ longer infusion duration, and hence dramatically reduces the potential for renal damage, it is still recommended to closely monitor a patient's kidney function during the course of therapy. It is worth noting that alendronate, an oral bisphosphonate, has been investigated for use in cats with persistent idiopathic hypercalcemia, and appears to be well tolerated (14,25), but further

investigation is warranted to evaluate its efficacy, given its extremely poor oral bioavailability, and if it should be recommended above other bisphosphonates in this species.

Mithramycin, **calcitonin**, and **gallium nitrate** are other theoretical therapies for medically managing hypercalcemia, but these all have limited utility due to their cost, side effects and administration schedules. Mithramycin (plicamycin) is an antitumor antibiotic which inhibits RNA synthesis in osteoclasts, leading to rapid inhibition of bone resorption (22). This medication has fallen out of favor in both veterinary and human medicine due to the potential to cause thrombocytopenia, renal and hepatic necrosis, and hypocalcemia. Calcitonin is another treatment option, as it attenuates bone resorption by inhibiting the activity and formation of osteoclasts. As a result, it rapidly decreases serum calcium concentrations within a few hours following administration, which is faster than any other treatment strategy, but its effects are relatively short-lived due to compensatory receptor down-regulation. Gallium nitrate is an antineoplastic agent that inhibits osteoclasts and decreases the resorptive solubility of hydroxyapatite by binding to hydroxyapatite crystals. This medication is typically used in cases that are refractory to bisphosphonates, and some studies have shown it to be more effective than bisphosphonates at reducing calcium levels in cases of hypercalcemia of malignancy. However, it is not considered a first-line treatment due to its potential for nephrotoxicity.

CONCLUSION

Ionized calcium concentrations are very tightly regulated within the body, and alterations can lead to significant and detrimental systemic multi-organ effects. Paraneoplastic hypercalcemia is a serious and relatively common complication in dogs, with various tumor types that can induce hypercalcemia through mechanisms that alter calcium homeostasis and lead to clinical illness. The most common canine neoplasia to cause hypercalcemia is T-cell lymphoma, but other types of neoplasia, and non-neoplastic diseases, should be considered whenever a patient presents with elevated calcium concentrations. Although clinical signs associated with hypercalcemia are often non-specific, early detection of the underlying cause is important. Once identified, instituting definitive treatment and supportive management will minimize life-threatening complications and maximize the chances for achieving a favorable outcome.

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