



# 2020 OVMA CONFERENCE & TRADESHOW

WESTIN HARBOUR CASTLE  
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**CONFERENCE PROCEEDINGS**

# FOREWORD

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# TABLE OF CONTENTS

## SMALL ANIMAL PROGRAM

### CARDIOLOGY

**Ashley Jones, BHSc, DVM, DACVIM**

*Staff Cardiologist, Veterinary Specialty Center, Buffalo Grove, IL*

1001 – Dilated Cardiomyopathy in Dogs

1002 – Approach to the Coughing Dog

1003 – Feline Cardiomyopathies

1004 – Cardiac Biomarkers

1005 – Practical Approach to Arrhythmias

### DENTISTRY

**Barden Greenfield, DVM, FAVD, DAVDC**

*Owner, MidSouth Veterinary Dental Referrals*

2001 – Feline Tooth Resorptions: When to Extract and When to Crown Amputate

2002 – A Step-by-Step Approach to Surgical Extraction of a Maxillary 4th Premolar and Maxillary 1st Molar Tooth

2003 – The Local, Regional and Systemic Complications of Periodontal Disease

2004 – Those Darn Oronasal Fistulas: How to Avoid Them, and How to Treat Them

2005 – When and When Not to Use Bonding Sealants

### EXOTICS

**Doug Mader, MS, DVM, DABVP (C/F), DABVP (R/A), DECZM(Herpetology), FRSM**

*Marathon Veterinary Hospital*

3001 – Adding Exotics to a Small Animal Practice

3002 – Basic Bunny Medicine

3003 – Basic Reptile Anatomy and Physiology

3004 – Treatment Techniques in Reptiles

3005 – Medical Issues in Common Pet Invertebrates

### GASTROENTEROLOGY

**Kenneth Simpson, BVMS&S, PhD, DACVIM, DECVIM-CA**

*Professor, College of Veterinary Medicine, Cornell University*

4001 – Chronic Diarrhea: What's the Cause?

4002 – Chronic Enteropathies in Cats: Diagnosis and Management

4003 – Update on the Diagnosis and Management of Canine Pancreatitis

4004 – Rethinking Canine HGE: Acute Hemorrhagic Diarrhea Syndrome

4005 – Chronic Vomiting: What's the Cause?

### ONCOLOGY

**Sarah Boston, DVM, DVSc, Surgical Oncologist**

*VCA Canada, 404 Veterinary Emergency & Referral, Aurora Ontario  
and*

**Paul Woods, DVM, MS, DACVIM (Internal Medicine, Oncology)**

*Professor of Internal Medicine and Oncology, OVC, University of Guelph, Guelph Ontario*

5001 – Making the Cancer Diagnosis

5002 – Managing the Cancer Patient

5003 – Practical Approach to the Management of Mast Cell Tumours in Dogs and Cats

5004 – Practical Approach to the Management of Osteosarcoma in Dogs and Cats

5005 – Practical Approach to the Management of Soft Tissue Sarcoma in Dogs and Cats

### CLICKABLE TABLE OF CONTENTS

Just "click and jump"  
to the proceeding  
of your choosing.

**PHARMACOLOGY****Lauren Trepanier, DVM, PhD, DACVIM, DACVCP***Professor and Assistant Dean of Clinical and Translational Research, University of Wisconsin-Madison, Madison, WI*6001 – Top 10 Potential Drug Interactions6002 – Drug Dose Adjustments for Disease6003 – Rational Therapy of Vomiting6004 – Practical Approach to Inflammatory Bowel Disease6005 – Choosing the Best NSAID for Your Patient**PRACTICE PEARLS**7001 – Growing Resiliency – The Connection Between Growth Mindset and Resilience**Colleen Best, DVM, PhD, CCFP**7002 – “You Only Care About the Money” – How to Navigate Financial Discussions with Clients**Sarah Bernardi, RSW, MSW***Veterinary Social Worker, Veterinary Emergency Clinic and Referral Centre, Toronto, Ontario*7003 – 2019 AAHA Canine Life Stage Guidelines**Jinelle Webb, DVM, MSc, DVSc, DACVIM***Medical Director, Associate Internal Medicine, Mississauga-Oakville Veterinary Emergency Hospital, Oakville, ON*7004 – Choose Your Weapons! Knowing What Dental Burs to Use Can Make or Break a Procedure**Barden Greenfield, DVM, FAVD, DAVDC***Owner, MidSouth Veterinary Dental Referrals*7005 – Dropless Cataract Surgery in Dogs (No proceedings submission for this talk)**Joe Wolfer, DVM, DACVO***Toronto Animal Eye Clinic, Toronto, Ontario*7006 – Consensus in Feline Medicine: Standards of Care**Matthew Kornya, DVM***Associate, The Cat Clinic*7007 – Minimally Invasive Surgery is Superior to Open Surgery: What is the Evidence?**Ameet Singh, DVM, DVSc, DACVS***Associate Professor, University of Guelph, Guelph, Ontario*7008 – Canine Rehabilitation Outcome Assessment Tools: Using Goniometry and Girthometry in Clinical Practice**Tiffany Durzi, DVM, CVA, CCRT, CVPP***Chief of Service, OVC Fitness and Rehabilitation Service***SURGERY****Ameet Singh, DVM, DVSc, DACVS,***Associate Professor, University of Guelph, Guelph, Ontario***and****Tom Gibson, BSc, Bed, DVM, DVSc, DACVS, DACVSMR***Associate Professor, Small Animal Surgery, Ontario Veterinary College, University of Guelph, Guelph Ontario*8001 – Advanced Gastrointestinal Surgery8002 – Getting Back to the Basics: Secure Knot Tying, Beautiful Closed Skin Incisions and Seroma Prevention8003 – Canine Cruciate Rupture: Conservative Treatment vs. Surgical Treatment8004 – Rehabilitation Modalities in the Management of Osteoarthritis8005 – Spay/Neuter Controversies

## TOXICOLOGY

**Justine Lee, DVM, DACVECC, DABT**

*CEO, VETgirl, LLC, Saint Paul, MN*

9001 – Top 5 Mistakes to Avoid in the Poisoned Patient

9002 – Top 10 Human Food Toxins Poisonous to Dogs and Cats

9003 – Top 10 Human Medications Poisonous to Dogs and Cats

9004 – Poisonous Plants Affecting Dogs and Cats

9005 – Rodenticide Toxicity: What's New?

## FOCUS ON INFECTION PROGRAM

10001 – Hot Topics in Infectious Disease

**Scott Weese, DVM, DVSc, DACVIM**

*Professor, Ontario Veterinary College, University of Guelph*

10002 – Leptospirosis

**Jinelle Webb, DVM, MSc, DVSc, DACVIM**

*Medical Director, Associate Internal Medicine, Mississauga-Oakville Veterinary Emergency Hospital, Oakville, ON*

10003 – Echinococcus Multilocularis: An Emerging Threat to Dogs & People in Ontario?

**Andrew Peregrine, BVMS, PhD, DVM, DEVPC, DACVM**

*Associate Professor, Dept. Pathology, Ontario Veterinary College, University of Guelph, Guelph, Ontario*

10004 – Care and Management of Community (unowned, free-roaming, "feral" cats) and Colonies

**Dr. Linda Jacobson, BVSc, MMedVet (Med), PhD**

*Senior Manager, Shelter Medicine Advancement, Toronto Humane Society*

10005 – Optimizing Pathogen Detection and Therapy in Granulomatous Colitis

**Kenneth W. Simpson, BVMS, PhD, DACVIM, DECVIM-CA**

*Professor, College of Veterinary Medicine, Cornell University*

## EQUINE PROGRAM

### SPORTS MEDICINE

**Heidi L. Reesink, VMD, PhD, DACVLSA**

*Assistant Professor of Large Animal Surgery, Cornell University, Lansing, MI*

11001 – Equine Joint Disease and the Value of Objective Gait Analysis

11002 – Frontiers in Management of Equine Joint Disease

11003 – Enigmatic Equine Tendon and Ligament Injuries

11004 – The Hitchhiker's Guide to Equine Regenerative Medicine

11005 – Advanced Imaging of Fatal Musculoskeletal Injuries in Race horses

### NUTRITION AND MORE....

**Robert D. Jacobs, BS, MS, PhD**

*Equine Technical Innovation Manager, Land O Lakes Purina Animal Nutrition*

12001 – Gastric Health in Horses: Feeding and Management Tools

12002 – Feeding (Fueling) the Performance Horse

12003 – Feeding for Certain Medical Conditions

**Luis G. Arroyo, Lic. Vet Med, DVSc, PhD, DACVIM**

*Associate Professor, Ontario Veterinary College, University of Guelph, Guelph, Ontario*

12004 – Current Status of Infectious Disease in Ontario

**Melanie Barham, DVM, PMP**

*Ontario Animal Health Network Coordinator, Animal Health Laboratory, University of Guelph, Guelph, Ontario*

12005 – New Drug Regulations and Veterinary Medicine

## PRACTICE MANAGEMENT PROGRAM

### FINANCE

**Darren Osborne, MA**

*Director of Economic Research, Ontario Veterinary Medical Association, Milton, Ontario*

13001 – Veterinary Disrupters (Part I)

13002 – Veterinary Disrupters (Part II)

13003 – Veterinary Innovators

13004 – Best Practices Not Used in Veterinary Medicine

13005 – Just the Numbers

### COMMUNICATIONS

**Mary Anne Vande Linde, DVM**

*Owner, Vande Linde & Associates*

14001 – Exam Room Communication Success

14002 – Money Talks the Easy Way: Defining and Assigning Value

### CONFLICT RESOLUTION (NO PROCEEDINGS SUBMISSIONS FOR THESE TALKS)

**Shawn McVey, MA, MSW**

*Co-Founder and Chief Culture Officer, Pathway Veterinary Alliance, Austin, TX*

15001 – The Case for Conflict

15002 – Self-Confrontation and Minding Your Manners

15003 – Conflict Dynamics and Characteristics

15004 – Constructive and Destructive Conflict

## PLENARY SESSIONS

**Maureen Anderson, DVM, DVSc, PhD, DACVIM**

*Lead Veterinarian, Animal Health & Welfare, OMAFRA*

and

**Scott Weese, DVM, DVSc, DACVIM**

*Professor, Ontario Veterinary College, University of Guelph*

16001 – Infectious Disease Roundup

## SPEAKER BIOS



# **SMALL ANIMAL PROGRAM**

## DILATED CARDIOMYOPATHY

Ashley E. Jones, DVM, Diplomate ACVIM (Cardiology)

### Introduction

Cardiomyopathy is a general term used to indicate an abnormality of the heart muscle cells. Dilated cardiomyopathy (DCM) is the most common form of cardiomyopathy in dogs and is the second most commonly diagnosed acquired heart disease in dogs after degenerative valve disease. DCM is characterized by systolic dysfunction, or the inability of the ventricle(s) to contract. Diastolic dysfunction (inability for ventricles to relax) is also a common finding. Typically the disease targets the left ventricle, but in some cases both ventricles may be affected. There are two stages of DCM: the occult stage is the period of time when the patient has systolic dysfunction but remains asymptomatic, whereas the overt stage is diagnosed once the patient becomes clinical for their condition and shows signs of congestive heart failure (CHF). Other factors that can cause a phenotype that mimics DCM such as hypothyroidism, nutritional deficiencies, infectious diseases, and toxins should be ruled out before a diagnosis of DCM can be made. Often the underlying cause of DCM remains unknown in both humans and dogs but is suspected to be genetic. Over 50 genes have been associated with dilated cardiomyopathy in humans, and several genetic mutations have also been linked to DCM in select dog breeds.

### Breed-Specific Dilated Cardiomyopathy

Doberman pinschers are the most commonly affected breed with DCM (reports of up to 30-50% affected). Two genetic mutations have been identified in association with DCM in Dobermans. Both demonstrate an autosomal dominant inheritance pattern with incomplete penetrance. The “DCM1” mutation is a defect in the pyruvate dehydrogenase kinase 4 gene (PDK 4), which is an important mitochondrial protein involved in production of ATP. The “DCM2” mutation appears to cause abnormal formation of a sarcomeric protein, thereby affecting the ability of the cardiac myocyte to contract. Genetic screening tests are available for these defects through the North Carolina Veterinary Genetics Laboratory (<https://cvm.ncsu.edu/genetics/>). Unfortunately these genetic mutations do not explain all forms of this disease, as there are some Dobermans with the mutation that do not have phenotypic changes of DCM, and others that do not have either mutation yet develop DCM. Dogs that are positive for both mutations have a 60% chance of developing DCM at some point in their life. Dobermans are unique in that some dogs will have an arrhythmogenic form of DCM where they maintain normal systolic function, but develop significant and often life-threatening ventricular arrhythmias. Sudden death can be the first sign of the disease.

Great Danes, Irish Wolfhounds and Newfoundlands are some of the giant breeds that are predisposed to developing DCM. Atrial fibrillation is not an uncommon finding in these breeds in association with DCM, and occasionally they can have ventricular premature complexes (VPCs). In Great Danes, a male predisposition was reported in one study, suggestive of an X-linked pattern of inheritance, but a specific mutation has not yet been identified for genetic testing. An autosomal recessive inheritance pattern with sex-specific alleles has been shown in Irish Wolfhounds, and males are over-represented in this breed as well.

While DCM is typically an acquired disease diagnosed in middle-aged dogs, Portuguese Water Dogs can have a juvenile onset of DCM that appears to be inherited in an



autosomal recessive manner, with the defect linked to a region on chromosome 8. The disease in this breed is very aggressive and affected puppies will typically die between 2 and 32 weeks of age.

Boxers with systolic dysfunction often are assigned the diagnosis of DCM, however it's unclear whether this is truly DCM or a different form of arrhythmogenic right ventricular cardiomyopathy (ARVC). The vast majority of Boxers with ARVC maintain normal cardiac structure and function, but a small subset will develop systolic dysfunction. In a recent study, the DCM phenotype in Boxers was associated with homozygous positive striatin mutation genotype.

Golden retrievers can develop a condition very similar (and genetically homologous) to Duchenne muscular dystrophy that has been described in humans. This genetic anomaly is X-linked and therefore affects predominantly males, but also homozygous females. Both skeletal and cardiac muscle is affected. Cardiac systolic dysfunction typically occurs between 30-45 months. Taurine-deficient DCM was also identified in a family of golden retrievers in 2005. Recently, an increase in prevalence of DCM in golden retrievers (and other uncommon breeds) was noted, with many dogs having low taurine levels. A common link seemed to be grain-free diets +/- exotic protein sources and particularly "boutique" brands, but research is ongoing to try to determine why these diets were not well tolerated and whether there are other factors that need to be considered. Current theories include a genetic predisposition to lower taurine levels, increased urinary or bile loss of taurine and impaired absorption, among others.

American Cocker Spaniels seem to be predisposed to a nutritional form of dilated cardiomyopathy associated with low taurine levels. An improvement in their myocardial function was reported after 4 months of supplementation with taurine and L-carnitine, though function did not completely return to normal. DCM in Dalmations is uncommon, but a nutritional component was suspected as the dogs were fed a low protein diet to prevent urate stone formation.

### **Secondary Dilated Cardiomyopathy**

Nutritional DCM – Historically some American Cocker Spaniels, Golden Retrievers, Newfoundlands and Dalmations have been identified to have taurine-deficient DCM. Recently, there have been several cases of DCM in apparent connection with the use of limited-ingredient, grain-free diets, or small-batch boutique diets. In July 2018, the FDA announced that it had begun investigating reports of canine dilated cardiomyopathy (DCM) in dogs eating certain pet foods, many labeled as "grain-free," which contained a high proportion of peas, lentils, other legume seeds (pulses), and/or potatoes as main ingredients. Some patients were identified with low taurine levels, but this was not present in all cases. Based on the data collected and analyzed thus far, the agency believes that the potential association between diet and DCM in dogs is a complex scientific issue that may involve multiple factors. Additional information can be found at: <https://www.fda.gov/animal-veterinary/news-events/fda-investigation-potential-link-between-certain-diets-and-canine-dilated-cardiomyopathy> For owners that are concerned about their pets being on a grain-free diet, it is advisable to test taurine levels and obtain an echocardiogram to determine if there are any concerns. Treatment and diet adjustment recommendations should be made based on findings of these tests. Carnitine deficiency has also been reported in one family of Boxers. Blood carnitine levels are not representative of myocardial carnitine levels, so this is a difficult diagnosis to confirm (myocardial biopsy required). Usually if this is suspected, dogs will be

supplemented with L-carnitine (N.B. not D-carnitine as this can interfere with normal physiologic processes) and if there is improvement in myocardial function based on recheck echocardiogram in 3-6 months, then supplementation is continued.

Myocarditis – a form of myocardial disease characterized by the presence of myocardial necrosis or degeneration and inflammation. A variety of physical, chemical, and infectious agents can damage the myocardial tissue and evoke an inflammatory response that may result in chamber enlargement, myocardial dysfunction similar to that observed in DCM, and a variety of tachyarrhythmias and bradyarrhythmias. Plasma troponin I (cTnI) levels are often elevated, suggesting myocardial injury. In the dog, protozoal and viral organisms are reported most commonly (region-dependent). Infectious causes of myocarditis reported in dogs include Chagas disease (*Trypanosoma ccruzi*), *Leishmania*, *Neospora caninum*, *Toxoplasmosis gondii*, parvovirus, West Nile virus, blastomycosis, Lyme disease (*Borrelia burgdorferi*). Definitive diagnosis can be challenging in cases of myocarditis, though titres can be performed for some diseases.

Doxorubicin Toxicity - an anthracycline antibiotic used commonly in many chemotherapy protocols. Toxic levels (cumulative doses > 180 mg/m<sup>2</sup>) can lead to myocardial damage, systolic dysfunction, dilated cardiomyopathy, and congestive heart failure. Arrhythmias, particularly ventricular, are common.

## Clinical Findings

Early detection of DCM can be challenging as there may be no appreciable abnormalities on cardiac auscultation or thoracic radiographs in the early stages of the disease. Echocardiography is the diagnostic test of choice and is essential for detection of patients with occult DCM. Echocardiographic findings include diminished systolic function, and potentially atrial enlargement depending on the stage of the disease. The wall diameter(s) may appear thin, however typically measure within normal limits. Many dogs will also have a small central jet of mitral regurgitation in addition to diastolic dysfunction. In later stages of the disease, thoracic radiographs can be useful for monitoring cardiomegaly and assessing for the presence of pulmonary edema. Electrocardiography (and potentially a 24-hour Holter) is often indicated as part of the work up for a patient with DCM as tachyarrhythmias are common.

Since systemic disorders can cause changes in the heart that resemble a DCM phenotype, it is important to perform diagnostics to rule out alternative causes of systolic dysfunction. Recently, there has been an apparent increase in the number of cases of canine dilated cardiomyopathy. These cases have been occurring in breeds that are not typically affected by DCM, and appear to be nutritionally mediated. Testing of taurine levels in these patients is recommended, in addition to ensuring they are transitioned to a nutritionally-sound diet that is formulated by a veterinary nutritionist. A thyroid panel should also be performed (can start with T4, but if this is low, then extended panel with free T4 and TSH should be done). Genetic testing can also be considered for at-risk breeds. Infectious disease screening should be performed in at-risk patients.

Treatment of DCM depends on the underlying cause. If a nutritional deficiency is suspected, then the patient should be supplemented with taurine and L-carnitine, and a diet change should be considered. Patients in the occult stage should also be treated

with an ACE inhibitor and pimobendan as these have been shown to delay the progression to CHF. Once the patient shows signs of CHF (typically pulmonary edema, but occasionally ascites in cases with biventricular failure), then diuretics should be added to their treatment regime. Antiarrhythmics should be used when clinically significant arrhythmias are present (e.g. atrial fibrillation or ventricular tachyarrhythmias).

Prognosis for dogs with occult DCM can be variable, as the time from diagnosis to the onset of CHF has been reported to be as short as about one year (though can be even shorter), and up to 4 years. There are several factors that contribute to this significant range including the underlying cause, the extent of disease at the time of diagnosis, the rate of progression for each individual patient and the presence or absence of arrhythmias. Following the onset of CHF signs, the average survival is reported to be 130 days, however clinically many cardiologists report average survival times of 6-12 months.

#### Selected References:

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## APPROACH TO THE COUGHING DOG

Ashley E. Jones, DVM, Diplomate ACVIM (Cardiology)

### Introduction

Coughing normally acts as a protective mechanism for the airways and lungs, however sometimes it can become excessive and non-productive, and even harmful to the airways and mucosa. Coughing is mediated by a complex reflex arc:

1. **Afferent pathway** – sensory fibers associated with cough receptors are triggered and impulses sent via vagus nerve to cough center. Many cough receptors have been identified in the pharynx, larynx, trachea, main carina, mainstem bronchi and more distal airways, in addition to ear canals, nasal sinuses, diaphragm, pleura, pericardium and stomach.
2. **Central pathway (cough center)** – located in the upper brain stem and pons, this is where the afferent signals are coordinated to trigger cough
3. **Efferent pathway** – impulses from the cough center travel via the vagus, phrenic and spinal motor nerves to muscles of the diaphragm, abdominal wall, larynx in addition to the inspiratory and expiratory muscles to execute the cough

In dogs, coughing can sometimes be misinterpreted as sneezing, gagging, reverse sneezing and even vomiting, as there can be a terminal retch with some coughing fits. It is important to ask in-depth questions to owners about coughing in order to avoid misdiagnosis. With cough receptors in several parts of the body, there are a variety of conditions/stimuli that can trigger a cough. The differential diagnoses can be divided into broad categories with examples as outlined below<sup>1</sup>:

- **Allergic/Inflammatory** - e.g. pharyngitis, tonsillitis, bronchitis, bronchiectasis, granuloma, pulmonary fibrosis, eosinophilic pneumonitis, pulmonary eosinophilia
- **Physical/Trauma** - e.g. tracheal collapse, hilar lymph node enlargement, esophageal dysfunction, foreign body, tracheal stenosis, left atrial enlargement
- **Neoplastic** - e.g. primary or metastatic lesion throughout airway (tracheal, laryngeal, mediastinum, ribs, sternum, lymph nodes)
- **Cardiovascular** - e.g. pulmonary edema, cardiomegaly, pulmonary emboli, pulmonary edema of vascular origin, pleural effusion
- **Infectious** - e.g. larval/parasitic – *Toxocara* spp, *Ancylostoma caninum*, *Strongyloides stercoralis*, *Filaroides* spp, *Paragonimus kellicotti*, *Dirofilaria immitis*, *Capillaria aerophila*, *Crenosoma vulpis*; fungal - pneumocystis, blastomycosis, histoplasmosis, coccidiomycosis, cryptococcosis, aspergillosis; pneumonia – bacterial, viral; abscess

### Clinical Findings

Differential diagnoses can often be prioritized based on history, signalment, physical examination and sometimes the owner's description of the cough can be helpful. When taking the history of a coughing patient, it's important to ask about chronicity, travel history, lifestyle factors (e.g. grooming facility, dog park etc.), any previously diagnosed conditions (e.g. heart murmur), triggers for the cough, character of the cough (including whether there has been any change in this), and whether the cough is productive, which might be more subtly noted by the pet swallowing after coughing. Chronic coughing would be more typical of allergic/inflammatory diseases and sometimes neoplasia, whereas acute onset of cough is more likely to be infectious or congestive heart failure

(CHF). Coughing due to CHF is going to be rapidly progressive unless treatment is instituted. Travel history is important to determine risk for fungal disease, heartworm disease and other parasitic infections. Young dogs, or dogs that frequent dog parks or boarding facilities are more likely to contract infectious respiratory diseases. Allergic, neoplastic and infectious conditions will typically cause more sporadic coughing, whereas pulling on the leash, excitement or sometimes eating/drinking can trigger tracheal collapse, which is often described as sounding like a “goose honk”. In contrast, CHF-related coughing is often described as a softer cough, and can be more common at night or upon rising. Chronic bronchitis can cause very harsh coughing with a terminal retch. Productive coughing can be noted with pneumonia and severe cases of CHF with fulminant pulmonary edema; hemoptysis occurs more commonly with neoplasia.

A thorough physical examination is always important, and it starts with observing respiratory rate and effort prior to any handling. Particular emphasis should be placed on cardiac auscultation, assessing a murmur, gallop or arrhythmia. Heart rate should also be recorded as this can be helpful in separating CHF from other causes of coughing – dogs with CHF will usually have a sinus tachycardia, whereas dogs with chronic airway disease or pneumonia may have high vagal tone contributing to a pronounced sinus arrhythmia. Detailed thoracic auscultation is also essential to detect and localize any crackles, wheezes or signs of pleural effusion. It is important to remember that crackles are non-specific. Inspiratory crackles are thought to occur due to explosive opening of airways, whereas expiratory crackles likely occur due to sudden airway closure. Closure of the airways tends to be less vigorous, thus making expiratory crackles harder to detect. Crackles associated with CHF occur secondary to narrowing of airways due to accumulation of peribronchial edema, thus are usually noted when the patient is in significant distress. CHF crackles resolve quickly with appropriate therapy and resolution of pulmonary edema. Crackles secondary to chronic airway disease such as bronchitis or bronchiectasis tend to be diffuse, chronic and can be ausculted in patients that are eupneic (though some patients with these conditions can also have increased effort). Wheezes are thought to occur due to fluttering of the airway walls and fluid together. While wheezes are classically associated with asthma, they can be noted with any abnormality/disease that causes narrowing of the airway lumen such as infections/secretions, tumors, foreign body or dynamic airway collapse.

Thoracic radiographs are an important diagnostic test for coughing patients. Proper technique and positioning is essential and will significantly help with interpretation. Ideally three views should be obtained (right and left lateral, as well as a ventrodorsal (VD) or dorsoventral (DV) projection), however sometimes this is not possible if a patient is very dyspneic. In these situations, sedation and flow-by oxygen can be given to ease dyspnea while trying to obtain at least a lateral or DV projection (whichever the patient seems to be able to tolerate). Once the patient is more stable, then the series can be completed. All structures on the thoracic radiograph should be reviewed and assessed. If the cardiac silhouette and pulmonary vasculature are normal, then a cardiac-related cough would be very unlikely. However, if there is an interstitial pattern noted in the perihilar or caudodorsal lung fields and cardiogenic-pulmonary edema is suspected, then left atrial enlargement and pulmonary venous dilation would be expected as concurrent findings. Caution should be used in assessment of the right side of the heart on thoracic radiographs and it should be noted that mild right-sided enlargement is not usually detectable with thoracic radiographs. A “reverse D” shape on a VD/DV projection (ensure the sternum and spine are superimposed for correct positioning), and increased sternal contact with the apex of the heart starting to be pushed dorsally off the sternum

on lateral projections are supportive of right-sided cardiomegaly, but typically only occur with significant enlargement. Right-sided heart enlargement does not typically cause coughing, however enlargement of the left atrium can cause compression of the mainstem bronchi and contribute to coughing. Measurement of a Vertebral Heart Size (VHS), with consideration for breed variability, provides an objective measure for assessing cardiomegaly and is very beneficial for monitoring progression of heart enlargement with serial radiographs. Assessment of the pulmonary parenchyma should include characterization of any abnormal patterns and localization of the abnormality.

- **Interstitial pattern** – partial obscuring of the pulmonary vessel borders
- **Alveolar pattern** – more severe interstitial with vessels completely obscured
  - Both of these patterns are the result of varying degrees of material accumulating within the interstitium or alveoli, including fluid (edema, hemorrhage) or cells (inflammation/infection, neoplasia).
- **Bronchial pattern** – due to thickening of the bronchial walls, creating the appearance of “donuts” or parallel “tram lines”
  - This pattern typically occurs in dogs secondary to allergies/inflammation (e.g. chronic bronchitis), or sometimes with infectious causes (e.g. tracheobronchitis, parasitic).
- **Vascular pattern** – prominent, enlarged pulmonary arteries and/or veins
  - Can occur due to high-output state (e.g. anemia, hyperthyroidism, fluid overload), increased pulmonary blood flow (e.g. left to right shunt), left-sided CHF, pulmonary hypertension
- **Mixed pattern** – when 2+ patterns present simultaneously; can occur with many disease states and presents diagnostic challenge

Localization of pattern distribution can also provide insight into the underlying cause of changes in the lungs. There are four main regions of distribution:

- **Cranioventral** – includes right cranial, right middle and left cranial lung lobes
  - DDX: bronchopneumonia, hemorrhage, neoplasia, lung lobe torsion
- **Caudodorsal** – right caudal, left caudal and accessory lobes
  - DDX: cardiogenic or noncardiogenic pulmonary edema, pulmonary fibrosis, neoplasia
- **Multifocal** – any lung lobe
  - DDX: fungal, protozoal, granulomatous disease, neoplasia
- **Asymmetric** – any lung lobe
  - DDX: trauma/contusions, bronchopneumonia, neoplasia

Additional diagnostics are also typically required to look for systemic abnormalities that could predispose to certain respiratory conditions, or findings that may support a specific diagnosis (modified from (Cohn, 2010)):

<b>Complete Blood Count</b>	<b>DDx to consider:</b>
○ Neutrophilia	Pneumonia, inflammation (incl ALI/ARDS)
○ Neutropenia	Sepsis, ALI, ARDS
○ Eosinophilia	Pulmonary eosinophilia, parasitic, hypersensitivity
○ Monocytosis	Fungal or histiocytic disease
○ Thrombocytopenia	PTE, sepsis, vasculitis, pulmonary hemorrhage
○ Polycythemia	Supportive of chronic hypoxemia
<b>Biochemical Profile</b>	
○ Hypoalbuminemia	PTE (secondary PLE, PLN), systemic inflammatory condition with secondary pulmonary signs

○ Hyperglobulinemia	Infectious, inflammatory disease
○ Hypercalcemia	Neoplasia, granulomatous, fungal
○ Increased ALT	Supportive of hypoxemia
<b>Urinalysis</b>	
○ Proteinuria	PTE secondary to PLN, systemic inflammation
○ Bacteruria	Sepsis

A Baermann fecal sedimentation should also be performed to look for signs of pulmonary parasitic infection. Unfortunately intermittent shedding may cause a false negative, but this test will be more sensitive than routine fecal flotation. A heartworm test should be performed if not recently done (within 6 months). Lung ultrasonography has also recently shown some promise in diagnosing cardiogenic edema, and potentially even differentiating between pneumonia, neoplasia and pulmonary edema. Ultrasound can also be helpful for obtaining FNA samples, though extreme caution must be used to ensure it is safe to obtain a sample and potential risks must be considered.

Echocardiography can be used to evaluate cardiac structure and function, and to provide support for suspected cardiogenic pulmonary edema or pulmonary hypertension. More advanced diagnostics such as transtracheal wash and bronchoalveolar lavage can be helpful for obtaining samples for cytologic analysis and culture, and in particularly challenging cases, these tests are an essential part of the diagnostic work up. CT scans are the most sensitive for detection of metastatic lesions and can also provide important information for surgical planning in certain cases (e.g. lung lobe torsion, primary lung mass). Sedated oral exams and/or fluoroscopy are indicated for patients with significant upper airway signs.

### Treatment

Treatment ultimately depends on the underlying diagnosis/cause of the cough. Some can be readily improved with appropriate therapy, however cases of tracheal collapse, chronic bronchitis, and cough due to left atrial enlargement/mainstem bronchus compression can be difficult to control. It must be relayed to owners in these situations that the cough is unlikely to resolve completely, and instead the goal is to decrease the frequency and/or severity to a point where it is tolerable for the patient and family.

### Acute/Emergency Setting

In patients with an acute exacerbation of their cough, sedation (e.g. butorphanol 0.2-0.4 mg/kg IM or IV) and oxygen can help to ease clinical signs, and also allow a more detailed physical examination and diagnostics to be performed with less stress on the patient. If there is an overt heart murmur, the patient is tachycardic and the cough has just started (or maybe worsening over the past few days, or prior CHF), CHF would be a very plausible diagnosis, so a dose of furosemide could be administered. For a first-time (potential) CHF patient, 2mg/kg furosemide IV or IM would be the typical dose of choice. For patients with a history of CHF, their previous dose of furosemide was not sufficient to control their clinical signs, so a higher dose than their current regime should be given (e.g. for a patient currently on 2mg/kg furosemide PO BID at home, consider giving 3-4 mg/kg IV or IM on presentation, and then further doses will be based on initial response). It is important to keep in mind, once a dose of furosemide is given, a true understanding of baseline renal function cannot be assessed as the urine will trend toward isosthenuria and it's likely that an increase in BUN and/or creatinine will occur. Thoracic radiographs (with flow-by oxygen) should then be performed as soon as it is reasonably safe for the

patient. In patients where bronchoconstriction is suspected, a puff of albuterol and fluticasone can be administered.

### Chronic therapies

CHF – furosemide 2mg/kg PO BID (or more depending on clinical signs, history), pimobendan 0.2-0.3 mg/kg PO BID, enalapril/benazepril (0.25-0.5mg/kg PO q12-24h), +/- spironolactone (1-2mg/kg PO q12-24h)

Pneumonia – antibiotic selection should be made based on patient risk factors, suspected underlying cause or ideally based on culture and sensitivity (especially important with lack of therapeutic response or in the presence of bronchiectasis). Reasonable first-line choice would be amoxicillin/clavulanate (20mg/kg PO BID). For recurrent cases or where there is no improvement with first-line treatment, a reasonable second-line option would be clindamycin (5-10mg/kg PO BID) + enrofloxacin (10mg/kg PO q24h). Antibiotic therapy should be continued for 2 weeks beyond radiographic resolution of pneumonia. Longer therapy may be needed for patients with bronchiectasis.

Deworming – can be done empirically depending on patient history and risk factors with fenbendazole (50mg/kg PO q24h for 3-5 days)

Fungal – itraconazole (5mg/kg PO q12-24h), or fluconazole (5mg/kg PO BID)

Chronic bronchitis - patients with chronic cough and no identifiable/rectifiable cause identified on thoracic radiographs (i.e. no evidence of pneumonia, pulmonary edema, metastatic lesions etc.), chronic bronchitis becomes a very likely diagnosis. Coughing in chronic bronchitis cases can be challenging, and sometimes frustrating to treat.

- Doxycycline trial can be considered (5 mg/kg PO BID)
- Bronchodilators
  - o Theophylline 5-10 mg/kg PO BID, Albuterol – inhaled or nebulized
- Steroids
  - o Prednisone (0.5-1 mg/kg PO BID, tapered to lowest effective dose)
  - o Fluticasone – inhaled or nebulized
- Cough suppressants
  - o Hydrocodone (0.2-0.5 mg/kg PO q6-12 hours), Diphenoxylate/atropine (0.2-0.5 mg/kg PO q8-12 hours), Butorphanol 0.5-1 mg/kg PO q6-12 hours), Maropitant (2 mg/kg PO q48 hours)

Tracheal collapse – cough suppressants are the mainstay of therapy (as outlined above). Lifestyle management can also be very helpful, including weight loss, use of a body harness rather than collar, avoid environmental triggers (such as smoke, scents etc).

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## FELINE CARDIOMYOPATHIES

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### Introduction

Cardiomyopathy is a general term used to describe abnormalities of the heart muscle. An expert panel of the American Heart Association (AHA) defined cardiomyopathy as “a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic.”<sup>1</sup> Categories of feline cardiomyopathies typically include hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), dilated cardiomyopathy (DCM), unclassified cardiomyopathy (UCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC). The AHA panel recommended that human cardiomyopathies be classified into the broad categories of “primary” cardiomyopathies and “secondary” cardiomyopathies, with primary cardiomyopathies considered to be genetic or idiopathic in origin, and secondary cardiomyopathies to describe patients with cardiac changes secondary to systemic disorders. In cats, the most common systemic disorders that can cause cardiac abnormalities include hyperthyroidism, systemic hypertension, acromegaly in addition to nutritional deficiencies and toxic insults such as anthracyclines. The precise diagnosis of primary cardiomyopathies in cats can be challenging – echocardiography is the gold standard, but there can be overlap between the phenotypes of the various cardiomyopathies, particularly in patients with advanced and end-stage disease. In a clinical setting, the stage of the disease is often sufficient to determine treatment/therapy, even when a precise classification is unclear. Staging of a cat with heart disease can be done using a modification of the ACVIM Classification Scheme outlined for degenerative valve disease:

STAGE	DESCRIPTION	TREATMENT
A	At-risk cats (Maine Coon, Ragdoll, Sphynx, DSH etc)	None
B1	Asymptomatic with early, mild or equivocal for heart disease (eg. borderline thickening of the LV, normal atrial size)	None
B2	Asymptomatic with moderate or severe myocardial changes (eg. overt thickening of the LV +/- left atrial enlargement)	Maybe – consider clopidogrel; atenolol? (see below)
C	Symptomatic (past or present) – CHF, ATE	Yes – see below
D	Refractory CHF	Yes, focus on QOL

### Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is the most common cardiomyopathy in both humans and cats, however the prevalence is much higher in cats vs. humans (estimated at 15% vs. 0.2% in humans). Hypertrophic cardiomyopathy is characterized by left ventricular (LV) concentric hypertrophy, in the absence of other predisposing factors (e.g. hyperthyroidism, systemic hypertension, (sub)aortic stenosis, acromegaly). The majority of human cases of HCM are attributed to a genetic defect in the myocardial sarcomere, with more than 1500 genetic mutations identified to date. Similarly in cats, two genetic mutations have been identified in the cardiac myosin binding protein-C gene (MYBPC3), which encodes the sarcomeric protein cardiac myosin binding protein-C. More specifically, the A31P mutation has been identified in Maine Coons, and the R820W mutation has been identified in the Ragdoll breed. Genetic screening tests are available for these defects through the North Carolina Veterinary Genetics Laboratory (<https://cvm.ncsu.edu/genetics/>). Unfortunately these genetic mutations do not

explain all forms of this disease in cats, as there are some patients with the mutation that do not have phenotypic changes of HCM, and others that do not have either mutation yet develop HCM. Cats that are homozygous for either mutation however, are at a very high risk of developing severe HCM.

The gold standard for diagnosis of HCM in cats is echocardiography. Many different echocardiographic phenotypes of HCM have been described, including mild cases of focal concentric hypertrophy, to more severe cases with significant diffuse wall thickening. Generally an LV end-diastolic wall thickness  $> 6$  mm is considered abnormal, however there is a gray zone between 5.5-6mm as the upper end of normal for LV wall thickness is considered 5.5 mm (and in some breeds, even 5.5 mm may be considered abnormal). For these equivocal/borderline cases, echocardiographic monitoring is helpful to assess for progressive hypertrophy, which would be consistent with HCM. It is important to ensure measurements are accurate and do not include false tendons that can run parallel to the septum, creating the illusion of wall thickening and leading to an erroneous diagnosis of HCM. This is particularly important if M-mode is used for measurements, so 2D images should be inspected carefully to determine if false tendon(s) are present. Another important finding that occurs in some cats with HCM is systolic anterior motion of the mitral valve (SAM). SAM causes a dynamic obstruction in the left ventricular outflow tract and can result in a significant pressure overload to the left ventricle. As a result, SAM can contribute to worsening concentric hypertrophy. Additionally, SAM causes an incomplete closure of the mitral valve, resulting in mitral regurgitation and another cause of increased left atrial pressure in these patients. When SAM is present, a diagnosis of hypertrophic obstructive cardiomyopathy (HOCM) is used.

### **Restrictive Cardiomyopathy**

Restrictive cardiomyopathy is the second most common form of cardiomyopathy in cats. There are two main forms of RCM in cats: endomyocardial and myocardial. A thick layer of fibrous tissue along the endomyocardial surface characterizes the endomyocardial form, whereas patients with the myocardial form of RCM can have some hypertrophied or thin myocytes in addition to varying degrees of necrosis and myocardial fibrosis. Both forms cause increased ventricular wall stiffness (decreased compliance) of either the left ventricle or both ventricles, resulting in secondary atrial enlargement and eventually CHF. The echocardiographic features of RCM include significant left or biatrial enlargement with normal wall thickness and normal wall motion. Documentation of a restrictive filling pattern is important to make a diagnosis of RCM, but this can be difficult to accomplish in patients that are tachycardic. Normally as the ventricles relax in diastole there is an early, passive phase of ventricular filling (E), followed by diastasis and finally an active (A) phase of diastole due to atrial contraction/atrial “kick”. Doppler can be used to measure the speed of blood flow from the atria to the ventricles during diastole. As the ventricle(s) become stiffer in cats with RCM, the E wave velocity will increase, while the A wave velocity decreases, resulting in an increasing E:A ratio ( $>2$ ). Arrhythmias are not uncommon in cats with RCM, and due to the severe atrial enlargement that can occur in these patients, spontaneous contrast +/- thrombus formation is not uncommon. In advanced cases, the wall motion can appear overtly stiff with eventual decline in systolic function.

### **Dilated Cardiomyopathy**

Dilated cardiomyopathy is a relatively uncommon type of heart disease in cats ever since the requirement for dietary taurine supplementation was discovered in 1987. Typically the left ventricle is affected with this condition, however both ventricles can be involved.

Echocardiographic features of DCM include eccentric hypertrophy of the ventricle(s) with significantly reduced ventricular wall motion, resulting in a decreased fractional shortening. The

left ventricle is considered dilated in cats with a diastolic left ventricular internal diameter (LVIDd) > 18 mm, and a systolic left ventricular internal diameter (LVIDs) > 11 mm. As a result of the decreased systolic function, the ventricular filling pressures increase, resulting in enlargement of the atria. Differential diagnoses for DCM-phenotypes include nutritional deficiency (taurine, thiamine), left-to-right shunting congenital heart disease, tachycardia-induced cardiomyopathy, or toxic insults such as anthracyclines. High-output states such as anemia, hyperthyroidism can also cause volume overload, but systolic function is usually preserved in such cases.

### **Unclassified Cardiomyopathy**

Unclassified cardiomyopathy is a bit of a controversial category of feline heart disease. It's used to describe cats with left or biatrial enlargement, which typically is indicative of underlying heart disease, but their ventricular changes do not fit into the criteria of the other forms of cardiomyopathy. For example, cats with heart rates > 150 bpm will have summation of E and A waves on Doppler interrogation of mitral inflow velocities, thus making a definitive diagnosis of RCM difficult. Therefore some cardiologists will use this category to describe cats that appear to have RCM (atrial enlargement, normal or near-normal LV wall thickness and normal LV wall motion), but where a definitive restrictive filling pattern cannot be documented. Other considerations for this category could include atrial myopathies that cause primary atrial dilation without necessarily any ventricular abnormality.

### **Arrhythmogenic Right Ventricular Cardiomyopathy**

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an uncommon form of heart disease diagnosed in cats (< 1% of cats with cardiomyopathy). The cause is unclear, however the disease seems similar to that diagnosed in Boxers and human with replacement of the right atrial and right ventricular myocardium by fatty or fibrofatty tissue. Sometimes this will extend into the left side of the heart as well. Several mutations of desmosome components have been identified in human cases of ARVC but no specific genetic mutations have been identified in feline cases to date. The vast majority of cats are not diagnosed until they progress to right-sided congestive heart failure; pleural effusion is the most common manifestation of CHF in these cats, but some will develop ascites. Arrhythmias are common with this condition – most will have some form of ventricular arrhythmias (either ventricular premature complexes or ventricular tachycardia) and many can have atrial arrhythmias such as atrial fibrillation. Echocardiographic findings include severe right ventricular eccentric hypertrophy and right atrial dilation +/- left atrial dilation. Right ventricular aneurysmal dilations may also be noted. The thinning of the walls can be remarkable, with transillumination through the heart walls reported on post-mortem exam of these hearts.

### **Ancillary Diagnostic Tests**

Additional diagnostic tests such as thoracic radiographs, electrocardiograms (ECGs) and biomarkers such as NT-proBNP can be helpful, however these are non-specific so a diagnosis of a specific cardiomyopathy cannot be made on the basis of these tests alone. Thoracic radiographs can demonstrate cardiomegaly and are the gold standard for diagnosing pulmonary edema in cats with congestive heart failure (CHF), but with the understanding that any type of heart disease can cause cardiomegaly and CHF. ECGs are helpful for characterizing arrhythmias and to some degree assessing for chamber enlargement, but again these abnormalities can occur due to any type of underlying heart disease. NT-proBNP is a cardiac biomarker that is released by the heart when it is stretched or under stress (volume or pressure overload). The Idexx Feline Cardiopet proBNP test has been most widely evaluated and using this test, a mild increase in NT-proBNP ( $\geq 100$  pmol/L) can be suggestive of occult/early cardiac

disease in cats, whereas a more significant increase ( $\geq 270$  pmol/L) in cats with respiratory signs is highly suggestive of CHF. This test should not be used indiscriminately for screening purposes, but rather performed in cats that are suspected of having underlying heart disease (eg. at-risk breeds, cats with a murmur, arrhythmia, gallop or respiratory signs). Several factors have been shown to falsely increase NT-proBNP values including systemic hypertension, chronic kidney disease and hyperthyroidism, so this must be taken into consideration when interpreting the test results.

### Clinical Findings

All forms of cardiomyopathy in cats can have a long asymptomatic (occult) phase. Unfortunately many cats will show no outward signs of their heart disease until they reach the CHF stage. Auscultation of a heart murmur can be suggestive of, but does not necessarily indicate the presence of heart disease in cats, as physiologic murmurs are not uncommon in this species. A gallop sound can be more indicative of underlying heart disease as this typically occurs due to increased ventricular filling pressures, however even these can be associated with other causes.

While some cats can have mild heart disease and remain asymptomatic, others will have progression of their heart disease leading ventricular dysfunction, either from stiffening of the ventricle with RCM or HCM, systolic dysfunction with DCM, or a combination thereof with UCM. Ventricular dysfunction results in increased ventricular diastolic filling pressure, which is translated to the atria causing atrial dilation and eventually CHF or arteriothromboembolism (ATE). Clinical signs of CHF are similar among all forms of cardiomyopathy, including tachypnea, dyspnea, lethargy, inappetance, vomiting, hiding. Coughing is an uncommon sign of CHF in cats, and more commonly is associated with asthma or heartworm disease. Cats are different from dogs in that left-sided congestive heart failure can result in pleural effusion, pulmonary edema or both. Some patients will also develop pericardial effusion. Less commonly cats can develop right-sided CHF with ascites +/- pleural effusion – this is usually associated with cases of RCM, DCM or ARVC. Clinical signs of ATE are referable to the location where the thrombus ends up following dislodgement from the left atrium – most commonly this is the aortic trifurcation, causing hindlimb paralysis (and considerable pain).

### Treatment – Asymptomatic (Stage B1-B2)

Treatment of asymptomatic cats with myocardial disease is controversial. There are no therapies that have been definitively proven to delay the onset of congestive heart failure in cats with cardiomyopathy. Beta-blockers and calcium channel blockers have been investigated for their potential beneficial effects in cats with HCM. One study showed some benefit of atenolol in reducing the severity of SAM and a slight decrease in wall thickness, whereas no significant changes were noted in the diltiazem group. Atenolol therapy in asymptomatic HCM cats without SAM did not confer any survival benefit. Angiotensin converting enzyme (ACE) inhibitors have the theoretical benefit of preventing angiotensin II and aldosterone-induced LV hypertrophy and myocardial fibrosis, but there are conflicting results among feline studies. There is also the question of when to consider starting clopidogrel therapy. The FATCAT study demonstrated superiority of clopidogrel over aspirin for cats with a prior ATE event, but it is unclear what degree of atrial enlargement warrants preventative antiplatelet therapy. The majority of cats that experience an ATE event have either moderate or severe enlargement of their left atrium, but it has been reported even in cats with mild or no atrial enlargement, so the author will generally recommend clopidogrel therapy to owners of cats with atrial enlargement.

## Treatment – Symptomatic (Stage C-D)

It is important to remember CHF is a syndrome rather than a diagnosis itself – CHF occurs secondary to underlying heart disease (usually cardiomyopathy in cats). Once a cat has progressed to the stage of CHF, the treatment plan is essentially the same for all, regardless of the underlying cardiac disease. Diuretic therapy must be instituted and cannot be discontinued. Generally cats with CHF will develop pleural effusion, pulmonary edema or a combination of both. Acute CHF patients should be given oxygen, furosemide +/- sedation (e.g. 0.2-0.3 mg/kg butorphanol IV or IM; 0.5-1 mg/kg alfaxalone IV or IM). The dose of furosemide to be used in the acute setting depends on severity of signs, current dose at home (if applicable), and (to some degree) renal function. Generally the author will give 2-3 mg/kg IV (or IM if necessary) once CHF confirmed. If there is no improvement within 30-60 minutes, this can be repeated (and reassessment of diagnosis should be considered as well). Once respiratory rate and effort are improving, then typically patients are given 1-2 mg/kg IV q4-8 hours. Higher doses or alternative medications may be needed for recurrent CHF patients. Handling should be kept to a strict minimum until patient is stable, however cats that have pleural effusion should have thoracocentesis performed as this can provide immediate improvement in dyspnea/tachypnea. The use of pimobendan in the acute setting is still somewhat controversial, but there is growing evidence that this therapy is well tolerated, even in cats with HOCM where a positive inotrope might be considered contraindicated. Clopidogrel should also be started once oral medications can be safely administered. Renal values and electrolytes should be monitored q24 hours during hospitalization. Diet change or supplementation should be implemented if a nutritional deficiency is suspected to be contributing to the underlying heart disease (e.g. DCM).

Once a patient is stabilized and ready for discharge, maintenance with furosemide, benazepril, clopidogrel and pimobendan is typically instituted. A recheck appointment should be scheduled in 1-2 weeks to monitor response to therapy with renal panel, thoracic radiographs +/- FAST thoracic scan if available in patients with historical pleural effusion. First-time CHF cats can generally be managed with the following doses:

Furosemide	1-2 mg/kg PO q 12 hours – escalating doses or additional diuretics required for recurrent CHF
Benazepril	0.25-0.5 mg/kg PO q 12-24 hours
Clopidogrel	18.75mg PO q 24 hours
Pimobendan	0.2-0.3 mg/kg PO q 12 hours

Since there is no cure for CHF, at-home monitoring is very important for owners to watch for signs of recurrence of CHF, as this is inevitable. Owners should be taught how to monitor resting respiratory rates (RRR) at home, and they should alert their veterinary care team if RRR > 35-40 bpm. For recurrent/refractory patients, a dosage increase of 25-50% for furosemide is generally effective initially, however with advanced disease and diuretic resistance that occurs with longer-term therapy, additional diuretics can be used as follows:

Hydrochlorothiazide/Spironolactone	6.25 mg PO q1-3 days (once daily dosing) in addition to current furosemide dose
Torsemide	0.1-0.3 mg/kg PO q 12-24 hours
Spironolactone	1-2 mg/kg PO q 12 hours

In patients with supraventricular tachyarrhythmias (eg. atrial fibrillation, atrial tachycardia), diltiazem (7.5-15mg/cat PO q 8 hours), atenolol (6.25-12.5mg/cat PO q 12 hours) or sotalol (0.5-2 mg/kg PO q 12 hours) are generally effective. In cats with concurrent small airway disease/asthma, sotalol should be used with caution as this medication includes non-specific beta-blockade. Additionally, beta-blockers are contraindicated in patients with CHF (though are occasionally used with caution and gradual up-titration). For patients with ventricular

arrhythmias, sotalol is the treatment of choice, though atenolol can also be effective in some cats.

### Prognosis

The asymptomatic phase is typically quite long, but can be extremely variable for cats with cardiomyopathy. In one study, the median time from diagnosis with HCM/HOCM to onset of CHF was 857 days, however the range was from 2 to 2954 days. Once the stage of CHF was reached for these cats, their survival was on average 1.3 years, with no difference between cats with HCM vs. HOCM. Cats with CHF secondary to RCM have a much more guarded prognosis, with average survival time reported to be 3.4 months (range 0.1-52 months). DCM carries a very poor prognosis, with the average survival reported as 11 days, however if the DCM is due to a nutritional deficiency then some of these cases are reversible. There is limited data on UCM in cats, but one study did report a median survival time of 925 days. Finally, cats with ARVC also have a very poor prognosis with a median survival time of 1 month. Unfortunately for all cats with heart disease, they could experience an ATE or life-threatening arrhythmia at any time, and owners should be warned of the unpredictable nature of cardiac disease.

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## CARDIAC BIOMARKERS

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### Introduction

A biomarker is a substance that is released in proportion to injury or disease from a specific organ or tissue. In order to be clinically useful, a biomarker must meet three criteria: (1) accurate test results can be obtained by a clinician in a short period of time and at a reasonable cost, (2) biomarker test result provides information that is not already available from a clinical assessment, and (3) should advance clinical assessment and decision making. Several cardiac biomarkers have been identified, however only a select few meet the criteria to be clinically relevant – these will be the focus of this lecture hour.

### Cardiac Troponin

Cardiac troponin I (cTnI) is a well-established cardiac biomarker. The cardiac troponin complex is made up of cTnI, along with troponin T (cTnT) and troponin C (cTnC). This complex helps to regulate the actin-myosin interaction involved with contraction and relaxation of cardiac myocytes. Normally cTnI is attached to the actin filament via cTnT, but with damage to the cardiac tissue, troponins are released into the extracellular space and enter circulation. It's important to note that there is also a troponin complex in skeletal muscle cells with a similar function, however the isoforms of cTnI and cTnT are distinct, allowing differentiation of skeletal troponins and cardiac troponins through the use of specific antibodies. The serum half-life of cTnI in dogs is approximately 6 hours depending on the severity of insult. Troponin can be detected in the blood within 5-7 hours following myocardial injury, with peak levels at 1-2 days post-injury, and then generally returns to baseline within 1-2 weeks (provided ongoing injury is not occurring). The half-life of cTnT is shorter (approximately 2 hours) and there is just one company with a cTnT assay available, so this is not used as frequently. The majority of tests available are for cTnI – this biomarker has been shown to increase earlier and more frequently in comparison to cTnT. There are several different companies that have an assay for measuring cTnI, however there is minimal standardization between these companies. Therefore it's important when doing repeated measures for monitoring that the same lab be used each time. Troponin molecules are highly conserved across mammals, and many human assays have been validated for use in dogs and cats, including newer high-sensitivity cTnI assays. Standard cTnI assays have a lower limit of detection of approximately 0.2 ng/mL. This level of detection is generally adequate for the significant increases in levels that occur with acute myocardial infarctions or myocarditis, but for dogs with mild to moderate degenerative mitral valve disease, cTnI levels less may be less than 0.03 ng/mL, requiring use of the high-sensitivity assay for detection. Several factors must be considered when interpreting troponin tests. First, the test is not specific to a certain type of heart disease – various types of heart disease (and some non-cardiac diseases such as GDV, pyometra) have been associated with increased troponin levels. Additionally, a normal test does not rule out heart disease, as it may be normal in the presence of mild cardiac disease. Excretion of troponin occurs via the kidney, so patients with acute or chronic renal disease may have false elevations. Finally, small increases in troponin can occur with increasing age even in the absence of (detectable) cardiac disease.

Several studies have been performed to assess cardiac troponin levels in association with both cardiac and non-cardiac diseases. Increased cTnI (indicating myocardial

injury) has been demonstrated in dogs with gastric dilatation and volvulus, pyometra, babesiosis, suspected cardiac contusions, in addition to patients with underlying heart disease including degenerative valve disease (DVD), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC) and pericardial effusion. In general, cTnI levels increase in association with the severity of cardiac injury, and higher levels are associated with more significant morbidity and mortality. For example, cats with hypertrophic cardiomyopathy (HCM) have increased levels of cTnI vs. normal cats, and higher troponin levels are associated with shorter survival times. It is important to keep in mind that an increased troponin level in a cat however, is not specific for HCM. Several studies have been performed in dogs with DVD and DCM, and troponin appears to be a reasonable complementary test to provide additional prognostic information. For instance, cTnI level of > 0.025 ng/mL was associated with 1.9 times risk for death in dogs with DVD. In Dobermans, a high-sensitivity cTnI concentration > 0.113 ng/mL had a sensitivity of 81.2% and specificity of 73.2% to identify the presence of DCM, and higher troponin levels have also been associated with higher risk of sudden death in Dobermans with DCM. The author primarily uses troponin tests when there is concern for myocarditis (e.g. new arrhythmia without any overt underlying cause), as some of these patients can have markedly increased troponin levels. Serial monitoring of troponin levels in these patients can be helpful from a prognostic standpoint - a steady decline typically indicates myocardial recovery from a one-time insult, whereas persistent elevations or increasing levels indicate ongoing myocardial damage and a poorer prognosis. Ultimately, specific guidelines for the use of troponin testing in veterinary medicine are not well established and further studies are needed.

### **Natriuretic Peptides**

Several natriuretic peptides have been identified. Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are the most commonly discussed in veterinary medicine. Both of these are primarily produced by cardiac myocytes as prohormones (proANP and proBNP). Enzymatic cleavage of these molecules separates the N-terminal (biologically inactive) and C-terminal (biologically active) fragments. C-terminal-ANP (C-ANP) and C-terminal-BNP (C-BNP) result in vasodilation and diuresis within the body, creating counter effects to the renin-angiotensin-aldosterone system (RAAS). This makes sense given that the prohormones are produced in response to myocardial stretch or stress. The C-terminal aspects of ANP and BNP have very short half-lives, so the N-terminals (NT) have been the focus for assay development. There is a test available through Antech to measure C-BNP, however the vast majority of veterinary studies have focused on NT-proBNP (available through IDEXX Laboratories). Special blood collection procedures are required for both tests to prevent degradation. Species-specific tests are required because unlike troponin, ANP and BNP are not highly conserved between species. In humans, C-BNP and NT-proBNP testing has been used to differentiate cardiac and non-cardiac causes of respiratory signs. Similar use has been described in veterinary patients. NT-proBNP increases in dogs with DVD or DCM, and in cats with HCM. Increased levels can also occur with hyperthyroidism and systemic and pulmonary hypertension, so it's important to keep this in mind when interpreting the results.

For dogs and cats with respiratory signs and chest xray findings are not conclusive to determine CHF vs. non-CHF, NT-proBNP can be somewhat helpful in these circumstances. In general, a low or normal NT-proBNP test would highly suggestive of noncardiac causes of the respiratory signs. Particularly challenging cases would be animals with mild heart disease, as these patients could have an increased NT-proBNP yet respiratory signs could be due to non-cardiac causes. The other challenge is that to



obtain a quantitative value for the NT-proBNP, the test must be sent out and if the patient is in respiratory distress, it is not possible to wait for results prior to implementing therapy. For cats, there is a point-of-care SNAP test available now through IDEXX and this is more useful for emergency situations. The SNAP test registers a level of > 100 pmol/L as abnormal and if negative, there is very little chance the cat has any heart disease. The SNAP test was able to differentiate between cats with moderate or severe heart disease with a sensitivity/specificity of 83.8%/82.6% and overall accuracy of 82.9%. A positive SNAP test increased the chances of those cats having underlying heart disease by a factor of 4.8. Important factors to remember with NT-proBNP test interpretation is that the test does not provide a diagnosis of the type of heart disease (e.g. HCM vs. restrictive cardiomyopathy vs. other) and should not be used as a replacement for thoracic radiographs and echocardiography as part of the diagnostic workup for patients with suspected heart disease. It is also not advisable to use this as an indiscriminate screening test for detecting heart disease in cats because there is a reasonably high false positive rate when the test is used in this manner. Instead it should be reserved as a complementary test in cats that are high risk (e.g. at-risk breed, murmur/gallop/arrhythmia detected, respiratory signs present). Blood pressure and thyroid status also need to be evaluated when performing an NT-proBNP test for accurate interpretation. In dogs, there is only a quantitative test available currently, and again this requires sending the sample to IDEXX. For this reason, the test is not readily used for differentiating CHF vs. noncardiac causes of respiratory signs. In asymptomatic dogs with DVD and heart enlargement (based on radiographic or echocardiographic evidence), an NT-proBNP greater than 1500 pmol/L indicates a high risk for development of CHF, so this result could be used to support closer monitoring of such a patient. NT-proBNP can also be helpful for identifying Dobermans with DCM and systolic function, however it is not useful for detecting Dobermans with the arrhythmogenic form of DCM. An echocardiogram would still be recommended with an increased NT-proBNP in order to get a diagnosis. The use of NT-proBNP for guiding therapy is controversial. There is some data to show that NT-proBNP will decrease in dogs treated for CHF, and dogs that had their NT-proBNP level decrease to < 965 pmol/L had improved survival, however definitive therapeutic targets have not been identified for guiding CHF treatment.

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## PRACTICAL APPROACH TO ARRHYTHMIAS

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### Introduction

An electrocardiogram (ECG, EKG) is the diagnostic test of choice for patients with arrhythmias. Interpretation of ECGs can be challenging, especially when not performed on a regular basis. Proper technique is important to obtain an ECG of diagnostic quality – this will make interpretation much easier! For standard positioning, the patient should be placed in right lateral recumbency, and ideally on a mat or material to insulate the patient from any potential electrical interference. Leads should be clipped distally on the limbs to minimize artifact associated with movement or respiration (white on RFL, black on LFL, green on RHL, red on LHL). Alcohol or coupling gel is then used to improve electrical conduction from the skin to the attached leads.

The goal of this lecture hour is to provide clinically relevant information on how to interpret ECGs so that appropriate treatment can be initiated (if indicated). The primary goal when treating arrhythmias (either bradyarrhythmia or tachyarrhythmia) is to control the heart rate so that adequate cardiac output is maintained.

### Normal ECG criteria (measurements performed on Lead II)

	Dog	Cat
Heart rate	60-160 bpm; up to 180-220 in toy breeds, puppies	140-240 bpm
Rhythm	Sinus, sinus arrhythmia, wandering SA pacemaker not uncommon	Sinus or sinus tachycardia
P wave	$\leq 0.4$ mV; $\leq 0.04$ sec	$\leq 0.2$ mV; $\leq 0.04$ sec
P-R interval	0.06 – 0.13 sec	0.04 – 0.09 sec
QRS	R wave 1.0 – 2.5 mV (up to 3.0 mV in larger dogs); QRS duration $\leq 0.06$ sec; MEA 40-100 degrees	R wave $\leq 0.9$ mV; QRS duration $< 0.04$ sec; MEA 0-160 degrees
Q-T interval	0.15 – 0.25 sec	0.12 – 0.18 sec
S-T segment	No elevation or depression $> 0.2$ mV from baseline; T wave $< 25\%$ R wave height, can be positive, negative, biphasic	No significant elevation or depression, T waves usually positive and $< 0.3$ mV

- Note: a normal ECG does NOT necessarily indicate a normal heart

### Conduction Disturbances

Any part of the electrical system within the heart can be subject to a disturbance or delay in impulse conduction. The normal pathway of conduction through the heart is as follows: impulses start in the SA node (has the intrinsic ability to spontaneously depolarize) → electrical activity washes through the atria (represented by P wave on ECG) → slower conduction through the AV node (allows time for atrial contraction to complete ventricular filling – represented by PR interval on ECG) → His-Purkinje system depolarizes to stimulate contraction of the ventricles (His bundle quickly divides into right and left bundle branches – represented by QRS complex on ECG) → ventricular repolarization (represented by T wave on ECG – pattern of repolarization is dictated by pattern of depolarization of the ventricles, so if there is abnormal depolarization (e.g. some cell-to-cell conduction due to bundle branch block), there will be abnormal repolarization).

### *Bundle Branch Blocks*

Bundle Branch Block (BBB) occurs due to delay or block of conduction in one of the bundle branches. When BBB is present, this means that part of the ventricle must be depolarized with cell-to-cell conduction since part of the Purkinje system is non-functional. Cell-to-cell conduction takes more time in comparison to the rapid depolarization associated with the Purkinje system. As a result, the ECG hallmark of a BBB is a markedly widened QRS complex ( $\geq 80$  ms in dog). These wide QRS complexes can be mistaken for ventricular-origin beats (eg. ventricular premature complex (VPC)), however it's important to recognize that BBB impulses still originate from the sinus node (and will have an associated P wave on the ECG), but then once the impulse reaches the ventricles, the pattern of depolarization is different. No specific therapy is required for BBB as they do not disturb the underlying sinus rhythm, nor cause hemodynamic compromise. Right BBB can be a completely incidental finding in both people and dogs (however can also be an indication of right-sided heart enlargement). Left BBB is more likely to be the result of underlying heart disease. An echocardiogram is recommended when BBB is present to evaluate for any structural cardiac changes.

### *AV Nodal Block*

1<sup>st</sup> degree and Mobitz type I 2<sup>nd</sup> degree AV nodal block are usually due to underlying vagal tone, and this can be proven by performing an atropine response test (0.04 mg/kg IV or IM). A complete response to atropine should be expected (sinus tachycardia (HR  $\geq 160$  bpm within 3-5 minutes IV,  $\sim 15$  minutes IM). Sources of high vagal tone can include intraocular disease, intracranial disease, respiratory disease, GI disease and occasionally urogenital disease. Dogs and cats are not usually symptomatic with 1<sup>st</sup> degree or Mobitz Type I 2<sup>nd</sup> degree AV block as the heart rate is usually within normal limits. Diagnostic work up to evaluate for a source of high vagal tone is indicated, and treatment would typically be aimed at the underlying cause. Treatment to speed up the heart rate with 1<sup>st</sup> degree and Mobitz type I 2<sup>nd</sup> degree AV block is not usually required as the heart rate typically remains within normal limits. Stimulants such as theophylline or hyoscyamine could be considered if deemed necessary. Mobitz type II 2<sup>nd</sup> degree, high grade 2<sup>nd</sup> degree and 3<sup>rd</sup> degree AV nodal block are usually due to structural changes (fibrosis) within the AV node in dogs, but can occur secondary to underlying cardiomyopathy in cats. Patients with 2<sup>nd</sup> degree AV block often don't show clinical signs, and sometimes with a sufficiently high escape rate (e.g. 50-60 bpm in dogs, 110-130 bpm in cats), even patients with 3<sup>rd</sup> degree AV block may be asymptomatic. An atropine response test is usually negative in these more advanced cases, indicating that high vagal tone is not the cause and instead it is a primary problem within the conduction system. Therefore medical management is not usually effective and a pacemaker would be required.

### *Sick Sinus Syndrome/Sinus Node Dysfunction (SSS/SND)*

SSS/SND is a disease of the conduction system that is thought to be degenerative in nature. The sinus node is most commonly affected, however other parts of the conduction system can also be affected, resulting in delayed rescue rhythms (escape beats). ECG features of SSS/SND include periods of sinus arrest (sometimes lasting 6-8 seconds). Various definitions of sinus arrest are used, but typically would be considered to occur when either a pause in atrial activity lasts  $> 2$  normal R-R intervals, or  $> 2$  seconds. In normal patients, junctional escape (40-60 bpm) or ventricular escape (20-40 bpm) rhythms should truncate pauses of this duration, however due to widespread conduction disease with this condition, these are often delayed allowing for much more dramatic pauses. Patients with SSS/SND may also have periods of supraventricular tachycardia, which can make it difficult to determine whether it is the prolonged pauses or rapid rhythms that are resulting in clinical signs (syncope). An atropine response test should be performed to test for influences of vagal tone and determine whether there is residual conduction system function when vagal tone is abolished. Some dogs may have a partial

response to atropine, but particularly in breeds that are predisposed to this condition (e.g. West Highland White Terriers, Miniature Schnauzers, Dachshund, Cocker Spaniels), this does not exclude the diagnosis of SSS/SND. This condition is particularly important to diagnose prior to anesthesia as patients with this condition can have profound bradycardia with induction of anesthesia (and often can't be rescued with atropine). A pacemaker is typically required for patients with syncope, and sometimes antiarrhythmic therapy (e.g. diltiazem) is required following pacemaker implantation if they have persistent supraventricular tachyarrhythmias as well.

### *Supraventricular tachycardias (SVT)*

This broad term is used to describe any tachyarrhythmia that originates from the SA node, atria or AV node/junctional region. Sometimes therapy is aimed at terminating the arrhythmia in order to allow the sinus rhythm to resume control of the heart rate, however this is not always possible. Rate control (treatment aimed at decreasing the number of impulses reaching the ventricles) is an alternative therapeutic approach and is usually successful in improving clinical signs and cardiac output. Vagal maneuvers can be attempted in patients with SVT – the goal of this is to increase vagal tone to slow conduction through the AV node. While these are often not successful in veterinary medicine, they are worth attempting, and multiple regions can be stimulated simultaneously: (1) ocular pressure – gentle pressure on both eyes, (2) carotid sinus massage – ideally palpate carotid pulse behind the angle of the jaw, then apply pressure and move fingers in craniocaudal direction, (3) diving reflex – sudden immersion of the head in cold water (not usually attempted).

Not all SVTs require emergency termination of the tachyarrhythmia, however if the patient is symptomatic and unstable (lethargic, syncopal, hypotensive), then usually the first-line treatment option in the acute/emergency setting would be diltiazem (0.15-0.25 mg/kg IV slowly; can be repeated). This is a calcium channel blocker that has minimal effect on vascular tone and inotropic state, which is beneficial when it is unknown whether the patient has any underlying heart disease. Diltiazem primarily works at the AV node to slow conduction. Verapamil is an alternative calcium channel blocker and works well to block conduction through the AV node. Unfortunately this drug has much more profound negative inotropic and vasodilatory effects, both of which could be very detrimental if the patient has underlying cardiac disease and therefore this drug is rarely used. Injectable beta-blockers such as esmolol would usually be the second-line choice. Esmolol (0.1-0.5 mg/kg IV) is short acting, so a CRI (0.025-0.2 mg/kg/min) can be used if this medication is successful in terminating the arrhythmia and then oral agents such as atenolol or sotalol can be used for long-term management at home. Because beta-blockers are more profound negative inotropes, the use of these medications is contraindicated in the presence of congestive heart failure. If the above options have failed, then a class I antiarrhythmic agent could be considered (e.g. procainamide, flecainide). These agents can cause vasodilation and hypotension and should be administered slowly (over 5-10 minutes). Flecainide should not be used in patients with underlying structural heart disease, particularly with systolic dysfunction. Finally, amiodarone (class III antiarrhythmic) is not used very commonly, however if all other attempts have failed and the patient remains tachycardic and unstable, then this can be considered. Standard IV amiodarone contains a solvent that can cause mast cell degranulation, so pretreatment with diphenhydramine +/- dexamethasone is often given. There is a newer formulation (Nexterone) that does not contain this solvent and seems to be well tolerated in dogs.

For chronic management (and for SVTs that do not require emergent termination of the rhythm), the choice of drug usually depends on what the patient responded to in the acute setting. A slow up-titration may be necessary to maintain cardiac output while gradually decreasing the heart

rate. Again, return to sinus rhythm is not always necessary and often just slowing down the overall heart rate (i.e. ventricular response rate) is sufficient and a more realistic goal. Historically the goal was to attain a maximum ventricular response rate of 160 bpm (on ECG in hospital), however more aggressive rate control is likely to be associated with improved survival based on recent human and canine studies. Intermittent Holter monitoring is really ideal in order to assess average heart rate over a 24-hour period and to ensure the heart rate is adequately controlled at home. Diltiazem (0.5-2mg/kg PO TID) is the most commonly used chronic therapy in the author's practice. Sustained-release formulations can be used for BID dosing (e.g. Dilacor XR – 1.5-6 mg/kg PO BID), however finding the appropriate version (i.e. capsules containing pellets/tablets rather than beads) of these medications to allow dosing in dogs has been challenging recently. Digoxin (0.002-0.005 mg/kg PO BID) can be added to diltiazem for improved rate control (particularly for patients with atrial fibrillation), but this medication does not work very well on its own. Caution should be used when using digoxin in patients with renal dysfunction as this can lead to accumulation and toxicity. Atenolol (0.2-1.0 mg/kg PO BID) is another good option for treating SVT. Occasionally this medication will be added to diltiazem for improved heart rate control, however very gradual up-titration must be performed with careful monitoring of blood pressure and markers of cardiac output as this combination can cause hypotension due to significant bradycardia and depression of systolic function. Sotalol (1-3 mg/kg PO BID) can also be considered as it has some beta-blocker function, but also has some class III effects. Oral amiodarone works really well especially for refractory cases, however it can cause significant side effects and careful monitoring of several bloodwork parameters is necessary. As a result, this medication is not used very commonly. Dronaderone is a newer class III antiarrhythmic agent that functions similarly to amiodarone, but seems to have a much lower risk of side effects. This agent can have negative inotropic effects and this needs to be taken into consideration for patient selection. Finally, oral class I antiarrhythmic medications such as propafenone and flecainide are options for refractory cases, but must be used very cautiously with systolic dysfunction.

#### *Atrial fibrillation*

While this is technically considered an SVT, this is one of the most common arrhythmias diagnosed in dogs and deserves a separate review of management. Many of these patients will present on an emergency basis with rapid heart rates (220-300 bpm). Usually this arrhythmia occurs in dogs and cats with significant underlying cardiac disease, and for this reason, conversion to a sinus rhythm is typically not a realistic goal. Even in patients with "lone" atrial fibrillation (absence of underlying heart disease), attempting cardioversion is controversial. Therefore, the focus is usually on RATE control (keeping the ventricular response rate normal) rather than RHYTHM control (i.e. converting to a sinus rhythm). A similar approach to therapy is used as outlined for SVT, however gradual slowing of the heart rate is usually performed because the tachycardia in these patients with significant underlying heart disease is somewhat compensatory and likely helping to maintain cardiac output. Diltiazem is usually the first line drug, and the combination of diltiazem and digoxin has been shown to provide superior rate control for dogs with atrial fibrillation. Beta-blockers such as atenolol and sotalol are less commonly used because these agents have more profound negative inotropic effects, and this could be detrimental to patients with significant underlying heart disease or congestive heart failure.

#### *Ventricular arrhythmias (malignant ventricular premature complexes (VPCs) and ventricular tachycardia (VT))*

The goals of antiarrhythmic therapy for ventricular arrhythmias are (1) improve hemodynamics and (2) prevent sudden death. Trying to eliminate all ventricular ectopy is not realistic and actually has been shown to be more detrimental in humans. The most important therapeutic

goals are to decrease the rate, duration and malignancy (e.g. fast couplets or runs, R on T, polymorphisms) of the ventricular tachyarrhythmia. Holter monitors are the ideal way to assess for treatment success. Holters are also helpful for ensuring the arrhythmia does not worsen with therapy, as it is important to remember that any antiarrhythmic medication can also have proarrhythmic effects. Not all ventricular arrhythmias require treatment - if there are just single VPCs or the rhythm is not fast (e.g. accelerated idioventricular rhythm/"slow VT") and the patient appears otherwise stable, then monitoring may be a reasonable approach. However very fast VT or a fast coupling intervals of VPCs increase the chances of a beat occurring during the "vulnerable period" and induce ventricular fibrillation, so these would be more likely to warrant treatment. Additionally, polymorphism is thought to be a higher risk in comparison to monomorphic VT. There are also some breeds that have a higher risk for sudden death with VT such as Doberman Pinschers, Boxers, Rhodesian Ridgebacks, German Shepherds, etc. so therapy should be more strongly considered if there are concerning arrhythmias in these breeds.

In an emergency setting, a precordial thump can be attempted – this is where a carefully aimed (and firm) blow with the fist is applied to the chest over the heart with the aim to interrupt a life-threatening rhythm. There is certainly controversy as to whether this technique should be used, so generally this technique is reserved for situations where defibrillation is not available.

The primary drug used for acute/emergency treatment of ventricular arrhythmias in dogs is lidocaine. It is administered as an IV bolus (2mg/kg), and this can be repeated if necessary (up to 8 mg/kg within a 10 minute period, or less if any neurologic signs noted). If the rhythm terminates with bolus therapy, then a CRI must be started quickly (50-80 ug/kg/min). Reasons for lack of efficacy of lidocaine include hypokalemia, incorrect diagnosis (e.g. wide SVT or accelerated idioventricular rhythm rather than true VT), or insufficient dose/too much time between boluses so therapeutic levels not attained. If lidocaine is not effective and the above reasons have been ruled out, then the next drug of choice would be procainamide IV. Beta-blockers can be considered, and sotalol is typically administered if safe to do so in the author's practice (keeping in mind that the combination of procainamide and sotalol can result in prolonged QT interval, though this seems to be less of a concern in dogs in comparison to humans). Magnesium can be helpful in some cases as this acts as a membrane stabilizer within the myocardium (0.15 mEq/kg diluted and given over 15 minutes; can be repeated). Finally, class III antiarrhythmics can be used with similar precautions as outlined above in the SVT section.

For chronic management, many patient factors are considered in selecting a drug (or combination of drugs). Sotalol is often the drug of choice for ventricular arrhythmias. In patients with significant myocardial dysfunction however, the beta-blocker component could exacerbate clinical signs. In these cases, the author will often use a very low dose of sotalol (or atenolol) in combination with mexiletine (5-8 mg/kg PO BID-TID). Procainamide is also an option, but it has been more difficult to obtain this medication in oral form. Amiodarone, propafenone or flecainide can also be considered in refractory cases with consideration of their respective side effects.

References available from the author on request

## Feline Tooth Resorptions (TR)...When to Extract and When to Crown Amputate?

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### Tooth Resorptions (TR)

Tooth resorptions have previously been called cervical neck lesions, feline odontoclastic resorptive lesions (FORL), feline resorptive lesions, and odontoclastic resorptive lesions). The correct terminology is a TOOTH RESORPTION. The prevalence is from 28.5% to 72.5%.

The lesions begin in the cementum, and can occur anywhere on the root surface of the tooth. Therefore, they do not necessarily have to be on the cervical area. These lesions progress into the dentin and pulp cavity of the tooth on both the crown and the root.

Clinical impressions can sometimes have a gingival enlargement of inflamed granulation tissue that actually covers the crown defect, smaller defects at the gingival margin, and /or no visible crown lesions and clinical signs. Pets can exhibit excessive drooling, anorexia, weight loss, halitosis, dysphagia, and dropping food while eating. Some lesions are asymptomatic as they are below the gumline without any exposure to oral bacteria or salivary fluids.

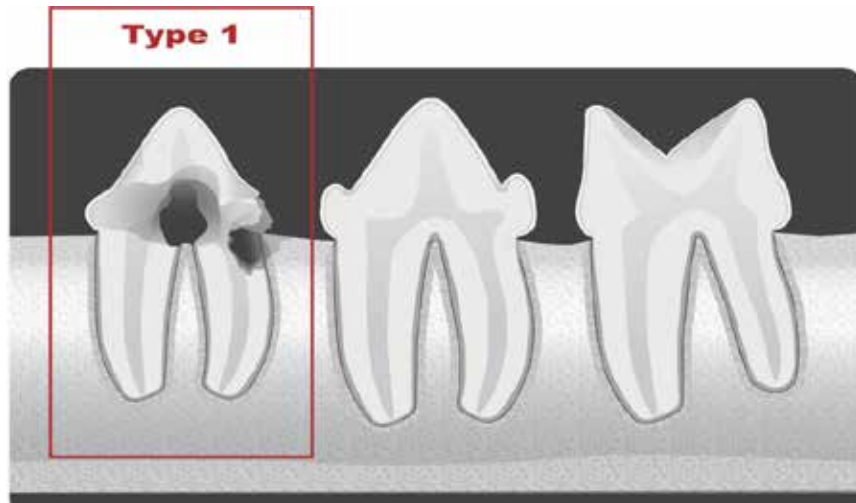
Cause is not fully understood but we do know that lesions are created by odontoclasts which start resorption of mineralized tooth surface on several regions of the root simultaneously. We don't know what the stimulation for this event is. It has been speculated that diet, minerals, water sources, periodontal disease, inflammation, Vitamin D and abfraction as causative agents, but many have been disproved with research. We still do not know the exact etiology.

### Types of Tooth Resorption (TR1, TR2, TR3)

Before distinguishing between Type I and Type II TR, one must understand tooth anatomy. The key between the two types is the presence or absence of the periodontal ligament (PDL). The PDL is the distinct space around the tooth root that separates itself between root and the white line of wall of the alveolus called the lamina lucida. The PDL is basically the shock absorber of the tooth and this prevents the tooth from being ankylosed into the surrounding bone.

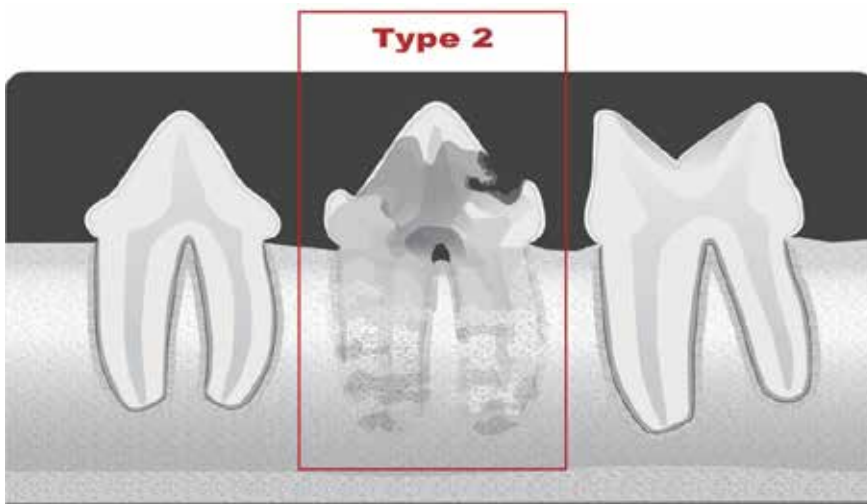
The only way to differentiate TR1 and TR2 is via dental radiography. Therefore, one should not undertake treatment of a cat with tooth resorption without the benefit of visualization of the PDL to discern whether complete extraction versus crown amputation and intentional root resorption is performed.

TR1: Characterized by radiographic evidence of a periodontal ligament space around the entire root with the resorptive lesion affecting the neck of the tooth and the crown. The radiographic density of the root of the affected tooth is the same as that of a non-affected tooth root.



REF: AVDC.org

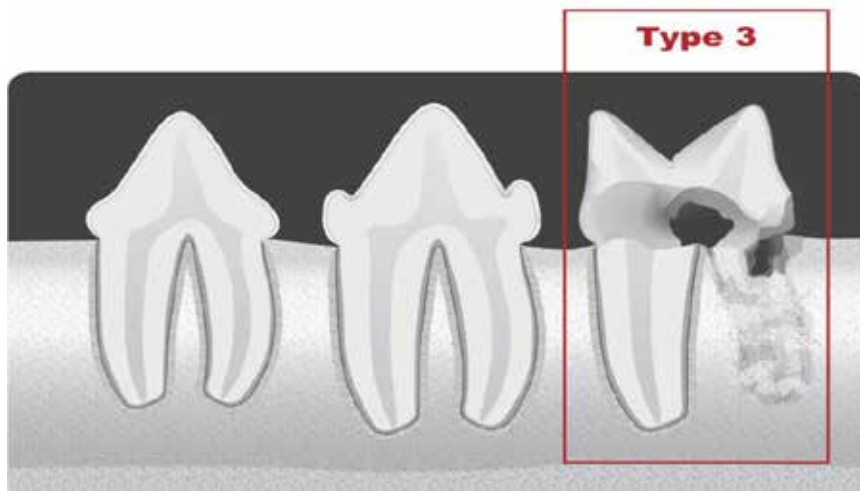
Type 2: The tooth root has undergone significant resorption and have a different opacity. There is a loss or a narrowing of the lamina lucida (PDL space). The root structure is basically blending in with the surrounding alveolar bone. The crown may or may not be affected.



Ref: AVDC.org

TR3: There is evidence of both TR1 and TR2 in the same tooth. This is very common with the mandibular 1<sup>st</sup> molar tooth.





Ref: AVDC.org

In a recent study published in 2009, Type I TR is 8 times more likely to be associated with periodontitis compared to Type 2 TR. In a different study, supereruption is also present of the canines in many instances. Another study indicated that purebreds are more likely to have TR lesions, 60% of all cats with TR had Type 2 and 40% had Type 1.<sup>ii iii iv</sup>

#### Treatment options for Tooth Resorptions

Type I tooth resorption teeth must be extracted. However, as mentioned earlier, the only way the clinician will know if it is in fact a Type I or Type II is via dental radiography. Surgical flap (envelope) is recommended and removal of buccal bone with a round bur (#2) helps facilitate extraction. Making a moat around each root tip helps and this is done via the use of a #1/2, #1 round bur or via a #170 crosscut bur on a high speed handpiece. After removal, radiographs must be performed to insure all tooth root structures are removed. Surgical closure is with a 5-0 chromic gut or Poliglecaprone 25 (Monocryl or Monomed) with an FS2 needle. Tension free closure is essential.

Type II tooth resorptions can be treated differently provided radiography has been performed to confirm this type. Ideally, extraction is needed, however, crown amputation and intentional root resorption can be performed if the following criterion are met:

1. Roots must clearly be Type II
2. There is no evidence of endodontic disease
3. No evidence of existing periodontal disease
4. The cat does not have evidence of concomitant gingivostomatitis. (especially caudal mucositis)

With Type II treatment, it is important to follow the patient radiographically every 6-12 months. This is to follow the progression of intentional root resorption and also look for other evidence of tooth resorption in the mouth, as this can occur.

<sup>i</sup> Stepaniuk KS. Feline Tooth Resorption. Fundamentals Series Veterinary Dental Forum. 2011.

<sup>ii</sup> Hennes F. Feline tooth resorption in a colony of 109 cats. In J Vet Dent. Sept 2008; 25(3); 166-174

<sup>iii</sup> Type ITR and type 2 TR identified to be significantly different manifestations of TR. J Vet Dent. Winter 2009; 26(4); 211.

<sup>iv</sup> Mincheff C. Recognition and Treatment of Tooth Resorptions. Fundamental Series Veterinary Dental Forum 2010. Boston, MA.

## A Step-by-Step Approach to Surgical Extraction of a Maxillary 4<sup>th</sup> Premolar and 1<sup>st</sup> Molar Tooth

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The premise for any dental extraction of flap procedure is to appreciate the anatomy as well as the surgical principles necessary for this procedure to be accomplished.

Before any dental extraction should be undertaken, it is ESSENTIAL that a veterinarian has prior appreciation of the root structure of the tooth being removed. The only way this can be accomplished is via dental radiography. While many times complete removal of the affected tooth can be accomplished without radiography, can the veterinarian absolutely claim that there are no tooth shards, bone fragments, or tooth root structures remaining? Failure to completely remove the tooth in entirety without any remnants is tantamount to malpractice. In many clinical situations, existing endodontic disease causing apical periodontitis (abscess) will remain unless the entire tooth root is removed.

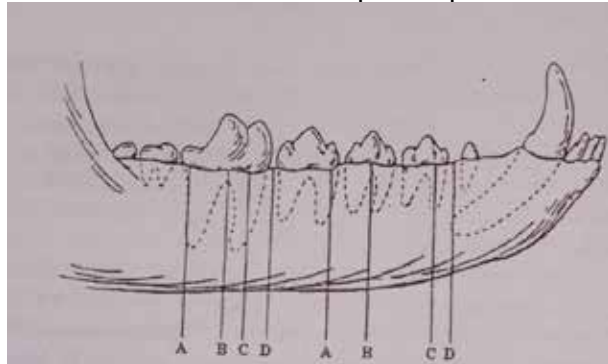
The flap procedure is an important consideration, as the veterinarian must choose a flap that allows exposure of the affected tooth and TENSION FREE CLOSURE without disruption of the neurovascular component of the gingiva. The ENVELOPE flap is considered with marginal amount of buccal or labial bone is needed to be removed to accomplish this extraction. This flap, as with others, must extend beyond the mucogingival line to allow for unattached gingiva to be released and facilitate a tension-free closure.

Vertical releasing flaps (single or bilateral) are mucoperiosteal flaps that allow the veterinarian full exposure of the tooth to be removed, thus allowing more buccal bone to be removed to facilitate extraction.

Three (3) Principles of flap surgery are as follows: If a vertical release is to be made, make it on the adjacent tooth at the appropriate LINE ANGLE, not the tooth to be removed. This is important in that you do not want your suture line over the alveolus, but rather over healthy bone (no suture line over a defect). Secondly, preserve blood supply and thirdly, selection of instruments that minimize tissue damage.

### Line Angle definition

This is an imaginary vertical line forming the intersection of two adjacent vertical dental surfaces. This denotes a specific position on a tooth and are important surgical landmarks.



Wiggs, RB, Lobprise HB Veterinary Dentistry Principles and Practice

The flap exposure is best accomplished after extraction by excision of the mucoperiosteum. Utilization of a scalpel blade nick followed by sharp dissection of this is made to allow the flap to fully cover the surgical extraction site. Any marginal tissue that looks irregular and inflamed should be removed.

4-0 poliglecaprone-25 with a reverse cutting-edge needle is chosen as the oral suture material. This suture is rapidly absorbed and the reverse cutting edge is used to minimize inadvertent tissue tears. Since it is a monofilament suture, it pulls freely through tissue, has good knot security, stays in the mouth longer than chronic gut, and does not require removal. Simple interrupted patterns (2-3 mm apart) are needed.

Scalpel blade selection should be via a #15 or #15C blade. Rarely, a #11 surgical blade is needed. Proper instrumentation is needed to adequately remove large teeth. It is recommended to have a winged elevator kit (2-8) which allows one variability in selection of elevators. Periosteal elevators are ESSENTIAL for adequate flap preparation and a couple of sizes are needed for both the small dog and cat as well as for large breeds.

In order to facilitate extraction of teeth, a high-speed dental unit is a must. One cannot adequately remove large single rooted or multirooted teeth without the benefit of a good high-speed unit. BEFORE undertaking any dental extractions, the veterinary would be wise to consult with his/her distributor for a unit. There are many good units in the marketplace, and each has their own benefit or even restriction. It is recommended, however, to go the extra mile and purchase fiberoptics in your high-speed handpiece. Swivel-tip handpiece is also recommended.

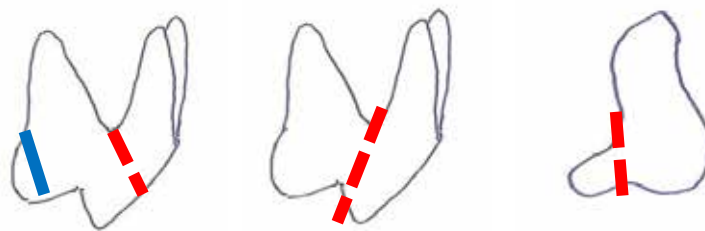
Bur Selection: #330, #1/2, #1, #2, #4, #6 round; 701 cross cut; medium grit football diamond; medium grit round diamond (I recommend surgical length burs in addition to the regular length)

Bone graft materials aid in filling the open socket with bone and connective tissue rather than allowing it to collapse or granulate in with soft tissue. Collapse of the socket can further alter facial features slightly because there is no longer any crown structure to support that portion of the upper lip, which is now vulnerable to trauma by the mandibular canine tooth. (for maxillary canine extraction). If there is marginal amount of ventral cortex remaining from extraction of a mandibular 1<sup>st</sup> molar tooth, a graft is warranted. Graft of mandibular canine teeth is also recommended if stability of the bone is needed. However, there is no substitute for a good clot formation in the site to help promote new bone formation.

Tips for extractions of the following teeth

#### **Maxillary 4<sup>th</sup> premolar tooth**

- Single or bilateral diverging incision. Make sure you DO NOT make incision over tooth you are extracting
- Careful of the parotid papilla if making a bilateral diverging incision
- Remove buccal bone with #4 or #6 round bur
- Moat with same burs you use in canine
- Section all 3 roots prior to removal, regardless if tooth is mobile or not



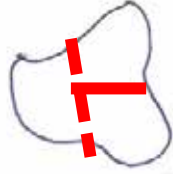
- Remove caudal crown cusp adjacent to the maxillary 1<sup>st</sup> molar tooth to facilitate straight-line luxation/elevation. Care needed to avoid contacting the 1<sup>st</sup> molar tooth
- Remove middle section of tooth if need be to allow straight line removal (OR amputate crowns for better visualization of crowns to facilitate extraction)
- Remove interradicular bone between the mesiobuccal root and the palatal root (after removal of the mesiobuccal root)
- Make a moat around the palatal root carefully with very fine cross cut (#170, 701, or 699) or round (1/4-1/2 round)
- Surgical burs are a must in difficult extractions so keep some on board (#2, #1, #1/2, 701)
- Alveoplasty needed using a medium grit football diamond.
- Avoid neurovascular bundle at infraorbital foramina
- Release the underlying periosteum and ensure that there is a tension-free flap.
- Take post-operative radiographs to ensure no tooth root remnant or chard of bone is present. A skyline view may be needed to look for possible root tips remaining.
- Surgically close with 4-0 poliglecaprone-25 with a reverse cutting edge needle in a simple interrupted or cruciate pattern with at least 4 throws. Simple continuous pattern may be used if the surgeon feels comfortable with this surgical pattern. Smaller pets (<5 kg use 5-0 poliglecaprone-25 with a P3 needle).

### Maxillary 1<sup>st</sup> molar tooth (and the maxillary 2<sup>nd</sup> molar tooth)

Depending on whether this tooth is to be surgically removed alone, or in conjunction with the maxillary 4<sup>th</sup> premolar tooth is important. If the 4<sup>th</sup> premolar is to be surgically removed a well, then I would extend the envelope flap caudally with a vertical release on the mesial aspect of the 4<sup>th</sup> premolar tooth (as described above)

- Envelope flap extending from the furcation of the maxillary 4<sup>th</sup> premolar extending distally past the 2<sup>nd</sup> molar tooth. (*Author's suggestion is to avoid a vertical releasing incision between the 4<sup>th</sup> premolar and 1<sup>st</sup> molar as there is a tendency of losing the attached gingiva on the distal aspect of the 4<sup>th</sup> premolar tooth*)
- Release the gingival mucosa carefully
- Make sure you have 4-handed dentistry by utilizing a technician to retract the gingival mucosa after the release
- Use a #2 or #4 round OR a #330 pear bur to remove the buccal bone on the mesial and distal buccal roots. **DO NOT USE A CROSS CUT BUR AS THIS CAN TRAUMATIZE THE CHEEK GINGIVAL MUCOSA.** Remember the buccal bone is very thin so delicate bone removal is needed to avoid inadvertent root transection or trauma.

- Section the tooth between the mesial and distal roots as well as at the mid cusp extending mesially to distally using a #330 pear bur (see below). This sectioning technique is also recommended for the maxillary 2<sup>nd</sup> molar tooth.



- Gently luxate or elevate using the appropriate # elevator or luxator. It is recommended levering the distal root first to allow for full visualization of the mesial and distal buccal roots. Using a #4 or higher winged elevator is advised for levering the palatal root.
- Once the roots are removed alveoplasty must be performed.
- Release of the underlying gingival mucosa via the buccal and distal aspect to allow for a tension-free closure. The distal release is important and care is needed to avoid traumatizing underlying vessels.
- Take a post-operative radiograph to confirm all roots out and no bone chards. A skyline view is also helpful if you suspect root remnants present.
- Close with 4-0 poliglecaprone-25 with a reverse cutting edge needle in a simple interrupted or cruciate pattern with at least 4 throws. Simple continuous pattern may be used if the surgeon feels comfortable with this surgical pattern. Smaller pets (<5 kg use 5-0 poliglecaprone-25 with a P3 needle).

Recommended texts:

Verstraete FJM, Lommer MJ. Oral and Maxillofacial Surgery in Dogs and Cats (2<sup>nd</sup> ed)

Bellows J. Small Animal Dental Equipment, Materials, and Technique (2<sup>nd</sup> ed)

Lobprise HB, Dodd R. Wiggs's Veterinary Dentistry Principles and Practice (2<sup>nd</sup> ed)

## The Local, Regional, and Systemic Complications of Periodontal Disease

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### Overview

Periodontal disease (gingivitis, periodontitis) is a common chronic, oral, infectious, and inflammatory problem of dogs, cats and humans. The destruction of periodontal tissue is a result of the host's response to a shift in bacterial presence in the mouth.<sup>1</sup>

### Objectives

The objectives of this lecture are to educate the practitioner on the local and systemic effects of periodontal disease. Based on this new knowledge, a more aggressive approach to early periodontal disease should be made to prevent the negative cascade of events that lead to bone loss and organ changes. Understanding the potential correlation between systemic consequences and periodontal disease will help the practitioner lean towards a more aggressive proactive treatment response versus a reactive one.

### Bacterial colonization and transition to unfavorable (Gram – anaerobes) pathogens (Pathophysiology)

It takes 1000 X antibiotics to effectively kill bacteria in sulcus. Therefore, PD treatment should be relegated to mechanical removal vs. antibiotic killing the bug. Within a few hours post cleaning, bacteria coat the pellicle-coated tooth surface. Initially, there are G+ facultative bacteria (Strep, Actinomyces) in the mouth. Over time, bacteria colonies adhere to pellicle via ADHESIONS. Plaque then matures through growth of species, and colonization.

There is a transition from early (aerobic) to highly O<sub>2</sub>-deprived environment of which G- anaerobes predominate. Secondary bacteria do not initially colonize tooth surfaces but adhere to cells of bacteria already in plaque (coaggregation)

Catalase + *P. gingivalis* is considered key periodontopathogen in cats and dogs and recognized as *P. gulae*.

*Pellicle* is the initial phase of plaque development This is derived from saliva, crevicular fluid and bacteria along with host tissue cell production and debris. Bacteria colonize on tooth surface within a few hours post prophylaxis. It takes 2-3 days for plaque to mineralize to form calculus. Calcium salts more likely to be deposited in alkaline environment (dogs and cats vs humans). The gram-negative anaerobes secrete thiols, which are a sulfur compound. This sulfur compound gives us the noxious rotten-egg smell of periodontally-compromised patients. Finally, the plaque bacteria are up to 500,000 times more resistant to concentrations of antiseptics than would kill singular bacteria.<sup>2</sup>

As mentioned earlier, calculus formation occurs within a day or two after a professional scaling and polishing. It is composed of 70-90% inorganic material, which are predominately various calcium salts. Calculus adheres to the tooth surface via adhesion of a dental pellicle to the tooth enamel. However, it may attach via irregularities in the surface of the tooth such as enamel hypocalcification or enamel etching via aggressive scaling and minimal polishing of the tooth surface.

It is VERY important to understand that calculus in itself is relatively non-pathogenic. While it may be a local irritant, it is not the primary cause of periodontal disease. It is the SUBGINGIVAL PLAQUE that extends under the free gingival margin and into the area of the gingival sulcus. However, supragingival plaque may protect the underlying subgingival plaque that has formed by providing protection and this formation can cause reduced oxygen availability. Once the subgingival pocket forms, removal of the supragingival plaque and calculus have marginal effect on the arresting of periodontal disease associated with the subgingival plaque. *Therefore, the visualization of a clean crown surface in itself does not constitute a healthy periodontium...subgingival scaling and treatment must accompany this event. The false narrative of anesthetic-free dentistry thus gives the client a false sense of a 'healthy, clean tooth' which could be far from the truth. Underlying periodontal pockets must be identified and treated to complete a true ATP/COHAT.*

### **Host Response (Pathobiology)**

"The host response to bacteria and periodontal infection requires expression of a number of bioactive agents, including proinflammatory and anti-inflammatory cytokines, growth factors, and enzymes that are the result of the activation of multiple signaling pathways."<sup>3</sup>

The local inflammatory response results in: Increased blood flow, enhanced vascular permeability, and influx of cells from the peripheral blood to gingival crevice. (This is triggered by histamine, bradykinin, PGE<sub>2</sub>, and nitric oxide). Neutrophils are attracted and there is also an increase in monocytes and macrophages, as well as T and B cells.<sup>3</sup>

Once the immune and inflammatory processes are initiated, MMP (matrix metalloproteases) are involved in stimulating inflammatory cells. MMP's are released by macrophages, leukocytes, and fibroblasts. This, along with other mediators, lead to bone loss (osteoclast stimulation).<sup>3</sup> Treatment of periodontal disease at the local level helps reverse/arrest this osteoclastic activity. Systemic involvement can also help control PD as well.

### **Predisposing factors that contribute to periodontal disease**

A rough tooth surface (especially subgingival) will attract plaque and is one of the most common predisposing factors of periodontal disease. Other potential factors to be shown are enamel hypocalcification, tooth trauma (uncomplicated crown, uncomplicated crown-root fractures), crowding and rotation of teeth (seen with small breed dogs), malocclusions, persistent primary teeth (retained puppy teeth), gingival growths and foreign bodies, and radiation therapy.<sup>2</sup>

The non-oral predisposing factors can also contribute to periodontal disease as well. An exaggerated immune response by the host (dog and cat) to plaque bacteria can lead to an aggressive response, which can lead to secretion and formation of pro-inflammatory, and inflammatory responses, which can lead to periodontal ligament and bone destruction. Conversely, a patient with a weak immune response may not be able to mount an effective host response to subgingival microorganisms, which can lead to a more rapid and severe periodontal response.<sup>3</sup>

*Corticosteroids* that are given exogenously, or endogenously (Cushings DX) can decrease the immune response via a variety of methods. These can be via suppression

of neutrophil activity, blocking the acquisition and expression of CMI, and decreasing circulating lymphocytes, to name a few.<sup>1</sup> While in humans, administration of cortisone and ACTH appear to have no effect on the incident or severity of gingival or periodontal disease, there is an adverse effect on bone quality and physiology. The periodontal ligament and gingival connective tissue experience capillary dilation and engorgement as well as degeneration and reduction of collagen fibers in PDL and increased destruction of the PDL tissue associated with inflammation.<sup>3</sup>

*Diabetes mellitus* has been proven to be deleterious to gingival health and the main reason is that DM increases the susceptibility to infections and decreased wound healing. Having a higher concentration of glucose in the gingival crevicular fluid may affect bacterial populations. There is altered collagen synthesis as well as delayed renewal of diseased collagen. An unregulated diabetic state can result in the production of accumulated glycation end products (AGE's), which are responsible for many of the severe diabetic complications.<sup>2</sup>

In a study of humans, individuals with severe periodontitis at the baseline exam had a greater incidence of worsening glycemic control over a 2-4 year period than did those without periodontitis at baseline. In that study, periodontitis was known to have preceded the worsening of glycemic control. Also, periodontitis has been associated with the classic complications of diabetes.

Other disease processes such as leukemia can exacerbate periodontal disease by the direct leukemic infiltration, increased gingival bleeding, and increased oral ulceration.<sup>1</sup> All leukemia's tend to displace normal components of bone marrow with leukemic cells. Anemia results in poor tissue oxygenation, making tissue more friable and susceptible to breakdown. A reduction of normal WBC's in the circulation leads to a poor cellular defense and an increased susceptibility to infection.<sup>3</sup>

Patients undergoing chemotherapy should have their oral cavity thoroughly cleaned and examined. Proper dental therapy has been shown to markedly decrease the oral complications associated with cancer therapy.<sup>2</sup>

### **Local/Regional consequences of periodontal disease**

The primary result of periodontal disease is the loss of alveolar bone resulting in a compromised tooth. However, periodontal disease can have more reaching effects within the oral cavity and surrounding organs.

*Pathological fractures* – Pathological mandibular fractures can occur with any dog or cat with advanced periodontal disease. This is most commonly associated with smaller breed dogs due to a combination of anatomical and physiological events. First, smaller sized pets have a higher incidence of periodontal disease due to crowding and competition for surrounding bone space. Smaller breed pets also have a mandibular 1<sup>st</sup> molar that is larger size wise to the mandible compared to larger breeds that have a higher % of mandible/tooth ratio.<sup>2</sup> Vertical bone loss during PD can be problematic, as this loss can extend to the apex of the tooth, which is close to, or at the ventral cortex. Any mild stress on the mandible, such as chewing on rawhides or toys, can cause a tooth fracture. Iatrogenic fracture secondary to advanced PD can also occur from over-manipulation of the mandible, using a spring-loaded mouth gag, or attempting to extract a periodontal compromised tooth without first radiographing the mouth to assess bone status.



*Oronasal fistula (ONF)* – This condition can occur with any breed pet and even in cats, but is most relegated to dachshunds and basset hounds. While an oronasal or oroantral fistula may occur with any maxillary tooth, the maxillary canine tooth is most affected. A vertical bone loss defect due to advanced PD on the palatal aspect of this tooth leads to this event. Clinical signs of ONF may include sneezing, nasal discharge, halitosis, and even anorexia.<sup>2</sup> However, in many instances, the owner is unaware of the pathology. Probing of the palatal aspect of the canine tooth is essential in confirming a diagnosis. (Make sure the probe is not deflected due to subgingival calculus giving the DVM/tech a false probing reading).

*Class II Perio-endo lesion* – This occurs when apically progressing periodontal disease pathogens enter the root canal system at the apex and causes tooth death and secondary apical periodontitis. Therefore, a classic vertical bone loss component is noted as well as apical lucency, giving the interpreter two separate but connected disease processes.

*Ocular manifestations of PD* – A well-documented article in the JAAHA showed the link between periodontal disease and ocular pathology. *Orbital manifestations* such as rapid onset and progression of exophthalmos, protrusion of the nictitating membrane, resistance to retropulsion of the glob through closed eyelids and severe pain when opening the mouth. One may see rapid development of unilateral chemosis or conjunctival hyperemia, with or without fever or anorexia. Moderate to increased IOP may be noted secondary to obstruction of orbital venous drainage by an orbital abscess. Teeth associated with ocular manifestations are the maxillary 4<sup>th</sup> premolar tooth and 1<sup>st</sup> or 2<sup>nd</sup> molars. In cats, ocular pathology may be a result of a maxillary canine tooth as well.

*Periorbital manifestations* – facial and periorbital swelling or a draining tract ventral to the palpebral fissure is noted. Blepharitis of the lower eyelid and concurrent draining tract ventral to the palpebral fissure are noted. Ptosis or lagophthalmos may occur if chronic or recurrent.

*Conjunctival manifestations* – Conjunctival hyperemia, chemosis, or purulent ocular discharge.

*Nasolacromal* – This can occur most commonly as a sign of chronic involvement of the maxillary canine tooth causing formation of a draining tract through the skin overlying the lacrimal canaliculi or the proximal nasolacrimal duct.<sup>4</sup>

*Osteomyelitis* - Periodontal disease and other dental infections are the most common causes of mandibular and maxillary osteomyelitis. This necrotic bone does not respond to antibiotic therapy and aggressive removal of the necrotic bone is necessary for surrounding tissue to heal.<sup>2</sup>

*Oral Cancer* – In humans, there is a link between chronic periodontal disease to the increased risk of oral cancer. This is most likely due to chronic inflammatory state that exists with periodontitis and the significant inflammation (chronic) that acts as a confounder to the body's defenders.<sup>2</sup> The association between chronic periodontitis and squamous cell carcinoma in cats has been postulated as a potential increased risk factor.

### **Systemic health as it relates to periodontal disease**

While this no true cause and effect with the relation to PD and systemic health at this time, there are possible influences by PD in humans: (Arthrosclerosis, CHD, MI,

Cerebral vascular accident, diabetes mellitus, low birth weights, COPD, acute bacterial pneumonia)<sup>3,4</sup>

A study in dogs showed the following: "...shows that periodontal disease is associated with histological changes in the kidneys, liver, and myocardium. The study demonstrated an association between increased severity of periodontal disease and increased histological changes in these organs."<sup>1</sup>

These histological changes were:

*Liver*- mild increase in lymphocytes and plasma cells in the liver parenchyma. ALT and ALKP levels were NOT elevated in these dogs.<sup>1</sup> Bacterial invasion of the liver has been shown to increase parenchymal inflammation and portal fibrosis. One study showed a significant relationship between PD burden and increased inflammation in the hepatic parenchyma.<sup>2,5</sup>

*Heart*- papillary muscles showed degeneration of small and medium vessels<sup>1</sup>. Studies showed increase in the incidence of AV valve changes with perio disease in dogs. One report even showed the risk of endocarditis at approximately 6-fold higher for dogs with stage 3 periodontal disease, compared with the risk for dogs without periodontal disease. Vegetative endocarditis lesions, when cultured, showed that many of the same pathogens inhabit the oral cavity. Historically, these lesions were blamed on previous dental procedures but recent studies report that the majority of endocarditis cases in humans and dogs were not associated with a recent dental procedure, but rather by normal activities such as eating and chewing.<sup>2</sup>

*Kidney* – mesangial thickening in the glomerulus and lymphoplasmacytic inflammation in the renal interstitium.<sup>1</sup> Chronic infectious and inflammatory diseases have been shown to contribute to formation of immune complexes in the kidneys, resulting in glomerulonephritis.<sup>2,6</sup>

Periodontal disease and mortality – Studies have not been conducted on dogs or cats as of yet, but in humans, a number of studies suggest increased mortality rate is associated with inflammatory periodontal disease. In a human study of 804 people with dentition, for those subjects averaging more than 21% alveolar bone loss at time of baseline, the risk of dying during the follow-up period was 70% higher than for other subjects. Amazingly, alveolar bone loss increased the risk of mortality more than smoking (52%).<sup>3</sup>

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## Those Darn Oronasal Fistulas..How to Avoid Them and How to Treat Them

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Oronasal fistula (ONF) formation can occur either iatrogenically or due to underlying periodontal pathology. This lecture will review the main causes of this as well as the treatment options available. The rate of surgical failure has not been established, but recurrence is frequent (up to 65% in humans). (1)

### CAUSES OF ONF

The main cause of ONF formation is due to Stage 4 periodontal disease (>50% bone loss), occurring either on maxillary incisors, maxillary canines, or premolars. Inflammatory cells within the gingival sulcus and underlying periodontal pocket cause a localized reaction leading to osteonecrosis. As the maxillary and incisive bone is thin, this apical migration can lead to communication to the underlying nasal passage.

Clinical signs are sneezing after eating or drinking, nasal discharge, and face rubbing. Chronic exposure of the nasal cavity to oral rubbing may occur. With regard to chronic ONF, rhinitis, destruction of nasal turbinates and subsequent pneumonia may occur. (2)

This is most common with the palatal aspect of the maxillary canine teeth. Unfortunately, technicians and DVM's do not probe the palatal aspect carefully and this pathology continues to occur unabated. Dental calculus on the palatal aspect of the canine that has an ONF may cause the periodontal probe to be deflected, giving the tech/DVM the illusion the pocket is not that deep.

In addition to Stage 4 periodontal disease, the other main cause of ONF's is iatrogenic due to poor flap design when extracting a maxillary canine tooth. The tooth may already have an ONF and the surgeon did not adequately close the defect due to tension on the surgical flap. In addition, a maxillary canine that is surgically removed for other reasons (complicated crown or crown/root fracture) may not have an ONF, but aggressive elevation and luxation may cause an iatrogenic ONF. Then a poor flap design then contributes to the presence of an ONF that would require additional oral surgery.

Finally, trauma to the maxilla can lead to ONF. Therefore, when any maxillary trauma occurs, the DVM needs to probe and assess for any possible communication with the nasal passage and oral surgery must be done when the patient is stabilized to correct this defect.

### TREATMENT OF ONF

The basic tenets of oral surgery must be adhered to when repairing an ONF. Those tenets are as follows:

- Tension-free flap
- Sutures must be over bone and not over the defect
- Removal of epithelial tissue on the margins
- Base of the flap must be wider than the ONF site
- Vertical releases must extend beyond the mucogingival line
- Periosteum release
- Absorbable suture (4-0 with FS2 needle or 5-0 with P3 needle Poliglecaprone-25)

Preoperative radiographs should be performed to rule out any possible nasal foreign body or tooth root remnant present. Performing a regional nerve block with 0.5% bupivacaine + 0.1 mls 0.3 mg/ml buprenorphine will provide analgesia for up to 72 hrs.

### **VESTIBULAR FLAP**

A wide envelope or diverging vertical flap should be made. This flap must be approximately 2.5X the width of the existing defect, and the vertical component **MUST** extend beyond the mucogingival (MG) line. This is critical as the unattached gingiva must be released to allow for adequate tension-free flap. Removal of epithelial tissue is needed either via a scapel blade or a medium grit football diamond bur. Palatal tissue must be removed to allow for the palatal tissue to be overlying bone, and not the defect. Surgical closure in an interrupted pattern with the above-mentioned suture. (2, 3)

### **DOUBLE-LAYER FLAP**

When a defect is large or chronic, or insufficient tissue is present to provide a single vestibular flap, a double layered flap may need to be incorporated. However, in narrow faced dogs with bilateral ONF's, this procedure may not be able to be performed bilaterally. The palatal edge of the defect provides the base or hinge, with releasing incisions advanced palatally and joined across to provide an adequate closing flap. The dorsal aspect of the defect is to be preserved and is the anchor for the edge of the palatal flap that is flipped over and secured. The edges of the flap are sutured and the buccal mucosal flap, already having periosteal release, then overlies this palatal flap and is sutured over the harvest site.(2,3)

### **FREE AURICULAR CARTILAGE AUTOGRAFT**

An article written by Soukup, Snyder and Gengler in the JoVD (26:2; 2009) reviewed a clinical case of utilizing a free auricular graft to repair a maxillary canine ONF. The edges of the defect are freshened, and epithelial tissue removed, and a compartment is made to receive the cartilage graft. Scapha cartilage is then surgically removed via a U-shaped skin incision to harvest the cartilage. The donor graft is then sutured between the oral mucosa and hard palate with a vest-over-pants pattern to secure the graft to the oral mucoperiosteum. (1)

### **POST OPERATIVE CARE**

Care must be made to avoid rubbing the face and traumatizing the surgical site. Oral antibiotics should be reserved for those systemically compromised patients, or if the patient has secondary rhinitis or pneumonia. Anti-inflammatory agents and analgesics are recommended post operatively and should be administered after reviewing pre-anesthetic blood work to insure there is no deleterious action of those medications. Softened food for 14 days with no hard chews or toys is needed.

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## WHEN AND WHEN NOT TO USE BONDED SEALANTS

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### Overview

There are indications for the use of bonded sealants in veterinary dentistry. However, it isn't without restrictions and warnings. This lecture will review what clinical presentations are favorable for placement of bonded sealants, how it is placed, how long it is effective, and what contraindications there are for placement of them.

### Objectives of the Presentation

- Understand and appreciate dentin anatomy (gross and microscopic)
- Understand types of tooth fracture and which one(s) are ones to receive dentin bonding
- Types of dentin bonding sealants (unfilled resins)
- How to apply bonded sealants
- What to do going forward after the bonded sealant is placed
- When to avoid bonded sealants

### Discussion

Tooth fracture can occur with many different results. Enamel fractures are the least traumatic tooth injury, requiring smoothing loose enamel and either placing an unfilled resin (bonding agent) or composite restoration. The fact that there is underlying dentin that has not been exposed provides internal protection from bacterial ingress to the pulp tissue. Exposed dentin can lead to oral sensitivity. These dentin tubules contain fluid that communicate with nerve endings, and anything causing fluid contraction or expansion, such as thermal change, results in sensory nerve stimulation. People feel this pain when a dentist blows cold air on their sensitive tooth causing sensitivity. When dentin has been compromised, bacteria could ingress through the dentin micropores and kill the tooth. The roughened surface from a tooth fracture serves as a plaque-retentive substrate, fostering bacterial (plaque) adhesions. When a tooth fracture involves the pulp cavity being exposed, the tooth will become non-vital within 48 hrs without proper therapy. We will be focusing on the latter two tooth fracture scenarios.

**Causes of tooth fracture** include chewing on hard materials such as deer/elk antlers, long bones, and other commercial hard materials. Tugging by pet owners can also cause tooth fracture, especially maxillary and mandibular canine teeth. As the temporomandibular joint does not allow for lateral movement of the mandible, the occlusal forces related to chewing do not allow for a sliding effect between the mandibular 1<sup>st</sup> molar and the maxillary 4<sup>th</sup> premolar tooth, thus contributing to tooth fracture. With both of these teeth having occlusal points, one can see how a hard object being chewed can contribute to a tooth fracture.

**Dental radiography** – Any dentin fracture should be radiographed. Visualization of the width of the root canal of the roots is needed and look at contralateral tooth for comparison. Multiple views may be needed for complete visualization of all roots, especially the maxillary 4<sup>th</sup> premolar tooth. Assess the apex of each root as well. **ONE MUST NOT PLACE ANY DENTIN BONDING AGENT ON ANY TOOTH WITHOUT FIRST EVALUATION VIA DENTAL RADIOGRAPHY.** (The author highly recommends having a dental radiography textbook for review)

**Dentin exposure** – Under electron microscopy, cut dentin has the appearance of swiss cheese. The size of dentin pores is larger than oral bacteria, therefore, bacterial could ingress through dentin via the canal system and penetrate the vital pulp. Under most conditions, hydrostatic forces within the dentin canals will prevent this bacterial ingress. It is via this method that many dentin fractures still have vital pulp tissue.

It is these tooth fractures that placement of a bonding agent will help seal those dentinal tubules and prevent further bacterial ingress. The addition of a composite restoration further protects the underlying dentin.

## Materials Overview

**Composite Resins:** These materials are most commonly used for restoration of tooth defects. It is best to select a small number of these products in order to become proficient using these materials. It is very important that the manufacturer's instructions be followed. Composites are made of a resin matrix, inorganic filler (usually various sizes of silica particles) and a coupling agent to bond the resin and filler particles together. Hybrid composite resins contain large and small silica particles and have the advantage of providing strength and a very smooth finish. Depending on the product, composites come in a variety of shades/colors and may be "flowable" (thick liquid in a syringe, fewer silica particles for strength) or "packable" (higher concentration of silica particles for greater strength) consistency.

**Glass ionomer:** Conventional glass-ionomer (GI) cements have a large number of applications in dentistry. They are biocompatible with the dental pulp to some extent and are composed of a mixture of glass and an organic acid. Glass ionomers are tooth-colored, do not wear as well as composite resin fillings and the cavity preparation for a glass ionomer filling is essentially same as a composite resin. One of the advantages of GI compared to other restorative materials is that they can be placed in cavities without any need for bonding agents. In humans they are generally considered good materials to use for root caries and for sealants. Newer GIs require a curing light for setting just like composite resins. Compomers and Resin-modified Glass Ionomers are restorative materials comprised of combinations of glass-ionomer and composite resin.

**Bonding agents** are materials used to bond the composite resin to the tooth and typically are supplied in a liquid form. These liquid adhesive resins are applied to the tooth prior to the restoration composite to make a dental composite filling material adhere to both dentin and enamel. In veterinary dentistry, they are also used as a bonded sealant applied to uncomplicated tooth fractures. Bonding agents are often methacrylates with some volatile carrier and solvent like acetone. They may also contain diluent monomers. For proper bonding of resin composite restorations, dentin should be conditioned with acids to remove the smear layer, created during mechanical treatment of the tooth with dental burs.

**Adhesive resin** creates a "hybrid layer" consisting of a collagen network exposed by etching and embedded in adhesive resin. This layer is an interface between dentin and adhesive resin and the final composite restoration. Modern dental bonding systems typically include a primer and adhesive in a liquid form. They can be either premixed for single liquid application or individually applied. For convenience, composite resins systems may be purchased in kit form. A kit may include acid etchant, the bonding system, application brushes, various shades of composite resin and a color shade selector. A special light-curing unit must be used to cure these products.

## Bonded sealants for uncomplicated crown fracture in the dog and cat

In human's restorative dentistry commonly involves treating caries or decay. Caries are uncommon in veterinary patients, dental trauma and tooth fractures are very common. Tooth fractures are often painful, and treatment varies depending on the fracture type encountered. Complicated fractures with exposed pulp never heal spontaneously and should receive endodontic treatment or be extracted. Uncomplicated fractures with exposed dentin have historically not been treated, as it was felt they were not a problem. This may or may not be true, as exposed dentin is often associated with pain from two different pathways; nerve stimulation and bacterial migration.

The enamel thickness in dogs and cats varies from .1 to 1mm in thickness. Dental fractures frequently result in the loss of this thin layer of enamel and expose the underlying dentin tubules. The tubules contain fluid that communicates with nerve endings, and anything causing fluid contraction or expansion, such as thermal change, results in sensory nerve stimulation. People feel this pain because when a dentist blows cold air on their sensitive tooth with dentin exposure they can relate to this phenomenon. Dentinal tubules are also large enough to allow bacteria to migrate through the tubules and into the vital pulp tissues. The abscessed teeth that result are some of the more severe endodontic cases seen. Additionally, the rough surface associated with a fracture serves as a plaque-retentive substrate, which fosters calculus formation.

A tooth does have some capacity to heal itself when the dentin is exposed, by forming a layer of reparative dentin. This reparative dentin is characterized by a tan to brown color visible in the dentin. Once this process occurs, the fluid filled tubules no longer communicate with nerves and pulp chamber. During this healing process, the tooth is uncomfortable and at risk for developing endodontic infection.

Instead of waiting on the tooth to potentially 'heal itself', one may consider smoothing the tooth fracture by performing an odontoplasty followed by a placement of a light-cured acrylic bonding sealing. This bonding immediately seals dentin tubules, helping to prevent infection, decrease pain, and accelerate the healing process. This process is similar to the sealant placed on a child's tooth via a pit and fissure lesion. Once the sealant is placed, it may provide approximately 3-12 months of protection. After that time, the tooth will have either healed itself internally or become non-vital (dead). All treated teeth should be re-radiographed in 6-12 months to ensure no pathology associated with death of the tooth or infection is developing. This treatment is generally only done once to each fracture site, and most useful on fresh fractures. Since the age of a fracture is difficult to determine, it is recommended that all fractures that do not visibly show evidence of reparative dentin.

### Materials need for bonded sealants

- High speed delivery system with integrated water supply in handpiece.
- Oil and moisture-free air source (either from high speed delivery system\* or compressed air)
- Conical white stone or medium and fine diamond burs
- Latch-key contra angle for low speed motor system
- Finishing discs and mandrel for low speed system (coarse to extra-fine)

- 37% phosphoric acid etch
- Bond-1, 3M Adaper-single Bond or other dentin bonding agent or unfilled resin
- Microbrushes and disposable wells
- Light curing gun (LED preferred)
- Dental radiograph system (CR or DR)

### Step-by-step procedure

- Obtain a baseline radiograph image. Make sure all roots are completely visible
- Use a conical white stone or medium fine diamond bur attached to the high speed handpiece, smooth the fractured dentin and enamel, removing rough edges. Conservative smoothing is needed. DO NOT PENETRATE THE PULP CAVITY
- Additional smoothing can be used with finishing discs attached to a mandrel on the reduction gear contra angle. Start at course (black) progressing to very fine (pink). Rinse with water between using each disc.
- Apply 37% phosphoric etch to the fracture site for 15-20 seconds, rinse for 15 seconds, then gently air dry. DO NOT DESSICATE. The etched area will appear to be slightly frosted when over dried. Once etched is removed, avoid contamination.
- Using a well and microbrush, place a thin layer of unfilled resin (Bond-1) on the smoothed fracture site, and light cure for 15-20 seconds, depending on the light cure gun used. The unfilled resin penetrates and bonds the prepared dentin and etched enamel to provide a sealed surface.

### Contraindications for dentin bonding

- Complicated crown or crown/root fracture
- Uncomplicated crown root fracture with secondary periodontal disease
- Caries
- Tertiary dental already in place

### References/Suggested Reading

Craig RG, Powers JM, et al. Dental Materials Properties and Manipulation, 8<sup>th</sup> Ed. 2004. Mosby.

Sakaguchi RL, Powers JM. Craig's Restorative Dental Materials, 13<sup>th</sup> Ed. 2012. Elsevier.

Robertson TM. Art and Science of Operative Dentistry, 5<sup>th</sup> Ed. 2006. Mosby Elsevier

Ahmad I. Predictable Aesthetic Dental Restorations. 2006. Blackwell.

Wiggs RB, Lobprise HB. Operative and Restorative Dentistry, In Veterinary Dentistry Principles and Practice. 2006.



## **ADDING EXOTICS TO A SMALL ANIMAL PRACTICE**

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So often you hear, "I can get a new bird/lizard for \$10." How then, can you justify to yourself and to your clients the cost of a \$300 procedure? The fact is that many exotic pets are free (Mommy, I found this snake!) or very little (you can buy a mouse for less than \$5 in most pet stores). Since these pets have little intrinsic physical cost value, many owners assume that their care should also be discounted. An understanding of the nature and importance of the human-animal bond, AND, the extra time/expense in training and equipment needed to care for these unique pets will help the novice exotic practitioner properly invoice for their services without having to feel "guilty" for charging for their worth.

Learning exotic pet care takes extra time and training. Providing that care also, generally, takes extra time and often times specialized equipment. If anything, I think that veterinarians should be charging more for their exotic medical services.

The popularity of exotics continues to grow. With high density living and the ever present need for that special human pet bond, people are turning to the non-traditional species that require less space and maintenance.

People like the concept of "one stop shipping." Adding exotics to your practice will not only satisfy your current dog and cat clients that also have exotic pets, but, once the word gets out, it will also bring in a new client/patient base.

### **Let your Investments pay off**

American Airlines is the largest airline company in the world. They have over 600 airplanes in their fleet. If a 767 is in the hanger for maintenance and not flying, AA is not making any money with it. It is only when those planes are in the air filled with passengers that the income is flowing.

That same analogy can be used for your empty cages, radiology unit, surgery room, dental drill, etc. You get the picture.

If you have a dog and cat practice, but are only using your dental unit on one or two patients a day, and it is left idle for the rest of the day, that is income lost.

### **Getting Started**

You MUST learn the normal if you want to be able to recognize the abnormal animal. As an example, there are over 12,000 species of reptiles. You certainly don't need to learn them all, I never have and have no intention to ever do so, but, you need to at least learn the most commonly kept species.

If the interest is not there on your part, perhaps you can bring in a new veterinarian that has experience with exotics. This is a great marketing/PR tool that the hospital can use to help promote their willingness to provide services to a constantly changing client base.

Caution should be taken not to bring on a novice that needs mentoring if you don't have the experience to give it or are not willing to provide it.

Not only does the veterinarian need experience, but, so does the support staff – this includes the entire hospital roster from the receptionist to the technicians to the kennel staff. If a receptionist tells a bird client to fast their pet for 12 hours prior to surgery as they might for a dog or cat, it could be a disaster.

There are a number of excellent references available. See the list after my lecture on "Survival Guide: The Dos and Don'ts of Managing Exotic Species in your ER."

## Equipment

Most modern dog and cat practices have the majority of equipment that will be needed to incorporate exotics. As mentioned in the intro, that equipment that you have purchased or is on a lease, is not generating any income if it isn't being used.

There will be a small amount of specialty equipment that is required. The extent that you will need will depend on how involved you want to get. For instance, I recommend starting out with wellness care for exotics. This will require a minimal investment. However, for example as you advance and move into diagnostic and therapeutic endoscopy, you will obviously need much more specialized equipment.

In addition to a reference list in the previously mentioned lecture, I also have a minimal equipment list that is needed to provide basic care.

## Services Offered

As mentioned, when starting out, walk before you run. Begin with well care for exotics like annual exams, vaccines, routine fecals and deworming, nail trims, wing trims, etc. This will give you the chance to learn as you go. Remember, it is critical to know the normal!

If your hospital is not set up to hospitalize patients outpatient care may be all you can offer. You will still need specialized, escape proof, temperature and humidity controlled cages whether it is for just day care or overnight hospitalization. If you only offer outpatient care you will need to make arrangements for a 24hr facility that will monitor your critical patients overnight.

For some exotic clientele a house or field call service may be more appropriate. For instance, clients with aviaries or large reptile breeding collections appreciate your availability to come to them rather than bring individual animals to your office.

On the same lines as house calls is striking a relationship with pet stores. Many of these pet outlets offer live pets and often they are in need of medical care. Of course, the cost of the care must be weighed against the potential income from sale. In some instances, euthanasia may be the most appropriate option, as distasteful as it may be.

Some veterinary offices choose to offer pet products. I think it is important that if you are recommending a specific product, one that is not readily available at pet stores, you should have that product available to the client. That provides both convenience to the client and ensures that the client will comply with your recommendations rather than substitute items with a lesser quality.

## Basic Hospital Reuirements

A room with low ceilings (9' or less), no ceiling fans, no open topped cabinets or any under cabinet recesses where a small rodent or reptile could escape to and hide. Nets, towels, blankets, soft cotton and heavy leather gloves should all be available. Exam tables should be fitted with non-slip surfaces.

A gram scale (1 g increments) is mandatory for evaluating the patient and calculating dosages. O<sub>2</sub> should be available in the exotics room. Included in this would be an induction chamber, various sized facemasks and cuffed and un-cuffed endotracheal tubes. Other useful equipment includes penlights, otoscopes, oral speculum (soft and lighted bi-valve), medical tape, paper tape, band cutter, Dremel with diamond blade, nail trimmers and either 1 cc or U-100 syringes for dosing small patients.

Because of the greater potential of zoonotic diseases with exotic pets appropriate disinfectants and established protocols are necessary.

25 and 27g syringe needles and small 24 – 26 g IV catheters may be needed. IO catheters are available and useful, but, spinal needles can be used if needed.

Proper anesthetic monitoring equipment such as capnograph, pulse oximeter, Doppler are essential. However nothing replaces a neonatal or pediatric stethoscope and an attentive technician.

Most of the necessary skills needed to draw blood or place an IV catheter are skills used in dogs and cats. See the web references below for some excellent training videos on these procedures in exotic pets.

In house chemistry analyzers capable of processing small samples and patient-side monitoring equipment, such as a glucose meter, are essential. Having a technician that can read exotic differentials is valuable but not essential.

Lacrimal cannulas are useful for rabbit conjunctivitis and 3-3.5 Fr Slippery Sam urinary catheters are more useful for ferrets than the standard Tom Cat urinary catheters.

If the hospital facility is going to be hospitalizing exotic patients it must have proper caging and food available for these animals. There are several companies that make assist feeding formulas for herbivores, omnivores, piscivores and carnivores (e.g. Oxbow Hay Co., Lafeber Co.).

There are a handful of medications that are “go to” for exotics. Regarding fluids, the standard fluids used in small animal medicine will all apply. Commonly used antimicrobials include the aminoglycosides, fluoroquinolones, chloramphenicol, tetracyclines, metronidazole, ceftazidime and injectable procaine penicillin. Again, not every drug is safe in every exotic! It is imperative to look up the drug in the formulary before dispensing it to a patient.

### **Pricing Strategies**

Unfortunately, it is common, especially among exotic pet veterinarians, to minimize care and costs in order to save the client money and reduce the risk of rejection of services. It is not a good idea for a veterinarian to ever minimize the care recommended because of a perception of the client’s financial wherewithal or any rationalization that takes cost into consideration. Clients visit veterinarians to receive the best possible care and recommendations. It does not necessarily serve the client or the veterinarian for cost to play a part in development of the initial medical recommendations. It is the client’s right and responsibility to take care of his or her own finances. A client may elect to refuse any services that are unwanted after the value of said services has been established. A veterinarian should consider the best quality care only when developing a medical plan, and during that initial component of development, cost is irrelevant.

It is clear however, that for a veterinarian to be able to practice the best medicine possible and make the exotic practice profitable, the client must be willing to pay for the care. As with any type of veterinary medicine, it is critical to understand your client's perspective including motivations and valuations. Again, our overriding goal in the exam room should be to get the client to accept in full, an estimate of charges to provide the animal with the best possible care. All that is required to obtain this result is to ensure the client believes that the intrinsic cost of the pet is not the same as the value that pet brings to the human-pet bond. In other words, value needs to be established.

A knowledgeable technical staff member should speak with the client and form a relationship before the doctor enters the room. The doctor should perform an exam, and discuss what care the exotic patient needs and how that care will benefit the patient. The doctor should not discuss money because this is a waste of a doctor’s time and puts a cloud in the client’s mind about the purity of the doctor’s motivation.

The doctor should write the chart and construct an estimate of charges.

The original staff member will discuss with the client what the doctor recommends and how that care will benefit the patient. Options for lesser care should not be given. The relationship

previously established fostered trust for this exchange and the repetition of the doctor's recommendations will provide greater understanding as well as an increased perception of correctness of the plan.

### **Marketing**

Once you decide to incorporate exotics into your practice let people know. Include pictures of exotic pets in your logo, your stationary, business cards, advertisements, etc.

Identify someone on your staff with Social Media experience, and if one does not exist, make an effort to hire one. Start with a simple but easy to use, mobile friendly website. Develop campaigns on Facebook, Google, Yahoo, Bing, Twitter, etc.

Collect e-mail addresses from all of your clients. E-mail marketing is easy and inexpensive and can be targeted to specific clients and pets.

Keep your website and FB page up to date and fresh. Don't overdue it, but, keep it active. Include both educational and fun posts. The more appealing it is the more it will be shared. That is free word of mouth!

Be cautious, however, as the Internet can be cruel. Just as you can get excellent promotion and marketing from it, one bad review can do severe damage. It is imperative that you monitor it on a regular basis and respond accordingly.

Join pet clubs, specialty organizations (e.g. House Rabbit Society) and get active in your community. Make an effort to write short articles for your local paper and offer to give talks to the Rotary, Kiwanis or other groups in your practice area.

### **Summary**

Whether a client only pays \$5 for a mouse, adopts a bunny out of a basket in front of the grocery store for free, or finds a snake out in a field, there is an established human-pet bond. This is evidenced merely by the fact that they made the effort to bring that pet to the veterinarian for care. In no way should the veterinarian discriminate between one of these clients with their relatively "low cost" pet vs. a person that paid \$2500 for a pedigree show dog. The human-pet bond is priceless. As such, the services you offer and the prices you set should reflect the level of training that you have and the quality of care that you offer.

### **References:**

The following is a very basic list of periodicals, websites and conferences that are beneficial to the novice exotic animal practitioner:

#### **General -**

[www.veccs.org/facility-certification/requirements](http://www.veccs.org/facility-certification/requirements) (for exotic patients)

Carpenter J. Exotic Animal Formulary. 5th ed. Elsevier; 2019.

Radiology of Rodents, Rabbits and Ferrets - E-Book: An Atlas of Normal Anatomy and Positioning (note – this is available as an e-book)

Atlas of Diagnostic Radiology of Exotic Pets, Small Mammals, Birds, Reptiles and Amphibians. Rubel, GA et. al. W B Saunders Co., Philadelphia. 1993. (note – this is out of print, but, if you can find it grab it!)

Manual of Exotic Pet Practice. Mitchell MA, Tully TN. Elsevier, St. Louis. 2009.

Mayer J, Donnelly TM. Clinical Veterinary Advisor: Birds and Exotic Pets. Elsevier; 2012.

#### **INTERNET -**

Veterinary Information Network

[www.Oxbowvetconnect.com](http://www.Oxbowvetconnect.com)  
[www.lafebervet.com](http://www.lafebervet.com)

### **Periodicals –**

The Veterinary Clinics of North America – Exotic Animal Practice.  
 Journal of Exotic Pet Medicine  
 Journal of Avian Medicine and Surgery  
 Journal of Herpetological Medicine and Surgery

### **Reptiles -**

Divers S, Stahl S. (in) Mader's Reptile and Amphibian Medicine and Surgery. 3rd ed. Elsevier; 2018.

Mader D, Divers S. Current Therapy in Reptile Medicine and Surgery. Elsevier; 2013.  
 (Note - Much more advanced, than 2<sup>nd</sup> ed. Not as practical for a quick clinical reference in an ER setting)

### **Rabbits, Rodents, Ferrets and other Small Mammals**

Quesenberry K, Carpenter JW. Ferrets, Rabbits, and Rodents, Clinical Medicine and Surgery. 3rd ed. Elsevier; 2012. (4<sup>th</sup> edition in the works)

Oglesbee B. Blackwell's Five-Minute Veterinary Consult: Small Mammal. 2nd ed. Wiley-Blackwell; 2011.

### **Avian**

Speer BL. Current Therapy in Avian Medicine and Surgery. Elsevier; 2016.

Avian Hematology and Cytology 4<sup>th</sup> ed. Campbell, TW. Wiley Blackwell, 2015.

Doneley B. Avian Medicine and Surgery in Practice: Companion and Aviary Birds (2<sup>nd</sup> ed). CRC Press; 2017.

A Color Atlas of Avian Anatomy. McLelland, J. W. B. Saunders Co., Philadelphia. 1991.

Backyard Poultry Medicine and Surgery: A Guide for Veterinary Practitioners 1st Edition. Grenacre C, Morishita TY. Wiley Blackwell. 2014.

### **Conferences -**

All of the specialty groups have annual conferences – many times in conjunction with the other groups – AEMV, ARAV, AAV (Exoticon)

The NAVC (now VMx) and WVC generally have excellent exotic tracts in addition to many hands on wet laboratories.

The ICARE conference held biannually in Europe is an excellent place to get Exotic CE

## **RABBIT MEDICINE FOR THE SMALL ANIMAL PRACTITIONER**

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Adding rabbits to an existing dog and cat practice can be the first step to an easy transition toward practicing non-domestic pet medicine. There are very few alterations that need to be made to an existing practice in order to accommodate rabbit patients. The majority of the challenges merely involve additional training for your staff regarding husbandry, handling and laboratory sample collection.

### **Handling, Restraint and Physical Examination**

Evolution has created a relatively delicate skeleton for the rabbit. Skeletal mass comprises only 8% of the rabbit's total body weight as compared to 13% for a comparably sized cat. In contrast, the rabbits muscles are extremely strong and well developed for running. As a result, an improperly handled rabbit which kicks out or fights while being handled is at risk of fracturing its long bones and spine.

Rabbits should never be picked up by their ears. Rather, they should be scruffed with one hand and have their hindquarters supported with the other. You should never let a rabbit's rear legs dangle when they are being carried. Your examination table should be covered with a non-slip surface. If a rabbit is placed on a formica or stainless steel type of surface, they have a tendency to slip and kick. During the examination always maintain control of the rabbit. These animals will often launch off the table for no apparent reason. A conscientious practitioner will keep this in mind and prevent a potential catastrophe.

If manual/mechanical restraint is not enough to perform a proper oral examination, position the patient for radiographs or collect laboratory sampling, additional control can be obtained by chemically sedating the rabbit. Ketamine HCl is commonly used. By itself relaxation is not complete. administered at 20 mg/kg gives adequate relaxation for most minor procedures. When used in combination with any of the following: acepromazine at 1 mg/kg, IM, midazolam at 0.5-1 mg/kg, IM or xylazine at 2.5-5 mg/kg, IM, you get excellent deep sedation to minor anesthesia for brief, non painful procedures.

For prolonged procedures the rabbit can be placed on a volatile anesthetic such as isoflurane. The gas can be effectively administered by face mask, or the patient can be intubated. Intubation is a difficult procedure in rabbits due to the deep, caudal placement of their glottis. However, with practice, patience and the aid of either a curved neonatal laryngoscope, an otoscope cone and a stylet, or an endoscope, intubation is possible and recommended for any involved procedures.

### **Laboratory Sampling**

To use an old saying, "Bad laboratory data is worse than no laboratory data at all," certainly holds true for rabbit medicine as well. Fortunately, unlike clinical pathology in avian and reptilian species, rabbit laboratory samples are relatively easy to evaluate and interpret. Any reputable domestic clinical pathology laboratory should have no problems evaluating rabbit samples.

Blood collection is most easily accomplished by sampling the marginal ear vein or the central ear artery. Even on the smaller Dutch breeds, these veins are readily accessible.

The fur over the vessel should either be shaved or gently plucked. If this does not dilate the vessel, then rub or tap the area with your finger. Once the target site is identified you should clean the skin with a mild soap or an alcohol wipe. If you still have difficulty raising the vessel you can either hold the ear in your hand for a few minutes, or wrap a warm cloth around the ear.

Using a small gauge needle, such as a 25 or 27, penetrate the vessel. Allow the blood to drip from the hub and free catch it in an appropriate collection tube. Using a syringe or vacutainer will generally collapse the vessel, but these techniques can be used on large-eared rabbits.

Rabbits do have accessible cephalic veins. However, due to their anatomy, having short antebrachia, the vessels can be difficult to locate and hold off in little patients, especially if the holder has big hands. When visualized these veins are a good source for venipuncture.

Another extremity vein which can be used for blood collection, but one which is more readily accessible than the cephalic vein, is the lateral saphenous vein. You'll find it coursing medial to lateral diagonally across the cranial aspect of the tarsus.

Rabbits have a pair of large jugular veins. For large samples these are your best choice. There are a number of methods suggested for jugular blood collection, but I have found that the easiest technique includes some sort of sedation, either with injectables or isoflurane via a face mask.

The neck area over the mid trachea cranial to the thoracic inlet should be shaved and prepped. With the patient in dorsal recumbency your assistant should hold the rabbit on the work table with its head over the edge. The assistant holds the rabbit's body with one hand and pulls the front feet back toward the rear with the other hand. Take the rabbit's head with your free hand and gently tip it back to expose the ventral neck region. In all but the grossly obese rabbits the jugular veins should be readily apparent. Large amounts of blood can be readily collected from this position.

Urinalysis is a useful diagnostic tool in rabbit medicine. Interpreting samples can be difficult due to the often times heavy, but normal, mineral or pigment content of the urine. Samples can be collected via cystocentesis in a fashion similar to that performed in cats.

An assistant can stretch the patient by holding the scruff in one hand and the rear legs in the other. This can usually be performed without tranquilizers in most rabbits. After appropriate prepping of the antepubic region the urine can be obtained using a small diameter needle (23 - 25 gauge) attached to a sterile six ml syringe. The sample can then be analyzed utilizing standard techniques.

On occasion it may be necessary to collect cerebrospinal fluid. This is one clinical technique which must be performed under anesthesia. Techniques are similar to those used in cats. The best place to collect spinal fluid is from the cisterna magna.

The patient is positioned in lateral recumbency with the head flexed toward the chest. The fur on the nape of the neck is shaved from the occipital protuberance to the level of the third cervical vertebrae, and laterally past the margins of the atlas.

The cranial margins of the wings of the atlas and the occipital protuberance are the landmarks for needle placement. The 22 gauge, 1.5 to 3.5 inch spinal needle should enter the skin midway between these points and be directed toward the patient's nose. Do the relatively small size of most rabbits a stylet is not usually necessary in the spinal needle. After the needle penetrates the dura and arachnoid membranes you need to pay close attention to the appearance of spinal fluid. After placement is confirmed you can then attach a manometer or syringe for whatever testing that needs to be performed.

## **Vascular Access**

All of the vessels mentioned for venipuncture can also be utilized for venoclysis. Simple injections are easily administered into the marginal ear vein, the cephalic or the saphenous veins. Prolonged infusions, such as with IV fluid therapy, should be performed through indwelling catheters.

Although the marginal ear veins can be used for small bore IV catheters, I have seen sloughing of the ear tips even with short term placement of catheters. This is most likely due to a chemical phlebitis initiated by infusion solutions and medications into the delicate ear veins, mechanical irritation from the catheter itself or from aggressive taping of the catheter to the ear.

Larger veins, such as the cephalic, the saphenous and the lateral thoracic vein in does are better suited for catheter placement. Large jugular catheters can be inserted but the procedure often requires some sort of sedation or anesthesia for the placement.

In an emergency, or when the rabbit patient is so severely dehydrated that finding a peripheral vein is not possible, fluids can still be administered intramedullary. Intraosseous (IO) catheters are best placed in the greater trochanter of the femur. The patient should be sedated, the fur over the head of the femur clipped and the skin prepped for surgery. The top of the greater trochanter is palpated with your finger while wearing a sterile glove. The needle (size depends on the size of the patient but can vary from an 18 - 23 gauge, 1 - 1.5 inch needle) is then passed directly through the top of the trochanter, parallel with the long axis of the femur, and into the medullary cavity. The needle is gently flushed with sterile saline and fitted with a male adapter. Antimicrobial ointment is applied to the insertion site and a light dressing is placed over the entire unit. Replacement fluids can now be administered via slow drip into this needle. When the patient is adequately rehydrated the IO catheter can then either be replaced with an IV catheter, or removed altogether.

## Injection Sites

Injection techniques in rabbits are no different than in cats. Subcutaneous (SC) injections can be administered over the scruff, or laterally, just cranial to the hips. Intramuscular (IM) injections are generally given into the large lumbar muscles on either side of the spine, just cranial to the pelvis. This is easily performed by one person simply by tucking the rabbit under your arm, just as is done when carrying the animal. Just before penetrating the skin the patient should be given a gentle squeeze with your arm to prevent it from jumping with the injection.

Caution should be exercised when administering IM injections into the rear leg. Because there is a risk of damaging the ischiatic nerve, especially with certain drugs such as Ketamine HCl, it is always best to give all injections into the cranial aspect of the rear leg, in the quadriceps group.

## Anorexia

Anorexia is a common problem in rabbit patients. The major task of the small mammal clinician when faced with an anorectic rabbit is to determine whether the condition is caused by pathologic, physiologic or psychologic embarrassment.

There are many diseases that can disrupt the normal neurologic, endocrine or mechanical processes involved in the feeding response. A pure division into categories is not possible, as many diseases have components that overlap. In some situations, the cause is obvious (such as gross malocclusion), and in others, elusive (cancer cachexia).

Categorizing signs and laboratory data may help in assessing the problem. In general, anorexia may be classified as either primary or secondary with respect to disease. In addition, there is a third, more category, called pseudoanorexia, which is not directly related to suppression of the feeding centers in the brain.

Primary anorexia should be considered in any case where the inciting factor directly involves the feeding centers of the hypothalamus, or from psychological disorders that have a direct impact of neural control of the feeding response.

Psychological disorders are more easily characterized in people, as our veterinary patients are less likely to articulate their emotional state. As a result, at the risk of anthropomorphizing, it is often necessary to attempt to interpret what the anorectic patient may be "feeling" in a given situation.

Any external influence that incites stress or anxiety (identified as fear or depression in people), such as changes in the environment (temperature, caging, air exchanges, noise etc.) can result in anorexia. Two common psychological influences include the alteration of social structure within the animal's environment (addition of a new animal to an established group) and the offering of a new food type.

Secondary anorexia includes diseases or influences from outside the brain and have a direct effect on the neuroendocrine control of hunger. Some conditions or diseases may produce signs associated with anorexia such as nausea and vomiting (although the latter is not seen in rabbits). It is



believed that the stimuli associated with these conditions are similar and the controlling centers within the brain are most likely neuronally interconnected.

Abdominal pain is a common cause of anorexia in rabbits. Tympany (bloat), constipation and trichobezoars (fur balls in the stomach) may contribute.

Inflammatory conditions, such as peritonitis, pyometra, metritis or endometritis, hepatic, renal, pancreatic or visceral inflammation can all lead to anorexia by directly or indirectly stimulating the appetite centers.

Endogenously produced toxins, such as azotemia or hyperammonemia, as seen in renal or hepatic failure, respectively, have serious consequences on appetite.

Neoplasia and cachexia are frequently associated together. However, oftentimes, the cachectic patient still has an appetite. Cancer patients may not always desire food, as the peptides and nucleotides associated with certain neoplastic diseases are known to cause anorexia. Neoplasia should be on the differential list for anorectic patients.

Miscellaneous causes of anorexia should include any systemic illness. Cardiac, pulmonary or pancreatic disease (eg. diabetes - although not well documented in rabbits) can be contributing factors. In rabbits, Pasteurellosis, a common clinical finding, can lead to many of the causes mentioned. In addition, Pasteurellosis of the inner ear can initiate nausea associated with the head tilt, and can contribute to anorexia.

Lastly, pseudoanorexia, which is a physical inability to eat, rather than the lack of desire to eat, must always be considered with the clinically anorectic patient. Dental disease, more specifically malocclusion of either the incisors or the molars, is a frequent contributing factor in rabbits.

A thorough physical examination is warranted for every case, including cases with apparent obvious explanations for the anorexia. In addition, a proper cranial nerve examination must be conducted. An open mouth oral examination (using sedation as needed) must be performed.

Radiographs, laboratory analysis (including complete blood counts, serum chemistry analysis and urinalysis) should be a part of every minimum data base.

Anorexia and food deprivation has serious consequences on a patient, especially to those which are convalescing. Lack of food results in a lower blood glucose, decrease in serum levels of glucose, a decrease in the insulin-responsive thyroxin-deiodinase converting enzyme and a resultant decrease in active T3, with a consequential decrease in the animal's basal metabolic rate. Rabbits are prone to developing fatty livers if the anorexia is not corrected quickly.

Anorectic rabbits need to be supported with appropriate diets. Vegetable gruels can be administered via syringe feeding, and when necessary, nasogastric tubes. Attention must be given to the animal's fluid balance and other medical needs, such as the administration of antimicrobials and analgesics, as required.

### **Pasteurellosis**

*Pasteurella multocida* is one of the more common bacteria isolated from rabbit pathology. The bacterium can be found in all organ systems, and can be responsible for several different disease symptoms. There are several serotypes that vary in virulence.

Transmission of *Pasteurella* spp. can be through direct contact, aerosols or vertically from doe to kits. As a result, most house rabbits should be considered to at least have been exposed to or are carriers of the organism. It is believed that the organism cannot be eliminated from the host, thus resulting in a permanent carrier state. Diagnosis and identification can be made through serology or bacterial culture.

Stress, such as improper housing, overcrowding, trauma etc., can act as an inciting factor in inducing clinical pasteurellosis. Symptoms can include "Snuffles" (ocular/nasal discharge, mild respiratory signs), dermatitis, dental disease (tooth abscesses), severe respiratory infections (pneumonia), torticollis and abscesses. These abscesses are usually dermal, and can occur anywhere on the body, or can be internal, commonly arising in organs such as the kidneys, the liver and the lungs.

Dermal abscesses can literally arise in a short period of time, with owners often reporting their presence in as little as a couple of days. Although the abscesses can be found anywhere on the body, I have seen them between the mandibles, below or between the ears, and attached to the mandibular or maxillary bone, associated with dental abscesses.

In pasteurella conjunctivitis, the periorbital tissue is oftentimes so inflamed as to make the entire orbit/globe appear enlarged. Intraocular pasteurellosis can result in a buphthalmic globe. It is not uncommon for the lacrimal glands to be occluded with inflammatory debris, thus exacerbating the pasteurella conjunctivitis. It is a benefit to the patient to gently flush the lacrimal glands prior to initiating ophthalmic antibiotics.

Whenever possible the abscess should be surgically debulked. Simple draining of the caseous material within the abscess, even with the aid of a penrose drain, will not suffice as it does in feline abscesses. It is necessary to surgically remove the entire capsule surrounding the abscess. This necessitates anesthesia, and because of the propensity for pasteurella abscessation in the lungs, it is prudent to radiograph the thorax prior to administering any anesthetics.

Intraocular pasteurellosis necessitates enucleation. Lesser cases, those involving the periorbital tissue, should respond to antimicrobial therapy.

As mentioned, it may not be possible to completely eradicate the pasteurellosis from a rabbit. Culture, surgical debulking and appropriate antimicrobial therapy should always be considered. In some instances, animals may require prolonged administration of antimicrobials, sometimes lasting as long as one year.

The antibiotics of choice for pasteurellosis include trimethoprim/sulfa (30 mg/kg, combined drug, PO, BID) or enrofloxacin (10 mg/kg, PO, BID). Either drug should be administered for at least 14 to 21 days, or as long as is necessary to control the infection. Procaine Penicillin G has been reported successful in some cases at 40,000 U/kg IM or SC, q24hrs for 5 days, but then followed up with trimethoprim/sulfa at the above dose. An alternate penicillin dosage regimen is 40,000 U/kg IM or SC, q 72 hrs for 14 days.

### **Tooth Root Abscess**

It is not uncommon for rabbits to present with abscesses of dental roots. These manifest as simple anorexia, or present with large, firm swellings adhered to the adjacent maxillary or mandibular bone. There may be an associated fluid or purulent pocket associated with the abscess, over the lesion.

Rabbits, in general, do not like their oral cavities examined. Proper restraint is in order, and a thorough oral examination is a must when masses are identified around the oral region. If necessary, use chemical sedation. Ketamine HCl at 25 mg/kg, combined with midazolam at 0.5 mg/kg, IM give excellent relaxation and allows for a complete oral cavity examination.

Use either a canine vaginal speculum or two loops of gauze and fully open the patient's mouth. Then, using a bright light source, examine each tooth. It is not uncommon to see purulent exudate oozing from the alveolar socket around the affected tooth.

While the rabbit is still sedated, obtain cranial radiographs. Properly positioned Vento-Dorsal and Lateral radiographs are a minimum. In addition, it is wise to get an oblique view, highlighting the region of the suspected lesion.

Once the pathology has been identified, it will necessary to remove the tooth. Simple medical therapy will not suffice. The signs may temporarily resolve, but, once the medication has ceased, the problem will recur. Always warn you clients about this, and, to protect yourself, document your warnings in the record, should they opt not to go with dental extractions.

### **Rabbit Syphilis**

Rabbit syphilis, or venereal spirochetosis, is caused by the bacterium called *Treponema cuniculi*. The disease is spread by direct contact through breeding and vertically from the doe to the kits. Although the lesions commonly are found on the genitals, pathology is occasionally seen around the lips, the nose and the eyes. There may be swelling with vesicles, open ulcers and ultimately crusts. These lesions may become secondarily infected with Staph bacteria, making the lesions appear even larger. The animals usually do not show signs of systemic illness. However, if the facial lesions are severe enough, the animal may go off food and water.

Diagnosis is based on clinical signs, skin cytology and histopathology using silver stains. In addition, several serological tests are available. If your local small animal laboratory is not equipped to handle such requests, take a serum sample to your local hospital and request a Wasserman Venereal Disease test.

Treatment of rabbit syphilis is effective, with the patient responding to injectable procaine penicillin at 40,000 - 60,000 U/kg, q 24 hrs for 7 days.

References available on request

## Basic Reptile Anatomy

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The objective of this presentation is to present a very basic approach to reptilian anatomy. This will help the student/practitioner better interpret radiographs, perform surgery and a more thorough physical examination.

In general, all reptiles are covered with scales. They can have four legs, or none. There are no snakes with legs, but there are lizards without legs. Thus, it is important to be able to distinguish a snake from a legless lizard. Snakes do not have eyelids. Lizards and turtles do have functional eyelids (with some exceptions such as some members of the gecko family). The snake eye is protected by a transparent scale called the spectacle. When a snake goes through ecdysis, or shedding, it will slough this spectacle with its skin. Occasionally this spectacle will not come off with the skin, and results in a retained eye cap.

A second obvious difference between snakes and legless lizards is that snakes do not have external ears. But, to complicate matters, not all lizards have ears. Fortunately, all legless lizards do! The snake lacks not only the external ear, but also the middle ear cavity, tympanic membrane and eustachian tube. They do have an internal ear which functions in detecting motion, static position and sound waves which travel through the ground, and limited audio frequencies. Lizards and turtles lack external pinnae, but most have a conspicuous tympanic membrane. There are a few species of lizards which lack this feature.

Snakes and some lizards have a special sensory structure called the vomeronasal or Jacobson's organ. Its paired openings are just rostral to the choana. The flicking tongue picks up minute scent particles in the air and places them in direct contact with this organ.

The teeth of snakes and lizards are both acrodont (attached to the bone) and polyphydont (capable of having several sets throughout life). Turtles do not have teeth, but instead, they have a horny beak that they use for biting. Non-venomous snakes have four rows of upper teeth: two rows on the maxilla and two rows on the palatine-pterygoid bones. There are only two rows on the lower jaw, one attached to each mandible. Venomous snakes substitute fangs for the maxillary teeth.

There is a small opening caudal to the tongue called the glottis. Unlike mammals, the reptile glottis is always closed unless it is taking a breath. It forms a vertical slit in the closed position. Snakes are able to extend their glottis out the side of their mouth while they are eating to allow for respiration.

The trachea is usually long and is supported by cartilaginous rings. These rings are complete in the turtle and the crocodile, and incomplete in the lizard and snake. The trachea usually terminates just dorsal to the heart. In the lizard and turtles the trachea bifurcates into two bronchi which then enter the left or right lung. In the snake the trachea branches into a short left bronchus which terminates in a vestigial left lung. The size and functional capacity of this left lung varies from species, and can be complete in some of the water snakes where it is used for hydrostatic purposes. The right bronchus terminates in the functional right lung.

All reptiles, except the crocodile, lack a diaphragm. Breathing (inspiration and expiration) is accomplished principally by the intercostal muscles. These are assisted by other muscles of the trunk and abdomen, as well as smooth muscles in the walls of the lungs themselves.

The three chambered reptilian heart is composed of two atria and a large ventricle. There is an incomplete ventricular septum which allows the heart to function as a four chambered heart.

Reptiles have a renal portal system. In the snake the parietal veins from the body wall and the caudal vein from the tail pass through the kidneys before anastomosing with the ventral abdominal vein. In the lizard the caudal tail vein and the internal and external iliac veins all feed through the kidneys before returning to the heart. In the turtle the renal portal system receives veins from the carapace, the musculature posterior to the kidneys and the external iliac veins.

Reptiles, except the snapping turtle, do not have lymph nodes. However, the lymphatic system in reptiles is complex. There is an extensive network of perivascular lymph channels around the major vessels and perivisceral lymph spaces which drain the viscera.

The spleen is a small, spherical, reddish organ located between the gall bladder and the pancreas. It is usually tightly adhered to the pancreas, and the two organs collectively are often referred to as the splenopancreas.

The pancreas is found caudal to the gall bladder on the mesenteric border of the duodenum. It has both endocrine and exocrine functions much the same as in mammals.

The single or double lobed thymus is found cranioventral to the thyroid gland, closely associated with the vagus. It does not involute when the animal matures as it does in higher vertebrates. Just caudoventral to the thymus is the thyroid. It is a spherical reddish-pink structure cranioventral to the heart and ventral to the trachea.

Reptiles have one or two pairs of parathyroid glands which can be found either cranial or caudal to the thyroid. In turtles the glands may be found imbedded in the thymus. These glands are difficult to find and are often obscured in the adipose tissue.

All reptiles have a pair of adrenal glands. They are found closely associated with the gonads and urogenital structures of the lizard and snake and with the kidneys in the turtle. The adrenals are pinkish filiform structures found medial to the gonads. Unlike mammals, the medullary and cortical tissue is indistinguishable, but nonetheless still produces the appropriate hormones.

For the most part the mouth does little more than catch the food. Very little mastication, if any, occurs. The saliva that is produced has little digestive significance, its role being mostly lubricatory. The esophagus has a special adaptation of several longitudinal folds which allow for great distensibility of the gut to accommodate large food items. The esophagus is dorsal to the trachea and extends from the pharynx to the stomach.

The stomach of the snake is fusiform, and in the lizard and turtle its shape grossly resembles the mammalian stomach. The stomach is rather short in the snake. Its junction with the esophagus is clearly noted at a site approximately equal to three-fourths the length of the liver. The stomach ends in a stricture, the pylorus, at the pyloroduodenal junction.

The small intestine may be either straight or have short transverse loops. The small intestine in the lizard and turtle has many loops and convolutions much the same as in the mammal. The small intestine terminates at the ileocolic junction. A cecum is present in some snake species. A cecum is present in both the lizard and the turtle.

The large intestine terminates at the cloaca. It is a short, straight tube. As in the bird, the reptilian cloaca has three chambers. The feces are discharged into the anterior chamber called the coprodeum. The next, or middle chamber, called the urodeum, receives the urogenital ducts. The posterior proctodeum acts as a general collecting area for digestive

and excretory wastes. The male intromittent organs open into this compartment, and both the male and the female have scent glands that also open here.

The reptile has a metanephric kidney. It is situated in the posterior part of the body positioned adjacent to the body wall, with the right kidney anterior to the left. They are brown in color and consist of twenty-five to thirty lobes. Since the snake lacks a bladder the ureters enter directly into the urodeum. The lizard and turtle the ureters enter the bladder, which then empties directly into the urodeum.

Both the male and female gonads are found in the posterior half of the body. They are medial to the kidneys and in the snake, the right is cranial to the left. The testes are off-white to yellow, and the ovaries are a yellowish pink.

### **Ambient Temperature affects on Reptile Physiology**

An increase in body temperature, or fever as it is referred to in mammals, has been noted to be beneficial to the health of the individual as far back as 2500 years ago. Although reptiles, which are ectotherms - that is, animals whose body temperature depends directly upon the ambient temperature or environmental factors such as the sun - are incapable of developing a fever response as can mammals, they can develop a fever behaviorally when exposed to certain pyrogens.

Fever in mammals, or its equivalent in reptiles, results when the thermoregulatory "set point" becomes elevated. The elevated "set point" is due to a response to a triggering agent such as a bacteria or virus. After the arrival of the foreign substance in the body the host's macrophages release a hormone called an endogenous pyrogen (EP). The EP acts directly on a region in the brain, the hypothalamus, the portion of the brain generally thought to be responsible for thermal regulation.

In mammals this increase in "set point" is manifested by increasing metabolic heat production (shivering), surface vasoconstriction and behavioral means. Reptiles depend entirely on behavioral means of thermoregulation.

Specimens of *Dipsosaurus dorsalis*, the desert iguana, were placed in cages which had a temperature gradient ranging from 30 - 50C. Lizards injected with a bacterial containing solution consistently chose a temperature that was 2C warmer than non-infected lizards. The lizards began to seek the warmer temperatures within four to six hours post-infection.

The antibody response of *Dipsosaurus dorsalis*, which had been infected with *Salmonella typhosa*, was evaluated at different ambient temperatures. At various intervals post-immunization agglutination titers were run to determine the antibody response. The antibody response was poor to non-existent at 25C, good at 35C, and moderately good at 40C. It was also noted that if the lizards were immunized at 35C and then transferred to 25C the antibody response was inhibited, but if moved from 35C to 40C after immunization the antibody response was enhanced.

During infection in mammals serum iron falls due to a release of EP. Bacteria uses the iron as a growth factor. The ability of bacteria to utilize iron is diminished at elevated temperatures. This fact, coupled with the drop in serum iron by the host, makes growth and continued propagation difficult for the bacteria.

Leukocyte activation, including increasing phagocytic, bactericidal and viricidal activity, leukocyte mobilization, and augmented production of immunologically active T-cells, are all factors that are increased by the release of EP. EP also stimulates interferon, an antiviral agent elaborated from the host's cells.

Elevated temperature, in and of itself, has a direct effect on viral and bacterial kinetics. Studies done on viral activity in the pig, ferret and puppy show that the virulence of viruses is attenuated at elevated body temperatures.

There are a combination of factors, due to elevated ambient, and hence, body temperature, work synergistically to help fight infection. The augmented antibody response, the increase in leukocyte activation, the stimulation of interferon and lysosomes, the decrease in serum iron and the decreased effectiveness of the bacterial siderophores combined with the actual decreased growth and replication of the bacteria and viruses represent a coordinated effort by the host to overcome disease.

References on Request

## TREATMENT TECHNIQUES IN REPTILE PATIENTS

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There are a lot of similarities between small animals and reptiles. That said, there are also differences, but these differences can make a difference between treatment success and failure when not heeded.

The FUNDAMENTAL principle to be followed when treating reptiles is to make sure that they are at their Preferred Optimal Temperature when administering treatments. The Preferred Optimal Temperature Zone (POTZ) for numerous reptile species can easily be found in the literature or on line at a number of sites.

When a reptile is at its POTZ the response to medications can be predicted – as they tend to respond like a mammal when properly warmed. When their core body temperatures are too low, there is no way to anticipate how their ill bodies will handle the medication.

It is the rare reptile patient (exceptions are severe traumas) that cannot wait 12 – 24 hours to be properly warmed up and prepared for diagnostics and therapeutics.

### Administering Medications

Before administering any treatment to an ill reptile you should always take the patient's core body temperature. This is done in a fashion similar to the procedure in mammals. Caution should be taken when inserting the thermometer in the vent as there is a blind pocket in the cranial portion of the cloaca (the coprodeum). This is easily, accidentally, penetrated, when using a pointed or sharp plastic thermometer. Soft, flexible, electronic thermometers are the best to use.

### Oral route (PO)

There is an old adage in small animal medicine that “if the mouth works, use it.” I believe that this is true in reptiles as well. Of course, you have to remember the caveat – they have to be properly warmed.

There has always been a belief that you should not use oral medications in herps. It has been shown that oral medications work fine in the properly prepared patient. Even if the patient is aggressive, has facial injuries or just can't be manipulated, it is still possible to place an esophagostomy tube and is commonly done in chelonians, and occasionally lizards and crocodilians. Snakes are generally easy to tube and E-tubes are rarely warranted.

This author prefers to send home reptile patients on oral medications rather than injectable drugs. When the owner is properly prepared and the patient is properly maintained, oral medications are an effective and safe way to prescribe home therapy.

### Subcutaneous (SC)

Reptiles don't have the voluminous SC space that is seen in mammals. More importantly, the SC space is not well vascularized in herps, making administration of medications in this location less efficiently absorbed.

Snakes have a SC lateral sinus that runs along the entire side of the animal. It is readily found between the epaxial muscles and the top of the ribs. When entered with a needle the fluid medication (chemotherapeutics or fluids) readily runs along this space down the side of the patient. By utilizing this space you minimize the obvious stretching of the skin seen with SC injections and theoretically, decrease any potential pain associated with administration of larger volumes of fluids.

In squamates there is generally an obvious lateral skin fold extending from just cranial to the thigh to the axilla. In most lizards there is minimal SC space between the scapula, a site commonly used in mammals, and is not recommended.



In chelonians, if it is possible to access the axillary or prefemoral regions, there is ample SC space for administering fluids or injections. Some chelonians will withdraw into their shell making access difficult. It may be possible to administer SC by using long needles inserted between the limb and the shell, but, this is not recommended as there is no way to adequately prep the skin before the injection.

Crocodylians can be administered SQ fluids along their lateral body wall similar to lizards. Hyaluronidase (an enzyme derived from bovine testicular tissue) administration has been advocated for enhancing SC fluid absorption in various species, including reptiles. Hyaluronidase lyses hyaluronic acid, which is part of the ground substance that binds the interstitium. In humans, it has been used for facilitating fluid and drug absorption from the subcutaneous space and reducing pain during chronic fluid administration. However, studies performed in cancer patients found no comparable difference between the duration of fluid at the administration site or the presence of pain in patients who received hyaluronidase during chronic subcutaneous fluid administration to those who did not. No studies have been performed to advocate its use for fluid replacement in the reptile.

Finally, regarding SC administration of medications in herps, some drugs are irritating or have extreme pH values have been shown to cause scarring and depigmentation to the skin post treatment. Clients should be warned of this possibility.

### **Intracoelomic (ICe)**

Ice fluid administration is commonly performed in reptile patients. Again, if the patient is properly warmed, this route can be effective, especially for larger amounts of fluid.

Caution should be taken to avoid damaging internal structures when inserting the needle. Gently placing the patient in dorsal recumbency, with the head angled slightly down, allows the viscera to slide forward with gravity, providing a small target just ventrocranial to the thighs. If the needle is directed parallel to the body wall and aimed slightly ventrally, it is less likely that organs, or lungs and airsacs, may be entered.

Always aspirate before administering – if blood, air or any fluid is withdrawn, remove the needle, and start fresh with a new syringe of medication.

### **Intramuscular (IM)**

Before a discussion of IM injections locations is covered it is necessary to have a brief discussion on the reptilian Renal Portal System (RPS).

Many of the drugs, especially the antibiotics, that are used in reptile patients are eliminated via the kidneys. Historically, authors have stated that drugs should not be administered in the caudal half of a reptile's body in order to avoid the RPS. Thoughts have concentrated on the fact that either the drugs would suffer a first pass effect (and subsequently be rendered ineffective) or, enter the kidneys in such high concentrations that renal toxicity might be a concern (especially with drugs such as the aminoglycosides).

Studies on the RPS in chelonia (Holz and Lewbart) have demonstrated a difference in the plasma concentrations of certain drugs when administered either in the forelimb or the hindlimb musculature. In one study, there was a significant difference between the two injection sites for the drug cephazolin, a drug known to be cleared by tubular secretion, but not gentamicin, a drug that is cleared by glomerular filtration.

In regards to the significant decrease in blood levels for the former drug, the author speculated that there was in fact no clinical significance since, although the levels had dropped, they were still above the MIC necessary for successful therapy.

The conclusion here was that drugs eliminated via tubular secretion may be affected by the RPS, owing to the fact that the blood returning from the caudal limbs and the tail appears to course through the

kidneys prior to returning to the systemic circulation. Drugs cleared from the body by glomerular filtration were not affected, apparently because the blood bypasses that anatomical location.

In reality, that is a gross oversimplification. Blood may change flow in and around the RPS dependent on many different factors. Body temperature and hydration status are the main two determinants. In addition, there are 10,000+ species of reptiles, and hundreds of medications that have yet to be studied. The work done so far is an important first step in understanding the black box of therapeutics in reptilian patients, but, caution must be taken when making generalizations. If necessary, it would be best to err on the conservative side, and if any doubt exists regarding the best administration site for a given medication, the cranial half of the patient's body should be chosen.

Remember, when giving medications by the IM route the patient must be properly warmed prior to administration. IM sites are limited in snakes to the epaxial muscles along either side of the spine. In some emaciated, or very small animals, this can be challenging and the injections are often SC rather than IM.

In lizards IM sites include the epaxial muscles as in snakes, the quadriceps and triceps. I try to avoid the caudal thigh so as not to accidentally traumatize the sciatic nerve. I have seen animals develop paresthesias in the rear feet secondary to ketamine and enrofloxacin administration in the biceps femoris group.

Although theoretically IM injections can be administered into the large tail muscles in the larger lizards, I generally don't use this site. I had one case in a Water Dragon where calcium gluconate was given into the tail, and within a week the tail sloughed off distally to the injection site.

Several medications can be irritating or even caustic. For example, enrofloxacin (United States product) has a pH of 11. It is only labelled for a SINGLE IM injection. When given IM it can cause severe muscle necrosis and sloughing of the skin.

IM injection in crocodylians are similar to those given in lizards.

In chelonians, again, the limiting factor is access to the limbs. If possible, for the appropriate medications, this author prefers the quadriceps muscles. In addition, the large pectoral muscles, just under the front legs and dorsal to the plastron, are an excellent place for IM injections. There is generally a large muscle mass present and minimal critical structures present that may cause potential injection site complications.

### **Intravenous (IV)**

The IV route is preferred in life-threatening conditions. Hypothermia and dehydration will not interfere with systemic absorption when drugs are given IV. That said, remember that whenever possible, the patient should be properly warmed, or at least in the process of being warmed, when IV therapy is started.

IV administration is possible in snakes but is limited. Intracardiac administration is possible in emergency situations – caution being taken not to administer medications that could be caustic to the myocardium. In addition, IV administration can be performed into the ventral coccygeal tail vein or the jugular vein. If a continuous IV is needed or if repeat IV administration is warranted, placing a jugular catheter is advised and not difficult.

The dorsal palatal vein is readily visible in snakes, and theoretically, can be used for IV access. But, extreme caution should be taken as this vein tends to bleed excessively and, especially in a conscious patient, can be difficult to establish adequate hemostasis. I do not recommend using this vein unless the animal is under general anesthesia.

In lizards IV medications can be given in the ventral coccygeal vein or the jugular veins. It is possible to utilize the brachial veins or the femoral veins in larger animals, but, they are surrounded by nerves and lymphatic channels, making placement difficult if not risky.

Again, if repeat IV access is needed, placing an IV catheter is recommended. The jugular veins or the cephalic vein in larger lizards are the preferred sites.

This author adamantly recommends against using the ventral abdominal vein due the risk of accidentally penetrating abdominal viscera thus resulting in iatrogenic celomitis.

### **Intraosseous (IO)**

Administering medications via the IO route are generally limited to fluid therapy via an IO catheter. Caution should be taken not to administer any medication IO that may be caustic to the bone marrow.

IO catheters are generally placed into either the proximal tibia, through the crest, directed distally into the tibia. Alternately, some clinicians prefer to enter the femur since it is a larger bone, entering the femur just proximal to the stifle and directing the needle proximally toward the hip. I caution against this technique, especially in species with a patella.

Finally, IO placement generally requires general anesthesia as it is painful, and, if not properly prepped and maintained, can result in permanent damage to the bone (osteomyelitis) and joint if it is accidentally penetrated during placement. I recommend attempting IV placement prior to IO access.

References available on request

## MEDICAL ISSUES IN COMMON PET INVERTEBRATES

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Invertebrates been proposed as alternatives to dogs and cats. These animals are known for their numerous hairy legs, multiple eyes, clawed hands, armor plated skin and pointed stingers. In spite of this formidable, somewhat ominous appearance, many people are attracted to their esoteric beauty, intriguing lifestyle and unique biology.

These creatures belong to the group of animals in the phylum arthropoda. Arthropods are all invertebrates; that is, they lack both a boney skeleton and a back bone. Invertebrates get their rigid support by a chitinous exoskeleton, which in turn gives them the outward appearance of wearing armor. Another important biological fact is that all invertebrates are ectothermic.

The most common invertebrates available in the pet trade include the large spiders such as the tarantulas and the wolf spiders (bird eating spiders and monkey spiders), scorpions, millipedes, snails, ants and land hermit crabs. All are relatively inexpensive and readily available. As with anything new, information on their captive husbandry and medical problems is scarce. There are a few anecdotal books which have been written, and some obscure technical articles available in the libraries. However, a synopsis of this information has not yet been made available to the general pet owning public.

This discussion is not intended to be an all-inclusive guide to the care and maintenance of invertebrates in the pet industry, but rather a focus to get the interested veterinarian started on a fascinating new pet group. The discussions will center around the most common invertebrates available in the legal pet trade and their common maladies.

### Why Keep Invertebrates?

Invertebrate pets offer numerous advantages over the more commonplace dogs, cats and birds. First off is there size. The majority of the invertebrates available in the pet market range in size from a marble to a lemon. This means that their requirements for housing/caging is minimal. In fact, most require nothing extraordinary in terms of equipment to keep them healthy, exotic food items or exorbitantly expensive caging. Small aquaria/terraria, gravel, feed dishes, cage decorations (bark, wood, rocks) and a secure lid will suffice for most of the invertebrates.

Along with their small size goes a quiet disposition. About the most noise you'll hear coming from an invertebrate's cage is the rustling of the animals as they saunter across the bottom of their cages. To hear this, you'll have to listen quite hard! This is a distinct advantage for those wishing to have pets in areas where space is a limitation and noise is a factor.

Another important consideration is the intensity of care required to keep the animals healthy. Most invertebrates do well on weekly or bi-weekly feeding. Of course fresh water needs to be available at all times. Do to the infrequent feedings the animals also infrequently soil their cages, thus they are non-odiferous and upkeep is a simple task.

Although the invertebrates as a group do not offer the attributes of being as warm and cuddly as a kitten or puppy, they are uniquely interesting to watch and observe their lifestyles. They offer an excellent learning device for children and adults alike.

### General Care

Some of the invertebrates are susceptible to a wide range of diseases. However, in practicality, the majority of diseases observed are related to improper husbandry and nutrition, and contaminated caging. Prevention of disease is much more successful than treatment of existing diseases. Disease control in the captive environment, therefore, is based on stringent husbandry practices, meticulous hygiene and a balanced diet.

Treatment of individual animals is possible, especially in some of the larger animals. Amputation of injured limbs, disinfecting surface wounds and arresting bleeding are common procedures. Often times simply altering some aspect of the husbandry or management, such as increasing the ambient humidity or temperature, or altering the housing, will correct the problems.

Regular cleaning of cages, which includes removing old feces and sloughed skins, helps control bacterial contamination of the environment. A solution of sodium hypochlorite (bleach) diluted 1:32 in water (1/2 cup bleach to one gallon of water) is an excellent disinfectant. It is imperative that the cage be rinsed thoroughly numerous times with fresh water prior to returning live animals into the clean cage.

Symptoms of a sick invertebrate vary depending with the species, but in general include one or many of the following signs: lethargy, loss of appetite, change in color, change in behavior, diarrhea and secretions or discharges from the joints of the exoskeleton. If any of these symptoms are seen the affected animal should be immediately separated from other animals in its cage to prevent any possible spread of disease.

There is evidence that certain species of invertebrates may harbor diseases which can be transmitted to humans. The most important of these is *Salmonella* spp., which can be carried and secreted by cockroaches and a number of other species. Although this is uncommon, it is prudent to emphasize that good personal hygiene should be employed by all those handling invertebrates.

All invertebrates are subject to traumatic injuries. Examples include being dropped, stepped upon and caught in the cage lid. Fractured limbs may need to be amputated. Bleeding can be stopped by drying the injured site and applying a small dollop of glue. Broken or amputated limbs will usually regenerate during the animal's next shed.

There are many different parasites that affect invertebrates from internal worms to external arthropods such as mites. In many species the mites don't appear to cause a problem, and it is probably not necessary to treat them.

Without a doubt one of the more common diseases to affect captive invertebrates is inanition, or lack of a proper diet. Some captive animals will suffer from maladaptation syndrome, or simply a refusal to eat anything offered. Others will exhibit the same symptoms if the husbandry, temperature or environment are otherwise inappropriate.

Disease entities specific to the various invertebrates will be discussed in turn under their appropriate sections. The basic principles mentioned apply to all of the following invertebrate pets.

### **Land Hermit Crabs**

Various types of hermit crabs have been available in the pet trade for about twenty years. Hermit crabs can be either aquatic, terrestrial or arboreal. The most common varieties come from Puerto Rico and Florida. The land hermit crab frequently found in the pet trade is *Coenobita clypeatus*.

As mentioned, all hermit crabs are arthropods. The group, or phylum Arthropoda, is further divided in to subphyla. The Mandibulata and the Chelicerata are two of the four. The distinction between the two groups is that the mandibulates have antennae and the chelicerates do not. Since the land hermit crabs have antennae, they are members of the subphyla Mandibulata. Other familiar mandibulates are the millipedes, centipedes and insects. The subphyla chelicerata include the spiders, scorpions and horseshoe crabs.

The classification of the hermit crabs can be further broken down by identifying their class. The class is the next taxonomic group after the subphyla. The class to which the hermit crabs belong has the distinction of possessing two pair of antennae, whereas all other mandibulates have only one pair of antennae. This class is the Crustacea. Other common crustacea include the lobsters, crabs and shrimps.

Husbandry

Land hermit crabs have the potential of living approximately ten years. This, of course, is only possible if housing and husbandry are proper. There are many caging types which are suitable for housing land hermit crabs. Plastic terraria and glass aquaria are the most commonly used.

The land hermit crab in its natural state lives just outside of the high-tide line of marine tidal zones. As such it is used to marine, or salt water. In captivity, however, it does well in either brackish or fresh water. The cage should be set up with a gravel substrate (aquarium gravel will work well). This substrate should be inclined from side to side so that the low end of the gravel will be submerged when a small amount of water is added to the enclosure. Water should not be so deep that a crab may drown. A few rough rocks and sturdy branches should be added to the cage for adornments and climbing items for the crabs.

The land Hermit Crabs should be housed at approximately 75° F. They also need high humidity. Being kept too hot or too dry will desiccate the crabs and may kill them if moisture is not supplied immediately.

Moisture is also needed for the crabs to molt. Molting is a hydrostatic process where the outer shell is split off by a build up of water pressure within. If the animal is not adequately hydrated it will be unable to shed its old shell. Immediately after shedding the crabs new outer skeleton is very soft. Because of this it is highly susceptible to predation and attack by other hermit crabs. It will usually hide in the substrate for a few days until its new exoskeleton hardens, and then it will begin a search for a new shell in which to take up residency.

All hermit crabs live in discarded snail shells. The soft body of the crab itself is shaped like a cornucopia, with a counterclockwise spiral. As the crab grows it inevitably outgrows its current shell and must find a new "house." They will occasionally compete with other crabs which are currently occupying a shell. If successful, the crab will actually usurp a resident and take its shell. If the crab is failed in its attempt to procure the shell, it must find a vacant shell or it will die. Since the crabs will not give the owner any hint as to when they are going to shed, it is important that a variety of different size shells be available for the crabs at all times.

As mentioned, fresh water is adequate for land hermit crabs. The important thing is that the water be clean of debris and old food. Stagnant or soiled water can be a source of contamination and disease to the crabs.

Hermit crabs are omnivorous by nature. In the wild they forage along the tidal zone of the beaches they inhabit. In captivity they do well on commercially available Hermit Crab diets, or other substitutes such as dry kibbled dog food, poultry mash, fruits and vegetables. Care should be taken not to overfeed these animals so that spoiled food be left around in the cage.

Although Hermit Crabs are gentle animals by nature, they do have one large claw which can yield a nasty pinch. Immersing the animal under water for a brief moment will usually stimulate them to release their grip.

#### Reproduction

Hermit crabs take on a primarily terrestrial existence as adults. They only return to the water for breeding. After the eggs hatch the larva go through several life stages and molts. When the new crabs reach adulthood they migrate to shore to live a terrestrial life. Due to the complex nature of their reproductive cycle, captive breeding is not recommended.

#### Medical Problems

Other than the medical problems which are common to all invertebrates, such as trauma and improper husbandry, there are no specific medical maladies unique to hermit crabs. Some hermit crabs will be infested with mites, but the mites don't seem to cause the crabs any ill-effects.

## Scorpions

The scorpion is one of the oldest living animals on the face of the earth. Having been morphologically unchanged for the last 200 million years, it is one of the more successful life forms ever to evolve. Most of the wild species found in the continental United States are non-poisonous and would make acceptable pets. The exception is the highly poisonous *Centruroides sculpturatus*. The three most common species found in the pet trade are *Pandinus empirator* the "AFRICAN EMPEROR", *Heterometrus* spp. the "MALASIAN EMPEROR," and *Hadrurus* spp. the "HAIRY SCORPION."

The Emperors are probably the most sinister appearing of all the scorpions, although they rarely, if ever, rely upon their stingers for defense or aggression. Rather, they depend upon their large pedipalps, or claws, for the capture and dismemberment of their prey.

Members of the genus *Hadrurus* are collectively referred to as the "Hairy Scorpions." These individuals range in size from three to eleven centimeters in length, and vary in color from light green to what has been described as an "Earthy Brown". This genus is found widely throughout the Southwestern United States. Hairy scorpions make hardier pets than Emperors. They are better adapted to withstand longer periods of water and food deprivation. These species, unlike the Emperors, do use their stingers for aggression, predation and defense. However, the Hairy scorpion's sting is about as poisonous and irritating as that of a Bee.

### Husbandry

There are two important considerations in establishing the living environments for these pets. Assuring proper humidity and providing appropriate hiding places are essential to maintaining healthy animals. Scorpions evolved in tropical climates and as such have never escaped a biological dependence upon moist conditions. Since they are nocturnal animals, direct contact with sunlight should be avoided.

Most scorpions do well at temperatures ranging from 65 to 90° F. Environmental temperatures greater than 95° F will induce heat stress. Caging should provide space for these animals to retreat from the heat as well as the sun.

Scorpions fare well on a diet of soft-bodied grubs such as wax worms, moths, crickets, small spiders and mouse pups. Most captive animals will need to be offered fresh food on a weekly basis, however, the larger more active animals will need twice weekly feeding.

Caution should be taken when handling the Hairy scorpions since their sting is painful. The use of lightweight forceps is recommended for manipulating these animals. It is usually possible to herd the scorpions into a suitable carrier for transporting them short distances. The emperors can be hand held, and although they don't sting, they may pinch with their claws.

### Reproduction

Sexing scorpions is very difficult and poorly documented. In some species the female is distinguishable by shorter tail segments. The male in certain species has a posteriorly protruding spine above the stinger. Other than this information, little is known regarding sex determination.

Unlike many invertebrates, scorpions bear live young. Fertilization is internal in the female. For the first several days after the baby scorpions are born they are carried around on their mother's back. During this time the baby scorpions live in harmony, but after leaving the safety of the mother's back they become aggressive and may cannibalize each other. Babies should be separated and fed wingless fruit flies, grubs or any other appropriate small insects.

### Medical Problems

Scorpions are hardy animals and do not have many overt disease problems. The majority of the disease problems encountered center around improper husbandry practices as previously described.

Well kept scorpions can be expected to live upwards of four years. Scorpions molt throughout life. During the molt phase the animals will refuse food. Likewise, as they get older they eat less and less food, eventually dying of old age.

The actual molt takes approximately one to two hours. This usually occurs at night, and it is during this time that damaged limbs will be regenerated.

## TARANTULAS

Tarantulas, like the scorpions, are in the Class Arachnida. Many spiders that are commonly referred to as tarantulas, and sold through pet stores as tarantulas, are actually members of a group of related spiders called Wolf spiders. Some of the common varieties available are the Bird-eating spider, Monkey spider, Pink-toed spider, and the Mexican red-leg spider. Tarantulas and the wolf spiders share many of the same characteristics and require similar care.

### Husbandry

Tarantulas accept a variety of food items. Mouse pups (pinkies) and insects are the most commonly fed. Crickets, grasshoppers, meal worms and wax worms are readily available food supplies. Tarantulas need to be fed only once per week. Adults have been known to survive two years without food.

Fresh water should be available at all times. Water can be supplied either in a shallow dish, or by misting the walls and foliage of the enclosure daily with a hand held spray bottle. Care should be taken not to allow the entire cage to get wet, or to allow the water to build up on one end which could cause the plants to rot and pathogenic bacteria to build up within the cage.

The relative humidity within the cage should be maintained at approximately 70%. The reason for this is that Tarantulas breath through specialized structures called spiracles (round openings on the underside of the abdomen). These spiracles open up into the animal's respiratory organ called the book lung. The surface of the spiracular canals and the book lungs are normally moist. In an arid climate these animals can dessicate rapidly. This is probably the most common cause of death in captivity.

Aquariums/terrariums should be maintained at room temperatures from 75-85° F. Adults can usually withstand a mild freeze without perishing. At temperatures between 40-75° F little activity occurs. For breeding, ovipositing and hatching room temperature is sufficient.

The most important consideration when handling tarantulas is to be aware that they are extremely fragile. A common misconception is that they are able to jump many feet from a standstill, and that they are extremely hardy. This old wive's tale has been propogated through many poorly made B rated-horror movies.

The hearts of spiders are located just a small distance from the underside of the body. The abdominal organs are in a similar position. If the animal is dropped the resulting concussion can cause severe damage to these delicate organs, and may be potentially fatal.

There are two acceptable methods for picking these animals up. Grasping the spiders by the section of the body to which the legs are attached will prevent the fingers from placing excessive pressure on the delicate internal organs of the abdomen. The animals should be lifted quickly. This will prevent them from struggling between your fingers, since spiders tend to remain motionless once they are removed from the surface.

The second method, which is much less traumatic, is to coax the spider into one hand by gentle prodding from behind with the other hand. Care should be taken to keep the spider from falling out of your palm. This method takes a little practice, and also takes a while to get used to if the handler is not accustomed to touching the spiders. Tarantulas are very fast runners and may try to run off the end of



your hand when lifted with this open-palmed technique. With practice this gentle handling method should foster a better relationship between the pet and the owner.

Although these creatures are not aggressive toward humans, there are some precautions which should be followed when they are handled. These animals should never be held close to your face and eyes. When disturbed or otherwise annoyed, tarantulas can flick hairs off of the dorsal part of their abdomens. These hairs can be hyperallergenic to some people, and can cause severe eye irritation and temporary blindness. In select individuals the dermal hairs may elicit skin allergies. The frequency of this skin reaction is less common than reactions to bee stings.

Tarantulas infrequently bite humans. Due to their quiet nature they must be tormented greatly before they will attack. A female guarding her eggs might be an exception to this. The configuration and positioning of the tarantulas fangs are such that they must grasp their prey ventrally and inject their poison in a front to back direction. Therefore in order for them to inject venom into a surface as large as a human finger, the finger just about has to be placed directly under the mouth parts.

Except for the rare allergic reaction to the venom, the tarantula bites from animals found in the continental United States are not poisonous to humans. This is not true for most of the specimens from other countries. Before purchasing any of these animals the buyer should be sure to identify the species.

### Reproduction

It is possible to distinguish the sexes in the tarantula and wolf spiders. In immature specimens sex differentiation is almost impossible. Both the male and the female tarantula reach sexual maturity during their seventh year. The mature male spider is identified by a sexual appendage called the ovigerous organ. This organ develops into a protrusion which forms at what would be considered the spider's knee on the first pair of legs behind the head (do not confuse the pedipalps, or sensory organs behind the head, as the first pair of legs). During reproduction the organ is used for fertilizing eggs by depositing spermatazoa into the female.

After breeding the male spider is genetically pre-programmed to die. The male will usually die one to two months after their seventh year molt, regardless of how well they are cared for in captivity. The females, if cared for properly, can last for 25 to 30 years.

The female deposits her fertilized eggs in a spherical web spun from her own silk. Egg cases should be separated from adults prior to hatching. Eggs hatch after three to four weeks. The spiderlets are highly cannibalistic and should be allowed to feed off each other for four to five days to thin out their numbers. After this time they should be separated and fed fruit flies or other suitable prey items.

### Medical Problems

Other than the medical disorders previously discussed for invertebrates in general the tarantulas have very few problems. The most common is one brought about as a defense mechanism by the tarantula itself. When the animal is threatened or agitated it will exhibit a flicking of its body hairs at the eyes of its antagonist. They do this by rapidly brushing their rear-most set of legs over their back which projects their stiff, short dorsal body hairs in the direction of their predator. These hairs can be very irritating to the eyes and skin.

Although this is an intentional behavior, it does leave the animal with a large bald spot over its back. These hairs will be replaced the next time the animal molts.

References available on request

## Chronic Diarrhea: What's the Cause?

Kenneth Simpson, BVM&S, PhD

A thorough and systematic approach is required to determine the cause of chronic diarrhea. An integrated approach based on patient history, physical findings, clinicopathological and intestinal function testing, and diagnostic imaging will be presented.

### Pathophysiology of Diarrhea

The most frequent clinical sign of intestinal disease is diarrhea - the passage of feces containing excess water, resulting in an increase in the fluidity, volume or frequency of bowel movements. The pathomechanisms in the genesis of diarrhea can be categorised as osmotic, secretory, permeability and motility. Most intestinal disease in dogs and cats involves several patho-mechanisms so attempts to categorise animals presented for the investigation of diarrhea using these criteria are usually redundant. e.g. the accumulation of inflammatory cells within the intestine in response to antigenic challenge and other less well defined stimuli, can exert its effects both directly and indirectly by the production of inflammatory mediators such as prostaglandins and leukotrienes. The net result is abnormal mucosal absorption, secretion, permeability and intestinal motility.

### General approach

Diarrhea which has lasted for 2 or more weeks is considered chronic. The approach to chronic diarrhea is based on the origin of diarrhea - large bowel or small bowel, and the presence of other specific or localising clinical findings. Differentiation is important as the diagnostic and therapeutic approaches to small and large bowel diarrhea are different. Differentiation is made on the basis of information furnished by the owner in response to questions about faecal characteristics, volume and frequency and related signs such as vomiting, weight loss, tenesmus and dyschezia.

**Small bowel diarrhea** is a consequence of diseases that affect the small intestine or related structures such as the exocrine pancreas.

### Causes of Chronic Diarrhea

<b>Infectious</b>	Salmonella, Campylobacter, Giardia, Tritrichomonas, Cryptosporidium, FeIV/FIV, FIP
<b>Metabolic</b>	Hyperthyroidism, liver disease, kidney disease
<b>Dietary</b>	Intolerance / allergy

### Exocrine pancreatic insufficiency

#### Small intestinal disease

<i>Structural</i>	Partial obstruction- intussusception, foreign object, neoplasia, congenital anomalies
<i>Inflammatory</i>	lymphoplasmacytic, granulomatous (FIP), eosinophilic
<i>Neoplastic</i>	Lymphosarcoma, adenocarcinoma, leiomyoma, fibrosarcoma
<i>Functional</i>	Motility disorders, idiopathic

### Patient evaluation and diagnostic approach

#### Signalment and history

Infectious and parasitic diseases are common in young animals, whereas neoplasia and metabolic disorders are more common in middle aged to older animals. Certain conditions appear more common in certain breeds e.g. IBD in Siamese. Small bowel diarrhea is generally associated with weight loss and large stool volume. Failure to thrive, changes in appetite, borborygmi, flatus, abdominal discomfort, ascites and oedema are also more common with small than large bowel diarrhea.

#### Physical examination

Particular attention should be paid to hydration status and examination and palpation of as much of the gastrointestinal tract and abdomen as possible. The thyroid gland should be palpated in cats >6yo. A thorough rectal examination should be performed.

#### Investigation of chronic small bowel diarrhea

The approach to patients with chronic small bowel diarrhea who are stable, have no specific localizing clinical findings and are negative for fecal parasites is usually to :

- Rule out endoparasites and pathogenic bacteria *Fecal*
- Screen for systemic disease *CBC, profile, UA ± T4, FeIV/ FIV*

- Rule out exocrine pancreatic insufficiency *TLI*
- Rule out partial obstruction *Palpation, radiographs, ultrasound*
- Evaluate intestinal structure and function *Biopsy - endoscopic / surgical, cobalamin/folate*

### **Laboratory evaluation of chronic small bowel diarrhea**

**Fecal analysis:** Giardia (cysts-ZNSO<sub>4</sub>, IFA, ELISA), Cryptosporidium (IFA), Coccidia, Tritrichomonas fetus (In pouch, PCR), other endoparasites (fecal float). Analysis for Clostridial endospores and endotoxin is fraught with difficulty in interpretation. Culture for Campylobacter and Salmonella in animals with bloody stools, or fever, or chronic undefined diarrhea. Fecal culture cannot be used to diagnose small intestinal bacterial overgrowth which has not been described in cats!

**Hematology:** Anemia - Microcytosis (MCV < 42fl cat) may occur secondary to GI blood loss. Macrocytosis (MCV > 53fl): ddx regenerative anemia, hyperthyroidism, FeLV or cbl/ folate deficiency.

Eosinophilia - intestinal parasitism, mast cell tumors, eosinophilic enteritis or hypereosinophilic syndrome. Neutrophilia ± a left shift may be encountered in inflammatory or infectious conditions. Lymphopenia may be associated with protein losing enteropathies and immunodeficiency.

Lymphocytosis is typical in stressed cats (adrenaline response).

**Serum Biochemistry:** R/O non-intestinal diseases which cause signs such as weight loss, vomiting and diarrhea that overlap with primary GI disease i.e. hyperthyroidism, kidney disease, renal disease, diabetes mellitus.

Metabolic consequences e.g. hypokalemia, hyponatremia. Mild to moderate increases in liver enzymes such as ALT (up to 500 IU/l) are common in cats with hyperthyroidism and intestinal disease. Serum bile acids - liver dysfunction or shunting in patients with GI signs.

Hypoglycemia with signs of gastrointestinal disease should arouse the suspicion of sepsis, liver disease, hypoadrenocorticism or pancreatic tumor. Hypoalbuminemia + hypoglobulinemia R/O protein losing enteropathies

Hypoalbuminemia with normal or increased globulin concentration has to be distinguished from protein losing nephropathy and liver disease.

Chronic diarrhea associated with hypoalbuminaemia usually requires intestinal biopsy to define the cause. Non-intestinal causes of protein losing enteropathy such as portal hypertension should also be considered. When globulin concentrations are normal or elevated renal and hepatic causes should also be pursued.

### **Protein losing enteropathies**

<b>Infectious</b>	Panleucopenia, Salmonella,
<b>Structural</b>	Intussusception
<b>Neoplasia</b>	<u>Lymphosarcoma</u>
<b>Inflammation</b>	<u>Lymphoplasmacytic</u> , eosinophilic, granulomatous
<b>Gastrointestinal haemorrhage</b>	Neoplasia, ulceration

**Urinalysis:** Part of a baseline evaluation to detect or rule out urogenital disorders in patients with signs of intestinal disease. Urate crystalluria may prompt the investigation of hepatic dysfunction as a cause of clinical signs. Urine Prot:creatinine for determining if the kidney is involved in the development of hypoalbuminaemia in patients with intestinal signs.

**Serology and hormone assays:** T<sub>4</sub>, FIV and FeLV.

**Tests of pancreatic function:** Exocrine pancreatic insufficiency is uncommon in cats and is usually associated with chronic diarrhea and polyphagia and a poor haircoat fTLI ≤ 8µg/l.

Pancreatitis can occur concurrently with chronic intestinal disease and cholangitis. Measurement of serum PLI (@sensitivity 67%, and specificity at 91%) and ultrasonography (sensitivity 35 to 67 %, with a specificity of @ 73%) may help to determine the presence of pancreatitis

**Radiography:** Survey abdominal radiographs are taken in patients with vomiting, but are low yield in patients with chronic diarrhea. Contrast radiography can be useful in evaluating partial obstruction and transit time/ gut length if ultrasonography is not available. Thoracic radiographs are often warranted in older cats with weight loss to screen for systemic disease.

**Ultrasonography:** Ultrasound is useful for detecting intestinal lesions such as intussusceptions, masses and foreign bodies, and for assessing intestinal wall thickness. The results of radiography and ultrasound provide a rational basis for selecting endoscopic biopsy (±duodenal juice analysis) or a laparotomy. Normal or diffusely thickened intestines can initially be evaluated endoscopically while focal lesions usually require

guided aspiration or laparotomy. Muscularis hypertrophy and mesenteric lymphadenopathy are frequently associated with inflammatory bowel disease and alimentary lymphoma.

### **Tests of intestinal function**

When a clinical problem cannot be adequately defined or localised to the small intestine a variety of tests can be used to assess small intestinal function. Intestinal function tests have the potential benefit of allowing an overall assessment of SI function, rather than the small snapshot provided by a biopsy. They should always be critically evaluated in the context of the whole patient.

### **Cobalamin and folate**

The measurement of circulating concentrations of cobalamin and folate may give an indication of the site and cause of intestinal dysfunction. Plasma concentrations of cobalamin and folate are labile and reflect the balance between dietary intake, bacterial utilisation and production, and intestinal absorption and body losses.

The interpretation of circulating cobalamin and folate concentrations with regard to small intestinal disease is only valid if exocrine pancreatic insufficiency, dietary supplementation, parenteral administration have been excluded and attention is paid to dietary vitamin content.

Subnormal concentrations of cobalamin are common in cats with EPI, intestinal, pancreatic or hepatic disease:

Forty-nine of 80 serum samples submitted from cats with signs of gastrointestinal disease during the period of January 1996-January 1998 had cobalamin concentrations below the reference range for healthy cats (range 900 - 2,800 pg/ml ; mean  $\pm$  SD = 1775  $\pm$  535 pg/ml SD ; n=33). Cats with subnormal cobalamin concentrations (mean  $\pm$  SD = 384  $\pm$  272 pg/ml, range 3 - 883pg/ml) were middle aged or older and were presented for weight loss, diarrhea, vomiting, anorexia and thickened intestines. Definitive diagnoses in 22 cats included inflammatory bowel disease, intestinal lymphoma, cholangiohepatitis or cholangitis, and pancreatic inflammation. Serum concentrations of cobalamin were particularly low in cats with intestinal lymphoma, 3/5 of which also had subnormal serum concentrations of folate (< 9ng/ml). The simultaneous presence of disease in the intestines, pancreas or hepato-biliary system in many cats made it difficult to determine the cause of subnormal cobalamin concentrations. The circulating half-life of parenteral cyanocobalamin was shorter in two cats with IBD (5 days) than in four healthy cats (12.75 days).

The presence of subnormal serum concentrations of cobalamin in 49 of 80 cats evaluated suggests that the measurement of serum cobalamin may be a useful indirect indicator of enteric or pancreatic disease in cats. The rapid depletion of circulating cobalamin in cats indicates that cats may be highly susceptible to cobalamin deficiency. From studies to date it appears that cats with a cobalamin below 200pg/ml consistently have increased MMA and require parenteral cobalamin.

**Intestinal Biopsy:** Biopsy of the intestine is frequently required to achieve a diagnosis in patients with chronic diarrhea due to malabsorption. In diffuse intestinal diseases and in animals with hypoproteinaemia endoscopy provides a minimally invasive low risk way of obtaining a biopsy. At least seven to 10 endoscopic biopsies should be acquired

Endoscopic biopsies are restricted to the mucosa and are small, difficult to process and orientate, and can be obtained only from the proximal duodenum and occasionally the distal ileum. Thus surgical biopsies are necessary in patients with focal intestinal lesions and in those whom endoscopic biopsy has not yielded a result. Surgical biopsies should be taken from multiple sites along the small intestine even if the intestine looks grossly normal. A small dermatologic punch aids the surgeon in obtaining full thickness biopsies and biopsy sites are sutured in an appropriate fashion. Extreme care is required where the bowel looks grossly abnormal and in hypoproteinemic patients to ensure leakage does not occur. Precautionary measures such as serosal patch or omental wraps may be employed. Biopsies of mesenteric lymph nodes should also be obtained. Other abdominal organs such as the liver, and pancreas can be grossly examined and biopsied. The information which can be obtained from intestinal biopsies depends on the expertise of the pathologist. Minimum evaluation should include routine microscopic examination of H&E stained sections. The pathologist should be able to give an indication of villus height and morphology, ratio of crypt to villus and the type and degree of cellular infiltrate and intraepithelial lymphocyte count. Recent studies suggest that changes in mucosal architecture are much more significant than subjective alterations in cellularity. Staining for different lymphocyte sub-types and clonality PCR may be useful in distinguishing IBD and low grade alimentary lymphoma

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**NOTES:**


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## Chronic Enteropathies in Cats: Diagnosis and Management

Kenneth Simpson, BVM&S, PhD

This presentation will focus on the two major chronic enteropathies of cats: inflammatory bowel disease and alimentary lymphoma.

### Feline Inflammatory Bowel Disease

Feline inflammatory bowel disease (IBD) is the term applied to a group of poorly understood intestinal disorders that are associated with vomiting, diarrhea and weight loss in cats. Diagnosis is usually based upon subjective analysis of intestinal mucosal biopsies and qualified according to the dominant mucosal infiltrate, typically lymphocytes and plasma cells. However, more objective studies have demonstrated increased expression of MHC class II antigen by leukocytes in the lamina propria and enterocytes, and upregulation of pro-inflammatory and immunoregulatory cytokines, rather than an increase in mucosal cellularity. Abnormalities in mucosal architecture, such as crypt distortion, villous blunting and fusion, and fibrosis have also been described, and have been associated with the severity of clinical signs, and the subjective histological grade of IBD. The cause of feline IBD has not been determined, but it is suspected that IBD in cats, like IBD in people, is a consequence of uncontrolled intestinal inflammation in response to a combination of elusive environmental, enteric microbial, and immunoregulatory factors in genetically susceptible individuals. Genetic susceptibility in people is linked increasingly to defects in innate immunity, exemplified by mutations in the innate immune receptor NOD2/CARD15, that in the presence of the enteric microflora may lead to up-regulated mucosal cytokine production, delayed bacterial clearance and increased bacterial translocation, thereby promoting and perpetuating intestinal inflammation. This possibility is supported by studies showing the pivotal importance of the enteric microflora in the development of IBD in rodents with engineered susceptibility and those demonstrating an abnormal mucosa-associated flora, considered to interact most closely with the innate immune system, in people with IBD. Knowledge of genetic susceptibility in cats with IBD is limited, with some studies reporting a predisposition for purebred cats such as Siamese. Culture based studies have shown fewer luminal microaerophilic bacteria in the duodenal juice of cats with clinical signs of gastrointestinal disease than healthy cats. More recent studies have revealed changes in the intestinal microflora of cats with chronic gastrointestinal disease, termed dysbiosis. The number of mucosa-associated Enterobacteriaceae was higher in cats with signs of gastrointestinal disease than healthy cats ( $P < 0.001$ ). Total numbers of mucosal bacteria were strongly associated with changes in mucosal architecture ( $P < 0.001$ ) and the density of cellular infiltrates, particularly macrophages ( $P < 0.002$ ) and CD3<sup>+</sup>lymphocytes ( $P < 0.05$ ). The number of Enterobacteriaceae, *E. Coli*, and *Clostridium* spp. correlated with abnormalities in mucosal architecture (principally atrophy and fusion), upregulation of cytokine mRNA (particularly IL-1, -8 and -12), and the number of clinical signs exhibited by the affected cats. These data establish that the density and composition of the mucosal flora is related to the presence and severity of intestinal inflammation in cats, and suggest that mucosal bacteria are involved in the etiopathogenesis of feline IBD.

### A Stepwise Approach to Treating Feline Inflammatory Bowel Disease :

How confident am I the cat has IBD?

- Clinical findings
- Clinicopathological tests
- Diagnostic imaging
- Intestinal biopsy

### Have I ruled out

Systemic/ metabolic disease  
 Dietary intolerance/ food allergy  
 Infectious agents  
   Protozoa  
     *Giardia*  
     *Tritrichomonas*  
 Pathogenic bacteria  
   Campylobacter / Salmonella

Viral?

Structural/anatomic abnormalities

- Does the cat have multiple problems or organ systems involved?
- Is the cat deficient in cobalamin or folate?
- Do I need a biopsy?
- **What and how should I biopsy?**
- How do I interpret the biopsy results and integrate gastric and intestinal histopathology?
- Is it IBD or small cell lymphoma?
- What diet should I use?
- When should I use antimicrobials? corticosteroids? chlorambucil?
- How do I manage concurrent disease in the liver and pancreas?
- How do I assess response?

### **An overview of diagnosis and treatment**

#### ***Clinical findings:***

Vomiting is the most common clinical sign in cats with IBD. Vomitus often contains bile. Other findings include diarrhea, changes in appetite, weight loss and less commonly excessive borborygmi and abdominal discomfort.

The severity of disease ranges from intermittent vomiting in mild cases to intractable small bowel diarrhea, inappetence and weight loss in severe ones. The severity of the disease correlates with the degree of intestinal damage, particularly villus atrophy and fusion

Physical findings range from normal to thickened intestines, mesenteric lymphadenopathy and loss of muscle mass. Ascites or edema are extremely rare in cats with IBD.

Routine laboratory testing may reveal mild to moderately elevated liver enzymes as a result of GI barrier dysfunction. However, IBD can be associated with concurrent hepatobiliary disease and pancreatitis- "triaditis"- so the clinician must consider these disorders (Ultrasonography and fPLI aid detection of intercurrent disease). The presence of hypocalcemia would ring alarm bells for pancreatitis. Hypoalbuminemia is rare. CBC is usually normal. Eosinophilia is encountered in some cats with LP enteritis, and should prompt consideration of parasites or food intolerance/allergy, as well as mastocytosis or hypereosinophilic syndrome. Measurement of serum cobalamin and folate can aid the detection of intestinal disease- low cobalamin concentrations are common in cats with IBD (EPI should be excluded by TLI assay). Cobalamin deficiency can produce identical signs to those associated with IBD. A combination of low folate and cobalamin tends to support a diagnosis of severe IBD or GI lymphoma.

Ultrasonographic findings in cats with IBD overlap with those of cats with lymphoma i.e. muscularis hypertrophy and mesenteric lymphadenopathy

#### ***Diagnosis:***

A diagnosis of idiopathic IBD is made by excluding systemic, parasitic, infectious, pancreatic and structural causes of chronic vomiting, weight loss or diarrhea and demonstrating histopathological abnormalities in intestinal biopsies. Keep in mind that IBD may co-exist with hepatobiliary disease and/or pancreatitis.

#### ***Treatment:***

Treatment of IBD is usually a "best guess least harm" approach employing dietary modification, vitamin supplementation, antimicrobial agents and immunosuppression. Treatment is to some extent based on the severity of the disease.

Mild to moderate disease may be associated with dietary sensitivity / intolerance, cobalamin deficiency or antibiotic responsive enteropathy.

A therapeutic dietary trial can be performed with either:1) a highly digestible diet which is gluten-free ,2) a diet limited to a single novel protein source or3) a diet containing protein hydrolysate, to determine if dietary sensitivity or intolerance are present. A response is usually observed within one to two wks. Re-challenge with the original diet is required to demonstrate intolerance.

Cobalamin deficiency is treated with parenteral cobalamin (0.5ml SC q 2-3wks). Folate should be given orally if serum concentrations are low.

A therapeutic trial (21days) with Tylosin (10mg/kg PO TID), metronidazole (15mg/kg PO BID) or oxytetracycline (10-20mg/kg PO TID) can be undertaken to determine if an antibiotic responsive enteropathy is present.

In patients who fail these trials and in those with moderate to severe disease, or hypoproteinaemia, immunosuppressive agents are usually added to achieve a response. Oral prednisolone (1-2mg/kg PO BID) is the initial drug of choice. It is usually administered at an immunosuppressive dose for 2-3 wks and then decreased by 50% every 2-3wks, and continued on an alternate day basis for 2-3 months. If clinical response is poor, chlorambucil (6mg/m<sup>2</sup> PO PO EOD (@2mg/5.3kg cat) and prednisone (5mg PO /cat/day) are initiated. Metronidazole (15mg/kg PO BID 10-14d then SID 10-14d) is frequently used in conjunction with corticosteroids to modify the microflora. However metronidazole is a potential mutagen and the author avoids long-term therapy.

Successful treatment is accompanied by a decrease in clinical signs, and an increase in plasma proteins (though low albumin is uncommon in IBD). Once a patient has had 2-3 months remission from signs it may be possible to

gradually withdraw immunosuppressive therapy. If signs recur daily medication is continued until signs resolve then gradually reduced. In patients who respond poorly to therapy or relapse after an initial response lymphoma should be ruled out.

**Prognosis** The prognosis for lymphoplasmacytic enteritis is variable and depends on its severity and the presence of concurrent disease. Many patients require prolonged treatment with glucocorticoids and diet. As no accurate criteria exist for predicting response it is wise to give a guarded prognosis.

### Alimentary lymphoma

*The changing and variable phenotype of feline alimentary lymphoma:*

Lymphomas represent up to ninety percent of hematopoietic tumors in the cat and are one of the most frequently diagnosed tumors of domestic cats. During the feline leukemia virus (FeLV) era of the 1960s through the 1980s, FeLV was the most common cause of up to 70% of cases of lymphoma that were predominantly cranial mediastinal, multicentric, renal and central nervous forms, associated with FeLV antigenemia. However, despite a decline in FeLV-associated lymphoma and contrary to expectations the prevalence of lymphoma has increased in the post-FeLV era, and there has been a change in the frequency of affected anatomic sites and patient demographics. Alimentary lymphoma is now the most common anatomic form and predominantly affects middle age to older cats, in contrast to mediastinal or multicentric lymphoma that typically affect younger cats. This increase in alimentary lymphoma has also been accompanied by a change in immunophenotype, from predominantly high grade B cell to predominantly low grade T cell. In a study of 41 cats with low-grade lymphocytic lymphoma evaluated at the Cornell University Hospital for Animals and South Carolina Veterinary Internal Medicine between 1995-2005, the median age at diagnosis was 13 years 148 (range, 6-17 years) and 40/41 were Domestic Shorthair (n = 33) or Domestic Longhair (n = 7). Lymphoma was confined to the gastrointestinal tract in 68% of cats and eighty-nine percent (32 of 36) of lymphomas were determined to be of T-cell origin by immunohistochemistry, while 8% (3 of 36) were of B-cell origin. A search of our pathology database for feline alimentary lymphoma during the years 2007 to 2011 yielded a total of 136 small cell lymphoma (SCL) and 16 cases of large cell lymphoma (LCL). The immunophenotype of a randomly chosen subset of 33 of the 136 cats with SCL indicated they were all T-cell. Surprisingly, we found that LCL were divided evenly between T- (8/16) and B-cell (7/6), with one tumor considered B&T-cell. This diversity in cell morphology and immunophenotype has potential implications for etiopathogenesis and treatment, and subsequent studies should be stratified on the basis of tumor immunophenotype and cell morphology.

The response to therapy has also changed, with overall median survival time reaching 704 days in low-grade lymphoma versus weeks to months in high-grade large cell lymphoma. Until, recently the large B cell phenotype predominated in Australia and the UK, but small T- cell phenotype has recently emerged. The sequential temporal emergence of low-grade alimentary lymphoma in the USA, Great Britain and Australia echoes the appearance of feline hyperthyroidism and raises the possibility of an underlying environmental or infectious etiology. The factors responsible for the changes in prevalence, immunophenotype and biology of feline alimentary lymphoma are not known.

**Clinical findings:** Middle aged and older cats (median 13yrs), predominantly DSH cats are reported. Weight loss, vomiting, chronic small bowel diarrhea and progressive inappetence are common features of GI lymphoma. Physical examination may reveal diffusely thickened or nodular intestines ± mesenteric lymphadenopathy. Hepatosplenomegaly, renomegaly, generalized lymphadenopathy and abdominal mass may also be detected. Acute abdominal pain and shock may be present if intestinal perforation has occurred.

**Diagnosis:** Routine biochemistry may reveal hypoalbuminemia. Anemia which is either normocytic normochromic non-regenerative or microcytic and hypochromic, and neutrophilia may also be present. Serum concentrations of cobalamin are often very low in cats with GI lymphoma and serum folate concentrations may also be reduced. High PLI concentrations are found in some cats and may indicate concurrent pancreatitis or pancreatic lymphoma. Ultrasound is useful for evaluating intestinal thickness / layering, presence or absence of mucularis hypertrophy, and detecting mesenteric lymphadenopathy and abnormalities in liver/kidney/spleen and pancreas. However it cannot distinguish lymphoma from IBD. Diagnosis can be made by demonstrating neoplastic lymphocytes in aspirates or biopsies from enlarged intestinal or peripheral lymph nodes, but is more often made by intestinal biopsy. The absence of lymphoma in a fine needle aspirate does not rule it out : there is a high degree of discordance between FNA and biopsy results of LN aspirates from cats with confirmed alimentary lymphoma. Endoscopic visualization and biopsy can enable the accurate diagnosis of GI lymphoma. However, endoscopy can also miss submucosal and serosal lesions or yield a diagnosis of "lymphoplasmacytic enteritis". Many cats with signs of intestinal disease including GI lymphoma have concurrent evidence of hepatic and pancreatic disease and undergo exploratory laparotomy and circumvent the endoscopy surgery debate.

**Treatment and prognosis:** In a recent study of 41 cats with low-grade lymphoma, lymphoma was confined to the gastrointestinal tract in 68% of cats, while 32% had other organ systems affected with or without gastrointestinal involvement. Extra-gastrointestinal sites involved included mesenteric lymph nodes (n = 6), liver (n = 10), spleen (n



= 1), and pancreas (n = 1). Some cats had more than 1 site affected. Eighty-nine percent (32 of 36) of lymphomas were determined to be of T-cell origin via immunohistochemistry, while 8% (3 of 36) were of B-cell origin. Fifty-five per cent of cats achieved a complete response to therapy and 37% achieved a partial response. The majority of cats (n = 31; 76%) received prednisone at a dose of 5 mg, PO, q 12-24 hrs and most (n = 35; 85%) received chlorambucil at a dose of 2 mg, PO, every other day. Eight percent of the cats experienced no response. There was no association between any risk factors and response to therapy. Overall median remission duration was 948 days. Partial response to therapy was associated with shorter remission duration ( $P = 0.002$ ). Overall median survival time was 704 days. No factors were significantly associated with survival time. Interestingly, 78% of cats tested in this study had hypcobalaminemia, which was associated with short remission duration, but only in the univariable analysis. Thus supplemental cobalamin (0.5ml SC q 2-3wks) and folate should be given as required. Lymphoblastic lymphoma, is much more aggressive than lymphocytic lymphoma, is generally treated with combination chemotherapy, and carries a poor prognosis.

***Given the dramatic differences in outcome of lymphocytic vs. lymphoblastic lymphoma is there any way to distinguish these forms of the disease without a biopsy?***

In the study of Fondacaro et al clinical signs, physical exam findings and endoscopic localization of disease overlapped in cats with lymphoblastic and lymphocytic lymphoma. Lethargy and the presence of an abdominal mass tended to be more frequent in cats with lymphoblastic lymphoma.

***Can I diagnose intestinal lymphoma with an endoscopic biopsy?***

Yes and No! Endoscopic visualization and biopsy can enable the accurate diagnosis of GI lymphoma. However, endoscopy can miss submucosal and serosal lesions or yield a diagnosis of “lymphoplasmacytic enteritis”. Many cats with signs of intestinal disease including GI lymphoma have concurrent evidence of hepatic and pancreatic disease and undergo exploratory laparotomy circumventing the endoscopy surgery debacle. Diagnosis also depends on the pathologist! Some pathologists are unwilling to diagnose lymphoma on endoscopic biopsies.

***How can I distinguish gastrointestinal lymphoma from inflammatory bowel disease?***

The signalment, clinical presentation, physical examination and results of clinical investigation are often very similar in cats with IBD and alimentary lymphoma. Hypoalbuminemia is a rare feature of IBD in cats and it's presence makes me think of high grade IBD or lymphoma. Intestinal perforation should place lymphoma high up the list. Concurrent renomegaly or splenomegaly should also prompt consideration of lymphoma and aspiration/biopsy. The presence of intestinal thickening, muscularis hypertrophy and mesenteric lymphadenopathy is consistent with IBD and lymphoma. Moreover, fine needle aspiration of enlarged lymph nodes can yield reactive hyperplasia in cats with GI lymphoma. Endoscopy may reveal marked thickening of the gastric mucosa and increased friability of the intestinal mucosa in cats with lymphoma, but there is an overlap between cats with IBD and alimentary lymphoma. At the present time the accurate distinction of GI lymphoma from IBD relies on histopathological evaluation. This can be relatively straightforward where biopsies are considered adequate in size and number, and unequivocal lymphoblastic cells or a monomorphic population of small lymphocytes are present. However, some biopsies display features of lymphoma and IBD, and others such as endoscopic biopsies do not allow thorough evaluation of all tissue compartments, and make it difficult to distinguish IBD from lymphoma. Immunophenotyping for T and B cell lineage, and PCR to detect clonal expansion of B (feline immunoglobulin heavy chain variable region genes) and T cells (T cell receptor gamma variable region genes) have been developed to aid this process.

***What is driving the development of feline alimentary lymphoma?***

Low-grade alimentary lymphoma in cats does not appear to be related to FeLV or FIV. There is strong evidence in people that low grade mucosa associated lymphomas develop as a consequence of a genetic predisposition (typically chromosomal translocations that impact mucosal inflammation or apoptosis) and a chronic infections with bacteria and viruses are increasingly associated with lymphoma. In people, infections with *Helicobacter*, *Borrelia*, *Chlamydia* and *Campylobacter* are associated with gastric, cutaneous, periocular and intestinal B cell MALT-lymphomas, respectively. The observation that 8-13% of people with celiac disease develop non-Hodgkin's enteropathy-associated T cell lymphoma is of high relevance to cats with alimentary lymphoma. Lymphomatous transformation in celiac disease is associated with unresolved chronic lymphocytic inflammation, villus blunting, an IL-6 and IL-8 rich cytokine environment, and global shifts in the enteric polymicrobial environment, towards proteobacteria and *E.coli*. We have established that cats with lymphoplasmacytic enteritis have shifts in mucosal Enterobacteriaceae, *E. coli*, and *Clostridium* spp. that correlate with abnormalities in mucosal architecture (principally atrophy and fusion), proinflammatory cytokine upregulation (IL-1, -8 and -12), and clinical severity, that parallel human coeliac disease. In preliminary studies, we found that the mucosal cytokine environment in feline alimentary lymphoma is dominated by IL-6 upregulation, and have detected invasive bacteria in 14/17 large cell lymphomas (a mix of T and B cell lymphomas) and 6 of 33 small cell lymphomas (T cell) relative to 0/18 controls.

While it is well established that persistent viral infections can drive lymphoma in cats, the relationship of FeLV to alimentary lymphoma in cats is controversial, with discordance between antigenemia (0-38%) and PCR positivity of

tissues for viral sequences. It is conceivable that latent FeLV infection drives feline alimentary lymphoma, but this possibility has to be weighed against the falling prevalence of FeLV in the cat population. In people a variety of viruses have been associated with lymphoma including: the  $\gamma$ -herpesvirus Epstein Barr Virus (EBV), which is associated with Hodgkin's lymphoma and various non-Hodgkin's lymphomas, including B-cell lymphoma in immunocompromised patients, Kaposi Sarcoma herpesvirus in individuals with immunosuppressive conditions, Human T-cell Leukemia Virus-1 with Adult T-cell leukemia-lymphoma (ATLL), a peripheral T-cell malignancy and Hepatitis C virus (HCV), which has been implicated in the development of some cases of non-Hodgkin lymphoma (NHL). Recent studies have expanded our knowledge of the role that viruses may play in promoting chronic intestinal inflammation, which is a known risk factor for tumorigenesis. A new dimension in understanding the multifactorial basis of chronic inflammatory diseases such as Crohn's disease has emerged from the discovery that a virus trigger (norovirus) is required to observe intestinal abnormalities in IBD susceptible *Atg16/1HM* mice. Mucosal inflammation depended on the presence of the intestinal microbiome and pro-inflammatory cytokines. Thus, variations in a host autophagy gene, exposure to a specific virus and the microbiome can act together to trigger intestinal inflammation in mice that is similar to that in patients with Crohn's disease.

Taken as a whole, the evidence to date supports the possibility that an underlying bacterial or viral infection could be involved in the etiopathogenesis of feline alimentary lymphoma

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## Update on the Diagnosis & Management of Canine Pancreatitis

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From a clinical perspective pancreatitis can be broadly categorized as acute, recurrent acute or chronic. It can be further classified according to its effect on the patient as mild or severe, non-fatal or fatal, and also by the presence of sequela such as abscess formation. Histologically, acute pancreatitis is characterized by findings that range from pancreatic edema to necrosis, variable infiltrates of mononuclear and polymorphonuclear cells, and local changes such as peri-pancreatic fat necrosis and thrombosis. Acute pancreatitis may resolve or persist and can be complicated by secondary infection and pseudocyst or abscess formation. It is tempting to equate mild acute pancreatitis with pancreatic edema, and severe or fatal pancreatitis with pancreatic necrosis, but this relationship has not been critically examined in patients with naturally occurring pancreatitis. Chronic pancreatitis is characterized by fibrosis and low grade mononuclear inflammation and may be a sequela of recurrent acute pancreatitis or a subclinical disease process that may present as diabetes mellitus or exocrine pancreatic insufficiency (EPI).

### *Etiology and Pathogenesis*

The etiology and pathogenesis of spontaneous pancreatitis is poorly understood. The major factors which have been implicated (by association) as causes of acute pancreatitis in the dog and the experimental evidence to support their involvement are summarized as follows:

<u>Potential aetiology</u>	<u>Clinical</u>	<u>Experimental</u>
Hyperlipidemia	Lipemia Abnormal lipid profiles Lipodystrophy	High fat diet IV Free Fatty Acids
Diet	Diet indiscretion Obesity	Fat >>protein diet Ethionine supplementation
Bile reflux	Concomitant biliary disease (?cats)	Bile infusion
Hypercalcemia	Ca infusion ? Hyperparathyroidism	Ca infusion
Corticosteroids	? Hyperadrenocorticism ? + Disc surgery?	Increased CCK sensitivity Pancreatic duct hyperplasia
Drug/toxin related	Organophosphates L-asparaginase Azathioprine, sulphonamides Potassium bromide and Phenobarbital Zinc	Organophosphates
Ischemia/reperfusion	Post-GDV	Ex-vivo pancreas
Hereditary predisposition	? Miniature Schnauzer, Min. poodle, Terriers, non-sporting dogs	
Endocrinopathies	? Hypothyroidism, diabetes mellitus	

Irrespective of the initiating cause pancreatitis is generally believed to occur when digestive enzymes are activated prematurely within the pancreas. In the normal pancreas safeguards are present to ensure that harmful pancreatic enzymes are not activated until they reach the intestinal lumen. Enzymes are stored in zymogen granules within the acinar cell in the presence of pancreatic secretory trypsin inhibitor (PSTI) and are released at the apical surface directly into the duct system. They are only activated in the intestine, by trypsin, following the cleavage of trypsin activation peptide (TAP) from trypsinogen by enterokinase. Potential sites for the intrapancreatic activation of pancreatic enzymes can therefore logically be divided into interstitial

(within the duct system and interstitium) and intracellular (within the acinar cell). Experimental studies suggest that bile and enteric reflux, and intravenous free fatty acid (FFA) infusion initiate pancreatitis by an interstitial mechanism whereas hyperstimulation with caerulein or organophosphates, pancreatic duct obstruction and choline deficient methionine supplemented diet (CDE diet) result in intracellular activation. Experimental pancreatic hyperstimulation with cholecystokinin (CCK: or its analogue cerulein), dietary supplementation with methionine, and obstruction of the pancreatic duct lead to the formation of large intracellular vacuoles in acinar cells. Vacuole formation is thought to be a consequence of the uncoupling of exocytosis of zymogens and abnormal intracellular trafficking of digestive and lysosomal enzymes. These subcellular alterations are considered to precipitate the intracellular activation of digestive enzymes. Pancreatic hyperstimulation may be of direct relevance to naturally occurring pancreatitis in dogs. CCK is normally released by cells in the duodenum in response to intraluminal fat and amino acids and coordinates and stimulates pancreatic secretion and gallbladder contraction during digestion. It is possible that high fat diets exert their effects via the excessive release of cholecystokinin and that hypercalcemia, organophosphates and high levels of circulating glucocorticoids also facilitate (potentially by changing pancreatic sensitivity to hyperstimulation), or cause pancreatic hyperstimulation; however, this is not proven. Edematous pancreatitis induced by CCK hyperstimulation in dogs is characterized by a rapid but self-limiting, burst of trypsinogen activation suggesting that the pancreas has a feedback mechanism to limiting trypsinogen synthesis and activation (see nutritional management). This concept of pancreatic down regulation is important when considering nutritional intervention in acute pancreatitis.

Often pancreatic inflammation is a self-limiting process, but in some animals reduced pancreatic blood flow and leukocyte and platelet migration into the inflamed pancreas may cause progression to pancreatic necrosis. Secondary infection may arise by bacterial translocation from the intestine. Release of active pancreatic enzymes and inflammatory mediators from the inflamed pancreas, such as Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 (IL-1) and phospholipid platelet activating factor (PAF), amplifies the severity of pancreatic inflammation, and adversely affects the function of many organs (systemic inflammatory response), and cause derangement in fluid, electrolyte and acid-base balance. It is the development of multisystemic abnormalities that separates mild from severe, potentially fatal pancreatitis.

## **Diagnosis**

There is currently no single specific test for pancreatitis in dogs and diagnosis is based on a combination of compatible clinical, clinicopathological and imaging findings. Surgical biopsy may be required to confirm a diagnosis, and to distinguish inflammation from neoplasia.

## ***Clinical findings***

### **Signalment and History**

Middle aged to old dogs (>5yrs years old) who are overweight appear at higher risk. Miniature Schnauzers, Yorkshire and Silky Terriers, non-sporting breeds and perhaps miniature poodles may be at increased risk of developing pancreatitis. There is no clear sex predisposition. Endocrinopathies such as hypothyroidism, diabetes mellitus and hyperadrenocorticism may also be risk factors. Thirteen percent of 221 dogs with diabetes mellitus had histological evidence of acute pancreatitis. Hyperlipidemia is another potential risk factor.

The history may reveal a recent episode of dietary indiscretion, toxin ingestion or drug administration. Common clinical signs include lethargy, anorexia, hunched stance, vomiting ( $\pm$  blood), diarrhea ( $\pm$  blood), increased respiratory rate and enlarged abdomen. Some dogs have a

history of icterus preceded by vomiting. Polyuria and polydipsia may be present in dogs with diabetes mellitus and pancreatitis.

#### Physical Examination

Physical findings in dogs with acute pancreatitis are variable and range from depression, to mild dehydration with signs of abdominal pain, to acute abdominal crisis with shock (tachycardia, prolonged capillary refill time, tacky mucous membranes, hypothermia), petechiation, icterus and ascites. An abdominal mass is palpated in some dogs.

#### **Diagnostic approach and differential diagnosis**

The differential diagnosis of acute pancreatitis in dogs is usually centered round the problems of vomiting and abdominal pain.

In vomiting dogs the initial approach is to distinguish self-limiting from more severe causes of vomiting on the basis of physical findings and a minimum database (e.g. Packed cell volume, total protein, azostick, urinalysis, plasma concentrations of sodium and potassium). Where vomiting is associated with systemic signs of illness, or is persistent, the clinician has to differentiate metabolic, polysystemic infectious, toxic and neurologic causes from intra-abdominal causes. This is usually achieved on the basis of combined historical and clinical findings coupled with a minimum database and the evaluation of hematology and serum chemistry profile, urinalysis and abdominal radiography. Measurement of serum amylase or lipase is often reported on routine serum chemistry profile. Additional procedures such as ultrasonography, abdominal paracentesis or assay of trypsin-like immunoreactivity, TAP or immunoreactive canine pancreatic lipase (cPLI, spec cPL etc) are usually performed on the basis of these initial test results and help to distinguish pancreatitis from other intra-abdominal causes of vomiting.

Where abdominal pain is the major finding localizing abnormalities such as abdominal distension are rapidly pursued with radiography, ultrasonography and paracentesis while providing supportive treatment on the basis of physical findings and a minimum data base and awaiting the results of hematology, serum chemistry profile and urinalysis. Abdominal pain can arise from any intra-abdominal structure. Musculoskeletal disorders such as discospondylitis and prolapsed discs can be hard to distinguish from abdominal causes of pain.

Diarrhea, which was bloody in some cases, is reported as a more frequent sign than vomiting in dogs with experimental acute pancreatitis. Acute pancreatitis and its complications (infection, pseudocyst or abscess formation) should also be considered in the differential diagnosis of icterus and pyrexia. Some dogs with pancreatitis exhibit few localizing clinical signs. Diagnosis in these animals requires a high index of suspicion and use of versatile diagnostic tests such as ultrasonography.

#### **Clinicopathological findings**

##### **Hematology:**

Extremely variable, ranging from mild neutrophilia and slightly increased haematocrit, through marked leukocytosis with or without a left shift, to thrombocytopenia, anemia and neutropenia with a degenerative left shift. Thrombocytopenia in dogs with pancreatitis is often associated with DIC and additional tests of hemostasis (OSPT, APTT, FDP or D-dimer, fibrinogen, antithrombin III) are performed to determine if DIC or other coagulopathies are present.

##### **Serum biochemistry :**

Serum biochemical abnormalities include azotemia (pre-renal and renal), increased liver enzymes (ALT, AST, AP), hyperbilirubinemia, lipemia, hyperglycemia, hypoproteinemia, hypocalcemia, metabolic acidosis and variable abnormalities (usually decreased) in sodium, potassium and chloride.

**Urinalysis:**

Enables azotemia to be characterized as renal or pre-renal. Proteinuria occurs in some dogs with acute pancreatitis and is usually transient. The presence of glucose or ketonuria should prompt consideration of diabetes mellitus.

**Pancreas specific markers:**

Classically, elevations in serum amylase and lipase activity have been used as indicators of pancreatic inflammation in dogs. However these enzymes can be increased in non-pancreatic disease, and dogs with confirmed pancreatitis may also have normal amylase and lipase activity. For example, in dogs with histologically confirmed pancreatitis, lipase is normal in 28 to 61% of dogs, and amylase is normal in 31 to 47% of dogs.

These limitations have led to the development of assays for enzymes or markers considered pancreatic in origin such as trypsin-like immunoreactivity (TLI), trypsinogen activation peptide (TAP), pancreatic lipase immunoreactivity (PLI, cPL) and pancreatic elastase. Experimental studies have documented high concentrations of TLI, TAP and PLI in dogs with experimental acute pancreatitis. The utility of TLI, TAP, PLI and elastase for the diagnosis spontaneous pancreatitis in dogs has not been thoroughly evaluated. Normal, subnormal and increased concentrations of TLI have been observed in dogs with confirmed pancreatitis. Elevations of TAP have been observed in the serum and urine (TAP:creatinine) of dogs with severe pancreatitis, and TAP may be a better prognostic than a diagnostic indicator of pancreatic inflammation. Experience with PLI/cPL is increasing and it appears better than serum amylase, conventionally measured serum lipase, TLI and elastase in the diagnosis of pancreatitis.

1. i. A negative cPL (<200 µg/l) or SNAPcPL is better at predicting the absence of pancreatitis than a positive cPL (McCord et al)
  - ii. In 40 dogs classified as having no pancreatic disease because of an absence of clinical signs and no inflammation on histology- Thirty-eight had a Spec-cPL value ≤ 200 µg/L, and 39 had values < 400 µg/L. This resulted in a specificity using the lower cutoff value of 95% (95% confidence interval 83.1-99.4), and using the higher cutoff value a specificity of 97.5% (95% confidence interval 86.8-99.9) ( Neilson Corley et al)
2. Spec-cPL more likely to be positive in severe than mild disease: A study of 70 dogs presented consecutively for post-mortem at a tertiary referral center (Trivedi et al) : The estimated sensitivity of canine pancreatic lipase was 21% for mild disease and 71% for moderate disease. This was a lower sensitivity than for total lipase (54% and 71%, respectively) in the same cohort of dogs! Although only 7 dogs were classified as having normal pancreatic histology, there was a specificity of 86% for Spec-cPL as compared with 43% for total lipase reported.
3. Recent studies show dry chemistry serum lipase correlates with cPL: The results showed a good correlation ( $r = 0.91$ ), and the normal and pancreatitis dogs identified based on the PLI values were correctly separated based on lipase activity. (Ishioka et al)

**Radiography:**

Radiographic findings in dogs with acute pancreatitis are generally non-specific and include loss of serosal detail, increased opacity in the right cranial quadrant of the abdomen, displacement of the duodenum ventrally and/or to the right, dilated hypomotile duodenum and caudal displacement of the transverse large intestine. Punctate calcification may occasionally be identified in dogs with long-standing pancreatitis; it indicates saponification of mesenteric fat around the pancreas.

Thoracic radiographs may enable the detection of pleural fluid, edema or pneumonia which has been associated with pancreatitis in dogs and cats.



**Ultrasonography**

Ultrasonographic findings include enlarged, hypoechoic pancreas, cavitory lesions such as abscess or pseudocyst, dilated pancreatic duct, swollen hypomotile duodenum, biliary dilatation and peritoneal fluid. One study of dogs with fatal acute pancreatitis indicated that ultrasound supported a diagnosis of pancreatitis in 23/34 dogs. Disorders other than pancreatitis e.g. pancreatic neoplasia, pancreatic edema (associated with hypoproteinemia or portal hypertension) and enlarged peri-pancreatic structures, can have identical ultrasonographic appearance to pancreatitis. Fine needle aspirates of cavitory lesions may be useful to distinguish abscess from pseudocyst.

**Abdominal paracentesis:**

Examination of peritoneal fluid may aid the detection of various causes of acute abdominal signs such as pancreatitis, gastrointestinal perforation or ruptured bile duct.

**Prognostic indicators**

Stratifying the severity of pancreatitis is useful when deciding how aggressive to be with medical and nutritional support, and in offering a prognosis. Severe pancreatitis requires aggressive support and carries a guarded prognosis, whereas mild pancreatitis often responds to short term symptomatic therapy and has a good prognosis. Clinical and clinicopathological criteria can be used to predict the severity of acute pancreatitis. The presence of shock or abnormalities such as oliguria, azotaemia, icterus, markedly elevated transaminases, hypocalcaemia, hypoglycaemia, hypoproteinaemia, acidosis, leukocytosis, falling haematocrit, thrombocytopenia and DIC should be considered likely indicators of severe pancreatitis in the dog and cat.

The measurement of components of the systemic inflammatory response such as TNF- $\alpha$ , and C-reactive protein, and IL-6 may also yield information about the severity of pancreatitis that in the future might lead to the administration of specific antagonists of this response.

Potentially useful prognostic indicators that are pancreas specific include assay of trypsinogen activation peptide (TAP), trypsin complexed with inhibitors, and phospholipase A<sub>2</sub>. Trypsinogen activation peptide has been shown to accurately predict severity in humans with pancreatitis. This peptide is released when trypsinogen, a pancreas-specific enzyme, is converted to its active form and rapidly accumulates in the urine and plasma of dogs with experimental acute pancreatitis. In spontaneous pancreatitis. Plasma and urinary TAP concentrations, as well as urinary TAP to creatinine ratio, were all increased in dogs that died with necrotising pancreatitis. Values were not increased in mild, interstitial pancreatitis. Increased plasma TAP concentrations were also present in dogs with severe renal disease. Phospholipase A<sub>2</sub> is elevated in dogs with severe pancreatitis.

A recent study determined that PE-1 had an overall sensitivity of 61% and specificity of 92%, comparable with published sensitivities for other pancreatic markers such as lipase and pancreatic lipase.

Morphologic assessment of severity is accomplished in humans by use of contrast enhanced computed tomography (CE-CT). Where lack of pancreatic perfusion is encountered i.e. necrosis, fine needle aspiration is used to distinguish infected from sterile necrosis. Substantially reduced mortality has been achieved by the detection and surgical treatment of people with infected necrosis. CE-CT has recently been reported in 2 dogs with pancreatitis. Contrast-enhanced computed tomography (CT) findings in both dogs were compatible with pancreatic necrosis. In one dog managed medically for 11 days the follow-up CT scan disclosed decreased pancreatic size and increased contrast enhancement compatible with partial resolution of pancreatitis.

## **Treatment**

Medical treatment is based on maintaining or restoring adequate tissue perfusion, limiting bacterial translocation and inhibiting inflammatory mediators and pancreatic enzymes; surgical treatment consists principally of restoring biliary outflow, removing infected necrotic pancreatic tissue, or coping with sequela such as pseudocysts. No studies have critically evaluated treatment modalities in dogs or cats with naturally occurring pancreatitis.

### **Initial management:**

The initial medical management of dogs with acute pancreatitis is based on the presenting clinical findings and the results of an initial database. Dehydration or hypovolemia are supported with intravenous fluid therapy e.g. LRS or 0.9% NaCl. Potassium and glucose should be supplemented where necessary. The type of fluid is tailored on the basis of electrolyte and pH measurements to restore normal electrolytes and acid-base balance. E.g. vomiting and mild dehydration are usually given crystalloids such as lactated Ringer's solution at a rate that will provide maintenance and replace both deficits and ongoing losses over a 24h period. Dogs with signs of shock require more aggressive support. The volume deficit can be replaced with crystalloids at an initial rate of 60-90ml/kg/h, then tailored to maintain tissue perfusion and hydration. Plasma (20ml/kg i.v.) or colloids (eg. Hetastarch, Dextran 70: 10-20ml/kg/day i.v.) may be indicated in the presence of hypoproteinemia or shock. Colloids such as dextran 70 and hetastarch may also have antithrombotic effects that help maintain the microcirculation.

Insulin therapy is initiated in diabetic patients.

Where vomiting is a problem, antiemetics (metoclopramide, chlorpromazine, maropitant, ondansetron) and antacids (e.g. famotidine) can be prescribed.

Prophylactic broad-spectrum antibiotics (e.g. amoxicillin ± enrofloxacin depending on severity) may be warranted in patients with shock, fever, diabetes mellitus or evidence of breakdown of the GI barrier.

Analgesia can be provided using buprenorphine (0.005-0.01mg/kg SC q6-12hrs) or oxymorphone (0.1-0.2mg/kg dogs IM, SC Q 1-3hrs). It may be necessary to administer low dose sedation with acepromazine (0.01mg/kg IM) to patients who become dysphoric after opioids. Buprenorphine is a partial agonist and may antagonise the administration of more potent analgesics in animals with severe pain. A transdermal fentanyl patch (Duragesic, Janssen) applied to a clipped clean area of skin provides a longer duration of analgesia in dogs (10-20kg, 50µg/hr patch q 72hrs). Adequate fentanyl levels are not attained for between 6-48 hrs after application, so another analgesic should be administered in the short term. The author avoids using non-steroidal analgesics in patients with acute pancreatitis due to concerns for GI ulceration, renal failure and potentially hepatotoxicity.

### **Specific therapy**

Many dogs with acute pancreatitis respond to fluid therapy and nothing by mouth for 48h. Hence, specific therapy is usually reserved for dogs that do not respond to fluid therapy or those with signs of multiorgan system involvement or DIC.

The specific treatment of pancreatitis has evolved along two paths, 1. Stopping further pancreatitis from occurring, and 2. Limiting the local and systemic consequences of pancreatitis.

Therapies aimed at inhibiting pancreatic secretion (e.g. glucagon, somatostatin) or the intracellular activation of proteases (e.g. gabexate mesilate) which have been of benefit in ameliorating the severity of experimental pancreatitis have shown little benefit in the treatment of patients with spontaneous pancreatitis, unless they are given before pancreatitis is induced (e.g. before ERCP). The lack of success with inhibiting the progression of spontaneous pancreatitis has led to increased emphasis on damage limitation; ameliorating the effects of inflammatory mediators or pancreatic enzymes on the patient and maintaining pancreatic perfusion.

Where a coagulopathy e.g. DIC, or hypoproteinemia are present, or the patient with pancreatitis is deteriorating, fresh frozen plasma (10-20ml/kg) may be beneficial in alleviating the coagulopathy, hypoproteinemia and restoring a more normal protease-antiprotease balance. Heparin (75-150IU/kg TID) may be potentially useful in ameliorating DIC, promoting adequate microcirculation in the pancreas and clearing lipemic serum. In experimental pancreatitis isovolemic rehydration with dextran has also been shown to promote pancreatic microcirculation in dogs. Therapy to abrogate the systemic inflammatory response with antagonists of PAF (e.g. lexipafant), IL-1 and TNF- $\alpha$  holds promise for the future.

Oral pancreatic enzyme extracts have been reported to reduce pain in humans with chronic pancreatitis, though this is controversial. They are less likely to be effective in dogs as they do not appear to have a protease mediated negative feedback system.

**Nutritional support:**

The initial aim is to identify and prevent, or treat, nutritional factors associated with pancreatitis:

Where obesity, hyperlipidemia and dietary indiscretion are reported it would seem prudent to address their underlying cause in an attempt to prevent future bouts of pancreatitis.

Precise recommendations for the dietary management of acute pancreatitis in dogs are hampered by the absence of controlled studies, and are often based on empirical wisdom and a best guess least harm approach.

**The dilemma between feeding and stimulating the pancreas**

Pancreatic secretion in healthy dogs occurs in response to ingested nutrients, particularly fats and amino acids delivered into the duodenum. Pancreatic secretion in response to food is mediated by hormones such as CCK and secretin, parasympathetic stimulation, and duodenopancreatic nerves. Restricting oral intake, or providing nutrients intravenously, does not stimulate pancreatic secretion. Thus it has been largely accepted that to provide “pancreatic rest” oral intake should be withheld until clinical signs resolve, or when signs persist for @72-96hrs that parenteral nutrition is introduced. This dogma is still prevalent in veterinary and human medicine.

However, there is growing evidence in people, and animals, that enteral nutrition is superior to parenteral nutrition in the treatment of acute pancreatitis. Jejunal feeding (distal to the site of pancreatic stimulation) does not exacerbate acute pancreatitis in people or experimental animals. People with acute pancreatitis fed via jejunostomy tubes (these can be oral transpyloric tubes), have lower morbidity, shorter hospital stays and less cost than those treated with TPN. As it is now feasible to place jejunostomy tubes non-surgically in dogs, through the nose, esophagus or stomach, clinical application of this feeding strategy is not restricted by a surgical procedure. However, it remains open whether dogs with acute pancreatitis really require jejunal delivery of nutrients. There is evidence that the pancreas of dogs with acute experimental pancreatitis, and people with naturally occurring severe pancreatitis, is not as amenable to stimulation as the normal pancreas. Dogs recovering from naturally occurring pancreatitis have also been shown to have subnormal circulating TLI concentrations suggesting that pancreatic enzyme synthesis is downregulated. In addition, it appears that the major benefits of enteral support in acute pancreatitis in people and experimental dogs are due to reductions in the systemic inflammatory response and the translocation of enteric bacteria rather than a reduction in pancreatic stimulation.

Intestinal permeability and morbidity in dogs with parvovirus are positively impacted by feeding a liquid diet (41%protein, 18% fat, 3%CF) through a nasoesophageal tube supporting the concept

that enteral feeding in general, rather than jejunal delivery, is the reason for the beneficial effects of EN, though this needs to be critically evaluated.

Resistance to enteral feeding of dogs with pancreatitis is anticipated, despite evidence of a beneficial effect. One common argument used to promote PN in dogs with pancreatitis is that they vomit too frequently to be fed enterally. However, studies in dogs with parvovirus should also help to allay this fear as these dogs tolerated nasoesophageal feeding despite severe vomiting and diarrhea, with enterally fed dogs showing faster recovery rates, greater body weight gains and lower intestinal permeability than dogs that were held NPO. A recent pilot study in dogs showed that esophagostomy tube feeding was well tolerated in dogs with pancreatitis and associated with less complications than TPN.

This is not meant to imply that parenteral nutrition should be discarded, but its use be restricted to patients that really need it, for instance those in whom caloric intake is severely and persistently impaired by persistent vomiting. When parenteral nutrition is indicated a choice has to be made between total and partial parenteral nutrition. Partial parenteral nutrition (PPN) is a more practical and manageable procedure than TPN in most settings and has been shown to be a safe and effective way of providing nutrition to dogs with pancreatitis and gastrointestinal disease. Interestingly dogs that received a combination of enteral and PPN survived more often than those receiving PPN exclusively.

#### **What diet should be fed to dogs recovering from pancreatitis?**

Free choice feeding is usually resumed when the appetite returns and vomiting and abdominal pain have subsided. Fat is frequently regarded as the major stimulus for CCK release and pancreatic secretion. However amino acids are also potent stimulators of pancreatic enzyme secretion and they are not restricted. Perhaps a more rational basis for fat restriction (?<15%DM) is the presence of hyperlipidemia. Avoidance of other dietary factors associated with pancreatitis, such as high fat diets, and high fat protein restricted diets designed for struvite dissolution, that have a nutrient profile similar to diet known to induce pancreatitis in dogs, is also reasonable. Obesity, a risk factor for pancreatitis, should be controlled with a balanced nutritional approach. Elemental diets cause a similar degree of pancreatic stimulation as normal diets.

#### **Patient Monitoring**

Minimal monitoring for stable patients includes regular assessment of vital signs and fluid and electrolyte balance. In those with systemic abnormalities, monitoring should be more aggressive and may include vital signs, weight, haematocrit, total protein, fluid intake and output, blood pressure (central venous and arterial), electrolytes and glucose, acid-base status, platelets and coagulation status. Monitoring pancreas specific markers and clinical signs on a sequential basis should help to support resolution or progression of pancreatic inflammation.

Ultrasound-guided fine needle aspiration of the pancreas may enable infected pancreatic necrosis to be detected. Ultrasonography may also enable detection of delayed consequences of acute pancreatitis such as pancreatic abscessation, pseudocyst formation and biliary obstruction.

#### **Surgical intervention**

Surgery is potentially indicated to remove devitalized tissue in patients with infected pancreatic necrosis and to investigate and relieve persistent biliary obstruction. The removal or drainage of abscesses is another indication for surgery. Resection or surgical drainage of pancreatic pseudocysts is not always necessary as these can resolve spontaneously or following percutaneous drainage. Pancreatitis that is recurrent or is unresponsive to treatment may also require surgery to confirm a diagnosis and to exclude pancreatic cancer.

**Prognosis**

The prognosis for dogs with mild acute pancreatitis is good. Severe or recurrent pancreatitis is associated with a guarded prognosis.

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## Rethinking Canine Hemorrhagic Gastroenteritis (HGE): Acute Hemorrhagic Diarrhea Syndrome?

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Hemorrhagic Gastroenteritis (HGE) is the name given to a **syndrome** that is characterized by acute hemorrhagic diarrhea that is associated with an elevated hematocrit. It is most commonly described in small breed dogs and is frequently associated with vomiting, depression and abdominal pain. While a specific underlying cause is frequently undetermined, *Clostridium perfringens* and dietary hypersensitivity are considered likely etiologies.

The differential diagnosis of HGE includes other causes of melena / hematemesis / GI bleeding, acute vomiting and abdominal pain. At the present time a diagnosis of HGE is considered a diagnosis of exclusion.

Exclusion diagnoses included nonsteroidal anti-inflammatory or corticosteroid toxicosis, hypoadrenocorticism, inflammatory bowel disease, severe hepatitis, hepatic neoplasia or hepatic failure, acute and chronic renal failure, pancreatitis, anticoagulant toxicosis, gastrointestinal neoplasia or foreign bodies, and enteric infection with parvovirus, *Giardia* spp., or endoparasites.

### Causes of melena / hematemesis

#### Gastrointestinal erosion/ulceration

<i>Metabolic</i>	uremia (?), severe liver disease, hypoadrenocorticism
<i>Inflammatory</i>	gastritis, enteritis, <b>HGE</b>
<i>Neoplastic</i>	leiomyoma, adenocarcinoma, lymphosarcoma
<i>Paraneoplastic</i>	mastocytosis, hypergastrinaemia/ other APUDomas
<i>Vascular</i>	A-V fistula, aneurysms
<i>Ischaemia</i>	hypovolemic shock , hypoadrenocorticism, thrombosis / infarction, reperfusion
<i>Foreign objects</i>	
<i>Drug induced</i>	non-steroidal and steroidal anti- inflammatories
<b>Coagulopathies</b>	thrombocytopenia, factor deficiencies, D.I.C.
<b>Ingestion of blood</b>	oral, nasal, pharyngeal, pulmonary bleeding

### Causes of abdominal pain:

<b>Gastric</b>	Dilatation/volvulus, ulceration,
<b>Intestinal</b>	Obstruction, intussusception, rupture, torsion, acute enteritis, <b>HGE</b>
<b>Pancreatic</b>	Pancreatitis
<b>Hepatic</b>	Acute hepatitis, ruptured bile duct, hepatic neoplasia
<b>Splenic</b>	Torsion, ruptured neoplasm
<b>Urogenital</b>	Nephritis, pyelonephritis, ruptured bladder, ureteral / urethral calculi, pyometra, prostatitis
<b>Peritoneum</b>	Primary or secondary peritonitis (e.g. chemical - bile and urine : septic-ruptured viscus)
<b>Musculoskeletal</b>	Discospondylitis, prolapsed disc

**Causes of Vomiting**

<b>Gastric</b>	Gastritis , Ulceration, Neoplasia, Outflow obstruction, Foreign bodies, Motility / functional disorders
<b>Intestinal</b>	HGE, Inflammatory Bowel Disease, Neoplasia, Foreign bodies, Intussusception, Functional disorders
<b>Intra-abdominal non-GIT</b>	<ul style="list-style-type: none"> <li>Pancreas Pancreatitis, Pancreatic Neoplasia</li> <li>Liver Hepatitis, Cholangitis, Biliary Obstruction</li> <li>Spleen Torsion</li> <li>Genitourinary Nephritis, Pyelonephritis, Nephrolithiasis, Urinary obstruction, Prostatitis, Pyometra,</li> <li>Peritonitis</li> </ul>
<b>Metabolic /</b>	Uremia, Hypoadrenocorticism, Diabetic Ketoacidosis,
<b>Endocrine</b>	Hyperthyroidism, Hepatic Encephalopathy, Hypercalcemia, Septicemia
<b>Infectious</b>	Distemper, Parvovirus, ICH, Leptospirosis, Feline Panleukopenia, Heartworm (cat), FIP, Salmonella, FeLV/FIV related
<b>Drugs</b>	Digoxin, Erythromycin, Chemotherapy, Apomorphine, Xylazine
<b>Toxins</b>	Strychnine, Ethylene Glycol, Lead
<b>Dietary</b>	Indiscretion, Intolerance, Allergy
<b>Neurologic</b>	Vestibular disease, Encephalitis, Neoplasia, Raised intra-cranial pressure
<b>Infectious</b>	Distemper, Parvovirus, Infectious Canine Hepatitis, Leptospirosis, Feline Panleukopenia, FIP, Salmonella

A thorough history and physical examination provide valuable clues to the site and cause of hemorrhagic diarrhea, vomiting and abdominal pain.

e.g. A Black Standard Poodle with melena, hematemesis and bradycardia should immediately trigger suspicion of hypoadrenocorticism.

A Shitzu with sudden onset hematemesis, melena and injected mucous membranes would be a prime suspect for HGE.

An eight week old puppy with melena and a painful abdomen and a thick segment of gut would rapidly raise suspicion of parvovirus and potential intussusception.

Has the patient had access to NSAIDs, rodenticides? What food is fed- raw (salmonella)? Grain based (aflatoxin)? What treats are fed (jerky)?

A patient with hematochezia that is accompanied by mucus and tenesmus is likely to have colitis, whereas focal streaking of fresh blood on a relatively normal stool suggests an ulcerated polyp or tumor.

**Routine clinicopathological testing will help to determine cause:****PCV/TP/CBC/Profile/UA:**

Finding a PCV of 75 and a total protein of 6.5 would be highly suggestive of HGE in a small breed dog with sudden onset clinical signs.

A PCV > 55 with a TP lower than predicted by the degree of hemoconcentration (e.g. less than upper limit of normal < 7.5) due to protein loss in GIT is considered a key feature of the classic syndrome of HGE.

**Integrate diagnostic findings to rule out HGE:**

Anemia - *Microcytosis* (MCV < 63fl), decreased red cell haemoglobin and *thrombocytosis* are common in dogs with iron deficiency secondary to GI blood loss from intestinal parasites or tumors (Ddx portosystemic vascular anomalies or fibrosing liver disease in young dogs with signs of gastrointestinal disease).

Eosinophilia may suggest mastocytosis, hypoadrenocorticism, parasitism or food intolerance.

White cell count varies depending on degree of inflammation and dogs with low white cell counts and melena and hematemesis are suspects for Parvovirus, Salmonellosis, sepsis pancreatitis, intestinal perforation etc.

Elevated liver enzymes and hyperbilirubinemia in the absence of anemia would be consistent with severe hepatic or biliary disease. Melena in association with clinicopathological evidence of liver dysfunction, particularly low cholesterol should raise the suspicion of end stage liver disease or where acute in presentation aflatoxicosis.

Patients with hematochezia accompanied by tenesmus and mucus should undergo fecal evaluation for endoparasites (whipworms) and culture for *Campylobacter* and *Salmonella* and rectal cytology for *Histoplasma* may be warranted.

Isosthenuria and azotemia with renal disease.

#### Screening for coagulopathies:

Where no underlying disease is apparent to explain GI bleeding a thorough evaluation of coagulation status should be performed. However, many systemic diseases associated with GI bleeding can also have concurrent coagulopathies. Physical exam may show evidence of an underlying coagulopathy e.g. petechiae, ecchymoses. Tests used to evaluate hemostasis include:

#### Diagnostic imaging:

Radiographs and ultrasound can help to localize the underlying disease associated with GI bleeding/vomiting and abdominal pain.

Radiographs in dogs with HGE may be normal or suggest ileus. Sonography may be normal or reveal findings consistent with a non-specific enteropathy or ileus.

**Treatment:** Dogs with HGE typically respond well to symptomatic therapy with crystalloids, anti-emetics (e.g. maropitant), analgesics (e.g. buprenorphine) ± antacids (H<sub>2</sub> antagonists or PPIs). Many dogs are given empirical antibiotics on the basis of perceived damage to the gut in the absence of signs of septicemia. Dogs with suspicion of septicemia can receive antibiotics.

#### **Recent Findings in HGE:**

##### Acute Hemorrhagic Diarrhea Syndrome (AHDS) or HGE?

Recent studies in dogs with the syndrome of HGE have revealed that histological lesions are restricted to the intestines with no evidence of gastric involvement. This has led to the proposal that the name should be changed to Acute Hemorrhagic Diarrhea Syndrome (AHDS).

However, it is reported that vomiting precedes the development of bloody diarrhea in 80% of 108 dogs with AHDS and that 40% of dogs having hematemesis preceding diarrhea. It has also been reported that while the median hematocrit of 108 dogs with AHDS was 57%, 52% of dogs with AHDS had hematocrit within the normal range.

Thus the population of dogs described with AHDS is different from the population of dogs traditionally considered to have HGE on the basis of a clinical syndrome of vomiting, bloody diarrhea of acute onset, and a hematocrit >50-55% in a small breed dog.

Remember, the syndromes of HGE and AHDS are based on the exclusion of other causes of acute vomiting, bloody diarrhea and abdominal pain, typically in a small breed dog.

##### What causes AHDS/HGE?

Recent studies have revealed necrosis and neutrophilic inflammation of the small intestine, and dense colonization with adherent *Clostridium perfringens* in dogs with AHDS/HGE.

A toxin produced by *C.perfringens*, NetF, is suspected of causing the intestinal damage. Intestinal “dysbiosis” associated with increase *C.perfringens* and NetF toxin has been described in @48% of cases with AHDS.

##### Should dogs with AHDS/HGE receive antibiotics?

Dogs with aseptic AHDS show a rapid decrease in netF and clinical signs without antibiotics.

Of 105 dogs (97.2 per cent) recovered with a median hospitalization time of 3 days (range 1–8 days).

Increased body temperature and reduced heart rate at 1day correlated with clinical improvement.

Dogs with evidence of septicemia and AHDS/HEGE can receive antimicrobials.

##### How beneficial are probiotics?

In dogs with aseptic AHDS a rapid decrease in netF and clinical signs was observed in the absence and



Presence of probiotics. Neither group required antibiotics.

Treatment recommendations:

- Rapid resolution in non-septic cases of AHDS/HGE is typically achieved with fluid therapy and antiemetics without antibiotics or probiotics.
- Dogs with evidence of septicemia and AHDS/HEGE should receive antimicrobials.
- The role of antacid therapy remains to be determined. PPIs have been associated with increased risk of *C.difficile* associated disease. In the absence of gastric ulcers and evidence of hyperacidity related intestinal disease should we avoid antacids/PPI therapy?
- The syndromes of HGE and AHDS are based on the exclusion of other causes of acute vomiting, bloody diarrhea and abdominal pain, typically in a small breed dog. Failure to respond to empirical therapy should be investigated aggressively.

Further reading:

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## Chronic Vomiting: What's the Cause?

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

### Initiation of vomiting

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

### Causes of Vomiting

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

### Patient evaluation and diagnostic approach

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

If the animal is systemically unwell, has been vomiting for more than a week, or has vomiting associated with hematemesis, bloody diarrhea or abdominal pain a more

aggressive work-up is necessary to define the nature of the problem.

Most non-gastrointestinal causes of vomiting, and gastrointestinal causes such as a foreign body or intussusception, are usually detected, or ruled out, by taking a detailed history, performing a thorough physical examination, routine laboratory tests (e.g. CBC, profile, UA, fecal, with evaluation of cobalamin, folate, lipase/PLI, T<sub>4</sub>, FeIV, FIV where indicated) and abdominal radiographs. Abdominal ultrasound is useful for detecting pancreatic, hepatic and splenic lesions, GI thickening (focal or diffuse) and sampling masses and parenchymal abnormalities. If these tests are negative or show abnormalities compatible with primary gastric or diffuse intestinal disease, endoscopic examination of the stomach and upper duodenum or contrast radiography are the principal diagnostic options. Endoscopy enables detailed examination and sampling of the gastric and duodenal mucosa with minimal patient discomfort and is generally accepted as the best method of evaluating mucosal abnormalities.

Radiographic contrast studies ( $\pm$  fluoroscopy) are generally restricted to examining functional (emptying) disorders of the stomach and the anatomy and patency of the intestinal tract distal to the duodenum. Patients with evidence of focal intestinal disease or concurrent involvement of multiple organs (e.g. liver, pancreas, intestine in cats with triaditis) are often best evaluated surgically.

### **Overview of therapy for vomiting**

Patient management should be aimed at detecting, and treating the cause and consequences of vomiting. Parenteral fluid therapy (usually IV) should be tailored to correct volume depletion, and electrolyte and acid base abnormalities. Dietary alteration in patients with acute vomiting is traditionally NPO for 24-48hrs followed by a transition to a bland, carbohydrate rich diet (to facilitate gastric emptying) when vomiting decreases. However, this notion has been challenged by the results of early enteral nutrition in dogs with parvovirus enteropathy, where feeding was associated with decreased duration of hospitalization and reduced intestinal permeability. Modified diets may be useful in patients with delayed gastric emptying, or chronic gastroenteropathies associated with food intolerance. Gastric protectants (e.g. sucralfate) can be used to bind toxins and protect the GI mucosa where vomiting is associated with gastritis or gastric ulceration. Inhibitors of gastric acid secretion (usually H<sub>2</sub> antagonists) are used to limit gastric erosion/ulceration in patients with gastritis / ulceration and those considered at risk of developing GI ulceration (e.g. shock) or esophagitis. Inhibition of gastric acid may also limit the hypochloremia and alkalosis associated with gastric outflow obstruction. Analgesics may decrease vomiting associated with acute abdominal conditions e.g. buprenorphine for pancreatitis. Antiemetics are indicated in patients with vomiting that is compromising hydration status, affecting electrolyte and acid base balance, and those at high risk for esophagitis or aspiration pneumonia, and those distressed by repeated vomiting. Antibiotics are usually limited to suspected infections, acute abdominal conditions or gastritis associated with Helicobacter infection. Prokinetic agents are used to promote gastric and intestinal motility in patients with a patent GI tract. Surgery is indicated to remove large foreign bodies, treat some causes of pyloric outflow obstruction, and to obtain biopsies of the GI tract and concurrently diseased organs.

### Pharmacological control of vomiting

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

Some antiemetics have more than one mechanism of action e.g. Phenothiazines (e.g. chlorpromazine) are antagonists of  $\alpha_1$  and  $\alpha_2$  adrenergic,  $H_1$ - and  $H_2$ -histaminergic and  $D_2$ -dopaminergic receptors; Metoclopramide antagonizes  $D_2$ -dopaminergic and  $5HT_3$ -serotonergic receptors and has cholinergic effects on smooth muscle.

Antiemetics are generally contraindicated in patients with gastrointestinal toxicity where they may limit expulsion of the toxic agent. Antiemetics can effectively mask signs of serious underlying disease hence a clinical response to antiemetics should not preclude a search for the underlying cause of vomiting. Non-selective cholinergic receptor antagonists (other than the  $M_1$  specific antagonist- pirenzepine) e.g. atropine, scopolamine, aminopentamide, isopropamide, may cause ileus, delayed gastric emptying and dry mouth. It is recommended that phenothiazines and the  $NK_1$  antagonist maropitant are not given to hypotensive patients. Phenothiazines may also cause unwanted sedation and decrease the seizure threshold in animals with epilepsy. Maropitant is metabolized by the liver and is heavily protein bound, hence careful monitoring is suggested in patients with liver disease and hypoproteinemia, and maropitant should not be used for more than 5 consecutive days. Maropitant can prolong the Q-T interval and is contraindicated in bradycardia. Antiemetics with prokinetic activity, such as metoclopramide, are contraindicated where there is a suspicion of intestinal obstruction.

The animal species, and age may also impact selection of antiemetic. Certain antiemetics are not recommended / require caution / are ineffective when used in the cat e.g. the cat is resistant to apomorphine induced vomiting suggesting the  $D_2$ -dopaminergic metoclopramide may have less activity than  $\alpha_2$  adrenergic antagonists. Maropitant is currently not licensed for use in dogs <12 wks of age due to dose dependent bone marrow hypoplasia.

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

The comparative efficacy of commonly used antiemetics against vomiting induced by apomorphine (central stimulus) and ipecac (peripheral stimulus) in laboratory dogs indicates that maropitant, chlorpromazine, and metoclopramide have similar activity against apomorphine induced emesis (all had greater activity than ondansetron), and that ondansetron and maropitant have equal activity against ipecac (both had greater activity than metoclopramide and chlorpromazine). Maropitant has been shown to reduce vomiting induced by xylazine in cats and has an analgesic effect in cats undergoing ovariohysterectomy..  $5HT_3$  antagonists have been shown to reduce cisplatin and dexmedetomidine-induced emesis in cat, but do not block the effect of xylazine

Clinical trial are lacking in cats. Two recent clinical trials in dogs, one in Europe, the other in

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

### **Strategies for managing persistent vomiting**

#### *Uremia*

Vomiting in uremia is mediated via the effects of uremic toxins on the CRTZ and afferent inputs from the inflamed stomach. Control of vomiting is focused on ameliorating uremia with fluid therapy, antagonizing the effects of uremic toxins on the CRTZ and limiting potential afferent input from the GI tract e.g. uremic / hypergastrinemic gastritis. Recent studies in cats and dogs have shown that gastric ulceration is rarely associated with uremia. In cats maropitant (1mg/kg SC/24hrs for no more than 5d) or ondansetron (0.5mg/kg BID) are typical first line antiemetics for uremia associated vomiting. H<sub>2</sub> antagonists (e.g. famotidine 0.5-1.0mg/kg SID-BID) and mucosal protectants (sucralfate 0.25-1g PO TID) are frequently prescribed to address concurrent gastritis, though recent studies have questioned the association of uremia with gastric ulcers in dogs and cats. Metoclopramide may not be an effective centrally acting antiemetic in the cat and its potential impact on renal dopamine receptors should be considered in cats with primary renal disease. Mirtazapine (1.88mg EOD) appears to be an effective appetite stimulant and anti-emetic for cats with CKD and could be a useful adjunct to the nutritional management of these cases.

#### *Pancreatitis*

Vomiting is likely due to direct afferent input to the vomiting center from the inflamed pancreas and adjacent intestines and ileus secondary to inflammation. Analgesia (e.g. buprenorphine 0.01mg/kg SC BID) is used to decrease afferent stimulation of the vomiting center, and may also have direct central effects on emesis. 5HT<sub>3</sub> receptor antagonists such as ondansetron, and the NK<sub>1</sub> antagonist maropitant are increasingly used, and may offer the additional benefit of decreasing pancreatic or visceral stimulation of emesis.

#### *Motion sickness*

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

#### *Cancer chemotherapy*

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

#### *Persistent vomiting of undetermined etiology*

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

ingestion of toxic substances, and contraindications for specific agents e.g. age, hypotension, bradycardia.

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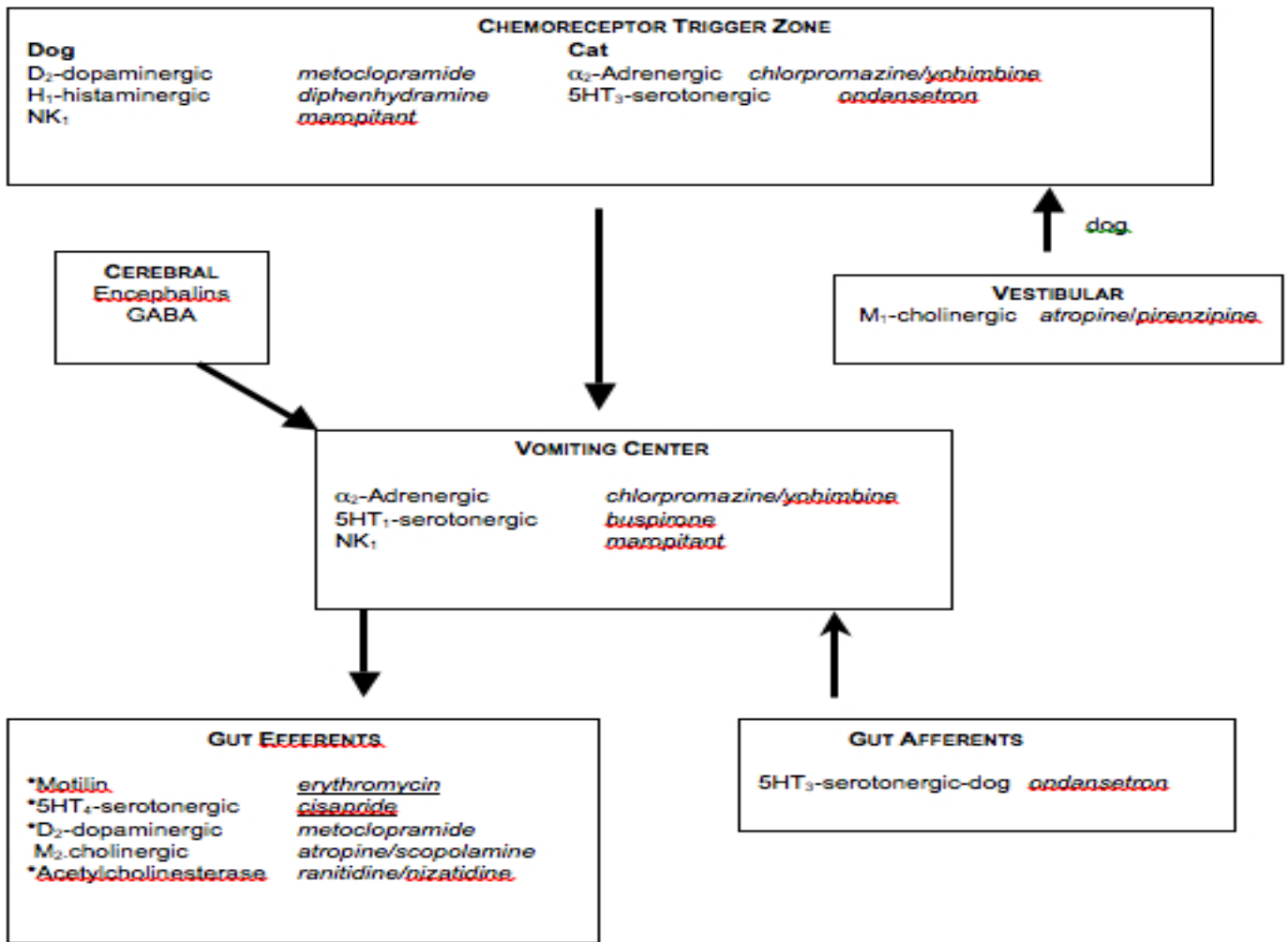
### Table 1. Causes of vomiting

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



NEUROPHARMACOLOGY OF ANTI-EMETICS AND PROKINETICS



Underlined = receptor agonists, \* = prokinetics

## MAKING THE CANCER DIAGNOSIS

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### Introduction

Throughout history, at various times certain diseases have been greatly feared by people (leprosy in biblical times, bubonic plague during the Middle Ages, tuberculosis in the last century). Today as a result of advances in microbiology and pharmacology, infectious diseases do not play such a major role in "developed cultures" that they did in the past. Today the disease that strikes fear in the hearts of laypeople is cancer. In Canada, cancer is the leading as a cause of death (with heart disease second) and accounts for approximately 30% of all deaths. In 2019, over 220,400 will be diagnosed with cancer and 82,100 will die from it this year. (An estimated 15% of all cancer deaths would be eliminated in several decades if Canadians stopped smoking cigarettes.) Although the basic nature of the neoplastic transformation that leads to cancer is still unknown, knowledge has been gained about the disease and its treatment. Today 1 in 3 cancer patients is cured (versus 1 in 5 in 1930) and it has been estimated that the medical cure rate could be improved to almost 1 in 2 simply by better application of the knowledge that exists today.

Similarly, in veterinary medicine efficacious therapy is available for many forms of cancer in pets. Therapy may increase the pet's quality of life by decreasing or alleviating pain and suffering, controlling the cancer, or rarely curing the cancer. Tumours in pets are often best approached with a multimodal approach, considering options in medical, surgical and radiation oncology. Surgery, however, is often a critical part of achieving a diagnosis and is often necessary in treatment. Surgery is also one method that is available that can cure some forms of cancer in animals and people.

When thinking through cancer diagnosis and treatment, it is very important to manage the work up in a logical, stepwise fashion to achieve the optimal treatment pathway. When faced with a patient with a tumour, the clinician should ask themselves three questions and work through answering these questions in order. These questions are:

1. ***What is it?***
2. ***Where is it?***
3. ***How bad is it?***

### **What is it?** (i.e. *Get a Diagnosis*)

This question refers to the tumour type. It is essential that this question is answered before any treatment is initiated. Removal of a neoplastic mass without knowing the tissue type will rarely give rise to a favourable result. In addition to a thorough history and physical examination, this question can be answered by several different methods, including cytology, biopsy for histopathology, and a presumptive diagnosis based on classic patterns of disease

Cytology is generally achieved by performing a fine needle aspirate. The advantages of this test are that it is quick, easy, inexpensive and can often direct us towards a diagnosis. It is a very good first step towards achieving a diagnosis. It can often diagnose lymphoma and mast cell tumours and it can help to differentiate between an inflammatory and a neoplastic process. The disadvantages are that it may be nondiagnostic in some circumstances, it can also give us

a vague diagnosis or even an incorrect one. For dogs that present every year with a large number of masses, it is recommended that their skin masses are mapped. This can be done using a standard histopathology submission form dog map and enlarging two of these pictures on one page. This sheet should be incorporated into the patient's record and should include patient information and a place to write information about each mass that corresponds to a number and location of the mass on the picture. The information about the mass should include the location (if there is any potential confusion based on the chart), size of the mass, mobility, firmness and whether the mass is in the skin, SQ tissue or deeper. It should also include the cytologic description of the mass and whether cytology was performed in-house or by a pathologist. Starting early with mapping masses will save a lot of time in the future and will allow you to keep track of your patient's masses so that new masses can be addressed and masses that were diagnosed as being benign (e.g. lipoma) can be monitored for growth. This method is very important in multi-doctor practices where different doctors may see a patient for their annual physical examinations, but is also important for single doctor practices because it is impossible to remember the exact character of a dog's masses over the years. If the mass is neoplastic, there are three possibilities for the types of cells present. Round cells, spindle cells and epithelial cells. With practice, you may become very adept at categorizing these cells and recognizing characteristics of malignancy, such as multiple nuclei or nucleoli, anisokaryosis, anisocytosis and mitotic figures.

If the cytology or the clinical impression of the mass is suspicious for a malignant process, a biopsy for histopathology is recommended. There are several different ways to achieve a histologic diagnosis and the method for achieving a biopsy should always be chosen with the eventual definitive resection in mind. Options for a biopsy include an incisional biopsy or an excisional biopsy.

An incisional biopsy can be achieved by taking a sample of the mass without disrupting the architecture of the mass. For subcutaneous masses, care must be taken to go deep enough into the mass so that the biopsy does not include only skin, SQ and muscle, but actually contains a portion of the neoplastic tissue. A result of normal muscle or fat is likely an indication that the biopsy technique did not go deep enough, rather than that the mass is a benign process. An incisional biopsy can be achieved using a skin punch, taking care to penetrate deep enough into the mass. A wedge of the tissue can also be taken. If the mass is completely subcutaneous, then you can make a small incision in the skin directly over the mass and then take a wedge or punch of the mass underneath. A Tru-cut biopsy can also be used very effectively to obtain a representative sample of the mass. Keep in mind that the centre of a large mass may be necrotic due to the lack of a blood supply and biopsies in this area may not be diagnostic. It is also important to keep in mind that if the tissue is a malignant process, the biopsy tract must be resected with the definitive resection, so the biopsy should be in a location that will be easily removed with the definitive resection. As well, the biopsy tract should be small (2 cm maximum) and should be in one location only. For example, multiple incisions taken from multiple locations around the mass could result in multiple areas needing to be resected in a definitive surgery and this may compromise the ability to achieve clear margins of resection. The sutures used to take a biopsy should be left in place until definitive surgery so that the biopsy tract can be removed. Another area to keep this principle in mind is oral tumours. A mass arising from the maxilla may appear to be most easily biopsied by going through the upper lip. This will, however, result in the need to resect the lip when, in most cases, this is not necessary for oral masses of the maxilla. The need to remove a portion of the

upper lip would lead to a less cosmetic end result for the patient. Osteosarcoma is another tumour type where the biopsy location may be important if a limb spare procedure is the owner's choice for a definitive tumour resection. If you are unsure of the best method of biopsy for one of your cases that you think will eventually require a major resection, contact your friendly neighborhood surgical oncologist to discuss the case and biopsy techniques before you biopsy.

An excisional biopsy may be performed in certain instances. It is, however, very important that a curative intent resection is not compromised by this technique. Examples of excisional biopsy that are appropriate include:

- 1) A 2 mm mass on the lateral aspect of the digit in a large dog. The mass is removed as a marginal excision. If the mass is benign, there will be no further treatment. If the mass is malignant, a digit amputation will be necessary and the biopsy tract will not affect this definitive surgery.
- 2) A 1 cm mass over the flank of a dog. Cytology was nondiagnostic. Options would include an incisional biopsy or an excisional biopsy. The owner just wants the mass removed. You explain to the owner that you will remove the mass with large margins (2-3 cm laterally and one fascial plane deep to the mass). If the mass is malignant, it has been removed appropriately. If the mass is benign, you have given a larger dose of surgery than necessary, but the mass is gone.
- 3) In cases of a presumptive diagnosis, such as hemangiosarcoma of the spleen or osteosarcoma, the tumour is often excised (e.g. splenectomy or amputation) without a definitive histopathologic diagnosis. This is appropriate in cases where the histopathologic diagnosis will not change the treatment of the patient and the pattern of disease is extremely suggestive of a common form of neoplasia.

An example of when an excisional biopsy is not appropriate for the patient is removal of a mass with moderate margins with no knowledge of the tissue type. If this mass is then diagnosed as a malignant process, the definitive resection has been compromised. A very dangerous logic is "removing as much as you can", without knowing what the mass is. If you do not know what the mass is, remove as little as you can and do not disrupt the tissues around the mass. This is because the tissue surrounding the mass contains tumour cells and the excision will disrupt the tissue architecture and the fascial planes, making it more difficult to determine and achieve clean margins of resection. The resection also becomes much larger than it would have been prior to mass removal because the entire scar must be removed using 3 cm and a fascial plane deep. If the fascial plane below the mass was already disrupted, you must go another fascial plane deep to achieve clean margins. This next fascial plane could be the body wall. It is also possible that a patient who would not have required radiation may need radiation to clean up the field. The potential consequences of a dirty resection of an unknown tumour include: a significant increase in morbidity to the patient, a significant increase in cost to the client, and the potential to lose the ability to cure the patient. The logic of "just removing the mass and then finding out what it is" is very dangerous and can have serious consequences. Do not be surprised by your results. The pitfalls of this approach are not always apparent to the doctor who has made this error because the problem is then referred on. It is also very important not to be completely guided by the client by the decision to just remove a mass. Most clients "just want the mass removed". They do not like looking at it, it bothers the dog and they do not want to think that their dog might have cancer. However, when clients are educated about the reasoning behind a logical, step-wise approach to tumour diagnosis and treatment, most of them are relieved to have this knowledge and will pursue more diagnostics, even if this is more costly up front. It is almost never more costly overall to take this approach.

A presumptive diagnosis is sometimes made in cases where the pattern of disease points very strongly to the diagnosis and/or the mass is in an area that is difficult or impossible to biopsy. As mentioned earlier, this type of diagnosis is also made in cases where the treatment will not change based on the type of tumour. Examples of this include a primary bone tumour. If the radiographic diagnosis is consistent with a primary bone tumour and the signalment of the patient is also consistent with the diagnosis, bone biopsy is considered unnecessary by some surgical oncologists. If, however, there is a bone lesion in a location or patient that is not consistent with a primary bone tumour, a biopsy is recommended. A bleeding splenic mass will need to be removed regardless of whether it is hematoma or hemangiosarcoma. A lung mass will need to be removed regardless of whether it is an abscess, granuloma or tumour. The advent of advanced imaging can help us to characterize these tissue types better in a noninvasive manner, but will only allow us to reach a more educated presumptive diagnosis.

**\*\*It is important to remember that when multiple masses are biopsied, the surgeon must change gloves and instruments to prevent seeding tumour cells to multiple sites. As well, it is critical to keep a very good record of where each biopsy came from, the use of a tumour map can be very helpful in these cases.\*\***

### Where is it?

Once the question of what is it? has been answered, the next question is where is it? This refers to staging of the disease. Staging of the tumour determines where exactly the tumour is locally and also if the tumour has metastasized to other sites. Local extent of tumour can be determined by palpation and ultrasound. Generally speaking, this question is most commonly answered by three-dimensional imaging such as CT scan or MRI prior to a large definitive surgery.

The methods for staging for metastatic disease will depend largely on the tumour type. For a benign mass, such as an epulis, no staging is required. For other masses, the staging tests performed will depend on the biologic behavior of the tumour type. In general, carcinomas tend to metastasize to lymph nodes and sarcomas tend to metastasize to lungs, however, this just a generalization and the reverse can be true in some cases. Three-view thoracic radiographs are always a good first step in staging. It is inexpensive and it is a very common site for metastasis. Although it does sound academic, three-views of the thorax are necessary to avoid missing a metastatic nodule. The upper lung field will be more aerated and therefore a nodule will be more apparent due to the contrast with the air in the lung. A nodule in the upper lung will also be more apparent due to magnification because of an increased distance from the plate. Multiple views will also allow the visualization of a nodule that was hidden by other thoracic structures. CT is becoming a tool that is much more sensitive for the assessment of pulmonary metastatic disease. However, thoracic radiographs should be performed as the initial screening test.

Staging can also be performed by evaluating regional lymph nodes. The local lymph nodes should be palpated in all cases and should be aspirated in cases that have a tendency to metastasize to lymph nodes. Any questionable lymph nodes should be biopsied (incisional or excisional biopsy). For some masses, the abdominal lymph nodes may need to be assessed using ultrasound or CT. An example of this is anal sac adenocarcinoma, which has a very high rate of metastasis to the sublumbar lymph nodes.

Abdominal ultrasound may also be appropriate in some cases, or as a method of evaluating older patients for overall health status prior to a major surgical intervention. Bone scan or long bone survey radiography should be performed in cases of osteosarcoma and should be considered in cases that have a tendency to metastasize to bone (for example TCC and other carcinomas).

For cancers that have a tendency to metastasize early in the course of disease, such as hemangiosarcoma or osteosarcoma, it is very important to explain the significance of the staging tests to clients. Most clients have a hard time understanding that if their pet is deemed clear of gross metastasis, the pet still has a high risk of microscopic disease. Spending time explaining this to clients early on will save a lot of confusion for them later in the course of disease. It is the reason why chemotherapy is recommended in these cases and why it extends their lifespan, but, unfortunately, does not cure their disease.

If the client cannot afford or does not desire therapy for a pet, then it is unnecessary to clinically stage the patient; diagnosis and prognosis are all that are required for good communication. However, if the client desires the best possible care for the pet then complete clinical staging is essential. By defining the extent of disease **BEFORE** therapy has begun, it becomes an easy task to determine if the tumour is responsive or not.

Clinical Staging of Tumours: defines the extent of disease; aids in planning treatment; allows more accurate prognostication; assists in evaluation of therapy; allows communication between clinicians; nomenclature: 'TNM' System (World Health Organization):

'T' describes size and invasiveness of primary tumour

'N' describes status of local lymph nodes

'M' describes presence of absence of distant metastasis

### **How bad is it?**

This question refers to both the stage of the disease and the grade. Grade refers to the histologic grade of the tumour. This is often designated as grade 1,2 or 3, with 1 having the least aggressive biological behaviour and 3 having the most aggressive biological behaviour. The grading system is particular to each tumour type and every pathologist may have a slightly different approach to tumour grading. It is important to keep in mind that although the grading system helps us to predict the biological behaviour of the tumour, each tumour type has a continuum of histological appearance and they are being categorized somewhat arbitrarily. It is also possible that the grade may shift from the incisional biopsy to the definitive resection because the pathologist will have more tissue to work with.

Information regarding the tissue type, stage of disease and histologic grade can now be assessed to give the owner a prediction of prognosis and a plan for treatment. The treatment plan will be based on the information from asking the three questions: What is it? Where is it? And How bad is it? From this point, recommendations and options can be presented to the owner. These plans will vary in aggressiveness of treatment and in cost and all options should be discussed with the owner. In general, the goals of therapy may be curative intent, palliative, or the owner may not wish to pursue further treatment and may elect for euthanasia when the patient's quality of life declines.

**References available on request**

## MANAGING THE VETERINARY CANCER PATIENT

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Advanced cancer treatment in dogs and cats often involves a multidisciplinary approach to disease. It is important to consider the treatment options available in each case prior to initiating any therapy, because each therapy can have an effect on the others. The three primary modalities that are used to treat cancer in animals are medical oncology (chemotherapy), surgery, and radiation.

Documenting tumour response to therapy:

**Complete Remission (CR):** disappearance of all clinical evidence of active tumour

**Partial Remission (PR):** 50% or greater decrease in size of the tumour

**Stable Disease (SD):** steady state or response less than partial remission or progression.

No appearance of new lesions or worsening of signs.

**Progression of Disease (PD):** unequivocal increase of at least 50% in the size of any measurable lesion

**Relapse (R):** the appearance of new lesions from complete remission. The reappearance of old lesions in patients who had CR. For patients in partial remission an increase of 50% or more in the size of the measured tumour over that obtained at the time of maximum regression.

The **ultimate goal** of cancer treatment is **CR** (and occasionally cure) which may be obtained by a number of methods (modalities) (e.g. surgery, chemotherapy, radiation therapy, immunotherapy).

Clinical staging defines the beginning point and the practitioner needs only to compare the stage of disease after treatment to the stage before therapy. If therapy does **NOT** provide objective decrease or at least stabilization of tumour burden, that particular treatment modality should be abandoned. Some tumour-bearing animals provide very minimal objective measurements for determining response to therapy. In such cases, paraneoplastic markers may allow the practitioner to monitor treatment.

### ***Always treat the patient in addition to treating the tumour.***

In addition to the neoplasm, most cancer patients have systemic disorders which need therapy, even before treatment of the neoplasm can be instituted (e.g. supportive and nutritional therapy).

### **Local disease requires Local therapy while Systemic disease requires Systemic therapy.**

Local disease may be defined as tumour confined to a single site, while systemic neoplasia describes tumour that has spread to distant sites by direct extension, lymphatic drainage, or hematogenous spread. Surgery, cryotherapy, and radiation therapy treat selected local tumours. Chemotherapy, hormonal therapy, or immunotherapy treat disseminated cancer or unresectable localized cancer. The only reason for using local treatment for systemic disease is for palliation.

### **Treatment Modalities:**

#### **Chemotherapy**

Indications: systemic neoplasia (e.g. lymphoma); metastatic neoplasia or likely (e.g. osteosarcoma); cytoreduction; nonresectable neoplasia.

Contraindications: severe underlying multiple organ dysfunction because this will increase the possibility of developing systemic toxicity.

Generally, chemotherapy should NOT be used as a substitute for surgery.

Chemotherapy most often involves cytotoxic chemotherapy, but can involve other forms of therapy. Cytotoxic chemotherapy drugs have different mechanisms of action, but the general principle is that these medications kill fast growing cells. The medication can not distinguish between fast growing tumour cells and normal fast growing cells in the body and for this reason, we have a maximum tolerated dose (MTD) of each medication and potential side effects. Common side effects are related to damage to cells that line the GI tract and bone marrow. These can give rise to nausea, vomiting and diarrhea, and bone marrow suppression. It is prudent to pretreat animals receiving some types of cytotoxic medication with anti-nausea medications (such as maropitant [Cerenia®], metoclopramide, or ondansetron) to prevent nausea. As well, symptomatic treatment for diarrhea (metronidazole or tylosin) can be started should this occur.

A complete blood count (CBC) should be performed at the nadir and prior to the next dose of chemotherapy. The nadir is the point when the bone marrow is maximally suppressed and can vary slightly depending on the medication administered but is usually around 7-10 days after administration of chemotherapy. Patients undergoing chemotherapy should have their temperature monitored. If patients become febrile or their WBC becomes low, prophylactic oral or intravenous antibiotics are recommended to prevent systemic infection.

Some dogs have a mutation in the MDR1 gene that prevents efficient excretion of chemotherapy from cells by p-glycoprotein. This can lead to a relative overdose of chemotherapy and severe toxicity in these dogs. It is possible to test dogs for this condition, called MDR1 (multiple drug resistance). In general, dogs that are predisposed to this condition are the same breeds that are susceptible to ivermectin toxicity, and for the same reasons. Herding dogs should be tested for the MDR1 mutation. Commonly used chemotherapy drugs that are excreted by this mechanism include vincristine, vinblastine and doxorubicin.

Depending on protocol, chemotherapy is administered every 1-3 weeks, after the assessment of a CBC to ensure that the white blood cell count is adequate. Each chemotherapeutic agent has specific side effects with necessary precautions that must be taken. Doxorubicin is cardiotoxic and for this reason, it is important to ensure that patients receiving this medication do not have underlying cardiotoxicity. As well, the maximum number of doses of doxorubicin is 5-6, or cardiotoxicity in the form of dilated cardiomyopathy will ensue. Doxorubicin is also a severe vesicant if extravasates. Untreated, this will cause severe wounds that will lead to amputation in most cases. Treatment with Dexrazoxane is the only known antidote, and it can prevent tissue necrosis if it is initiated early. However, this problem is best avoided. The way to prevent extravasation is to ensure that the person administering chemotherapy is experienced at venipuncture and that the catheter is placed on the first stick and is secured in place. Patients must be monitored closely during the infusion to ensure that the catheter does not become dislodged. This is just one example of potential side effects with chemotherapy, it is important to understand the drugs, indications, side effects and safety precautions necessary when administering chemotherapy.



It is also critical to ensure the safety of the staff when chemotherapy is administered in your practice. Exposure to chemotherapy is teratogenic and carcinogenic. A fume hood and/or a commercial closed system (Equashield or PhaSeal) for the preparation and administration of chemotherapy is critical. Further, the staff administering this medication should wear appropriate safety equipment, such as gowns, gloves and a safety mask.

Other forms of chemotherapy are oral medications. Some oral formulations are given at cytotoxic doses. There is also a type of administration of chemotherapy that is referred to as metronomic chemotherapy. This is low dose, continuous chemotherapy. These protocols are geared towards decreasing the blood supply to the tumour and slowing the progression of disease. They are often given in the palliative setting. There is not a lot of hard evidence that these protocols are effective because they are relatively new, but they may be appropriate in some cases and the incidence of side effects tend to be lower because of the lower dosing involved.

Targeted chemotherapy is a new form of chemotherapy that involves targeting mutations on the cancer cells (e.g. tyrosine kinase inhibitors). They work by targeting the mutations on the cancer cells that allow for unrestricted growth and proliferation. The same receptors in normal cells are only turned on when the receptor is bound. There has been some promise with this new class of chemotherapeutic agents. They appear to have fewer side effects than cytotoxic chemotherapy, but will still have an effect on normal cells, so side effects such as nausea, vomiting, diarrhea and bone marrow suppression still can occur and it is important to monitor these patients closely.

In general, chemotherapy is administered when systemic spread of disease is considered probably or has been diagnosed. The decision to administer chemotherapy will depend on the tumour type, grade and staging tests. In cases that stage negative, chemotherapy is recommended if the likelihood of metastasis is considered higher than 50%.

**Combination Chemotherapy** in general, is more effective than single agent therapy. Benefits: additive antitumour effects without additive host toxicity; delayed resistance to drugs; action on more than one cell stage simultaneously, with a resulting greater fractional cell kill per cycle of chemotherapy.

### **Surgery**

Indications: (1.) curative excision (the first surgery has the best chance for a "cure");  
 (2.) cytoreduction ("debulking") -incomplete excision to be followed with other treatment modalities;  
 (3.) palliation - decrease pain or signs

When surgery is part of multimodal therapy, it is important to consider the potential side effects of both chemotherapy and radiation. It is convention in veterinary medicine to wait until suture removal until chemotherapy is started to ensure that the incision has healed without complication prior to the potential to develop a low WBC after chemotherapy. Chemotherapy may delay healing slightly but it is not a clinically relevant concern. If you are planning a surgical procedure for a patient that is on chemotherapy, it is very important to consider the nadir and ensure that the patient has adequate WBC.

Radiation therapy and surgery both are used to treat local disease and because of this, they are often combined to treat tumours that cannot be treated with surgery alone. The decision to give radiation first and follow with surgery or vice versa is case and clinician dependent. It is important to consider that surgical treatment within a radiation field can lead to an increased complication rate because of the decreased ability of irradiated tissue to heal. Conversely, treating a scar with radiation after surgery can create concerns because the scar is typically hypoxic and oxidative damage by free radicals is the primary mechanism of DNA damage after treatment with ionizing radiation. It is critical to plan the approach with advanced imaging of the tumour and with involvement of both the surgical oncologist and radiation oncologist. If the plan is to remove a mass first and follow with radiation, it will be removed less aggressively than if radiation is not part of the plan. It should be removed with a marginal excision and metal hemostatic clips should be placed in the surgical site to mark the extent of surgery for the radiation oncologist. The worst case scenario is a wide excision that yields dirty margins, because this means the patient has to endure a big surgery and radiation of a large radiation field. Although this will happen occasionally, usually with very aggressive tumours, this scenario is best avoided with careful planning of the patient's optimal treatment pathway.

### **Radiation Therapy**

Radiotherapy is the treatment of neoplasia using ionizing radiation. Ionizing radiation is travelling energy that is energetic enough to result in the ejection of an electron from an atom creating a positive ion (atom minus electron). Ions created in tissue are highly reactive and cause structural alterations in critical intracellular macromolecules with lethal effects on cells. DNA is believed to be the primary target for radiation damage leading to cell death. Lesions in DNA prevent it from replicating normally. When a cell whose DNA has been significantly damaged by radiation enters the mitotic phase of the cell cycle, it dies (i.e. radiation injury shows itself when irradiated cells attempt to divide). This point is critical to understanding the effects of radiation in both tumours and normal tissues.

Theoretically, there is a dose of radiation that would sterilize any tumour. The most important factor limiting the dose that can be safely administered is normal tissue tolerance. The goal of radiotherapy is to deliver the maximum radiation dose to the tumour while keeping the dose to surrounding normal tissues below their tolerance level.

The response of normal tissue depends on the proliferation rate of the cells that compose it. In general, acute (or early) and chronic (or late) toxicities affect rapidly and slowly renewing tissues, respectively. Since toxicity is dependent upon the turnover rate of cells, acute effects develop and progress during the course of treatment with resolution within approximately 2 to 8 weeks after therapy. The most commonly affected tissues include skin, mucous membranes of the oral and nasal cavities, eyes (cornea, conjunctiva, tear-producing glands), and the lower gastrointestinal tract. Acute side effects are uncomfortable and often require supportive care including antibiotics and pain medication but they are self-limiting because of rapid cellular renewal. On the other hand, late radiation effects involve slowly or non-proliferating tissues such as bone, eyes (lens and retina), nervous tissue, muscle and connective tissue. Lethally irradiated late-responding tissues may be able to maintain full or complete function until they are stimulated to divide and will, therefore, not express radiation injury until months to years after being irradiated. Since cellular renewal is slow or absent in these tissues, late radiation toxicity is serious, irreversible and is often life threatening when a critical organ is affected. Late toxicity

should be avoided with appropriate treatment planning. Hence, the primary dose-limiting factor in radiotherapy is the tolerance of late-responding tissues in the radiation field.

We use radiation in three different settings, depending on the goal of therapy:

- 1.) Palliative radiation: This usually involves the administration of a relatively high dose of radiation (6-8 Gray) to a tumour site 1-4 times weekly. The goal of therapy is to decrease pain and inflammation and to slow tumour progression. Common applications of this type of radiation therapy include palliation of bone tumours, palliation of bladder tumours and course fractionated treatment of oral melanoma.
- 2.) Fractionated radiation therapy: Low doses of radiation are given daily for 15-20 fractions, usually given daily Monday through Friday. The fractionated dosing scheme allows the normal tissues to recover from the effects of radiation. Common applications of this type of radiation therapy include: bladder cancer, treatment of scars after incomplete resection of mast cell tumours and soft tissue sarcomas, nasal tumours, and preoperative irradiation of sarcomas.
- 3.) Stereotactic Radiation Therapy: This is the newest form of radiation and it requires very sophisticated equipment that allows for the highly conformal delivery of a high dose of radiation to the tumour, with a steep drop off in the radiation dose to the surrounding normal tissues. SRT is delivered in 1-3 doses over a period of 1-6 days. The major advantages of this type of radiation are that the treatment course is very short; the side effects are minimal because the dose to the surrounding tissues is small. The use of SRT dose requires a tissue target, so it is not appropriate to use this type of radiation after surgical removal of the tumour. The common applications of this type of radiation in veterinary medicine include: limb spare for appendicular osteosarcoma, brain tumours and nasal tumours.

Acute side effects are most common after a course of fractionated radiation therapy. Acute effects seen during the course of radiation are usually related to damage to epithelium of the skin, mucosa and foot pads. As mature epithelial cells are sloughed, new cells are not formed to replace them and the results is a mucositis (oral cavity is most common) or a radiation burn. The side effects are painful and will start about 2 weeks into a course of radiation therapy. Stopping radiation will not stop the progression of the side effects and will mean that the patient receives the side effects, but not the benefits of radiation. Pain management at the onset of radiation side effects is critical to ensure that the patient maintains a good quality of life during this period. In severe cases of oral mucositis, a feeding tube may be necessary to maintain hydration and nutrition for the patient if they are not eating. The side effects will resolve approximately 2 weeks after the end of the course of radiation. The area of skin affected often develops leukotrichia once the hair grows back. Late side effects of radiation are more severe and can include osteonecrosis, cataracts and neurological consequences. They occur 6-12 months after a course of radiation. Often it is related to a high dose of radiation and this may be more likely in cases that have received palliative radiation and then have lived for longer than expected.

**Investigational:** immunotherapy (biological modifiers, vaccines, monoclonal antibodies, etc.), electrochemotherapy, hyperthermia are early in development and understanding.

**References available on request**

## PRACTICAL APPROACH TO MANAGEMENT OF MAST CELL TUMOURS IN DOGS & CATS

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### Introduction

Mast cell tumours (MCT) (histiocytic mastocytoma, mast cell sarcoma, mastocytosis) are the most common cutaneous tumour in the dog representing 20-25% of all canine skin tumours. In the cat MCT represent 15% of all tumours (second most common cutaneous tumour). No sex predilection has been found in the dog, but in the cat the male:female ratio is 2:1. MCT occur most commonly in middle-aged dogs and cats with a mean age of about 8 years. Siamese cats, boxers, Boston terriers and other breeds of bulldog descendants are at higher risk to develop MCT.<sup>1,2</sup>

Mast cell tumours may exist in cutaneous or extracutaneous sites. In dogs the most common sites are the skin of the trunk and perineal region (50%), the skin of the extremities (40%), and the cutaneous head and neck (10%). MCT can arise in multiple cutaneous locations (11%). In cats most MCT are found in the head and neck region. Occasionally MCT are located only in the spleen in cats.<sup>1,2</sup>

The biologic behaviour of MCTs is extremely variable. Histologic grading can help determine the likelihood of recurrence or metastasis, but it will not predict the biologic behaviour of an individual tumour. Mast cell tumours have a high metastatic potential and many dogs will present with regional lymph node metastasis or rarely, splenic metastasis with splenomegaly. Dogs with advanced disease may have gastric or duodenal ulcers (related to histamine levels with secondary excess of hydrochloric acid secretion in the stomach), and present with vomiting, melena, and anemia. Occasionally mechanical manipulation during examination will result in degranulation of mast cells which results in erythema and wheal formation (Darier sign).<sup>1,2</sup>

Diagnosis of MCT can often be made by a fine needle aspirate (FNA) cytology but excisional biopsy is required for accurate histologic grading. Establishing a diagnosis prior to surgical treatment can be very helpful because the treatment should be aggressive and precaution may need to be taken to prevent or control heparin and histamine release. Diagnostic work-up may consist of staging with a complete blood count (CBC) (eosinophilia, basophilia, mast cells), buffy coat smear, bone marrow aspirate, FNA of the lesion and regional lymph node, abdominal radiographs or ultrasound (splenomegaly). In advanced canine MCT, a coagulogram (PT, PTT, FDP) may be performed.<sup>1,2</sup> The presence of the occasional mast cell in buffy coat or draining lymph node must be interpreted with caution because non neoplastic diseases can also result in mast cells.<sup>3</sup> Poorly differentiated MCT may be highly anaplastic without granules; therefore, they may represent a diagnostic challenge requiring special stains and immunohistochemistry (IHC). The tumour biopsy may be submitted for additional tests, such as immunohistochemistry (IHC) for markers of Ki67, c-kit mutations (CD117), and proliferation markers such as AgNOR staining and mitotic index.<sup>4,5</sup>

### Grading

The histologic grade of an MCT is determined by histopathology of the tumour and cannot be assessed simply by cytologic evaluation of fine-needle aspirates. The grade of an MCT is determined by the characteristics of the neoplastic cells (e.g., degree of granulation, cytologic

and nuclear pleomorphism), number of mitotic figures, and extent of tumour invasion into the underlying tissues. Histologic grade is the most consistent prognostic factor and correlates significantly with survival, but it does not predict the behaviour of every tumour.<sup>6</sup>

Histologic grading was based historically on a 3-tiered approach to histologic classification: Grade 1 well differentiated; Grade 2 intermediately differentiated; Grade 3 poorly differentiated. However the challenges with the grading system were inconsistency among pathologists accurately applying the criteria of the grading system, reproducibility of grading, interobserver variation, large number of cases assigned intermediate grade 2 (72%), and it was difficult to predict which grade 1 and 2 mast cell tumours would result in death due to the mast cell tumour. As a result, to provide better prognostic significance, a two-tier histologic grading system was established to identify MCTs that have a higher risk of aggressive biological behaviour (e.g. metastasis) and to increase interobserver consistency. The 2-tier system divides canine cutaneous MCTs into low-grade and high-grade based on the number of mitoses (< or  $\geq 7$  /10 high-power fields), presence of multinucleated cells (< or  $\geq 3$  /10 high-power fields), or bizarre nuclei (< or  $\geq 3$  /10 high-power fields), and karyomegaly (increased nuclear size). According to the two-tiered system, high-grade mast cell tumours are significantly associated with shorter time to metastasis or new tumour development and with shorter survival time. In one study, the median survival time was less than four months for high-grade mast cell tumours but more than two years for low-grade mast cell tumours.<sup>7</sup>

In conjunction with the two-tiered system and mitotic index (MI), several markers are being utilized to better define and predict mast cell tumour disease. Ki-67 determines the number of proliferating cells, and AgNORs (agyrophilic nucleolus organizer regions) correlates with the speed of cell proliferation. c-Kit mutations of exon 11 and 8 of c-Kit have been detected in canine cutaneous mast cell tumours, and aberrant KIT expression patterns have been linked with decreased survival. A major problem when evaluating proliferation markers is selection of the area to be evaluated and standardization of the evaluation methods.

### Staging

After diagnosis of a MCT, it is important to consider the staging that will be necessary for each patient. In all cases, the draining lymph nodes should be palpated, when external and a FNA and cytology should be performed. If the draining lymph nodes are internal, an abdominal ultrasound may be necessary to examine the regional nodes. The decision whether or not to do an abdominal ultrasound for staging of MCT is clinician and case-dependent. In cases with large and/or ulcerated masses, a location that may have a more aggressive behavior, recurrent disease or lymph node involvement, an abdominal ultrasound should be performed. Small dermal MCT that are amenable to wide resection can be removed with a wide margin and then staging decisions can be made once the histological grade is available. If an abdominal ultrasound is performed, further controversy exists about whether or not to perform a FNA of the spleen and liver if they are ultrasonographically normal. There is literature that suggests that because metastasis of MCT tends to be infiltrative, rather than nodular, the spleen and liver should be aspirated in all cases. There is also literature that supports the view that only spleen and liver that are abnormal on ultrasound should be aspirated because when the spleen/liver is normal on ultrasound, the diagnosis of metastasis is rare. The authors prefer to aspirate spleen and liver regardless of appearance. Although there are only a small number of studies evaluating the utility of thoracic radiographs for staging of MCT, the rate of detecting radiographic lung metastasis is low. Thoracic radiography may be warranted, however, as a method of ensuring that there is not concurrent disease in these patients or evaluating hilar lymph nodes. The evaluation of the buffy coat for mast cells is now considered historical only.

Further, bone marrow aspiration is also not routinely done because dogs with bone marrow involvement will have widespread and severe disease before the bone marrow is affected.

### Therapy

The therapeutic approach for MCT is based on the clinical stage and histologic grade of the tumour.

**Surgery** is the primary treatment for MCT, particularly for control of local disease.<sup>8,9,10</sup> In general, a wide resection is recommended for mast cell tumours. The exact margin required is not definitively known. A recent paper has suggested that 2 cm margins laterally are all that is required for tumours that are grade 1 or 2. However, a subsequent study indicated that when 2 cm margins are used for grade 2 MCTs, 10% of the cases had dirty margins. Because of this, we recommend 3 cm lateral margins when possible and one fascial plane deep to the tumour. It has also been suggested that neoadjuvant treatment with corticosteroids may facilitate resection. Corticosteroids will decrease inflammation of the tumour and this may make resection easier, however, the corticosteroids will not have an effect on the tumour cells that are peripheral to the tumour. It is possible that corticosteroid treatment may create a false sense of security and the ability to achieve clean margins. It is the author's opinion that corticosteroid use preoperatively should be reserved for cases where cytoreductive surgery and a marginal resection is the goal of surgical therapy.

**Radiotherapy** has played an important role in the management and treatment of canine cutaneous MCT. As with most tumour types, radiation therapy is used for the purpose of achieving local and regional control of the tumour. If excision of a cutaneous mast cell tumour is incomplete, a second and wider surgery should be considered. If, due to the location and/or size of the scar, re-excision is not possible, radiotherapy is the treatment of choice. Curative-intent radiation schedules of daily small-dose fractions for 3 to 4 weeks (total dose approximately 40-52 Gray) have proven to be effective for local control of incompletely excised cutaneous MCT.<sup>1</sup> Two-year control rates of 85-95% are reported when low or intermediate grade MCT are treated in this manner.<sup>1</sup> It is important to note that the reported recurrence rate of incompletely excised grade 2 MCT is approximately 23%, suggesting that a minority of incompletely excised MCT recur and that adjuvant therapies may not always be necessary.<sup>11</sup> However, local recurrence has been shown to negatively affect the survival of affected dogs,<sup>11</sup> and adjuvant radiotherapy remains the treatment of choice to minimize the risk of local recurrence if complete surgical excision is not possible. When regional lymph node metastasis is present, extirpation of the affected node is recommended along with excision of the primary tumour. It has been reported that dogs with low to intermediate grade MCT with metastasis limited to the local regional lymph node may have a favourable prognosis (median disease free interval of 41 months) when treated with a combination of surgery and definitive (curative-intent) radiation therapy.<sup>12</sup> These findings suggest that systemic therapy may not be necessary for some dogs with low and intermediate grade tumours that might intuitively be considered "high risk", such as those with lymph node metastasis. Additional studies are needed to confirm this conclusion. In the meantime, adjuvant systemic therapy should be considered in dogs with negative prognostic factors including high-grade tumours, lymph node metastasis, recurrent tumours, tumour ulceration, GI signs, tumours in unfavourable locations, rapid tumour growth and large tumours.<sup>1</sup> For incompletely excised grade 3 or high grade MCT, numerous radiotherapy schedules have been proposed, including standardly fractionated (daily, small-dose fractions for 3 to 4 weeks) and coarse-fractionated protocols (weekly, large-dose fractions for 3 to 4 weeks), but these have not been compared.<sup>1</sup> Systemic adjuvant therapy is recommended for grade 3 or high-grade tumours due to the higher metastatic potential. Interestingly, a report described positive outcomes in dogs with grade 3 MCT treated with

surgery and radiation alone, including the regional lymph node (median remission and survival times of 28 months).<sup>13</sup> Despite these interesting findings, the majority of veterinary oncologists feel that local therapy alone is insufficient for optimal control of poorly differentiated or high-grade MCT.

Radiotherapy can also serve as a means to achieve palliation of clinical signs associated with non-resectable tumours. Although irradiation of bulky MCTs is generally less effective than treatment of microscopic disease, excellent tumour responses may be observed, including complete responses. Coarse-fraction protocols (weekly, large-dose fractions for 3 to 4 weeks) are commonly used for palliation. Tumour response rates greater than 70-80% have been reported when MCTs were irradiated in the gross disease setting in combination with Palladia and/or glucocorticosteroids<sup>14,15</sup>. Degranulation of tumours in response to irradiation is possible, but rare. This may be of more concern when large tumours are treated. Ancillary medications such as those suggested below and glucocorticoids should be used when MCTs are irradiated in the gross disease setting.

Radiation therapy has reported a 50-75% control rate at one year. When possible radiation should be used as adjuvant therapy after incomplete surgical excision or as primary treatment if surgery is not an option.<sup>16-19</sup>

**Chemotherapy** is less effective than surgery or radiation. Chemotherapy is considered for patients with: high-grade (grade 3) histologic results; distant metastasis; lymph node metastasis; C-Kit positive results or high proliferation scores; nonresectable mast cell tumours; and/or multiple mast cell tumours in a short time period.

Multiagent protocols (e.g. prednisone and vinblastine) may achieve a higher response rate than single agent therapy.<sup>1,2,20</sup> Recently, tyrosine kinase inhibitors (TKI) (toceranib [Palladia®], have become available in veterinary medicine.<sup>21-29</sup> Kit, a tyrosine kinase, has been found to be mutated in 9-30% of high grade MCT in dogs.<sup>22</sup> In future, TKIs in combination with other chemotherapy may result in higher response rates. Toceranib phosphate (Palladia®—Zoetis), a novel anti-cancer drug in dogs, is an oral tyrosine kinase inhibitor that blocks activity of multiple receptors and selectively targets the split kinase family of RTKs. It exerts antiangiogenic and antiproliferative effects, and the oral bioavailability is 77%. Palladia is labeled for dogs with grade 2 or 3 recurrent cutaneous mast cell tumours with regional lymph node involvement. The recommended label dose for mast cell tumours is 3.25 mg/kg every other day, with dose adjustments downward based on regular assessments.<sup>23</sup> However, we dose Palladia at 2.5-2.7 mg/ kg on a Monday, Wednesday, Friday protocol.

Ancillary drug therapy is important with canine MCT. Dogs with mastocytosis, palpable MCT, or evidence of gastrointestinal bleeding should receive H<sub>2</sub> antagonists (i.e. famotidine, ranitidine) to reduce gastric acid secretion and prevent gastrointestinal ulceration. Sucralfate (0.5-1 g PO q 8h) may be given in cases with evidence of gastrointestinal ulceration and bleeding. H<sub>1</sub> antagonists (e.g. diphenhydramine 2-4 mg/kg PO q 12 h) are used along with famotidine prior to and following surgical removal of canine MCT to help prevent the negative effects of local histamine release on fibroplasia wound healing.<sup>1,2</sup>

### Prognosis

Prognosis is based on species, breed, tumour location, growth rate, extent of disease, and the histologic grading of the tumours. The grading is based upon cellular differentiation, cellular pleomorphism, cytoplasmic granules, mitotic figures, and depth of invasion. In general, cutaneous MCT carry a more guarded prognosis in the dog than in the cat. MCT in the boxer

are usually of a lower histologic grade than those found in other breeds. MCT in Siamese are of the less malignant histiocytic type. Tumours located in the perineal or preputial area are likely to metastasize both locally and to deep lymph nodes. Growth rate but not tumour size is also an important prognostic indicator. Dogs with MCT growth rates of greater than 1 cm/week have only a 25% chance of surviving an additional 30 weeks. The more undifferentiated tumour then the higher the grade and the poorer the prognosis.<sup>1,2,35</sup>

Regardless of local therapy chosen, even dogs with low to intermediate grade tumours should be evaluated regularly for local recurrence and possible systemic spread.

**Chemotherapeutic Protocols for Canine Mast Cell Tumour<sup>36</sup>**

**Prednisone/Vinblastine<sup>30</sup>**

Prednisone 2 mg/kg PO q 24 h; Vinblastine 2 mg/m<sup>2</sup> IV q weekly for 4 weeks followed by 4 treatments every 2 weeks

Continue Vinblastine 2 mg/m<sup>2</sup> IV every 2 weeks for as long as appears to have an objective response. Taper and discontinue prednisone over 12-26 weeks.

**Toceranib (Palladia)<sup>21-23</sup>**

(3.25 mg/kg PO q 48 h = label dose but actually too high)

2.5-2.7 mg/kg MWF

**CCNU (Iomustine)<sup>31</sup>**

CCNU (Iomustine) 70-90 mg/m<sup>2</sup> PO every 3 weeks

**CVP<sup>32</sup>**

(Cyclophosphamide/Vinblastine/Prednisone)

Cyclophosphamide 50 mg/m<sup>2</sup> PO q 48 h or for 4 days per week; Vinblastine 2 mg/m<sup>2</sup> IV once a week; Prednisone 20-40 mg/m<sup>2</sup> PO q 48h

or

Day 1 Vinblastine 2-3 mg/m<sup>2</sup> IV (start at 2 mg/m<sup>2</sup> and increase by 10-30% with each dose if tolerated); Days 8,9,10,11 Cyclophosphamide 50-75 mg/m<sup>2</sup> PO ; Daily Prednisone 1 mg/kg PO q 24 h

Repeat cycle at Day 21 for 6 months. Prednisone tapering began at 4 months and discontinued by 7 months.

**Chlorambucil/Prednisolone<sup>34</sup>**

Chlorambucil 5 mg/m<sup>2</sup> PO q 48 h; Prednisolone 40 mg/m<sup>2</sup> PO q 24 h for 14 days than 20 mg/m<sup>2</sup> PO q 48 h

Chemotherapy for MCT	Response rate	Complete Remission	Partial Remission	Reference
Toceranib (Palladia™)	43 %	14 %	28 %	25
Vinblastine & prednisone	47 %	33 %	13 %	30
Vinblastine, cyclophosphamide & prednisone	64 %	45%	18 %	32
Lomustine (CCNU)	42 %	5 %	37 %	31
Vinblastine or lomustine & prednisone	64 %	29 %	35 %	32
Chlorambucil & prednisone	38 %	14 %	24 %	34

**References available on request.**



## PRACTICAL APPROACH TO THE MANAGEMENT OF OSTEOSARCOMA IN DOGS AND CATS

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### INTRODUCTION

Osteosarcoma is the most common primary bone tumour in dogs and makes up approximately 85% of the tumours of the skeleton. This is primarily a disease of large and giant breed dogs. Older dogs are more commonly affected, with a median age of 7 years. Osteosarcoma has a predilection for the metaphyseal regions of long bones. The most common sites of osteosarcoma include the metaphyseal region of the distal radius, proximal humerus, distal femur and distal and proximal tibia.<sup>1,2</sup>

### DIAGNOSIS AND STAGING

A presumptive diagnosis of osteosarcoma is based on the signalment, tumour location and radiographic signs. A decision to biopsy the bone prior to treatment will depend on several factors. If the presentation of the case is very typical of a primary bone tumour and the owner's willingness to treat will not be altered by the tumour type, the clinician may opt to skip this step and move forward with definitive therapy. Cases with an atypical presentation for osteosarcoma should be biopsied prior to definitive therapy.<sup>1,2</sup>

Bone biopsy is performed using a Jamshidi needle or Michele trephine and a closed technique in most cases.<sup>3</sup> When planning the site of the bone biopsy, it is also important to take the options for definitive therapy into consideration. The biopsy tract is considered contaminated with tumour cells and will need to be removed during definitive therapy. This becomes important in cases where limb spare surgery is an option or in cases of flat bone osteosarcoma. If stereotactic radiosurgery is a consideration for limb spare, a bone biopsy should not be performed in cases that are typical of osteosarcoma. The reason for this is that one of the major complications associated with stereotactic radiosurgery is pathologic fracture and this has been seen at the bone biopsy tract sites. Another option for determining a pretreatment diagnosis is cytology via a fine needle aspirate, which is the preferred technique as it often yields a result with less cost, risk and morbidity to the patient. This technique has been used in concert with ultrasound in an attempt to improve the yield. The ultrasound can be used to look for a break in the cortex through which to insert a large gauge needle. A diagnostic sample was obtained in that study in 32/36 cases.<sup>4</sup> Alkaline phosphatase staining has high sensitivity and specificity for determining if a cell is of bone origin.

Staging is performed after a diagnosis of osteosarcoma has been made to determine if there is gross spread of disease. Almost all (90-98%) cases of osteosarcoma have metastasized at the time of diagnosis. However, this is micrometastatic disease in most cases, as the rate of diagnosing gross metastasis at the time of presentation is ~15%. The two most common sites of metastasis are the lungs and another bone site.<sup>1,2</sup> Three-view thoracic radiographs are an essential part of tumour staging. CT scan is the modality of choice for evaluating for lung metastasis in human osteosarcoma patients. This test has been shown to be highly sensitive but not specific for diagnosing gross metastasis to the lung in humans. As CT scans become more common-place in staging for osteosarcoma in canine patients, more information will become available as to how to interpret positive lesions on the CT scan. The probability of diagnosing gross bone metastases at the time of diagnosis is similar to the probability of finding gross pulmonary metastases (~ 8%). Evaluation for metastases to other bones involves a

complete orthopedic examination and long bone survey radiography or nuclear scintigraphy. Long bone survey radiography is an insensitive test for metastasis to bone and scintigraphy is superior, but less available in veterinary medicine. A complete orthopedic examination including palpation of the spine is important to determine if the dog is a good candidate for an amputation and to evaluate for possible metastatic disease. Areas that are painful should be radiographed.

The rate of metastasis to regional lymph nodes has been reported to be 4.4%.<sup>5</sup> Dogs with lymph node metastases have a much shorter survival time (approximately 2 months). The regional lymph nodes should be palpated and aspirated if enlarged. If the diagnosis of lymph node metastasis is not made prior to amputation, it is important that the lymph node is specifically examined histologically post-amputation.

## **SURGICAL TREATMENT**

### **Amputation**

The goal of surgical treatment is complete resection of the primary tumour to prevent further metastasis and remove the source of pain. Most commonly this is achieved by amputation of the affected limb. In most cases there is a significant reduction in weight bearing in the affected limb prior to surgery and the patient will adjust easily to walking on three legs post-operatively. A thorough orthopedic examination should be performed prior to amputation. In most cases, dogs will cope well after amputation, even if there is evidence of osteoarthritis. Dogs treated with amputation alone will generally live for 3-4 months until they succumb to metastatic disease.

### **Limb Spare**

The distal radius is the site that has been most successful for limb spare surgery. However, there are options available for other sites. Owner selection for this procedure to be successful is as important as case selection. The owners who choose to move forward with this option must be fully educated that this option carries with it a significantly greater financial and time commitment than amputation and that there is a much higher risk of post-operative complications. Common complications of limb spare surgery include infection and implant failure. Local recurrence is also a potential complication of limb spare surgery. In some limb spare cases, the complications are catastrophic and revision surgery or amputation is required and owners must be prepared for this. Guidelines for selecting candidates for distal radial limb spare are that the patient is negative for gross metastasis, has minimal soft tissue involvement and that less than 50% of the length of the bone is affected radiographically.

There are many limb spare techniques that are in the literature to treat canine distal radial osteosarcoma. These include: cortical allograft,<sup>2</sup> pasteurized autograft,<sup>6</sup> intraoperative radiation (autograft),<sup>7</sup> endoprosthesis, vascularized ulnar transposition,<sup>8</sup> stereotactic radiosurgery,<sup>9</sup> bone transport osteogenesis,<sup>10</sup> intraosseous transcortical amputation prosthesis (ITAP) and limb shortening limb salvage. With the exception of intraoperative radiation, stereotactic radiosurgery, ITAP and limb shortening, these techniques involve the resection of the distal radius with appropriate margins and the replacement of the defect that is created with an autograft, allograft, prosthesis or regenerate bone.<sup>11</sup> As with many surgical procedures with multiple techniques available, there is not one perfect technique that is without its own set of complications. Currently the endoprosthesis technique appears to be used most commonly by surgical oncologists.

The endoprosthesis limb spare technique uses a 316L stainless steel endoprosthesis that is commercially available. The original endoprosthesis was developed by Charles Kuntz and has

been modified over time. In a study that prospectively compared clinical cases of allograft limb spare and endoprostheses, significantly more of the radius was resected using the 122mm endoprosthesis.<sup>11</sup> The authors postulated that this might have increased the incidence of proximal radial screw pullout. The newer generation VOI endoprosthesis is available in two lengths and is coated with hydroxyapatite to encourage bone ingrowth. The screws are locking screws to help reduce screw pullout. In a study comparing allograft and endoprosthesis in clinical cases, there was no significant difference in infection rate, infection severity, median time to infection, surgical time, limb use, implant failure rate or oncologic outcome.<sup>12</sup> A biomechanical study of allograft vs. endoprosthesis in cadaveric limbs showed the endoprosthesis to be biomechanically superior to the allograft. This study also showed that there was no biomechanical advantage to preserving the ulna in either the allograft or the endoprosthesis group.<sup>12,13</sup> The reported complication rate for endoprosthesis is 95% with over 60% of these being major complications, which makes it difficult to endorse this technique. Limb shortening limb salvage, which was developed by Dr Boston, has only been reported in one case, but may offer a new alternative. This involves removal of the distal radius and then acute shortening of the limb and an arthrodesis. The resultant shortened limb is usually well-tolerated or can be managed with an endoprosthesis if necessary. Time will tell if this technique holds promise for the future.

SRS was reported as a limb spare technique that involves a single dose of radiation that is accurately delivered to the bone tumour with minimal radiation delivered to the surrounding tissues.<sup>9</sup> This delivery technique involves creating a frame around the limb that is used to ensure accurate positioning during the planning CT and the delivery of radiation. A contrast-enhanced CT is then obtained, which is used to plan a radiation dose that will conform to the shape of the tumour target by the use of a linear accelerator. After treatment planning, the patient was transferred to the radiation suite and a single dose of 3000 cGy was delivered to the tumour volume. There is a steep dose gradient between the tumour and surrounding tissues to minimize damage to healthy tissues. The main disadvantages are that SRS is not readily available and there is a risk of pathologic fractures, which is around 50%.

The complications rate for limb spare surgery is much higher than for other orthopedic procedures. The three major complications that occur are infection, local recurrence and implant failure.

The reported infection rate for limb spare varies widely but is 40-75%. Limb spare infections are difficult to manage because of the relative lack of blood supply to the distal antebrachium and because of the presence of a large implant and/or graft. With severe infections that fail to respond to antibiotics and result in poor limb use, amputation may have to be performed. The high infection rate has become a major pitfall in limb spare surgery. However, the silver lining is that dogs that develop infected limb spares with both cortical allografts and endoprostheses appear to have a survival benefit over dogs that do not develop infection.<sup>12,14</sup>

Local recurrence rates for limb spare are reported at 15-25%. The risk of local recurrence is increased when the tumour capsule is encountered intraoperatively and care must be taken to avoid this, especially during the dissection between the radius and ulna. Removal of the ulna en bloc with the radius, either proximal to the styloid process as in ulnar transposition or at the level of the radial osteotomy may help to decrease this complication. Dogs with evidence of a pathological fracture or a large amount of soft tissue involvement preoperatively also have an increased risk of recurrence.

The third major complication associated with limb spare is implant failure. Liptak reported a construct failure rate of 40% when 20 dogs that had either allograft or endoprosthesis limb spare were evaluated. The mode of construct failures will vary depending on the limb spare technique used. Liptak found that the failures in the allograft limb spare dogs tended to occur distally, whereas the endoprosthesis construct failures occurred proximally. After SRS or intraoperative radiation, the construct fails at the level of the irradiated bone. LBTO can result in failure of one of the wires, and this is generally managed by replacement of the wire and is a relatively minor complication. Recently, dogs that developed a construct failure after limb spare were reported to have a survival advantage.<sup>13</sup>

## ADJUNCTIVE TREATMENT

### Chemotherapy<sup>15</sup>

Chemotherapy has been shown to significantly increase the survival times of dogs undergoing surgical treatment of osteosarcoma. The median survival time varies in the literature from 202-540 days. Most reported median survival times are around 1 year. The options for chemotherapeutic agents are doxorubicin, carboplatin and cisplatin.<sup>16-20</sup> These drugs can be given as single agent therapy or in combination (doxorubicin and carboplatin or cisplatin). There has not been definitive evidence to suggest that one protocol produces a significantly longer survival time.

### Radiation

Palliative radiation is another treatment option for dogs with osteosarcoma.<sup>21</sup> This treatment involves treating the affecting bone with 2-4 doses of radiation. The dose of the radiation is low and will not cause side effects to the skin or surrounding tissues. The goal of palliative radiation is to reduce the pain and inflammation associated with the tumour and to improve quality of life. Advantages of this treatment are that it is significantly less expensive (\$1,000-1,200) and it is a good option for owners who do not want their dog to undergo surgical treatment. It is also a viable option for patients with evidence of metastatic disease where amputation is not practical. Dogs with more than one bone lesion can receive radiation to both sites at the same time. The disadvantage of this treatment is a relatively short survival time (the average is 3 months) and that not all dogs will respond to therapy (approximately 70% have a good response) as well there is a risk of pathological fracture. Full course, curative intent radiation is generally not frequently performed due to the side effects that can occur to the skin, the duration of radiation and the expense involved. The expense involved with full course radiation would be similar to that of limb spare surgery. The exception to this is the development of stereotactic radiosurgery.

### Palliative Therapy

Palliative radiation is the most common palliative treatment that is given. This option can be combined with other medications that may help with pain control and possibly slow the progression of disease. Chemotherapy can be combined with palliative radiation. The type of chemotherapy will depend on the owner and the clinician, but both full course chemotherapy and metronomic chemotherapy can be used.

If analgesics are the sole therapy for osteosarcoma, this treatment should only be employed for a short period. Most patients will have some improvement with NSAID and/or gabapentin and/or opioid analgesics. Bisphosphonates are a relatively new palliative therapy for osteosarcoma. This class of drugs is osteoclast inhibitors and therefore will decrease the rate of osteolysis. They may also have other antineoplastic effects. These medications have a poor oral absorption in dogs and the preferred route of administration is intravenously. The most commonly used bisphosphonate at OVC is zoledronate at a dose of 0.1 mg/kg as an infusion

with 60 mL of saline in a 15 minute CRI. This medication has the theoretical risk of causing renal toxicity and monitoring of renal function is recommended. The infusion is repeated every 30 days. In most cases, this therapy is combined with palliative radiation. Oral bisphosphonates are very poorly absorbed by dogs; therefore, should not be used.

Metronomic chemotherapy is another relatively new form of chemotherapy.<sup>22</sup> This is an oral, regularly administered (every day or every other day) low dose of chemotherapy that may slow the progression of disease. The combination of drugs includes an NSAID, low dose doxycycline and low dose cyclophosphamide (15 mg/m<sup>2</sup> PO daily). Potential side effects include bone marrow suppression and sterile hemorrhagic cystitis. The efficacy of this therapy has not been demonstrated. Studies at OVC have not shown the effectiveness of metronomic cyclophosphamide chemotherapy with adjuvant meloxicam administration as maintenance treatment for dogs with appendicular osteosarcoma following limb amputation and carboplatin chemotherapy.<sup>23</sup> Similarly, the addition of toceranib (Palladia®) to metronomic piroxicam/cyclophosphamide therapy following amputation and carboplatin chemotherapy did not improve outcome.<sup>24</sup> Unfortunately, a retrospective study of toceranib (Palladia®) treatment for canine metastatic appendicular osteosarcoma did not show an improvement in outcome.<sup>25</sup>

### **Immunotherapy**

Although there has been advancement in surgical techniques for OSA for both the human and veterinary patients the challenge has been the lack of advancement for the treatment of metastatic OSA in the last 25 years. Various combinations of cytotoxic chemotherapy result in the same outcome. However, immunotherapy offers a novel systemic therapy that may improve patient outcome. Various immunotherapies have been proposed over many years all the way from Coley's toxins in the late 1800's. More recently muramyl tripeptide (MTP) (a synthetic analog of a component of bacterial cell walls) was developed as a nonspecific immune modulator.<sup>26</sup> MTP targets and activates macrophages and when encapsulated in liposomes MTP-PE can deliver the agent selectively to monocytes and macrophages which become activated and tumouricidal. In people, treatment resulted in a decreased risk of recurrence and metastasis and MTP has been approved by the European Medicine Agency for the treatment of patients with osteosarcoma.<sup>27</sup>

Presently OVC as a member of the NIH Comparative Oncology Trials Consortium (COTC) is conducting a trial to determine the safety and efficacy of a live, attenuated, recombinant *Listeria monocytogenes* (ADXS31-164) expressing a chimeric human HER2/neu construct to induce HER2 specific immunity, to prevent metastatic disease, and to prolong overall survival in dogs with OSA in the setting of minimal residual disease following standard of care (i.e. amputation and carboplatin). The epidermal growth factor receptor HER2/neu expression has been demonstrated in canine OSA (similar to human OSA). Previously, in a phase I dose escalation clinical trial with 18 dogs, the vaccine resulted in a significant increase in median disease free interval (615 days) and median survival (956 days) when compared to a historical control group. Overall survival rates at 1, 2 and 3 years for dogs treated with ADXS31-164 were 78%, 61% and 50% respectively.<sup>28</sup>

**References available on request.**

## PRACTICAL APPROACH TO MANAGEMENT OF SOFT TISSUE SARCOMAS IN DOGS AND CATS

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### Introduction

Soft tissue sarcomas are a heterogeneous group of tumours that are named after their presumptive tissue of origin. The focus of this discussion will be tumours that are histologically diagnosed as soft tissue sarcomas, spindle cell tumours, nerve sheath tumours, hemangiopericytomas, and mesenchymal cell tumours. More broadly, soft tissue sarcomas can include other tumours of connective tissue origin including fibrosarcoma, liposarcoma, leiomyosarcoma, malignant fibrous histiocytoma, myxosarcoma, myxofibrosarcoma, lymphangiosarcoma, and hemangiosarcoma. Despite the varying tissues of origin, soft tissue sarcomas have many features in common. They are locally aggressive and recurrence is common after a marginal excision. They tend to metastasize hematogenously, rather than via the lymphatics. Overall the metastatic rate for these tumours is low and obtaining local control is the most important component of therapy.<sup>1,2</sup>

### Diagnostic Workup

Soft tissue masses should be approached with a FNA as a first diagnostic step. Even with a convincing cytological diagnosis of spindle cell tumour, mesenchymal cell tumour, or sarcoma, an incisional biopsy of the mass for histologic confirmation is recommended prior to definitive surgery. This is especially true if a wide or radical excision is the planned course of action, as this will result in considerable expense and morbidity to the patient. It is important to keep in mind the eventual surgical planning that will take place when performing an incisional biopsy. For subcutaneous masses, the skin incision should be made in the central portion of the skin involved. The skin incision should be small relative to the mass and should never approach the margin of tumour and normal tissue, as this may compromise margins of excision. A wedge of tissue can be removed or skin punch biopsy can be used to take the biopsy. A Tru-cut biopsy is another potential method for incisional biopsy and may be useful for sarcomas that are not in the skin or subcutaneous tissue. The disadvantage of this technique is that it provides a much smaller sample, making definitive diagnosis and grade assessment more difficult. It is important to note that although an incisional biopsy will help to give more definitive information regarding diagnosis and grade, the pathologist is only provided with a small amount of tissue with the biopsy and it is possible that the tumour will be upgraded or downgraded when the entire mass is received. Prior to definitive surgical removal, staging should be performed with three-view thoracic radiographs. The metastatic rate is dependent on the grade. Reported metastatic rates are 0-15% for a Grade 1 STS, 10-20% for a Grade 2 STS and 40-50% for a Grade 3 STS. Local staging should be performed in many cases prior to definitive surgical resection. This can be done with either CT or MRI, depending on availability.<sup>1,2</sup>

### Surgical Treatment

Surgery remains the mainstay of treatment for soft tissue sarcoma in dogs. Although chemotherapy and radiation may play a role, this class of tumours is not very responsive to these modalities, especially in the gross disease setting. Because of the high recurrence rate with soft tissue sarcomas that are not removed with adequate margins, a wide or radical excision is recommended. Wide excision refers to removal of the tumour with 3 cm margins laterally and one fascial plane deep to the tumour. A radical excision refers to the removal of an anatomic segment to achieve clear margins of excision. The margins of excision should be

inked with tissue ink and evaluated by a pathologist for completeness of excision. It is very important to communicate with the pathologist regarding margins of excision. It is also important that the deep margin is evaluated by the pathologist, not just the lateral margins of excision.

Soft tissue sarcomas tend to form a pseudocapsule of compressed tumour cells at the periphery. This can give the impression that they are mobile and can be easily shelled out. A marginal excision with minimal to no normal tissue surrounding the mass will leave tumour cells behind and a recurrence is very likely with this treatment. An unplanned excision is an excision that was performed without knowledge of the tumour type prior to removal and is generally a marginal or incomplete excision if the mass is then diagnosed as a soft tissue sarcoma. This scenario might then prompt the clinician who performed the unplanned excision to refer the case to a specialist in oncology. A study by Bacon et al evaluated the success of primary re-excision after recent inadequate resection of soft tissue sarcomas in dogs.<sup>3</sup> In 41 dogs, re-excision of the surgical scar resulted in a long-term favourable prognosis without the need for radiation or amputation. The local recurrence rate in that study was 6/39 (15%) and distant metastasis occurred in 4/39 dogs (10%). Residual tumour was identified histologically in only 22% of cases and this was not found to be predictive of local recurrence. If possible, re-excision of the surgical scar should be performed after unplanned excision of STS. Re-excision should be performed with wide margins, removing the fascial plane below the scar.

Kuntz et al evaluated prognostic factors of soft tissue sarcoma and found that the number of mitotic figures and necrosis on histopathology was predictive of survival time and the number of mitotic figures was predictive of distant metastasis. This suggests that tumour grade may play a role in how we treat these tumours both systemically and locally. A study evaluated whether or not tumour grade was a predictor of local recurrence in marginally excised subcutaneous soft tissue sarcomas.<sup>4</sup> The study evaluated 138 tumours, of which 34 were completely excised and 104 were marginally excised. None of the completely excised tumours with follow up information (0/30) recurred. Of the incompletely excised tumours, 3/41 (7%) of the grade 1, 14/41 (34%) of the grade 2 and 3/4 (75%) of the grade 3 tumours recurred after marginal excision. These comparisons were statistically significant. Overall this study concluded that histological grade is a strong predictor of recurrence of marginally excised subcutaneous STS. Clean histologic margins were also a strong predictor of nonrecurrence.

A retrospective study evaluated the recurrence rate for low-grade soft tissue spindle cell sarcoma of the extremities and found that with 37 tumours in 35 dogs the margins of excision in this study were dirty (12), clean but close (12), and clean (11).<sup>5</sup> Follow up ranged from 210-2,202 days. MST and DFI were not reached because <50% of the dogs died of disease-related events. There was not a significant difference between survival in the three groups of dogs. This could be due to the small number of dogs in each group. The DFI and ST were 697.8 and 703.5 days. This study does suggest that distal extremity, low grade soft tissue sarcoma may be amenable to a less aggressive treatment protocol for both local and systemic therapy.

A study by Chase et al evaluated the outcome after removal of canine spindle cell tumours in first opinion practice.<sup>6</sup> In 104 canine spindle cell tumours, the method of resection was described as marginal in 45 (43.3%), narrow in 18 (17.3%), wide in 5 (4.8%) and radical in 6 (5.8%) and not recorded in 30 (28.8%). Tumour recurrence occurred in 29 dogs (27.9%). The distribution of local recurrence was 13/45 (28.9%) of the marginal excision group, 3/18 of the narrow excision group (16.7%) and 1/5 (20%) in the wide excision group. The median survival time was 1,013 days. Of the 83 dogs that were dead at the time of the study, 18 (21.7%) of the deaths were tumour related. Of the 18 dogs that died, the MST was 878 days. An assessment of tumour invasiveness by palpation was predictive of DFI and ST.

The findings that some cases can do very well with a low grade spindle cell tumour, even with marginal excision, does not suggest that local therapy is not the most important part of treatment. It does, however, highlight the need to assess every patient as an individual and to take multiple factors into account when determining the best treatment approach. The tumour grade, size, location and how amenable the tumour is to wide excision are very important. In cases where a wide excision can be carried out with minimal morbidity to the patient, this should be the treatment pursued, regardless of grade. When the tumour is not amenable to wide excision without the need for amputation, other factors should come into play. The two important factors to consider are the tumour grade and the age of the patient. A low grade tumour in a geriatric patient removed with a marginal excision may not recur in that patient's life time, as was seen in Chase and Stefanello's studies, where a large proportion of the patients died of non-tumour related causes.<sup>5,6</sup> However, a higher grade in a younger patient will increase the risk of a local recurrence with a marginal surgical resection. When considering a surgical approach that is marginal, it is important to have a plan for long-term local control and/or for managing a recurrence. This may include amputation or re-excision and radiation therapy.

### **Adjunctive Treatments**

Because local control is crucial in soft tissue sarcoma, radiation is often used as adjunctive treatment after a marginal excision or when a wide excision is performed with inadequate histological margins.<sup>7-10</sup> It is very important that the surgeon performing the excision has a plan for either a curative intent surgery (wide excision) or a cytoreductive surgery (marginal excision) that will be followed with radiation therapy. The worst-case scenario is an attempted wide excision with dirty histological margins. This creates the most surgical morbidity and cost, increases the chance of healing complications, and creates the largest possible radiation field. Although this unfortunate circumstance will occur occasionally, it can be avoided in most cases with appropriate preoperative planning. If clean margins are unlikely to be achieved based on preoperative imaging, a better approach would be to plan for a marginal excision and follow with radiation. Radiation should not be used as a mop to clean up after a messy surgeon! Although it can be a safety net to fall back on when the margins of excision are not clear, it should not be relied upon in all cases. Full course radiation therapy has been shown to be effective adjunctive therapy to achieve local control after a marginal excision. However, local control is not achieved in all cases.

Chemotherapy is generally not recommended for grade 1 or 2 STS because of the relatively low metastatic rate. Systemic chemotherapy for the treatment of high grade STS is controversial. Selting et al retrospectively evaluated 39 dogs with high grade STS that were treated with adjuvant doxorubicin.<sup>11</sup> The overall DFI was 724 and the MST was 856. A significant difference was not found when dogs that received doxorubicin (21 dogs) were compared to dogs that did not (18 dogs). Although this data would suggest that a survival benefit is not provided by doxorubicin in cases of high grade STS, a prospective, randomized clinical trial is necessary to truly determine if there is a role for doxorubicin in cases of high grade STS. Such a study would be difficult because of the paucity of cases of high grade STS and the relatively long survival time.

Elmslie et al reported the beneficial effects of metronomic chemotherapy (continuous, low dose chemotherapy) in dogs with incompletely resected soft tissue sarcomas.<sup>12</sup> Thirty dogs with incompletely resected STS were treated with cyclophosphamide and piroxicam. These dogs were compared with 55 contemporary controls. The DFI in the control dogs was 211 days,



versus the treatment group, where the DFI was not reached. Metronomic chemotherapy appears to play an important role in local control of incompletely resected STS.

### **SOFT TISSUE SARCOMAS IN CATS: FELINE INJECTION SITE (VACCINE ASSOCIATED) SARCOMA**

Although there may be a trend towards a less aggressive approach to the management of some low-grade soft tissue sarcomas in dogs, the opposite is true for the approach to vaccine-associated sarcomas (VAS) in cats. VAS were first reported in the early 1990s and have been associated with FeLV and rabies vaccinations, as well as other subcutaneous injections. These tumours arise from sites of chronic, intense inflammation that leads to the proliferation and transformation of fibroblasts. Most commonly these tumours are high-grade fibrosarcomas. Recommendations from the Vaccine Associated Feline Sarcoma Task Force (VAFSTF) have been put in place in an attempt to decrease the incidence and the location of vaccine associated sarcomas. It is now recommended that cats are vaccinated over the lower limb to allow radical resection of VAS, should they occur. A study by Shaw et al evaluated the changes in VAS sites from 1990-2006 to determine if the recommendations of the VAFSTF resulted in different locations of VAS.<sup>13</sup> When sites were compared before and after the vaccination recommendations in 1996, there was a decrease in the percentage of interscapular and right and left thoracic VAS and a corresponding increase in the number of VAS over the right thoracic limb and the combined regions of the pelvic limb and abdominal wall bilaterally. The authors hypothesized that the VAS over the lateral abdominal wall were likely a result of an aberrant injection that was intended for the proximal pelvic limb but resulted in injection over the abdominal wall due to the position of the cat at the time of injection. The proximal limb and lateral abdominal wall remain problematic areas to treat with wide surgical resection and this study highlights the need for continued education of general practitioners to vaccinate over the lower extremity and for continued development of vaccines with a limited inflammatory response.<sup>14</sup> **The most significant finding of this paper is that we, as veterinarians have control over where these tumours occur, meaning where we vaccinate cats can have a direct impact on where tumours occur and how easy they are to manage. It is critical that cats are vaccinated below the elbow and stifle to ensure that they can be managed effectively with limb amputation.**

A mass in a cat that is present >1 month after vaccination at a vaccine site or any firm growing mass in a cat should be biopsied. Unfortunately, FNA and cytology in these cases can be misleading and is therefore not recommended. Similarly, these masses should not be excised, but should be biopsied with an incisional biopsy to determine tumour type first. Excision without knowledge of tumour type may lead to a larger definitive resection with a decreased chance of a successful outcome. Once diagnosed, referral to a surgeon is recommended for local and distant staging with CT scan and surgery.

Like other sarcomas, aggressive local control remains the mainstay of treatment for VAS. Surgery is the primary method of local control, and is often combined with radiation therapy pre- or post-operatively. Cohen et al evaluated 78 cats with VAS treated with conservative or wide excision followed by full course radiation therapy.<sup>15</sup> The median survival time for all cases was 730 days. 41% of the cats had a local recurrence and 12% developed metastasis. Whether the cats had a wide or conservative excision did not affect the recurrence rate. 26 cats received chemotherapy. There was no difference in the recurrence rate, metastatic rate or survival times in dogs that received chemotherapy compared with cats that did not. This study suggests that conservative excision and radiation therapy to 3 cm margins may be equivalent to wide excision with 3 cm margins and radiation therapy. However, the overall recurrence rate in this study was

high, and local control was not achieved in 41% of the cases. More aggressive local control appears to be necessary. Cohen's study found that the number of surgeries was inversely related to a successful outcome. This was also found in a retrospective study by Eckstein et al.<sup>16</sup> Kobayashi et al reported 92 cats with VAS treated with preoperative radiation therapy and found that clean margins of excision had a significant survival benefit, with a mean time to first event (local recurrence or metastasis) being 986 days in cases with clean margins, compared with 292 days in cases that did not.<sup>17</sup> This highlights the importance of an incisional, rather than an excisional biopsy, followed by expedient referral to an oncologic surgeon for aggressive local resection.

Phelps et al described wide or radical excision of VAS using 5 cm lateral margins and two muscle planes or bone as the deep margin of excision in 91 cats.<sup>18</sup> The recurrence rate was low compared with other studies at 14%, with a median survival time of 901 days. Incisional dehiscence was the most common complication. However, the overall complication rate was low. This study suggests that surgery alone can be an effective method of treatment of VAS. However, the margins of excision need to be extensive and this will require a surgeon with additional training and experience in surgical oncology. Even a 1 cm mass will require an excisional diameter of 11 cm, which is considerable in a small patient. Most VAS are much larger than this at the time of diagnosis and excision. Post operative care in an ICU is essential to provide adequate support and analgesia. Many of these patients will require a blood transfusion intraoperatively. **Again, this study highlights the need for primary care veterinarians to vaccinate cats below the stifle and elbow to ensure that if a VAS occurs, it can be treated effectively with amputation alone.**

Radiation therapy is often used in combination with surgery. It is difficult to determine if this should be performed before or after surgery, if at all. The benefit of performing radiation therapy first is that the margins of excision will be sterilized, and the radiation field will be as small as possible. The disadvantage of this approach is that there may be an increase in incisional complications due to the fact that the surgical site will be within the radiation field. Kobayashi et al reported 92 cats with VAS treated with preoperative radiation therapy and concluded that this is an effective treatment plan in cases of VAS, especially if clean margins of excision can be achieved post-irradiation.<sup>17</sup> Each case must be evaluated on an individual basis.

A retrospective by Bregazzi et al evaluated cats treated with surgery and radiation, with and without doxorubicin also failed to show a survival benefit with the addition of chemotherapy to the treatment protocol.<sup>19</sup> It is difficult to interpret retrospective studies because there may be a selection bias in the cases that are selected for chemotherapy. Eckstein et al did show a significant benefit in the PFI when chemotherapy was used in the gross disease setting in cases treated with coarse-fractionated radiation therapy compared with cases that did not receive chemotherapy.<sup>16</sup>

As far as the types of vaccinations, it is recommended that primary care veterinarians review the Feline Practitioner Guidelines for vaccinations. It is important to tailor the vaccination protocol to the needs of the individual patient, rather than vaccinating every cat with the same protocol. Feline leukemia virus vaccine should be given judiciously and in the appropriate location. Non-adjuvanted rabies vaccine is recommended. Even with non-adjuvanted vaccine, the vaccines should be given in the appropriate location as the development of this tumour is multifactorial.

**References available on request**

## Top ten potential drug interactions in dogs and cats

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In humans, the risk of adverse drug interactions multiplies as the number of administered drugs increases. Interactions can occur during IV drug administration, during oral absorption, at the target site, or during hepatic or renal elimination. Drug interactions may lead to loss of efficacy or increased toxicity. Although most of our knowledge of drug interactions comes from data in humans, many of these interactions are likely to occur in dogs and cats as well.

### TYPES OF DRUG-DRUG INTERACTIONS (DDI)

- Pharmacodynamic DDI
  - One drug affects the action of another drug at the site of biological activity
    - Leads to changes in drug response without changes in systemic drug concentrations
    - Often logical and predictable when drug mechanisms of action are understood
    - Mostly outside of the scope of this presentation
- Pharmacokinetic DDI
  - One drug affects the absorption, distribution, biotransformation, or excretion of another drug
    - Leads to changes in systemic drug concentrations
  - Absorption
    - Gastric pH
    - Drug chelation (by metal ions)
    - Drug adsorption (e.g. activated charcoal)
    - Altered GI motility
    - Altered intestinal CYP or transporter activity
  - Distribution
    - Altered protein binding (minor mechanism)
    - Interference with tissue uptake
  - Biotransformation
    - Inhibition of enzymes (major mechanism)
    - Induction of enzymes
  - Excretion
    - Alterations in GFR
    - Inhibition or induction of transporters

## THE TOP OFFENDERS

### Sucralfate

Aluminum-containing drugs such as sucralfate can form complexes with many other drugs in the GI tract, markedly decreasing drug absorption. In humans, sucralfate impairs the bioavailability of several fluoroquinolones, theophylline, aminophylline, digoxin, and azithromycin. **In dogs, sucralfate has been shown to decrease the bioavailability of ciprofloxacin, doxycycline and minocycline** (Kukanich 2014, 2015, 2016). Sucralfate co-administration may decrease the efficacy of these antibiotics. These interactions can be minimized or avoided by giving the antibiotic two hours *before* the sucralfate. The opposite regimen is not recommended (i.e. giving the sucralfate first, followed two hours later by the antibiotic) because of the persistence of sucralfate in the stomach. However, because of the difficulty in coordinating dosing at home, sucralfate should be prescribed only with strong rationale when other oral drugs are being given.

Sucralfate delays, but does not decrease the extent of, the absorption of H<sub>2</sub> blockers, and there are no reports of adverse interactions between omeprazole and sucralfate. Therefore, staggered dosing does not appear to be necessary for sucralfate and these antacids.

### Ketoconazole

Ketoconazole and itraconazole are best absorbed at acidic pH; therefore, these azole antifungal drugs should not be prescribed at the same time as omeprazole, H<sub>2</sub> blockers, or other antacids. Interestingly, antacids do not affect the absorption of fluconazole.

Ketoconazole inhibits cytochrome P450 CYP3A enzymes, which have a wide substrate range and high potential for drug-drug interactions. Ketoconazole is also an inhibitor of p-glycoprotein, an important drug efflux transporter. Inhibition of p-glycoprotein can decrease drug elimination through the bile and kidneys, and can also increase drug bioavailability across the small intestine.

**Ketoconazole may increase plasma concentrations of many drugs**, including ivermectin (shown in dogs), cyclosporine (shown in dogs and cats), digoxin, amitriptyline, midazolam (shown *in vitro* in cats; Shah 2009), and warfarin. Ketoconazole increases the bioavailability of tramadol more than 4-fold in dogs (Kukanich 2017); this might lead to excess sedation in some dogs. A suspected interaction between ketoconazole and colchicine, leading to colchicine toxicity, was recently reported in a dog (McAlister 2014). Like ketoconazole, itraconazole also inhibits the clearance of some drugs in humans.

The effects of ketoconazole to inhibit the clearance of cyclosporine can be exploited to allow lower doses of cyclosporine. Ketoconazole dosages as low as 2.5 mg/kg/day are effective (Myre 1991, Gray 2013). Monitoring of ALT is recommended during

ketoconazole therapy. Trough whole blood cyclosporine can be measured at steady state (by one week), just prior to the next dose. Target levels for immunosuppression in humans are 400-600 ng/ml, although lower concentrations may be associated with clinical responses in dogs and cats.

### **Cyclosporine**

As a substrate for both p-glycoprotein and CYP3A, cyclosporine has the potential for numerous drug interactions. Compounds that inhibit CYP3A, including diltiazem and even grapefruit juice, lead to increased cyclosporine blood concentrations and the potential for toxicity. Both cimetidine and metoclopramide have been reported to decrease cyclosporine clearance in humans; however, these drugs do not significantly impact cyclosporine concentrations in dogs, likely due to species differences in enzyme-substrate specificity (Daigle 2001, Radwanski 2011)

In addition to the use of ketoconazole to increase cyclosporine concentrations, **both fluconazole and clarithromycin have cyclosporine-sparing effects in dogs** (Katayama 2014, Katayama 2008). In fact, fluconazole at 5 mg/kg/day decreased the total daily dose of cyclosporine necessary to maintain therapeutic concentrations in dogs by 39% (Katayama 2010). In cats, clarithromycin at 10 mg/kg/day increased cyclosporine levels and allowed a cyclosporine dose reduction by 65% in one feline patient (Katayama 2012).

The nutraceutical St. John's Wort induces CYP3A in humans and accelerates elimination of cyclosporine, decreasing drug concentrations (Durr 2000); this has also been shown in dogs (Fukunaga 2012). **Supplements containing St. John's Wort should be avoided in dogs being treated with cyclosporine.**

### **Phenobarbital**

Phenobarbital is a potent inducer of several P450 enzymes in humans and dogs. Phenobarbital speeds the metabolism of many drugs in humans, including glucocorticoids, mitotane, theophylline, ketoconazole, clomipramine, lidocaine, digoxin, and others. Phenobarbital also induces glucuronidation pathways, and can reportedly speed the clearance of carprofen in dogs (Saski 2015).

Phenobarbital has clinically significant drug interactions with other anticonvulsants. Phenobarbital increases the clearance of zonisamide in dogs, possibly due to induction of CYP3A (Orito 2008). **Phenobarbital also increases levetiracetam clearance in dogs**, and can lead to a 50% shortening of levetiracetam half-life (Moore 2011) by a P450-independent mechanism (Munana 2015). Phenobarbital lowers the target therapeutic concentrations of bromide needed to maintain seizure control in dogs, although this interaction is likely pharmacodynamic rather than pharmacokinetic (Trepanier 1998). Finally, phenobarbital undergoes auto-induction of its own metabolism, necessitating phenobarbital dosage escalations in some dogs on long-term therapy (Abramson 1998).

Conversely, the **clearance of phenobarbital is inhibited by chloramphenicol**. This can lead to sedation and ataxia in dogs being treated with both phenobarbital and chloramphenicol (Houston 1989), and this combination should be avoided.

In cats, phenobarbital causes minimal cytochrome P450 enzyme induction, so phenobarbital drug interactions involving enhanced P450-mediated clearance are unlikely in felines.

### **Fluoroquinolones**

The **oral absorption of some fluoroquinolones, such as ciprofloxacin, is impaired by drugs that contain divalent or trivalent cations, to include aluminum, zinc, and iron**. In contrast, no interaction was seen between enrofloxacin and aluminum-containing sucralfate in a small number of Greyhounds (Kukanich 2016). However, this requires further evaluation before these two drugs can be recommended in combination.

Fluoroquinolone antibiotics inhibit the clearance of theophylline in both humans and dogs, due to inhibition of the cytochrome P450 enzyme CYP1A2. This has led to theophylline toxicosis in humans. In dogs, **enrofloxacin leads to higher plasma theophylline concentrations** by about 30-50%, and marbofloxacin increases theophylline concentrations by a lesser extent (~25%). The combination of enrofloxacin and theophylline could potentially lead to theophylline side effects in some dogs, particularly dogs with concurrent renal insufficiency when enrofloxacin concentrations might increase.

Other fluoroquinolone drug interactions occur independently of cytochrome P450 effects. Enrofloxacin delays elimination of flunixin meglumine (Banamine), possibly by competitive inhibition of renal tubular transporters, leading to higher flunixin blood concentrations in dogs (Ogino 2005). **Ciprofloxacin decreases blood concentrations of the immunosuppressive drug mycophenolate** in humans, by impaired enterohepatic recycling of its glucuronidated metabolite (this recycling requires deconjugation by a brush border glucuronidase, which is inhibited by ciprofloxacin; Kodawara 2014). Fluoroquinolones and other antibiotics need to be evaluated for interactions with mycophenolate in dogs.

### **Metoclopramide**

Metoclopramide, a dopaminergic (D2) antagonist and prokinetic agent, has several important drug interactions in humans. Metoclopramide **enhances the absorption of acetaminophen, aspirin, and alcohol overdoses via increased gastric emptying**. Metoclopramide can theoretically lead to enhanced extrapyramidal side effects (tremor) in combination with phenothiazines (e.g. chlorpromazine, acepromazine), or with selective serotonin reuptake inhibitors (e.g. fluoxetine). Tremors are also seen at standard metoclopramide dosages in dogs with renal insufficiency without dose adjustment.

Interestingly, metoclopramide reduces pain on injection of propofol in humans, as well as the amount of propofol needed for anesthetic induction (by 20-25%), although the mechanisms are not clear. Although metoclopramide is a dopamine antagonist, it has no effect on the use of dopamine for hypotension; this is mediated by D1 receptors.

### **Furosemide**

Furosemide can lead to dehydration and pre-renal azotemia, which will decrease the renal clearance of some drugs, including digoxin. Furosemide can also cause hypokalemia and hypomagnesemia, both of which exacerbate the cardiac toxicity of digoxin. These interactions can lead to digoxin toxicity unless serum digoxin levels are monitored.

In addition, **furosemide enhances the nephrotoxicity of amikacin and gentamicin**; because of this, mannitol may be preferred over furosemide for treatment of acute renal failure caused by aminoglycosides. When high dosages of furosemide are combined with ACE inhibitors, this can cause hemodynamic changes that can lead to acute renal failure. Initial doses of ACE inhibitors should be conservative when furosemide is also instituted, and clinical status and renal function should be monitored over the first 1-2 weeks.

Interestingly, the bioavailability and diuretic effects of furosemide are enhanced by **vitamin C** supplementation in dogs (Lee 1989). For example, 150 mg of vitamin C doubles the urine output from furosemide in dogs, which could lead to dehydration. Owners of dogs treated with furosemide should be warned against adding supplements containing vitamin C (ascorbic acid).

Furosemide can also affect the efficacy of other drugs. **Hypokalemia secondary to furosemide can blunt the antiarrhythmic effects of lidocaine**. Serum potassium should be evaluated in patients with ventricular arrhythmias, and potassium supplementation should be considered if patients do not respond to lidocaine. Furosemide administration will also **increase the renal loss of bromide**, and can lower serum bromide concentrations and lead to seizure breakthrough.

### **Cimetidine**

Cimetidine is a potent inhibitor of several families of cytochrome P450s in humans (CYP2D6, CYP3A4 and others). Cimetidine also inhibits a specific renal drug transporter (OCT2). Because of this, cimetidine decreases the clearance of many drugs in humans, to include chloramphenicol, lidocaine, theophylline, diazepam, midazolam, and others. Cimetidine may lead to toxicity from these drugs in humans.

**Cimetidine appears to be a weaker inhibitor of P450s in dogs**, but effects on renal transporters have not been well studied. Only a few cimetidine drug interactions have been reported in dogs, showing modestly decreased clearance of theophylline, (Gascon

1994) delayed absorption of cyclosporine (Daigle 2001) and a marked increase in the bioavailability of tramadol (Kukanich 2017).

Other H<sub>2</sub> blockers such as ranitidine, famotidine, or nizatidine are not P450 inhibitors at therapeutic concentrations. Ranitidine and nizatidine have the theoretical advantage of prokinetic effects. However, oral ranitidine had no effect on GI transit time in one study in dogs (Lidbury 2012).

### **Omeprazole**

The pump blocker antacid omeprazole is an inhibitor of some cytochrome P450's in humans (mostly CYP2C19), and may inhibit the clearance, and possibly increase the toxicity, of diazepam, midazolam, and warfarin (Wedemeyer 2014). Omeprazole can also inhibit p-glycoprotein, and may enhance the absorption of digoxin in humans.

Omeprazole inhibits the conversion of clopidogrel to its active metabolite, leading to decreased efficacy in humans. However, **a recent study in dogs showed that omeprazole (1 mg/kg q 24h) did not significantly reduce the antiplatelet effects of clopidogrel** (Thames 2016). This has not been evaluated in cats or at higher dosages in dogs.

As inhibitors of gastric acid secretion, omeprazole and pantoprazole can also decrease the absorption of iron supplements, ketoconazole, and itraconazole. It is wise to discontinue antacids when oral ketoconazole and itraconazole are being given. Alternatively, if antacids cannot be stopped, fluconazole can be considered.

**Omeprazole also decreases the bioavailability of mycophenolate mofetil** in humans, due to poor dissolution of this drug at a pH above 4.5 (Kees 2012). This combination should be avoided in dogs and cats until more is known in these species.

### **Clomipramine**

Clomipramine is a tricyclic antidepressant that inhibits norepinephrine reuptake. **Clomipramine can have serious pharmacologic interactions with monoamine oxidase (MAO) inhibitors**, which decrease the breakdown of norepinephrine and serotonin. This can lead to "serotonin syndrome" (twitching, tremor, tachycardia, myoclonic movements, hyperthermia) in humans, which can be fatal. This is a well-established interaction in humans. Examples of veterinary MAO inhibitors include selegiline (L-deprenyl) and amitraz. The potential for an interaction between clomipramine and these drugs has not been directly evaluated in dogs, but the Clomicalm® label recommends against clomipramine being given within 14 days of either L-deprenyl or amitraz.

Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, also inhibit neuronal reuptake of serotonin leading increased concentrations in the synapse. However, the risk of serotonin syndrome for SSRIs in combination with clomipramine appears to be lower than with MAOIs, at least in humans (Figuroa 1998). Other drugs that inhibit



serotonin reuptake, to include tramadol, have the *potential* for a drug interaction with clomipramine, but the risk appears to be even lower than with MAOIs or SSRIs.

In addition to these target site interactions, **clomipramine** is a fairly potent inhibitor of canine CYP2D15 (Aidasani 2008), which could lead to interactions with drugs such as **dextromethorphan** (in Robitussin®) that are metabolized by this pathway in dogs (Shou, 2013). Finally, the metabolism of clomipramine can also be impaired by ketoconazole or itraconazole in humans, and clomipramine should probably not be combined with these azole antifungals unless there is careful monitoring.

Summary Table: Drug interactions in humans that may also affect dogs and cats

Drug	May increase the toxicity of:	May decrease the efficacy of:	Toxicity may be increased by:	Efficacy may be decreased by:
<b>Sucralfate</b>		Ciprofloxacin, doxycycline, erythromycin, theophylline, digoxin		
<b>Ketoconazole</b>	Cyclosporine, warfarin, digoxin, amitriptyline, midazolam, cisapride, clomipramine, colchicine, tramadol			Antacids, H <sub>2</sub> blockers, omeprazole
<b>Cyclosporine</b>			Ketoconazole, itraconazole, fluconazole, diltiazem, clarithromycin, powdered grapefruit	St. John's wort
<b>Phenobarbital</b>		Glucocorticoids, clomipramine, lidocaine, digoxin, theophylline, mitotane, levetiracetam, zonisamide, carprofen?	Chloramphenicol	
<b>Fluoroquinolones</b>	Theophylline, flunixin meglumine	Mycophenolate mofetil		Sucralfate, iron, aluminum, zinc
<b>Metoclopramide</b>	Ethanol, aspirin, or acetaminophen overdoses; propofol?	Probably <i>does not</i> counteract the renal effects of dopamine	Aceprozamine, fluoxetine (tremor)	
<b>Furosemide</b>	ACE inhibitors, digoxin, aminoglycosides	Bromide, lidocaine (via hypokalemia)	Aminoglycosides, vitamin C	
<b>Cimetidine</b>	Lidocaine, theophylline, diazepam, propranolol, tramadol?	Ketoconazole, itraconazole, iron supplements, cyclosporine		
<b>Omeprazole</b>	Diazepam, midazolam, warfarin, digoxin	Ketoconazole, itraconazole, iron supplements, mycophenolate		
<b>Clomipramine</b>	Dextromethorphan?		L-deprenyl, amitraz, ketoconazole, itraconazole, fluoxetine, tramadol?	

Consider using the **Drug Interactions Fact Checker** at [www.drugs.com](http://www.drugs.com) to screen for known human drug interactions.

## Drug dose adjustments for disease

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### Introduction

Physicians have ready access to evidence-based recommendations for drug dosage adjustments in patients with organ dysfunction. In contrast, veterinarians lack similar guidance for most drugs. Although we need more veterinary studies, it is possible to make some reasonable recommendations for drug dosing in dogs and cats with heart failure, hepatic failure, and renal insufficiency, based on a few veterinary studies and existing data from humans.

### Considerations in heart failure

Decreased cardiac output in heart failure can lead to **prerenal azotemia**. This may necessitate lower chronic doses of renally cleared drugs, such as digoxin, furosemide, and enalapril. In contrast, benazepril, which can also undergo hepatic clearance, should not require a dose reduction in dogs or cats with mild to moderate azotemia (Lefebvre 1999; Kitagawa 2000; Toutain 2000; King 2002).

In right heart failure, the presence of **gastrointestinal edema** may lead to erratic oral absorption of some drugs, including oral furosemide (Ogawa 2014). When furosemide is given IV, it leads to an acute increase in venous capacitance within 5 minutes (Johnston 1984); this can offload the heart even before any diuretic effect is seen.

Peripheral vasoconstriction leads to decreased blood flow to the skin in fulminant failure. To assure adequate drug delivery **in heart failure, intravenous or intramuscular drug administration is preferable** to oral, SC, or transdermal routes whenever possible.

Cardiac drugs have many potential drug interactions, caused by additive drug effects, opposing drug actions, or competition for drug elimination. For example, diltiazem and atenolol in combination can lead to AV block and bradycardia. Furosemide can lead to hypokalemia, which can diminish the effectiveness of lidocaine and increases the risk of digoxin toxicity. ACE inhibitors and spironolactone can lead to hyperkalemia (although this is uncommon in dogs receiving concurrent furosemide).

In humans, dosing of digoxin and other drugs is based on nomograms that incorporate ideal body weight and creatinine clearance. In addition, cardiac drug dosages can be titrated to achieve target reductions in BNP or NT-pro-BNP, and this leads to better outcomes than following clinical signs alone (De Vecchis 2014). Similar evidence-based practices are not yet available in veterinary medicine.

Key points:

- In acute heart failure, parenteral dosing (esp. IV) is preferred when possible.
- Polypharmacy is common in heart disease – always consider possible drug interactions. One good resource is [www.drugs.com](http://www.drugs.com), **Drug Interactions Checker**.
- Frequent monitoring of appetite, hydration, body weight, electrolytes, and kidney function is important in dogs and cats that are treated with multiple cardiac drugs (e.g. every 3 months, sooner if problems noted).

**Hepatic insufficiency**

In humans with inflammatory liver disease without cirrhosis, hepatic drug metabolism is mostly conserved. With cirrhosis or substantial hepatic dysfunction, however, drugs that are normally extensively metabolized are not cleared efficiently. Common examples of hepatic dysfunction in our patients include **fulminant hepatic lipodosis, acute hepatic necrosis, cirrhosis, and large portosystemic shunts**. Based on human data, dosages of some drugs may need to be reduced in dogs and cats with these diseases.

There are many drugs that are extensively metabolized or rely on liver blood flow for clearance. Unless these drugs have a high margin of safety, **dosing at 25-50% of standard dosages** is recommended in humans. Otherwise, drug alternates can be used. For example, if metronidazole toxicity is a concern in liver failure, lactulose can be substituted when treating hepatic encephalopathy, and ampicillin/sulbactam can be used if systemic anaerobic coverage is needed.

Few drug pharmacokinetic studies have been published in veterinary patients with impaired liver function. In one study in cats with liver disease (many with hyperbilirubinemia), the clearance of ondansetron was impaired, leading to an approximately 60% increase in ondansetron exposure after a single dose (Fitzpatrick 2015). This probably means less frequent dosing in cats with liver disease (i.e. q12h rather than the recommended q8h in cats with normal liver function, Quimby 2014).

**Table 1: Drugs with recommended dosage reductions in humans with liver dysfunction/ cirrhosis** (from Verbeeck 2008; Amarapurkar 2011; Perianez-Perraga, 2012)

Amitriptyline	Fluoxetine	Ondansetron*
Azole antifungals	Lidocaine	Phenobarbital
Chloramphenicol	Metronidazole	Vinblastine
Cyclophosphamide	Midazolam	Vincristine
Diazepam	Morphine	Voriconazole

\*Also shown in cats

Hypoalbuminemia is a common complication of hepatic insufficiency, and could theoretically lead to increased acute adverse effects from highly protein drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) or benzodiazepines. However, this is not actually well documented.

Ascites can be seen in dogs with portal hypertension from hepatic fibrosis or cirrhosis. Lipid soluble drugs will not distribute to ascites fluid. The normal body weight (minus estimated ascites fluid weight) should be used to calculate dosages of lipid soluble drugs such as propofol, fentanyl, and vitamin K<sub>1</sub>. Water soluble (polar) drugs will distribute to ascites fluid (unless they are highly protein bound). For polar drugs such as aminoglycosides, the total body weight (including ascites fluid) should probably be used to calculate drug dosage.

Patients with shunts or loss of liver function have increased sensitivity to central nervous system (CNS) depressants. Barbiturates, acepromazine, and dexmedetomidine should be avoided, **Benzodiazepines at reduced dosages, along with lower doses of reversible opioids, are good choices.** Fentanyl is a good choice because of its short half-life. For encephalopathic seizures, consider using diazepam or midazolam at 20-30% of standard doses and titrating upwards to effect.

Some therapies can worsen hepatic encephalopathy. Avoid stored whole blood and stored packed red blood cell transfusions in patients with significant liver dysfunction, since **stored blood can have high ammonia concentrations.** Instead, use an in-house blood donor or a unit with a distant expiration date.

**Avoid NSAIDs** in dogs and cats with significant liver disease, because of the risk of gastrointestinal bleeding. GI bleeding is a protein load on the gut, and can worsen hyperammonemia. Furosemide can also worsen hepatic encephalopathy by leading to hypokalemia, dehydration, azotemia, and alkalosis. Spironolactone/hydrochlorothiazide is better tolerated than furosemide when treating ascites.

As for fluid therapy, avoid 0.9% saline IV in patients with liver disease, since this high sodium fluid can lead to volume overload. Instead consider 0.45% saline with 2.5% dextrose and added potassium for liver patients. Finally, **avoid glucocorticoids in patients with liver disease until signs of hepatic encephalopathy are controlled.** Glucocorticoids are catabolic, and will enhance muscle breakdown, deamination of proteins, and release of NH<sub>3</sub>.

Key points:

- No need to dose adjust drugs in patients with increased liver enzyme activities unless there is evidence of decreased liver function (increased bile acids, low albumin, increased bilirubin) or shunting.
- Caution with sedating drugs – these typically need lower dosages in liver failure.
- Avoid drugs that cause hypokalemia, GI bleeding, or sodium retention in patients with liver disease

## Renal failure

Renal failure leads to decreased filtration of renally eliminated drugs and metabolites, and can also lead to decreased tubular secretion of some drugs, such as trimethoprim, cimetidine, and digoxin. Renal failure is associated with less obvious effects on drug

disposition, such as decreased renal P450 and Phase II drug metabolism, impaired binding of some drugs to albumin, and reduced tissue binding of other drugs.

Given these complexities, it is unfortunate that there are very few studies on dosage adjustments in dogs or cats with renal failure. Creatinine clearance is used to make rational dosage adjustments in azotemic humans, but this measurement is typically not available for veterinary patients. Dosage reductions in humans are typically made when creatinine clearance values are less than approximately 0.7 to 1.2 ml/min/kg (depending on the drug); this corresponds to a serum creatinine of approximately 2.5 to 3.5 mg/dl (220-310 umol/L). Dosage reductions can be made by giving less drug at the same intervals, the same dose at less frequent intervals, or a combination of the two.

Drugs that require dosage reductions in renal failure include those with a relatively **narrow margin of safety that are primarily eliminated by the kidneys** (or have an active metabolite that is eliminated by the kidneys). Penicillins are renally excreted, but toxicity is unlikely. However, dose reduction would be appropriate and would decrease the cost of more expensive penicillins and related drugs (such as ticarcillin or meropenem) in patients with azotemia. Cephalosporins such as cephalothin and cefazolin can be nephrotoxic at very high doses in some animal models, so dose reduction of these two drugs may be indicated in dogs and cats with renal failure.

Most fluoroquinolones are renally cleared. Given the risk of retinal toxicity from enrofloxacin in cats, **less retinotoxic fluoroquinolones**, such as marbofloxacin, pradofloxacin, or orbifloxacin, should be substituted in cats with renal failure. If enrofloxacin is necessary (i.e. in the U.S. where it is the only injectable veterinary fluoroquinolone available), the dosage of enrofloxacin should be routinely adjusted for cats with renal insufficiency. Although the optimal method is not established, consider extending the dosing interval, which will still preserve peak plasma concentrations for this concentration-dependent antibiotic class.

Aminoglycosides are dose-dependent nephrotoxins. Aminoglycosides should be avoided whenever possible in azotemic patients, and other drugs should be chosen for resistant gram negative infections (e.g. marbofloxacin or orbifloxacin, ticarcillin, or cefotetan), with dosage adjustment. **When aminoglycosides are necessary, always rehydrate first, and use concurrent fluid therapy** (IV or SC). Consider the use of amikacin (15 mg/kg SC q. 24h), which is possibly less nephrotoxic than gentamicin in cats (Christenson 1977). Extend the dosing interval (e.g. to q48h) to minimize trough concentrations, which are associated with toxicity. Monitor for tubular damage by examining daily fresh urine sediments for granular casts. Do not use aminoglycosides in patients with urinary obstruction, and do not use furosemide or NSAIDs concurrently. Finally, limit aminoglycoside therapy to 5 days or less whenever possible.

Chloramphenicol is sometimes indicated for resistant infections such as MRSP or MRSA. In cats, 25% or more of chloramphenicol is excreted unchanged in the urine; therefore, its use should be avoided in cats with renal insufficiency, or at minimum, a CBC should be monitored weekly for dose-dependent leukopenia.

Potentiated sulfonamides should also be used with caution in azotemic patients, due to decreased renal clearance and decreased protein binding. If they are used in renal failure, it is important to reduce the dosage. In addition, sulfadiazine (found in Tribissen) should be avoided in azotemia since it is the least soluble sulfonamide, especially in acid urine. In dehydrated human patients, sulfadiazine can precipitate as drug crystals in the renal tubules and lead to hematuria and even tubular obstruction. It is unclear whether this is a risk in cats or dogs. When using potentiated sulfonamides, always rehydrate first, dose accurately, and avoid concurrent use of urinary acidifiers.

**Furosemide must be dosed conservatively** in azotemic dogs and cats (and only with good rationale, i.e. fulminant congestive heart failure). Patients with renal insufficiency that need to be treated with furosemide should be monitored very closely for dehydration, hypokalemia, and worsened azotemia (i.e. skin turgor, body weight, PCV/TP, potassium, BUN, and creatinine) at each recheck.

H<sub>2</sub> blockers such as cimetidine, ranitidine, and famotidine are cleared by the kidneys, and lead to CNS disturbances (mania, confusion) in elderly humans with decreased GFR. Therefore, the dosage of these drugs should probably be decreased in dogs and cats with azotemia. However, it **appears that H<sub>2</sub> blockers are not indicated routinely in chronic kidney disease** in dogs and cats, since post mortem studies have found that gastric ulceration is actually uncommon in renal failure in these species, in contrast to humans (McLeland 2014).

Metoclopramide is also renally cleared. Standard continuous rate infusion (CRI) dosages (1-2 mg/kg/day) can cause tremor and ataxia in azotemic patients, and lower doses (e.g. 0.25 to 0.5 mg/kg/day as a CRI) appear to be better tolerated (anecdotal observation).

**Mirtazapine** is an effective appetite stimulant in cats, and has also been shown to **decrease vomiting in cats with chronic kidney disease** (Quimby 2011). However, mirtazapine shows modestly delayed clearance in cats with renal failure (Quimby 2011). The suggested dosing is 1.88 mg every 48 hours in cats with azotemia; further dose reductions are indicated if excessive sedation or hypotension is noted.

Benazepril may be preferred over enalapril in dogs and cats with CKD, since benazepril can also undergo hepatic clearance, and does not require a dose reduction in dogs or cats with mild to moderate azotemia (Lefebvre 1999; Kitagawa 2000; Toutain 2000; King 2002). Although the incidence of hypotension or hyperkalemia has been reported to be low in cats with CKD treated with benazepril (Lavalley 2017), hyperkalemia can occur, particularly in combination with potassium-supplemented renal diets. It is important to monitor blood pressure, BUN, creatinine, and serum potassium in CKD patients on ACE inhibitors (initially after one week, then every 1 to 3 months depending on clinical status). **ACE inhibitors should also be discontinued for 24 hours prior to anesthesia** to allow the kidneys to respond to any intra-operative hypotension.

Gabapentin appears to be effective for post-operative and neuropathic pain (Crociolli 2015, Plessas 2015; Ruel 2019), and to reduce fear response behaviour in cats (Pankratz 2018). Gabapentin is renally cleared in humans, and at least 50% dose reductions are recommended with chronic kidney disease to avoid over sedation (Hartmann 2010).

NSAID's can have adverse effects on GFR, and can also accumulate in renal failure. **NSAIDs should be avoided or dosed carefully in CKD.** For analgesia, opioids, dose-reduced gabapentin, or acetaminophen (in dogs) may be safer choices. If an anti-inflammatory effect is needed, use conservative NSAID dosages and monitor carefully for dehydration and inappetance. Other options for osteoarthritis management in renal failure include diets supplemented with omega-3 fatty acids, physical therapy, and acupuncture.

**Coxibs are *not* safer in renal insufficiency;** they have the same potential for adverse renal effects as non-selective NSAIDs, since COX-2 is also important for renal blood flow. It is unclear whether grapiprant, the EP4 receptor antagonist newly approved for osteoarthritis, is safer than NSAIDs for patients with kidney failure.

#### Key points:

- Dose adjust renally cleared drugs with narrow safety margins in patients with CKD.
- Use extrapolated human guidelines for dose adjustment until better veterinary data are available.
- Find substitutes for drugs with adverse effects on GFR (NSAIDs, diuretics, aminoglycosides).

**Table 2: Empirical recommendations for drug dosage adjustment in renal failure** (based on human studies, reviews (Munar 2007; Goodman and Gilman's textbook), a few veterinary studies, and expert opinion).

Drug	Standard dosage	Method for adjusting	IRIS Stage 2 renal disease (cr 1.6-2.8 mg/dl in cats)	IRIS Stage 3 renal disease (cr 2.9-5.0 mg/dl in cats)	IRIS Stage 4 renal disease (creatinine > 5.0 mg/dl)
Amikacin	15 mg/kg q24h	Interval	q24-48h *Avoid if possible *Adjust interval for trough concs. < 2 ug/ml	q48h *Avoid if possible *Adjust interval for trough concs. < 2 ug/ml	Not recommended
Amphotericin B	1 mg/kg IV three times weekly		Use liposomal formulation only	Use liposomal formulation only	Not recommended
Atenolol	0.25 mg/kg q12h	Dose/Interval	0.19 mg/kg q12-24 h	0.125 mg/kg q12-24 h	0.06 mg/kg q24h
Azithromycin	5-10 mg/kg q24h	-	No adjustment	No adjustment	No adjustment



Benazepril	0.5 mg/kg q12h	Dose	No adjustment	0.25 mg/kg q12-24h	0.125 mg/kg q12-24h
Cefotetan	30 mg/kg SC q12h	Interval	No adjustment	30 mg/kg SC q24h	30 mg/kg SC q24-48h
Ciprofloxacin	25 mg/kg PO q24h	Dose or Interval	No adjustment (dogs; safety unclear in cats)	12-25 mg/kg q24h	12 mg/kg q24h
Doxycycline	5 mg/kg q12h	-	No adjustment	No adjustment	No adjustment
Enalapril	0.5 mg/kg q12h	Dose	0.375-0.5 mg/kg q12h	0.25-0.375 mg/kg q12h	0.25 mg/kg q24h
Enrofloxacin	5 mg/kg q24h	Interval	5 mg/kg q24-48 h	5 mg/kg q48h (not recommended in cats)	5 mg/kg q48-72h (not recommended in cats)
Famotidine	1 mg/kg q12h	Dose/Interval	No adjustment	1 mg/kg q24h	0.5 mg/kg q24h
Fluconazole	5 mg/kg q12h	Interval	5 mg/kg q12-24h	5 mg/kg q24-48 h	5 mg/kg q48-72h
Gabapentin	10 mg/kg q8h	Dose/Interval	5 mg/kg q12h	5 mg/kg q24h – adjust for sedation	Not recommended
Gentamicin	6-8 mg/kg SC or IV q24h	Interval	q24-48h *Avoid if possible *Adjust interval for trough concs. < 2 ug/ml	q48h *Avoid if possible *Adjust interval for trough concs. < 2 ug/ml	Not recommended
Ketoconazole	10 mg/kg po q12h	-	No adjustment	No adjustment	No adjustment
Maropitant	1 mg/kg SC q24h	Negligible renal clearance (Benchaoui 2007)	No adjustment	No adjustment	No adjustment
Meropenem	8 mg/kg SC q12h	Dose/Interval	No adjustment	4-8 mg/kg q12h	4 mg/kg q24h
Metoclopramide	1-2 mg/kg/day CRI	Dose	1.0 mg/kg/day CRI	0.5 mg/kg/day CRI; monitor for tremors	0.25 mg/kg/day CRI; monitor for tremors
Metronidazole	7.5-15 mg/kg q12h	Dose	No adjustment	No adjustment	3.75-7.5 mg/kg q12h
Mirtazapine	1.88 mg per cat q24h (Quimby 2011)	Interval	1.88 mg q24-48h	1.88 mg q48h (Quimby 2011)	Individualize dosing interval to minimize side effects
Ondansetron	1.0 mg/kg q8h (from Quimby 2014 in cats)	-	No adjustment (Fitzpatrick 2015)	No adjustment (Fitzpatrick 2015)	Unclear; not dose adjusted in humans with advanced CKD
Potentiated sulfonamides	15 mg/kg po q12h	Interval	q12h	q12-24h	q24h
Spironolactone	1.0 mg/kg q12h	Dose/Interval	0.5-1.0 mg/kg q24h	0.25 mg/kg q24h	Not recommended
Tramadol	1-4 mg/kg q8-12h	Dose/Interval	0.5-2 mg/kg q12h	0.5-1 mg/kg q12h	0.5-1 mg/kg q24h

## Rational therapy of vomiting in dogs and cats

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Vomiting is a common problem in veterinary patients, and can lead to dehydration, hypokalemia, reflux esophagitis, and weight loss. There are several clinically effective veterinary anti-emetic drugs. Choosing among these options depends on the likely cause of the vomiting and the mechanisms of action and side effects for each drug.

The first step before considering an antiemetic in a dog or cat is a reasonable work-up to rule out serious underlying disease. Acutely vomiting animals brought to a veterinary clinic deserve abdominal radiographs to evaluate for gastric foreign bodies or intestinal obstruction. Using an antiemetic empirically in an animal with unrecognized GI obstruction can delay the diagnosis and may worsen the outcome. If vomiting is severe or persistent, CBC, biochemical panel, and pancreatic lipase testing are indicated.

*“If they are sick enough for an antiemetic, they are sick enough for a work-up”*

### Anti-Emetics

#### **Maropitant (Cerenia®)**

Neurokinin-1 receptor antagonist.

- Inhibits substance P binding to NK-1 receptors in emetic center, chemoreceptor trigger zone (CRTZ), and enteric plexus of gut.
- Most effective anti-emetic available for dogs and cats
  - More effective than metoclopramide (Puente-Redondo 2007)

#### Indications:

- Ongoing vomiting due to diagnosed renal failure, liver disease, gastroenteritis, or pancreatitis
- Prevention of vomiting due to motion sickness
- Prevention of vomiting from opioid pre-meds, especially when given 30-45 minutes before the opioid (Claude 2014)
  - However, can cause ptyalism in this setting
- Prevention of vomiting prior to cisplatin or doxorubicin chemotherapy
- **Maropitant is not indicated in patients with acute nausea or poor appetite that are not vomiting.**
  - Does *not* significantly decrease nausea from many stimuli in dogs, including:
    - Doxorubicin, cisplatin, hydromorphone, morphine, and plant toxins (Rau 2010, Kenward 2017, Claude 2014, Koh 2014, Lorenzutti 2017, Kretzig 2011, Swallow 2017)
  - Exception: may be effective for *delayed* nausea from chemotherapy (de la Puente-Rendodo, 2007)
- **Maropitant for pain modulation?**
  - NK-1 receptors are distributed in the CNS, spinal cord and peripheral nerve terminals, and substance P mediates sensory pain pathways

- Some evidence for efficacy of NK-1 antagonists against visceral pain in animal models
  - Poor efficacy for somatic pain in humans
- Maropitant has anesthetic-sparing effect in dogs
  - 1 mg/kg/ IV, followed by 30 microgr/kg/hr CRI (Boscan, 2011)
  - 1 mg/kg SC at pre-meds (Marquez, 2015; Swallow 2017)
  - Modest decreases in inhalant anesthetic needs
- Potential indication for peri-operative pain control, especially in patients where opioids or NSAIDs are contraindicated
- Has anti-inflammatory effects in a mouse model of pancreatitis (Tsukamoto 2018)
  - This has yet to be proven in dogs or cats

#### Dosing:

- Dogs: 1 mg/kg IV or SC; 2 mg/kg PO
  - 8 weeks of age and older
  - Uninterrupted treatment now label-approved for dogs older than 7 months
    - Dosing still limited to 5 days in a row for puppies 8 weeks to 7 months old
- Dogs for motion sickness: 8 mg/kg PO once daily for maximum of 2 days
- Cats: 1 mg/kg IV, SC, or PO once daily
  - 16 weeks of age and older

#### Drug interactions/Contraindications/Side effects:

- Generally well tolerated
- More discomfort reported with SC maropitant compared to SC metoclopramide (Lorenzutti 2017)
  - Pain can be decreased by refrigerating maropitant vial (Narishetty 2009)
  - Pain on injection of maropitant appears to be due to metacresol preservative (Deckers 2018)
- Transient decrease in BP after IV administration, by 10-20 mmHg (Boscan 2011)
- Increased drooling in dogs when maropitant used in pre-meds (Claude 2014)

#### **Metoclopramide**

Increases release of acetylcholine in GI smooth muscle, leading to increased gastric emptying and net "downstream" intestinal motility, without ileus.

- Antagonizes the actions of dopamine on the chemoreceptor trigger zone in dogs (central antiemetic action in dogs).
- As effective as maropitant in blocking apomorphine-induced emesis in dogs (Selacek 2008)
- Traditionally thought to increase tone in the lower esophageal sphincter (reducing reflux), but has been shown to have little effect on LES pressure (at least after a single dose).
  - Cisapride is much more effective (Kempf 2014)

Metoclopramide in cats:

- Metoclopramide does not appear to be effective as a central D2 antagonist antiemetic in cats. Emesis in cats appears to be mediated through receptors other than D2, particularly alpha-2 receptors.
  - This is consistent with the finding that cats are also very insensitive to vomiting induced by apomorphine (a dopaminergic agonist), but are sensitive to emesis from xylazine (an alpha-2 agonist).
  - Further, metoclopramide can decrease xylazine-induced vomiting in cats (Kolahian 2010)
- **Metoclopramide does appear to clinically decrease vomiting in cats,** either due to its prokinetic effects or through indirect effects not involving D2 receptors.

#### Indications:

- Delayed gastric emptying
- Nausea associated with ileus
- Prevention of nausea and vomiting associated with morphine/dexmedetomidine premeds (most effective when given 30 minutes prior to premeds; Brioschi 2018)
- Prevention of nausea from an over-distended stomach during esophagostomy tube feedings
- Central antiemetic in dogs, especially when ileus is also suspected (e.g. infiltrative GI disease, pancreatitis, parvovirus)
  - Comparable efficacy to maropitant and ondansetron for vomiting in parvoviral enteritis (Yalcin 2016)
- Prevention of GI upset during cyclosporine treatment (anecdotal success)
- *Not* the drug of choice for prevention of chemotherapy-induced vomiting (Kenward 2017)

#### Dosing:

- 0.2-0.4 mg/kg q. 6 hours SC or PO.
- May be most effective when given by continuous rate IV infusion (1-2 mg/kg/day).
- Cover infusion set with foil (light sensitive)

#### Drug interactions/Contraindications:

- Rule out intestinal obstruction first
- Enhances acetaminophen and ethanol absorption in acute intoxications in humans
  - Should be avoided for acute treatment of vomiting due to intoxications; may enhance delivery of toxin to small intestine

#### Side effects:

- Tremor, hyperactivity, and anxiety after high doses (Parkinson's-like; stop the drug and treat with diazepam)
- Decrease dosage in renal failure (decreased metoclopramide clearance may lead to tremor).

**Ondansetron (Zofran®)**

Antiemetic that antagonizes serotonin (5-HT<sub>3</sub>) receptors in both the CNS and GI tract. Particularly effective for vomiting due to **peripheral** stimulation (Sedlacek 2008)

Indications:

- Vomiting in patients with diagnosed visceral disease (e.g. pancreatitis, GI neoplasia, hepatic disease).
  - Comparable efficacy to maropitant and metoclopramide for vomiting in parvoviral enteritis (Yalcin 2016)
- Prophylaxis of vomiting and nausea associated with chemotherapy (Kenward 2017)
- Prophylaxis of vomiting from dexmedetomidine in cats (0.22 mg/kg of ondansetron in same syringe as dexmedetomidine, given IM; Santos 2011)
- **More effective for nausea (without vomiting) than maropitant** (Kretzing 2011)

Formulations/Dose/Route:

- 2 mg/ml injectable; 4 mg tablet; oral solution 4 mg per 5ml.
- Best estimated dosage:
  - 1.0 mg/kg q. 8 hours in cats (from Quimby 2014)
    - SC route in cats has better bioavailability and provides longer duration of action than PO or IV (Quimby 2014)
    - The previously recommended dosage of 0.5 mg/kg PO q. 12h (extrapolated from humans) is likely sub-therapeutic
  - Marked variability in plasma concentrations in dogs makes dosing recommendations difficult (Baek 2015)
    - Empirical dosage in dogs: 0.5-1.0 mg/kg q. 8h

Drug interactions/Contraindications/Side effects:

- Headache or dizziness in humans
- Increases in ALT reported in humans
- Ondansetron is a p-glycoprotein substrate in humans but has not been evaluated in dogs– potential for adverse effects in Collies and other dogs with MDR1 mutations <http://www.vetmed.wsu.edu/depts-VCPL/drugs.aspx>

**Prochlorperazine (Compazine®), Chlorpromazine (Thorazine®)**

Phenothiazine central antiemetics with multiple mechanisms of action: dopamine antagonist, H1 antagonist, alpha-adrenergic antagonist, and anticholinergic. Inhibit vomiting at chemoreceptor trigger zone *and* directly at emetic center (therefore, potent antiemetic). **Less effective for peripheral triggers of vomiting** (Sedlacek 2008)

Indications:

- *Not recommended* for empirical outpatient use because of potential for hypotension and sedation (undesirable in a sick patient).
- Prochlorperazine or chlorpromazine may be useful for refractory vomiting in patients with diagnosed underlying disease and a central cause for vomiting (e.g. chemotherapy, uremia), for which IV fluid support can be provided.

- Additional effect of sedation may be beneficial in anxious dogs or fractious cats.
- Inexpensive
- Note: acepromazine (0.05 mg/kg IM) is also effective as an adjunct treatment to prevent nausea in dogs, for example prior to morphine pre-medication (Koh 2014)

Dosage: 0.1-0.5 mg/kg SC q. 8 hours.

Drug interactions/Contraindications/Side effects:

- Can cause hypotension (alpha-blockade) or tremors (dopaminergic antagonism).
- Can cause sedation and potentiate effects of sedatives, anesthetics, and organophosphates.
- Do not use these drugs in dehydrated patients or in those without a diagnosis.
- Do not use formulations that contain anticholinergics such as isopropamide.
- Do not use in combination with metoclopramide (additive anti-dopaminergic effects).

### **Mirtazapine**

Antidepressant with appetite-stimulating and anti-emetic properties. Complex mechanisms of action! Central antagonist at presynaptic alpha-adrenergic receptors. Increases central serotonergic (5-HT<sub>1</sub>) and noradrenergic activity, but inhibits other serotonin receptors (5-HT<sub>2</sub> and 5-HT<sub>3</sub>) and histamine (H<sub>1</sub>) receptors. Weaker inhibition of alpha-1 and muscarinic receptors.

- Effective as an appetite stimulant
- Anti-emetic and anti-nausea effects in humans (likely via 5-HT<sub>3</sub> blockade)
- Increases gastric emptying in dogs (Yin 2014)

Indications:

- Decreased appetite or anorexia unresponsive to treatment of the underlying disease
  - Effective in cats (Quimby 2013) and some dogs (anecdotal)
- Effective for vomiting in cats with CKD (Quimby 2013)

Formulations/Dosage: 15 mg tablets

- 1.88 to 3.75 mg (1/8 to 1/4 tab) every 24 to 48 hours in cats with normal renal function- start with the lower dose
- 1.88 mg (1/8 tab) every 48 hours in cats with CKD (Quimby 2011)

Drug interactions/Contraindications:

- Contraindicated with monoamine oxidase inhibitors, tricyclic antidepressants, and serotonin reuptake inhibitors because of risk of serotonin syndrome in humans (tremor, rigidity, myoclonus)
  - Do not combine mirtazapine with drugs that directly or indirectly increase serotonergic activity, to include fluoxetine, tramadol, buspirone, amitriptyline, clomipramine, amitraz (in Certifect®), dextromethorphan (in Robitussin), and even the antibiotic linezolid
- Because of many drug interactions, use the Interactions Checker on [www.drugs.com](http://www.drugs.com) prior to adding mirtazapine to other medications

- Contraindicated in patients with glaucoma

Side effects:

- Sedation, mydriasis common
- Idiosyncratic neutropenia in humans
- Overdose leads to vocalization, agitation, ataxia, tremors, hypersalivation (Ferguson 2015)
  - Do not dispense full 15 mg tablets to owners

Adjunctive Drugs for Vomiting Patients

**Famotidine (Pepcid®)**

Famotidine is an H<sub>2</sub> blocker that is more potent than ranitidine and unlike cimetidine, has no P450 inhibition. **Famotidine is not an antiemetic, and is overused in vomiting animals**, since hyperacidity is probably a relatively uncommon cause of vomiting in dogs and cats.

Indications:

- Persistent vomiting where secondary reflux and esophagitis are a concern
- Vomiting due to hyperacidity (mast cell disease).
- No direct antiemetic effects.
- In contrast to clinical dogma, gastric ulceration appears to be uncommon in cats and most dogs with CKD, at least based on necropsy data.
  - Instead, gastric fibrosis and mineralization are seen (Peters 2005; McLeland 2014).
  - Hyperacidity and high serum gastrin levels were *not* found in cats with CKD (Tolbert 2017)
  - Therefore, **antacids are of questionable benefit in feline CKD, despite widespread use.**

Dosing:

- 1 mg/kg po or IV twice daily has been recommended...however,
  - This oral dosage suppresses gastric acid for only 14-22% of the day in dogs (Tolbert 2011), and IV, suppresses gastric acid for ~45% of the day in dogs, and these are inadequate by human standards
  - Oral omeprazole is more effective than oral famotidine at suppressing gastric acid in dogs and cats
- 1 mg/kg IV loading followed by 8 mg/kg/day CRI
  - Contrary to intermittent famotidine dosing, this CRI protocol *is* effective in suppressing gastric acid in dogs (Hedges 2019), and appears to be an evidence-based alternative to IV pantoprazole

Side effects:

- Generally well tolerated.
- As for other basic drugs, rapid IV infusion may cause bradycardia.
- Prior anecdotal reports of hemolysis were unsupported in recent study; safe in cats given famotidine IV by slow bolus over 5 minutes (de Brito Galvao & Trepanier, 2008).
- Requires dose reduction in renal failure (shown in humans)

**Ranitidine (Zantac®)**

Also an H<sub>2</sub> blocker; has additional benefit of prokinetic effects (weak anticholinesterase activity)

Indications:

- No direct antiemetic effects.
- As an antacid in patients suspected of having both hyperacidity and either gastric atony or megacolon (cats)

Formulations and dosage: 75 mg tablets over the counter; Syrup 15 mg/ml available.

- Dosage in cats (based on pharmacokinetics): 3.5 mg/kg PO q. 12 hours.
  - Note: Ranitidine at 2 mg/kg PO q. 12 h was ineffective at suppressing gastric acid in dogs (Bersenas 2005) and in cats (Sutalo 2015)

Side effects:

- As for famotidine, requires dose reduction in renal failure (shown in humans).
- Unlike cimetidine, no clinically significant P450 enzyme inhibition with ranitidine at therapeutic dosages.
- Rapid IV infusion may cause hypotension.

**Omeprazole (Prilosec®; Gastrogard®)**

H<sup>+</sup>/K<sup>+</sup> ATPase pump inhibitor. Blocks the final step in gastric acid secretion.

- More potent than famotidine at acid suppression in dogs (Tolbert 2011) and cats (Parkinson 2015; Sutalo 2015)

Indications:

- Clinically proven gastroduodenal ulceration
- Erosive esophagitis
- NSAID overdose
- Prevention of NSAID-induced ulcers (humans)
- Portal hypertension
- (Gastrinomas - uncommon)

Formulations/Dose/Route: 10 and 20 mg capsules.

- Drug is enteric-coated to prevent degradation.
  - If reformulated, enteric-coated granules can be placed in a gelatin capsule.
  - **Split enteric coated tablets are effective** in suppressing acid production **in cats** (Parkinson 2015)
  - Note: equine preparation is much too concentrated to use safely in dogs and cats unless professionally reformulated.

Empirical dose:

- 1.0 mg/kg PO BID in dogs and cats (Bersenas 2005, Parkinson 2015)
- 1.5-2.6 mg/kg once daily (Tolbert 2011)

Drug interactions/Contraindications:

- Omeprazole is a P450 enzyme inhibitor in humans, but not as broad spectrum as cimetidine.
- Can inhibit bioactivation of clopidogrel (Plavix) in humans, but this does not occur in dogs (Thames 2017)
  - Not yet evaluated in cats



- Unnecessary to add famotidine during initial treatment with omeprazole (Tolbert 2015)

Side effects:

- Chronic administration of omeprazole is associated with gastric polyps in humans.
  - Omeprazole does lead to gastric mucosal hypertrophy in dogs at high doses given chronically.
- Can increase risk of bacterial pneumonia in human patients that aspirate

### **Sucralfate (Carafate®)**

Disaccharide complexed to aluminum hydroxide; at acid pH in stomach, acquires negative charge and adheres to positively charged matrix elements exposed in ulcer beds.

- Improves barrier function of the canine gastric mucosa after injury (shown ex vivo; Hill 2018)
- Binds pepsin and bile salts (which can otherwise contribute to ulcer formation)
- May enhance production by gastric mucosa of cytoprotective prostaglandins (increased blood flow and cell turnover lead to faster ulcer healing).

Indications:

- Gastric ulceration
- Esophagitis
  - Note: sucralfate has been shown to prevent acid-induced esophagitis experimentally in cats; may be useful prior to surgery when reflux is anticipated (recent meal; megaesophagus; esophageal or gastric foreign body).
- Gastric or duodenal neoplasia with ulceration
- Post-endoscopic retrieval of gastric or esophageal foreign bodies
- (Disappointing topical efficacy for radiation mucositis in humans)

Empirical dosage: 1/4 to 1 gram PO q. 6 to 8 hours.

- May be crushed and suspended in water; stable for 14 days in the refrigerator as a 200 mg/ml suspension.

Drug interactions:

- Very important! **Sucralfate binds other drugs and impairs their absorption** (tetracycline, digoxin, some fluoroquinolones)
- Important to give most other drugs at least 2 hours *before* sucralfate (not vice versa). This is difficult for many clients to achieve.
- Exception: sucralfate can be given concomitantly with H<sub>2</sub> blockers without affecting their overall absorption (Albin, 1986; Mullersman, 1986); therefore, no separation of dosing times is necessary.

Side effects: Constipation, chalky, unpalatable taste

### **Cisapride**

Prokinetic drug in the same family as metoclopramide; increases release of acetylcholine from myenteric plexus (via effects on serotonin receptors) in smooth muscle of esophagus, stomach, small intestine, and colon; increases lower esophageal sphincter pressure, gastric emptying, small intestinal motility, and

### colonic motility

- More potent than metoclopramide and no antidopaminergic effects
- Appears to be more effective than metoclopramide at increasing tone in the lower esophageal sphincter (Kempf 2014)

### Indications:

- Constipation, feline megacolon
- Gastroesophageal reflux
- Recurrent bloating due to gastroparesis
- Gastroparesis associated with inflammatory bowel disease

Formulations/Dosage: 10 mg tablets. Empirical dose: 0.5 mg/kg PO q. 8 hours (for cats, 2.5 mg q. 8 hours to start); use with lactulose if megacolon present; food enhances absorption in humans

### Drug interactions/Contraindications:

- Rule out GI or pelvic obstruction
  - Contraindicated for mechanical obstructions or for colonic strictures.
- Caution with ketoconazole or itraconazole: these antifungals inhibit cisapride metabolism in humans and can lead to cardiac arrhythmias.
- No direct efficacy as an antiemetic.

### Side effects:

- Diarrhea, cramping in some humans
- Unlike metoclopramide, no CNS side effects
- In cats, cisapride can also lead to QT prolongation, but at dosages 20 times higher than those used clinically.
  - These same ECG changes (QT prolongation) have been reported for dolasetron. Until more is known, the combination of cisapride and dolasetron should probably be avoided.

### **Key points**

- Maropitant is an excellent antiemetic, but it should not be used before ruling out GI obstruction or serious metabolic disease
- Maropitant is not a great choice for nausea or poor appetite without vomiting
- Metoclopramide actually *is* effective as an antiemetic in cats, and is useful whenever a prokinetic is also desired
- Ondansetron is particularly useful for nausea and visceral vomiting
- Omeprazole is preferred over famotidine when a potent antacid is needed on an outpatient basis
- Sucralfate has multiple drug interactions

<b>Underlying disease</b>	<b>Clinical approach to vomiting</b>
Renal failure	Hydration, treat hypokalemia if present Mirtazapine or maropitant Antacids probably <i>not</i> indicated
Hepatic insufficiency	Treat encephalopathy (lactulose, hydration) Treat hypokalemia Start omeprazole if portal hypertension suspected Metoclopramide if ascites and gastroparesis Maropitant if still vomiting Avoid metronidazole if GI upset already present
Inflammatory bowel disease	Treat underlying inflammation (hydrolyzed protein diet, glucocorticoids) Ondansetron if continued nausea and vomiting Metoclopramide or cisapride if gastroparesis
Pancreatitis	Metoclopramide, ondansetron, or maropitant acutely If painful, buprenorphine, butorphanol, or fentanyl CRI for visceral analgesia
Gastroesophageal reflux	Omeprazole and cisapride
Intoxication	Gastric lavage; then consider maropitant (CRTZ toxins) or ondansetron (direct GI irritants) Avoid prokinetics
Hairballs	Petrolatum products If no response, cisapride or metoclopramide
Chemotherapy	Maropitant, ondansetron acutely Prochlorperazine (e.g. fractious cat) Ondansetron for delayed GI toxicity (peripheral stimulation)
Motion sickness	Dogs: dimenhydrinate (Dramamine) or maropitant Cats: maropitant
Megacolon with vomiting	Treat megacolon (SC fluids, lactulose, cisapride)
Parvoviral enteritis	Maropitant or ondansetron Add metoclopramide if ileus suspected Palpate daily for possible intussusception
Post-operative ileus	Metoclopramide or cisapride

## Practical approach to inflammatory bowel disease

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Idiopathic inflammatory bowel disease is defined as:

- Gastrointestinal (GI) signs greater than 3 weeks in duration
- Incomplete response to dietary trials and anthelmintics
- Histologic lesions of mucosal inflammation on biopsy
- Clinical response to immunomodulatory therapies  
([www.wsava.org/StandardizationGroup.htm](http://www.wsava.org/StandardizationGroup.htm))

The underlying pathogenesis of IBD is thought to be a disturbance in GI mucosal permeability, endogenous microflora, and/or mucosal immunity, with loss of mucosal tolerance to luminal antigens. IBD typically presents in adult to middle-aged dogs and cats. Weimaraners, Rottweilers, German shepherds, and border collies are at higher risk. **Patients that are less than 1 year of age should be worked up for causes of GI signs other than IBD.**

Food-responsive enteropathy is considered a different diagnostic category, and is distinguished from IBD solely by response to elimination or hydrolyzed protein diet. The work-up is the same, up to the time of a food trial. Dogs with food-responsive enteropathy tend to be younger, (average age 3 years) and can be as young as 8 months at disease onset. More recently, the term “chronic enteropathy” has been adopted rather than IBD, since food-responsive disease and IBD are only distinguishable by response to diet therapy.

### Diagnostics

**Abdominal ultrasound** is indicated to help localize disease, and allows collection of FNAs from focal lesions and lymph nodes.

- **Loss of normal intestinal wall layering** suggests GI neoplasia
- **Muscularis wall thickening** (defined as greater than half the thickness of the submucosa) is suggestive of small cell lymphoma or IBD in cats (Daniaux 2014; Tucker 2015)
  - Older age and the presence of lymphadenopathy, particularly rounded hyperechoic nodes, are associated with lymphoma in cats
  - Lymphoma can be diagnosed by FNA of a mesenteric node, but lack of cytologic evidence of lymphoma does not rule it out.
- The presence of **hyperechoic striations** in the intestinal wall (in fasted dogs) is very suggestive of protein losing enteropathy due to lymphangiectasia
- **Intestinal adenocarcinoma** has the ultrasonographic appearance of segmental intestinal wall thickening with mixed echogenicity, and should be pursued surgically.
- Note: overall intestinal wall thickening may or may not be present in patients with IBD

**GI panel** (serum folate, cobalamin, TLI and PLI)

- Serum cobalamin should be measured in all dogs and cats with suspected IBD and small or mixed bowel diarrhea.
  - **Low serum cobalamin** can be caused by ileal disease or pancreatic dysfunction (either pancreatitis or exocrine pancreatic insufficiency).
    - (The relationship between cobalamin and small intestinal bacterial overgrowth (SIBO)/antibiotic responsive diarrhea is actually not strong)
  - Hypocobalaminemia (<200 ng/L) is associated with poorer outcomes in dogs
  - Low serum cobalamin is common in cats with GI disease, especially those with a low body condition score.
    - **Serum cobalamin is particularly low in cats with GI LSA**
- Patients with suspected IBD and low serum cobalamin should be presumed to have ileal involvement (especially if pancreatic disease is ruled out), and may require ileal biopsies via colonoscopy or surgical approach to get an accurate diagnosis.
- **A low serum folate suggests proximal small intestinal malabsorption.**
  - This finding, along with upper GI signs (vomiting) and/or duodenal thickening on ultrasound, may suggest that upper GI endoscopy will reach the affected areas.
- Pancreatitis (**increased fPLI**) commonly accompanies IBD in cats
  - Cats with low serum albumin and low cobalamin are more likely to have accompanying pancreatitis (fPLI  $\geq$  12.0 ug/L)
- **Increased cPLI** is found in some dogs with IBD, and may reflect accompanying histologic pancreatic inflammation.
  - Co-existing pancreatitis should be taken into consideration when choosing diets for dogs with IBD.
  - Increased cPLI concentrations (> 200 ug/L) are associated with poorer clinical response to IBD treatment if pancreatitis is not co-managed.

**Biochemical panel**

Serum biochemistry is typically normal in dogs and cats with uncomplicated IBD.

- However, the presence of low albumin, low globulin, and low cholesterol in dogs suggests lymphangiectasia, a more severe syndrome of small intestinal malabsorption that can be caused by idiopathic IBD, lymphoma, or Histoplasmosis.
- These dogs are more difficult to manage, and may have ionized hypocalcemia due to accompanying vitamin D malabsorption.

**Intestinal biopsies – endoscopic versus full thickness**

Mucosal biopsies, collected from the stomach and duodenum via endoscopy, are relatively non-invasive and less expensive than laparotomy or laparoscopy.

- However, upper GI endoscopic mucosal biopsies may miss a diagnosis of lymphoma in cats, especially those with distal intestinal but not gastric

involvement. **Including ileal biopsies (by also performing colonoscopy) increases the sensitivity of endoscopy for GI lymphoma in cats.**

Full thickness biopsies, obtained by abdominal exploratory or laparoscopy, are ideal for the diagnosis of IBD and the exclusion of lymphoma. Because disease severity can vary markedly by region of the GI tract, biopsies should be collected from **stomach, duodenum, jejunum and ileum**. Additional biopsies of the liver, pancreas, and lymph nodes can be based on clinical presentation and gross appearance. However, the additional cost, time of hospitalization, and potential complications of surgical biopsies can be a barrier to many owners.

No matter what the biopsy technique, your pathologist should follow the WSAVA GI standardization group guidelines for IBD histopathology, which includes scoring systems for cellular infiltrates, crypt distortion, villous blunting and fusion, and fibrosis. ([www.wsava.org/StandardizationGroup.htm](http://www.wsava.org/StandardizationGroup.htm))<sup>39</sup>

Treating without a biopsy: IBD cannot be definitively diagnosed without an intestinal biopsy. In some situations, however, a biopsy may not be possible, such as a client with financial constraints or a patient with contraindications for anesthesia (e.g. cardiomyopathy, biventricular effusion, or debilitation). If treating presumptively for IBD without a biopsy, make sure that owners would not pursue chemotherapy for lymphoma, if present, and understand that a definitive diagnosis is lacking. Abdominal ultrasound, fPLI or cPLI, and serum folate and cobalamin concentrations are still recommended even if a biopsy is not possible.

### **Treatment of IBD**

Diet is a critical first step in the management of chronic enteropathies in both dogs and cats.

- Although idiopathic IBD is defined by an incomplete response to dietary trials, patients with even severe inflammatory changes on GI histology may respond to dietary manipulation alone.
- Mucosal histopathology scores do not predict which patients will respond to diet and which will require glucocorticoids.

**Novel protein (elimination) diets** are designed to avoid exposure to proteins to which the gut mucosal immune system may have been previously sensitized. Most commercial elimination diets contain a novel protein source, are free of milk, corn, and wheat, and are highly digestible with moderate soluble fiber.

- Diet alone has a fairly high efficacy rate in treating chronic enteropathies in both dogs and cats, and avoids the side effects of immunosuppressive therapy.
  - **Up to 50% of cats and dogs with chronic enteropathies will respond well to an elimination diet**
  - Most cats respond to elimination diets within 2 to 3 days
    - Consider a **one-week trial in cats** allowing time for diet transition, as long as compliance is good and the owner is observant.
  - Most dogs respond to elimination diets within 5-7 days

- Consider a **7-10 day trial in dogs**, allowing time for diet transition
- Concurrent dermatologic signs increase the likelihood of diet response
- Serum screens for IgE against dietary allergens are **not predictive** of response to elimination diets, and should not be used.
  - False positives and false negatives are common, and IBD is thought to be mediated by IgA, not IgE.

**Hydrolyzed protein diets**, such as Hill's z/d Ultra Allergen Free, Purina HA, or Royal Canin hypoallergenic diets, are designed to minimize the antigenicity of intact dietary proteins.

- Royal Canin hypoallergenic canine diet (hydrolyzed soy protein) was comparable to a standard digestible GI diet in initial response rates in dogs with chronic small bowel diarrhea; however, the hydrolyzed diet showed a more durable response at 6-12 months and 3 years, with a greater reduction in clinical signs (Mandigers 2010)
- There are no studies comparing the efficacy of hydrolyzed protein diets to novel protein elimination diets. I choose hydrolyzed diets first because so many of the "novel" protein sources are now available in commercial over the counter pet foods.

### Immunosuppressive drug therapy

In dogs and cats with a biopsy diagnosis of moderate to severe inflammatory gastrointestinal disease, with clinical signs that are not responsive to dietary change, the standard of care remains immunosuppressive drugs. Hopefully this will be replaced in the future by more specific therapies as we better understand the pathogenesis of IBD.

**Prednisone or prednisolone:** Prednisone is a pro-drug and is converted into active prednisolone after administration.

- This conversion (or possibly the absorption of prednisone itself) is apparently poor in cats. Therefore, **prednisolone** is optimal for glucocorticoid administration **in cats**, especially those without a prompt response to prednisone. In dogs, there is probably no benefit of one over the other.
- Anti-inflammatory to low immunosuppressive dosages of prednisolone (1-2 mg/kg/day) are recommended initially.
  - Consider using 40-50 mg/M<sup>2</sup> dosing in large dogs to avoid debilitating glucocorticoid side effects (or do not exceed 60 mg total per day)
  - Once clinical signs improve, the dosage can be tapered every 3 to 4 weeks to the lowest dose that controls clinical signs.
  - Glucocorticoids should be accompanied by a highly digestible diet, ideally a hydrolyzed protein source if accepted.
- In patients with severe malabsorption, treatment with subcutaneous injections of glucocorticoids may improve drug response initially.
  - This can be accomplished with **dexamethasone**, given at about 1/7 the dosage of prednisolone, to allow for the increased potency of

dexamethasone (4 to 10 times that of prednisolone; I use a factor of 7 to convert).

**Budesonide** is an orally administered glucocorticoid approved for use in humans with Crohn's disease. Budesonide undergoes extensive hepatic clearance in humans, which leads to lower systemic drug concentrations and associated side effects.

- In dogs, budesonide has fewer side effects of polyuria and serum alkaline phosphatase induction.
  - However, budesonide can still be absorbed at concentrations sufficient to cause adrenal suppression in dogs.
- Budesonide is effective anecdotally in dogs and cats with IBD. The drug is supplied in 3 mg enteric coated gel caps, and must be reformulated to provide the recommended empirical dosage of 0.5 – 0.75 mg per cat per day, or 0.75- 2 mg per dog per day.
- Because the degree of systemic absorption has not been established in dogs and cats, patients should still be monitored for side effects of glucocorticoids, such as symptomatic urinary tract infections or glucosuria.

**Azathioprine** inhibits RNA and DNA synthesis, and thus affects rapidly dividing cells such as lymphocytes. Azathioprine is both anti-inflammatory and immunosuppressive, and may be used as an add-on agent for severe cases of chronic enteropathies dogs (e.g. PLE/lymphangiectasia)

- Azathioprine, chlorambucil, or cyclosporine can be used as a second line drug in dogs
- Dose azathioprine at 50 mg/M<sup>2</sup> daily to avoid overdosing big dogs
- Side effects:
  - Dose-dependent hepatopathy (increased ALT and ALP not due to glucocorticoids) in first 2 to 3 weeks
    - German shepherds are higher risk (Wallisch & Trepanier 2015)
  - Dose-dependent neutropenia or thrombocytopenia (typical onset after 6 weeks)
- Azathioprine is contraindicated in cats due to impaired detoxification of azathioprine by thiopurine methyltransferase (TPMT).

**Chlorambucil** is an alkylating agent that cross-links DNA, but is less potent than cyclophosphamide.

- Traditionally used as an add-on to prednisolone for GI small cell lymphoma in cats.
  - Efficacy as an add-on agent in feline IBD (compared to cyclosporine) has not been evaluated.
  - Chlorambucil is dosed at 2 mg per cat, every 48 to 72 hours, or alternatively, 20 mg/m<sup>2</sup> as a single dose every 14 days.
- In a recent retrospective study in dogs, chlorambucil appeared superior to azathioprine as an add-on to prednisone for protein-losing enteropathy (Dandrieux 2013)



- **Chlorambucil should be re-considered for use in dogs as a second line agent** in dogs with chronic enteropathy that is not responsive to prednisone alone
- Side effects:
  - Chlorambucil is well tolerated in most patients.
    - It does not cause hemorrhagic cystitis, and although leukopenia is possible, it is uncommon.
  - CBC should be monitored prior to the first 3 doses if the 20 mg/m<sup>2</sup> protocol is used, then periodically (e.g. every 2-3 months).
  - One apparently rare side effect of chlorambucil is a reversible myoclonus

**Cyclosporine** is a potent immunosuppressant that inhibits T cell function, specifically IL-2 production by T cells.

- Cyclosporine is effective for dogs with clinical signs that are refractory to glucocorticoids alone
  - Has not been compared directly to azathioprine or chlorambucil
- Cyclosporine is also effective in cats with refractory IBD, anecdotally, at dosages of 5 mg/kg once or twice daily.
- Inappetence and vomiting are common side effects, and typically respond to a 50% dose reduction.
  - Metoclopramide (0.2-0.4 mg/kg PO q. 12 h) is also effective anecdotally for cyclosporine-induced GI side effects.
- Less common side effects include:
  - Gingival hyperplasia, seen in both dogs and cats
  - Secondary fungal infections (often “street” fungi causing subcutaneous nodules)
  - Reactivation of subclinical latent infections, such as toxoplasmosis in cats
- The dosages of prednisone and cyclosporine should always be tapered to the *lowest effective doses* to avoid serious side effects from chronic immunosuppression.

### Other interventions

**Cobalamin** is involved in essential pathways such as hematopoiesis, DNA synthesis, and fatty acid metabolism. If present, low serum cobalamin should be treated.

- Cyanocobalamin is a synthetic but stable precursor of active B12 congeners
- The empirical cyanocobalamin dosage in dogs is 250-1500 µg SC weekly (<https://www.cvm.tamu.edu/gilab/research/cobalamin-information>)
- Subcutaneous cobalamin
  - The empirical cyanocobalamin dosage in cats is 250 µg SC weekly
    - Cobalamin supplementation (with no other treatment changes) is associated with weight gain, increased appetite, and diminished vomiting and/or diarrhea in deficient cats
  - Weekly doses for 6 weeks have been recommended by Texas A&M, with a 7<sup>th</sup> dose one month later and recheck of serum cobalamin after an additional month

- Oral cyanocobalamin (1 mg tablets)
  - 250-1000 micrograms po *daily* (Toresson 2018)

**Metronidazole** has excellent anaerobic and good antiprotozoal spectrum, and has been used anecdotally for IBD in dogs and cats.

- Although metronidazole has been reported to have direct immunomodulatory effects, it is unclear whether this is a clinical effect in IBD
  - For example, inhibition of human lymphocyte proliferation requires metronidazole concentrations  $\geq 50$  micrograms/ml, versus a Cmax in cats about 9 micrograms/ml.
  - However, doses of 14 mg/kg/day did inhibit macrophage phagocytosis and inhibit delayed type hypersensitivity reactions in rodents
- In a prospective randomized study in dogs with IBD, there was no difference in rate of remission in dogs treated only with prednisone (1 mg/kg/day; 88% response) and those with add-on metronidazole (10 mg/kg q. 12h; 83% response; Jergens 2010)
- Side effects of metronidazole
  - Metronidazole is unpalatable, and can cause inappetence in cats.
  - High doses ( $\geq 58$  mg/kg/day) are associated with neurologic toxicity in both dogs and cats
  - Metronidazole is mutagenic at therapeutic dosages in cats (Sekis 2009).

**Probiotics:** If IBD is indeed caused in part by a loss of mucosal immune tolerance to certain bacterial flora, then probiotics may have some benefit in this disease.

- Potential beneficial effects of probiotics include modulation of gut flora, inhibition of colonization by pathogenic bacteria, and inhibition of bacterial translocation across the gut wall.
  - Probiotic bacterial by-products can also have anti-inflammatory effects; for example, butyrate inhibits pro-inflammatory cytokine expression in intestinal samples from patients with Crohn's disease.
- There is some evidence for the efficacy of probiotics in ulcerative colitis in humans, although effects are strain- and dose-specific. Studies in vet med have enrolled small numbers of dogs
  - In one study, there was no demonstrated advantage of a probiotic cocktail over limited antigen diet alone in 21 dogs with IBD (Sauter 2006)
  - In a second study, another probiotic cocktail (VSL#3) improved both histology and clinical signs in dogs with IBD (comparable to pred plus metronidazole; Rossi 2013)
- Some marketed veterinary probiotics do not contain viable organisms as labeled or have no label claims and low viable counts as tested.
  - Use only products for which viable bacteria have been documented and that have been shown to colonize the intestinal tract of dogs or cats.

**Omega-3 polyunsaturated fatty acids (PUFAs):** Another option for adjunct therapy of IBD is omega-3 polyunsaturated fatty acids (PUFAs). These compounds decrease

generation of leukotrienes such as LTB<sub>4</sub>, which is a potent neutrophil chemotactant and pro-inflammatory molecule.

- PUFAs such as eicosapentanoic acid can reverse cytokine-induced intestinal permeability defects in animal models.
- Enteric-coated PUFAs have been effective in maintaining remission in people with Crohn's disease in some studies.
  - Enteric coated PUFAs are available over the counter in fish oil supplements such as Fisol (Nature's Way; 150 mg eicosapentanoic acid and 100 mg docosahexaenoic acid per soft gel).
- Dosing is empirical since studies are lacking.
  - A starting point would be the dosages used in humans: eicosapentanoic acid at 17-25 mg/kg/day and docosahexaenoic acid at 8-18 mg/kg/day.
- PUFAs should be added as a single agent with a dose titration, since they can be unpalatable, and diarrhea is a common side effect.

### **Additional treatment of specific syndromes**

#### **Histiocytic ulcerative colitis (a.k.a. granulomatous colitis)**

- Seen in young boxers, Frenchies, and English bulldogs
- Combined large and small bowel diarrhea – soft to liquid blood diarrhea
- Responds to 6 to 8 weeks of an oral fluoroquinolone
- Do not stop early!
- Immunosuppression or diet change not indicated

#### **Protein-losing enteropathy**

- Chronic enteropathy signs with panhypoproteinemia
- Treatment is similar to that for IBD, but more aggressive
- Novel or hydrolyzed protein diet
- Prednisone **and** azathioprine, chlorambucil or cyclosporine
  - If severe malabsorption, start with SC dexamethasone until in remission
- Diuretics for ascites
  - Spironolactone/hydrochlorothiazide at 1 mg/kg q. 12h
- Low dose aspirin or clopidogrel to prevent thrombosis
- Fair to guarded prognosis

#### **Lymphangiectasia**

- Chronic enteropathy signs with panhypoproteinemia, **low cholesterol**, and mucosal striations on intestinal ultrasound
- Yorkies predisposed
- Treatment is similar to that for PLE, but even more aggressive
- **Low fat diet**
- Glucocorticoids plus cyclosporine (or azathioprine, or chlorambucil?)
  - May need to start with SC dexamethasone until in remission
- Diuretics for ascites

- Spironolactone/hydrochlorothiazide at 1 mg/kg q. 12h
- Low dose aspirin or clopidogrel to prevent thrombosis
- **Oral calcium carbonate and calcitriol for ionized hypocalcemia**
- Guarded prognosis but can do well if managed carefully

## Choosing the best NSAID: comparative toxicity and drug interactions

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With the availability of many prescription veterinary non-steroidal anti-inflammatory drugs (NSAIDs), there are many choices for controlling acute and chronic pain and inflammation in dogs (but fewer for cats). Because patients with osteoarthritis may be older and have concurrent disease, the risk of toxicity and NSAID-associated drug interactions should always be considered when an NSAID is selected.

### I. NSAID mechanisms of action

- A. Cyclooxygenase 1 (COX-1)
  - 1. Constitutively expressed in many tissues
  - 2. Generates protective prostaglandins in stomach, intestine, and kidney
  - 3. Also generates thromboxane (TXA<sub>2</sub>), which mediates platelet aggregation
- B. Cyclooxygenase 2 (COX-2)
  - 1. Induced by inflammation
  - 2. Generates pro-inflammatory prostaglandins
  - 3. Also generates protective renal prostaglandins and is important for healing of gastric ulcers once they occur
- C. NSAID inhibition of COX 1 and/or COX 2
  - 1. Anti-inflammatory, anti-pyretic, and analgesic (via COX-2 inhibition)
  - 2. Anti-platelet (via COX-1 inhibition)
    - a) **Non-selective agents**
      - (1) Aspirin, ketoprofen, piroxicam
    - b) **COX-2 preferential**
      - (1) Carprofen, meloxicam
    - c) **COX-2 selective**
      - (1) Deracoxib, firocoxib, robenacoxib
    - d) Other agents
      - (1) Acetaminophen
      - (2) Dual COX and lipoxygenase inhibitors
        - (a) Tepoxalin (Zubrin) – no longer marketed
      - (3) Grapiprant

### II. Newest agents

- A. Robenacoxib (Onsior®)
  - 1. COX-2 selective veterinary NSAID
    - a) Prolonged COX-2 inhibition (for 16-24 hours) at sites of inflammation.
  - 2. Label approval in the U.S. for the management of acute pain in dogs and cats

- a) Dosage: 1 mg/kg/day (cats) or 2 mg/kg/day (dogs) for up to 3 days.
  - b) Lower bioavailability when given with full meal (King 2013)
  - c) In Europe, the drug is approved in cats for 6 days of administration.
  - 3. Better efficacy than either meloxicam or buprenorphine for post-operative pain control in cats (Kamata 2012, Staffieri 2013).
    - a) Robenacoxib has a short elimination half-life in feline blood (about 1 hour, compared to ~ 15 hours for meloxicam), which could translate to less off-target toxicity
  - 4. Less effective than meloxicam for post-laparoscopic pain in one study in dogs (Bendinelli 2019)
- B. Grapiprant (Galliprant)
- 1. Prostaglandin (EP4) receptor antagonist
    - a) Blocks binding of PGE2
  - 2. Not a true NSAID – targets downstream from COX
    - a) However, *should not be combined* with NSAIDs or glucocorticoids
  - 3. Approved for osteoarthritis in dogs
    - a) Like NSAIDs, can cause vomiting (Rausch-Derra 2016)
    - b) Unclear if grapiprant is safer in patients with renal disease or with risk factors for gastric ulcers
      - (1) PGE2 is protective in both the kidney and GI tract

### III. GI Toxicity of available NSAIDs

- A. Vomiting, diarrhea
  - 1. Common early side effect; direct gastric irritation
- B. Gastric ulceration
  - 1. Inhibition of PGE2 generation
    - a) PGE2 important for maintenance of gastric mucosa
      - (1) Epithelial turnover
      - (2) Mucus and bicarbonate secretion
    - b) NSAIDs also directly alter phospholipids in the mucus gel layer overlying the gastric mucosa
      - (1) Can damage this hydrophobic barrier
      - (2) Rationale for enteric coated aspirin
  - 2. Ulcer risk potentiated by:
    - a) Glucocorticoids
      - (1) Inhibition of prostaglandin synthase
      - (2) Decreased peroxidase-mediated scavenging of free radical precursors
    - b) Multiple or overlapping NSAIDs
  - 3. All NSAIDs have the *potential* to cause serious GI bleeding, but **which NSAIDs are safest for the GI tract?**

- a) Difficult to directly compare the relative GI toxicity of veterinary NSAIDs
    - (1) Most published studies that use endoscopy (the gold standard) enroll relatively few dogs, and dogs are typically young and healthy.
  - b) Lower risk with COX-2 preferential compared to non-selective agents
    - (1) Carprofen leads to less GI ulceration than aspirin in dogs (Reimer 1999)
    - (2) Carprofen associated with fewer and milder gastric lesions compared to ketoprofen in dogs (Forsyth 1998)
  - c) Coxibs (COX-2 selective) have a better safety profile than classical NSAIDs in humans
    - (1) May carry a lower risk of GI bleeding in dogs, but have not been compared directly within the same study to COX-2 preferential NSAIDs
    - (2) However, gastrointestinal ulceration and perforation have been reported in dogs with deracoxib
      - (a) **COX-2 is important for *healing* of gastric ulcers experimentally, and coxibs may impair healing of pre-existing ulcers**
4. The ulcerogenic effects of NSAIDs are potentiated by multiple NSAID use and by concurrent glucocorticoids, which are contraindicated

### C. Monitoring for GI bleeding from NSAIDs

- 1. Clinical monitoring:
  - a) Vomiting and diarrhea
  - b) Lethargy, inappetance
  - c) Darkened stools – late finding
  - d) Biochemical monitoring:
    - (1) PCV/TP
      - (a) Polychromasia with drop in PCV and TP (acute)
      - (b) Microcytosis (chronic)
    - (3) Albumin, globulin, and BUN
      - (a) Low albumin, low globulin, and increased BUN with no change in creatinine, suggest GI bleeding
  - e) Fecal occult blood
    - (1) Can detect GI bleeding before overt melena, but available fecal occult blood tests lack specificity in dogs and cats on standard commercial diets containing animal protein (Tuffli 2001)

2. Drugs that protect against NSAID ulcers
  - a) Note: gastric acid is necessary for the development of gastric ulcers with NSAIDs
  - b) Omeprazole
    - (1) Blocks HCl pump
    - (2) Drug of choice for preventing NSAID ulcers in humans
    - (3) Famotidine is not potent enough at standard dosages to decrease gastric acidity in dogs and cats
  - c) Misoprostol
    - (1) Synthetic PGE2 analog
    - (2) Effective in preventing aspirin-induced ulcers in dogs
    - (3) Drawback is diarrhea and cramping

#### IV. Renal decompensation

- A. Any NSAID can adversely affect renal perfusion
  1. Prostaglandins are critical for renal perfusion in patients with low renal blood flow
    - a) Prostaglandins increase renal arterial blood flow in response to a drop in renal perfusion
    - b) Prostaglandins also stimulate renin release
  2. Both COX-1 *and* COX-2 generate protective renal prostaglandins
    - a) Even COX-2 selective agents can decrease glomerular filtration to the same extent as classical NSAIDs.
  3. The risk of renal decompensation from NSAIDs is greatest with:
    - a) Pre-existing renal disease
    - b) Hypovolemia or dehydration
    - c) Congestive heart failure
    - d) Sodium-restricted diets
    - e) Cirrhosis
- B. Most studies on NSAID effect on renal function have been done in healthy animals undergoing elective procedures
  1. Carprofen at the label dose showed no adverse effect on glomerular filtration rate (GFR) in one study
    - a) However, in another study, carprofen and ketoprofen both led to a decrease in GFR in healthy dogs undergoing castration (Forsyth 2000).
    - b) In addition, ketoprofen has been associated with transient azotemia, even in healthy dogs being spayed (Lobetti 2000).
  2. Meloxicam in cats
    - a) Clearance in cats is *not* slower than in dogs
      - (1) Does not rely on glucuronidation
    - b) No adverse effect on GFR in healthy euvolemic cats (Goodman 2009)



- c) **However, meloxicam has led to acute renal failure and death in client-owned cats given the SC label dose (0.3 mg/kg) chronically**
  - (1) Chronic oral meloxicam dosing is label-restricted in cats in the U.S.
  - (2) Lower daily dosages (0.01-0.03 mg/kg daily) were clinically well tolerated in geriatric cats with osteoarthritis, but renal function was not consistently monitored (Gunew 2008)
  - (3) A dose of 0.02 mg/kg/day was well tolerated in older cats with IRIS stage 1-2 CKD (Gowan 2011)
  - (4) Meloxicam oral suspension (at a more dilute concentration of 0.5 mg/ml) *is* approved in Europe for chronic use in cats at a dosage 0.05 mg/kg/day.
- 3. Robenacoxib in cats
  - a) Well tolerated in cats with osteoarthritis treated for 1 month at 1-2 mg/kg/day (King 2015), including 40 cats with early CKD
- C. Use of NSAIDS with pre-existing azotemia
  - 1. Consider alternative agents for analgesia
    - a) Fentanyl CRI or transdermal patch
    - b) Adjunctive gabapentin
    - c) Buprenorphine
    - d) Tramadol?
      - (1) No efficacy for osteoarthritis in crossover study in dogs (Budsberg 2018)
    - e) Acetaminophen in dogs
  - 2. If NSAIDs are necessary in azotemic animals:
    - a) Use with fluid support if possible
    - b) Use conservative doses and titrate to effect
    - c) Add multimodal agents to minimize NSAID needs
      - (1) Omega-3 fatty acids, glucosamine, acupuncture
- V. **Platelet dysfunction and bleeding**
  - A. Classical NSAIDs inhibit platelet function most readily
    - 1. Aspirin, ketoprofen, piroxicam
      - a) Impaired platelet function via inhibition of COX-1 mediated TXA<sub>2</sub> generation.
      - b) Prolonged bleeding times with ketoprofen in dogs undergoing elective orthopedic surgery (Grisneaux 1999)
        - (1) One ketoprofen-treated dog developed a hematoma at the surgical site.
      - c) Bleeding from gingival or enhanced surgical hemorrhage
      - d) GI hemorrhage most common
        - (1) Impaired platelet function *and* altered gastric mucosa

- B. COX-2 preferential agents have less inhibitory effects on platelets
  1. Carprofen leads to mild subclinical decreases in platelet aggregation, but neither carprofen nor meloxicam prolong buccal mucosal bleeding times in healthy dogs
- C. COX-2 selective coxibs do not inhibit platelet function in dogs
  1. Deracoxib, firocoxib, and robenacoxib do not affect buccal mucosal bleeding time in dogs
  2. **Coxibs may be better NSAID choices in dogs with pre-existing coagulopathies** (e.g. von Willebrand's disease)
  3. Clinical monitoring for bleeding is always important
- D. What about coxibs in patients with **hypercoaguable** states?
  1. Traditional non-selective NSAIDs (esp. low dose aspirin) have a theoretical advantage in patients prone to thrombosis
  2. Coxibs, in theory, are contraindicated in hypercoaguable veterinary patients
    - a) Unopposed activity of COX-1 may lead to platelet over-reactivity and impaired small vessel dilation, resulting in thrombosis in at-risk patients
    - b) Until more is known, avoid coxibs in patients with protein losing nephropathy, immune mediated hemolytic anemia, vasculitis, and hyperadrenocorticism

## VI. Hepatopathy

- A. In humans, both cholestasis and fulminant hepatic failure have been reported with coxibs.
- B. In dogs, carprofen has been associated with rare acute hepatic necrosis
  1. Very high ALT with typically lesser increases in SAP
  2. This is an idiosyncratic, not a dose-dependent, reaction
  3. **It is very unlikely that modest increases in SAP with a normal ALT are due to carprofen**
- C. Icterus and hepatic enzyme elevations have also been reported with all other veterinary NSAIDs in dogs (see drug labels), although the incidence is not clear.
  1. Any NSAID has the potential to cause idiosyncratic hepatopathy
  2. Baseline CBC and chemistry panel indicated in older dogs
  3. Careful clinical monitoring is key
    - a) Watch for vomiting, inappetence, lethargy, diarrhea, dark urine
    - b) If even mild clinical deterioration during NSAID administration, evaluate blood work, with a focus on new elevations in ALT or bilirubin
  4. With idiosyncratic reactions such as these, careful clinical observation is probably a more effective monitoring tool than routine liver enzyme monitoring

## VII. Drug interactions with NSAIDs

- A. Glucocorticoids
  1. Contraindicated with NSAIDs
  2. Increased risk of GI ulceration
- B. Acetaminophen and phenobarbital
  1. Acetaminophen is metabolized to its toxic metabolite by a cytochrome P450 (CYP2E1) that is induced by phenobarbital
    - a) Chronic phenobarbital administration increases the hepatotoxicity of acetaminophen in experimental studies
    - b) Acetaminophen should probably be avoided in dogs treated with phenobarbital**
- C. Hemodynamic interactions
  1. Aminoglycosides
    - a) NSAIDs increase nephrotoxicity
    - b) Impaired compensatory PGs
  2. Furosemide
    - a) NSAIDs impair response to hypovolemia from furosemide
    - b) Impaired compensatory renal PGs
  3. ACE inhibitors
    - a) Both NSAIDs and ACEi impair response to hypovolemia
    - b) Caution prior to general anesthesia
- D. Herbs and NSAIDs
  1. Herbs that contain salicylate, such as meadowsweet and willow, could exacerbate the side effects of aspirin and other traditional non-selective NSAIDs
  2. Gingko, garlic, ginger, and ginseng inhibit platelet aggregation
    - a) Gingko has lead to spontaneous bleeding in humans in combination with aspirin

### Minimizing NSAID complications

- Obtain screening CBC and chem panel in older patients prior to starting NSAIDs
  - Rule out significant pre-existing azotemia, anemia, or hepatic dysfunction
- Maintain hydration
- Absolutely no concurrent glucocorticoids (including budesonide and potent topicals)
- Never use multiple NSAIDs concurrently
  - Consider a one-week washout between an NSAID and either glucocorticoids or another NSAID
  - Consider bridging with omeprazole during that week
- Provide client education about monitoring for GI upset, darkened stools, inappetence, or lethargy in any treated patient
- Schedule periodic CBC and chem panels in older patients or those with underlying risk factors for GI bleeding, such as hepatic disease.

<b>Non-selective agents</b>		
Aspirin	Both COX-1 and COX-2	Low doses selectively inhibit platelet function (0.5– 1 mg/kg q12h) May be useful for pro-thrombotic states (cardiomyopathies in cats, protein losing nephropathy in dogs) GI upset and bleeding at higher dosages
Ketoprofen	Both COX-1 and COX-2	Short term analgesia, but has been associated with bleeding and azotemia There are safer agents
Piroxicam	Both COX-1 and COX-2	Effective to slow growth of transitional cell, nasal, and colon carcinomas in dogs and cats Avoid if coagulopathy present

<b>COX-2 preferential agents</b>		
Carprofen (Rimadyl)	COX-2 > COX-1	Good pain control with minimal risk of bleeding Risk of renal decompensation remains Rare risk of idiosyncratic hepatic necrosis
Meloxicam (Metacam)	COX-2 > COX-1	Good pain control with minimal risk of bleeding Oral transmucosal formulation available for dogs (OroCAM) Risk of renal decompensation remains Acute renal failure with chronic dosing at label dose in cats

<b>COX-2 selective agents</b>		
Deracoxib (Deramaxx)	COX-2 >> COX-1	Good pain control with apparent low risk of new GI ulceration COX-2 selective agents can impair healing of pre-existing ulcers Minimal risk of bleeding Risk of renal decompensation remains
Firocoxib (Previcox)	COX-2 >> COX-1	Good pain control with apparent low risk of new GI ulceration COX-2 selective agents can impair healing of pre-existing ulcers Minimal risk of bleeding Risk of renal decompensation remains
Robenacoxib (Onsior)	COX-2 >> COX-1	As for other coxibs Better efficacy than meloxicam for post-operative pain control in cats.

<b>Other NSAID-like drugs</b>		
Acetaminophen (Tylenol)	Weak, reversible COX inhibition No significant anti-inflammatory effects	Antipyretic or analgesic in dogs intolerant of NSAIDs (acetaminophen 10-15 mg/kg q. 8 h; if combined with codeine, dose codeine at 1-2 mg/kg q. 8 h.) Acetaminophen contraindicated in cats, of course
Grapiprant (Galliprant)	Not a COX-inhibitor Prostaglandin (EP4) receptor antagonist	Not an actual NSAID Safety relative to NSAIDs of various classes requires more experience
Tepoxalin (Zubrin)	Both COX-1 and COX-2 Also inhibits 5-lipoxygenase	Safer than coxibs for dogs with pre-existing ulcers? Unfortunately, no longer manufactured

## Growing Resilience - The connection between growth mindset and resilience

Colleen Best, DVM, PhD, CCFP

Carol Dweck is a psychologist who studies the power of people's beliefs. Her theory of traits states there are two ways people can view the malleability of a person's basic characteristics – with a fixed mindset or with a growth mindset.<sup>1</sup> Those with a fixed mindset hold a belief that basic qualities, such as intelligence or musical ability, are fixed and cannot be changed. People with a fixed mindset frequently believe that talent leads to success, not effort. Those with a growth mindset believe that the most basic qualities can be cultivated with hard work and dedication; brains and talent simply provide a foundation.<sup>1</sup>

Resilience has been described as a “state of being that promotes wellness and decreases the impact of physical and psychological stress”.<sup>2</sup> One theory of resiliency describes five key principles that resilient individuals embrace: managing health, problem-solving, increasing strengths (self-esteem, self-confidence, and self-concept), developing positive response choices, and learning good lessons from difficult situations.<sup>2</sup> Research has demonstrated that individuals that possess higher levels of resiliency recovered faster from threats.<sup>3</sup> Self-compassion and mindfulness have been found to be positively associated with resiliency levels and protective against burnout.<sup>4</sup> It is in the areas of increasing strengths, developing positive response choices, learning good lessons from difficult situations, and self-compassion that mindset factors into the development of resilience.

The link between mindset and resilience is apparent when one considers the impact of the mindset one holds. Dweck's research has shown that one's mindset influences one's capacity for growth, perseverance, and willingness to try.<sup>5</sup> These are incredibly powerful qualities. It's also important to recognize that we can hold different mindsets about different characteristics; for instance, a growth mindset regarding athletic ability and a fixed mindset about intelligence. Therefore, it's important to reflect on the mindset we use to approach all manner of personal characteristics (e.g., intelligence, social skills, personality, cooking ability).<sup>5</sup> A growth mindset, believing that one can grow and change, reduces the fear trying a new thing, of failing, or of making a mistake.<sup>5</sup> This is because the outcome of the effort does not reflect back on one's basic personal characteristics or identity. Whereas, a fixed mindset makes one vulnerable to assaults on one's sense of self. For instance, if one considers themselves to be an excellent surgeon and holds a fixed mindset about surgical ability, a surgical complication or adverse outcome may be perceived as a threat to one's sense of self – you're not as good as you thought, you are a failure, you are a bad surgeon. However, if one holds a growth mindset about surgical ability, a failure or unexpected outcome does not reflect back on one's self-identity, as it's believe that one can learn and do better going forward – you made a mistake, it's possible to learn from it and do better next time. A growth mindset allows you to be resilient in the face of an unexpected outcome because you do not feel threatened and it does not elicit doubt in your identity.

One's mindset also colours the lens through which one sees the world. This is because one's mindset influences how one perceives another's actions and motivations.<sup>1</sup> In the case of a fixed mindset, one doesn't believe that another can grow and change a given personal characteristic. Consider how you would treat someone you don't believe has the capacity to change? You may determine you dislike who they are, versus disliking their performance or behaviour. Further, it's less likely that you would dedicate time or energy to teaching that individual or teaching them because it's not believed that is possible. However, in the case of growth mindset, where it's believed that personal characteristics are malleable, it's easier to give another the benefit of the doubt, to work with them to support their growth, and to be tolerant of their mistakes. Thus, if a

growth mindset is adopted, not only are you increasing your own resilience, but also your compassion and patience towards those around you.

It takes some purposeful intention to adopt a growth mindset, however, the benefits of doing so are multifaceted and abundant. One of the best parts about deciding to incorporate growth mindset into your life is that all that is needed to do so is an awareness of the power of the mindset one holds. Interventions show that when students are taught about fixed and growth mindsets, that the information they are given is all that is needed for them to make positive changes and go forward using a growth mindset.<sup>2,5</sup> Choosing to adopt a growth mindset will not only improve your own resilience and capacity for growth, it will strengthen your relationships with those around you and facilitate team performance.

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## Proceedings

### **“You only care about the money!” Setting the record straight: How to Navigate financial discussion with clients**

Sarah Bernardi RSW, MSW

#### **Retail Component**

- Vet medicine is a business! It has the retail component that human medicine does not in Canada.
- Clients may be confused, stressed, emotional, they might have financial issues and therefore take it out on frontline staff.
- This is a scary, volatile time for them, may not truly understand the scope of the situation.

#### **A difficult conversation...but one worth having**

- Money is an undercurrent of many relationships, but this is often overlooked or avoided
- Research shows us that although both Vet professionals and Human physicians acknowledge money as an important topic for discussion, this subject can create contention between themselves and clients. (Bonvicini, 2009)
- Two barriers of having this discussion in human medicine were listed as:
  1. Discomfort dealing with financial issues
  2. Insufficient time (Alexander, Casalino & Meltzer, 2003)
- When we leave estimate discussions until the end of the conversation, it fragments it. Finances are a key part of the decision-making process for many owners, so it should be discussed from the beginning. But what does this even look like?

#### **Challenges for the Staff & Client**

The experiences are often parallel to each other:

- Sense of identity
- Fear of judgment
- Emotional Response
- Additional stress

#### **Theme**

- *“Financial issues are often paired with a perception of caring and compassion...”*

- This may look like: “you are making me pay, so you must not care!” or the client may measure their own compassion by the money they are willing to spend.
  - Ex. The unwillingness or inability to pay for a private school for a child does not mean that the child is not cared for
  - Ex. Diamond ring for your partner- does not ensure that they are loved

### Tools for discussion

- Rapport building! You don't just work with animals; you work with people to.
- You already share a common ground with your client—you both love animals! Now you just need to build on this foundation.
- It doesn't take long to do this; clients appreciate being recognized and acknowledged. Just use that important tool of empathy.

### 'Where does the money go?'

- Know why this is a paid service- this tool is good to help you remember why you have to charge for the service provided. In some contexts, it is also valuable info to share with the clientele, and general public (family, friends).

### Helpful Comparisons

- People often draw on human experiences when trying to make sense of their animals' experiences.
- Being able to provide a comparison between the price of pet care vs. human care, can offer some perspective for clients.
- Of course, there is a time and place for this- i.e. if you sense that they won't receive this info well, or may not interpret it correctly, then avoid it.

### Verbal & Non-Verbal

- Three components of communication
  - Words
  - Tone
  - Body language
- We focus on words, but in reality, our body and tone are relaying 93% of the message.
- Non-verbal's show our true feelings
- Self-awareness- the more we know ourselves, the better we communicate!
- Observe clients, you can tell if they aren't processing what your saying.



## Quick Conversation Tips!

- Avoid using jargon
- Open-ended Q's
- Restate concerns/important info client shares with you
- Keep a neutral/non-judgmental tone
- Keep "open" body language (no arm crossing, remove physical barriers.)
- Be observational! Is the client receiving this information correctly? If not—clarifying Q's!

## Don't Assume

- Assuming intentions, depletes relationships.
- Not only can we make assumptions of others, we can also make assumptions of how others perceive us.
- Examples:
  - A client is afraid to raise concerns about cost of care in case they are perceived as uncaring.
  - Staff judge client's finances based on appearance, car, age, pet breed...etc.
  - Client assumes a young vet professional is too inexperienced to justify full payment.
- Be aware of your internal dialogue and how it presents externally.

## Dismantle the Hierarchy

- Advocate for yourself and your staff
- Everyone recognizes each role to hold equal importance and necessity, communication opens up and so does trust
- Educate clients about different clinic roles, the more they know, the more comfortable they feel in your environment!

## How does this knowledge help you?

- Equips you for difficult conversations
- Reminds you not to take a client's backlash personally. Money often adds another stressful aspect to the situation, they are not lashing out at you because you're a bad person, they are probably feeling a range of emotions and haven't had time to process them.
- Versatility in your workplace- communication is a valuable skill anywhere you go
- Rapport building is important to your business! A better relationship with clients = better communication, which may in turn decrease the amount of complaints and negative feedback received. Clients should feel comfortable asking questions, sharing financial concerns etc.

*References available from the author(s) on request*

## 2019 AAHA CANINE LIFE STAGE GUIDELINES

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### Introduction

Organizing a canine patient's lifespan into distinct life stages is a way of recognizing that a dog's physiology evolves as it matures, requiring different approaches to healthcare as the animal progresses from puppy to senior pet. The patient's life stage becomes a clinical tool that guides the clinician's risk assessment and preventive healthcare and treatment strategies. Equally important, the life stages described in the guidelines also represent a useful framework for developing and then explaining individualized pet healthcare to the pet owner.

### Definition and Utilization of Life Stages

Puppy	From birth through cessation of rapid growth (approximately 6-9 months of age, varying with breed and size)
Young adult	From cessation of rapid growth until completion of physical and social maturation, which occurs in most dogs by 3 to 4 years of age
Mature adult	From completion of physical and social maturation until the last 25% of estimated lifespan (breed- and size-dependent)
Senior	The last 25% of estimated lifespan through end of life
End-of-life	The terminal stage (length of time depends on the specific pathologies)

Physiological and behavioral developmental periods do not start and end abruptly, but phase in and out gradually. Team members should acknowledge the differences in life stages, and adapt the experience at the veterinary hospital to each life stage. This includes planning how to minimize client and pet anxiety associated with veterinary visits, planning the content and frequency of visits, and taking into consideration the dog's signalment and lifestyle to individualize as appropriate.

### Pet Lifestyle and Safety Assessment

Safety hazards vary with the patient's life stage, environment, and lifestyle, as well as with hearing/vision and mobility impairments. Client communication regarding potential hazards will reduce these risks, especially for new dog owners or new dogs at any life stage. This extends to discussions on registration and identification of the dog, and long term planning for care.

### Nutritional Assessment

Nutritional assessment, including evaluation of the body/muscle condition score and nutritional factors, should be a part of every visit to the veterinary practice and should utilize the entire practice team. Screening evaluation should be performed on every animal, with extended evaluations performed as necessary, and should be tailored to life stage. See the AAHA Nutritional Assessment Guidelines for Dogs and Cats.

### Parasite Control, Zoonoses and Human Safety

Parasitism remains common in dogs despite widespread availability of safe and effective treatments. Monitoring for parasitism, year-round broad-spectrum control, and routine treatment prevents both disease in dogs and contamination of the environment. Veterinarians play a crucial role in protecting dogs, their families, and the public from exposure to zoonotic disease. The risk of zoonotic disease must also be considered for the veterinary healthcare team. Consumption of raw or undercooked meat carries risk, both in the ability of the pet to carry zoonotic and disease causing agents, but also in handling of the food itself. See AVMA-AAHA Preventive Care Guidelines/AAHA Infection Control, Prevention, and Biosecurity Guidelines.

## Vaccination

Veterinarians make vaccination recommendations based on many factors, including the life stage and lifestyle of each dog. Every dog should receive immunization with core vaccines (rabies virus, canine distemper virus, canine parvovirus, canine adenovirus-2) that comply with state/provincial regulations. Customized plans for non-core vaccines are indicated in accordance with existing guidelines, based on geography, life stage, lifestyle and exposure risks. Dog owners should be informed about the benefits and risks from vaccines, and should be given the opportunity for questions. See the AAHA Canine Vaccination Guidelines.

## Behaviour

Canine behavior is influenced by developmental age, experiences, breed and environment. Because behavior problems continue to be a significant cause of relinquishment and euthanasia, it is essential that behavioral evaluations and interventions be incorporated into each patient's veterinary visit. Recommendations vary by life stage, however each pet should be approached as an individual. Furthermore, the general approach to veterinary visits should attempt to reduce fear, anxiety, and stress with patient response documented in the medical record. The veterinarian is the primary resource for accurate and current information regarding behavior; see the AAHA Canine and Feline Behavior Management Guidelines.

## Baseline Data

Prior to the development of occult disease, it is useful to determine a baseline for each individual dog. Determining an individual dog's baseline allows for the trending of values over time. Detection of occult disease in all life stages can allow for earlier diagnostic and therapeutic intervention, and the potential for increased healthy longevity. Veterinarians must use their judgement, considering the breed, life stage, and other factors such as pre-existing disease or use as a service dog, in order to determine the implementation and frequency of baseline data.

## Dental Care

Because so many dogs are affected by dental and periodontal disease, dental care must be incorporated into each dog's preventive healthcare plan and discussed at every visit. Preliminary information can be obtained on an awake patient, however only when the patient has been anesthetized can a complete and thorough oral examination be performed and an accurate periodontal disease diagnosis and assessment be made. Patient breed and life stage will present unique dental needs and concerns. Pet owner education is paramount to ensure proper dental care throughout the dog's life. See the AAHA Dental Care Guidelines.

## Reproductive Health

It is recommended to spay or neuter all dogs not intended for breeding. Those intended for breeding should follow responsible practices to reduce perpetuation of disease. Sterilized dogs of both sexes have greater average lifespans than intact dogs. Some diseases are prevented by sterilization, such as testicular tumors and pyometra, whilst the incidence of other diseases are increased with sterilization, such as urethral sphincter mechanism incompetence in female dogs. However, studies have indicated that the timing of sterilization may alter the risk of certain disease processes, including orthopedic disease, obesity, urethral mechanism incompetence in female dogs, and certain cancers. The risk of disease may be increased or decreased with sterilization, and in many cases, the risk also varies by breed and sex.

Based on the current literature, it is recommended that female and male dogs not intended for breeding and expected to be <45 pounds when full-grown should generally be sterilized by 5-6 months of age. Due to the possible orthopedic concerns, certain cancers in some breeds, and the phenotypical differences between large and giant breeds, males expected to be >45 pounds

should be sterilized when growth is complete, usually between 9 to 15 months. There may be a benefit to orthopedic health of postponing even longer. The recommendations are less clear in female dogs expected to be >45 pounds, therefore clinical discretion and extensive client communication and education will be needed to individualize the care in this population. These recommendations attempt to balance risk of orthopedic disease, USMI, and some cancers associated with early sterilization, against risk of mammary neoplasia, unwanted litters, and possible other cancers if sterilized later. These medical recommendations may need to be balanced against certain nonmedical extenuating circumstances, such as likelihood of future access to veterinary care, financial incentives provided by adoption groups, or the opportunity to perform surgical sterilization concurrently with another anesthetized procedure.

### **Breed-Specific Considerations**

It is recognized that physiology can vary by breed. With the presence of several hundred distinct canine breeds and many more mixed-breed combinations, it is important to recognize the potential for variability in physiology and clinical pathological normal values. Assessing and correctly entering the dog breed should occur at the first visit, and knowledge of the breed increases the recognition of genetic disease and expected variations in normal ranges of test results. It is important at the first visit for practice teams to engage in breed-specific education with the pet owner. This dialog should include specific, directed evaluations and diagnostic tests at each life stage for the individual patient in order to detect occult disorders earlier. Besides early detection, these diagnostic tests are also important to establish a baseline for the individual patient. When a known breed of dog undergoes breed-specific screening, those results should be shared whenever possible in a public database, e.g., collie eye screening or hip dysplasia screening.

### **Importance of Practice Team and Pet Owner Compliance**

The cost of prevention is often a fraction of the cost of treating a disease once it has become more advanced. The ultimate goal of preventive care is improved quality of life and longevity for the patient. The entire practice team's support is crucial to improve a client's understanding of the need for and value of routine examinations, and to ensure consistent practice team recommendations through all life stages. Guidance should be through the use of two-way communication and including the pet owner as a team member through eliciting their perspective. This includes discussion on the options available to increase predictability in the cost of care, such as preventive healthcare plans and pet insurance. It is vital to ensure that the pet owner's perspective is solicited and used to form the basis of an individualized life stage-specific recommendation to improve the likelihood of pet owner compliance.

### **Summary**

A patient's life stage is one of the most relevant aspects of clinical practice because it guides risk assessment, a preventive healthcare plan, and appropriate treatment. A canine patient's life stage also forms the basis for an ongoing dialog with the pet owner about a lifetime healthcare strategy for the pet. This is a critical aspect of the life stage concept because effective client communication is the key factor in pet owner compliance with the practice team's individualized recommendations.

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## CHOOSE YOUR WEAPONS! KNOWING WHAT DENTAL BURS TO USE CAN MAKE OR BREAK A PROCEDURE

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### Overview

A veterinary dentist has a large armamentarium of burs that accomplish a variety of tasks. Without them, many, if not most, procedures would be performed inadequately. This discussion will review burs needed in your private practice.

### Objectives of the Presentation

- Show different variety of burs used by veterinary dentists
- Application of each bur

### Discussion

Before consideration of burs, we need to look closely at the type of handpieces needed to adequately perform any oral surgical or restoration task. High-speed handpieces are used when rapid and efficient cutting of the tooth and/or supporting bone is needed. These run at 300,000-400,000 RPM. This lecturer recommends the use of a swivel tip handpiece that has either an LED or fiberoptic light capability. Using a modified pen grip for procedures adds to tactile sensitivity.

The burs that will be discussed today are friction grips (FG). Please refer to veterinary catalogues using such grips. A latch-tip bur is used for reduction gear contra-angle slow speed handpieces. These will only be discussed with regard to finishing discs and not any other bur.

Length of burs range from friction grip short shanked (FGSS); friction grip (FG) and friction grip oral surgery length shank (FGOS). Short shanked burs are rarely used in clinical practice.

**Cutting burs** – Uses for cutting burs are: section multirrooted teeth and/or removal of buccal bone to facilitate extraction; perform alveoplasty to smooth sharp bony edges after an extraction; provide access sites for root canal therapy; reduce or reshape teeth for crown reduction or crown preparation; remove part of the mandible or maxilla.

### Carbide steel burs

These burs are meant for single usage procedures! Each has blades and valley or flutes between each blade. The blade provides cutting action, while the flute acts to remove the cut material. Cutting burs have 6 flutes.

Round burs – These are used to provide endodontic access sites and bone smoothing. Size range 1/4-8. The smaller the number, the smaller the size of the bur.

¼, ½ round burs used for facilitating moats around retained tooth roots or feline roots (FG, FGOS)

#2, #4 and #6 round burs used for removing buccal bone (FG). Most practices can live with #3 and #4 and be very happy.

Pear shaped burs – These are wider at the tip with a slightly rounded corner for added protection against chipping. Many veterinary dentists use the #330 as the 'universal' bur to

remove buccal bone and section teeth . The most common bur is #330 (FG). There is also #331 and #332.

Fissure burs – have grooved heads and are used for sectioning teeth and reducing crown height. Sides of the straight fissure bur are parallel and the sides of the taper fissure bur converge toward to the tip. Fissure burs may also contain cross-cuts along the blades (called cross cut fissure burs).

The most common and practical is the #701 and #701L taper fissure bur (FG, FGOS)

### **Diamond burs**

These burs are covered with bits of industrial diamonds used for crown preparation, alveoplasty (smoothing of bone), scarification, and shaping teeth (odontoplasty). There are a variety of diamond burs used in a specialist's practice, but one could be happy with 1-2 different types of burs in general practice. Burs recommended are medium grit football diamond and #14 round diamond bur (medium grit).

Another less utilized way a diamond is used is via removal of buccal bone. By using a diamond instead of either a 6 fluted round or cross-cut bur, less chance of excess bone removal or even tooth gouging is performed. A few veterinary dentists teach this method in labs to help prevent too much bone removal.

### **Stones**

Stones are used for polishing and finishing restoratives as well as for smoothing enamel defects in the dog. White stones (Arkansas White) are the primary stone and use this in a flame tip. Green stones are used to smooth enamel and Gray stones for polishing fabricate crowns.

### **Trimming and Finishing burs**

These are the most underutilized but essential burs in a dentist's armamentarium. They are designed for completing restorations, odontoplasty and alveoplasty. The more flutes, the more smooth the polish. Most veterinary dentists use 12-fluted burs in a variety of shapes (egg, flame, round, and taper).

### **Discs**

Veterinary dentists DO NOT recommend the usage of any diamond cutting disc due to the great potential for patient/surgeon injury. Finishing discs, however, are used quite frequently for smoothing restoratives. They are used from coarse to super-fine.

### **Summary**

Having the right bur in your hands helps you perform dental procedures easier and with less patient trauma. Before using any new type of bur, it is recommended to practice on a cadaver or previously removed tooth.

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## CONSENSUS IN FELINE MEDICINE

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Guidelines and consensus statements provide a backbone of medicine by allowing a unified standard of practice across various regions and specialties.

While a wide range of guidelines are available on a broad range of subjects, a small subset have been chosen to discuss here due to their relevance to daily practice. Four sets of guidelines will be discussed in brief. The focus will be on the feline aspects of these guidelines, though many of them contain recommendations for dogs as well.

### Guidelines for the Management of Feline Hyperthyroidism (AAFP)<sup>1</sup>

Hyperthyroidism is among the most common diseases of older cats, and while treatable, leads to significant morbidity and mortality. The majority of cases are readily diagnosed through a combinations of clinical signs and an elevated total thyroxine. Some cases, however, are more difficult to diagnose due to atypical presentations or borderline results. As measurement of thyroxine concentrations has become common in health screens for many older cats, elevations may also be detected in animals with no identified clinical signs. These guidelines are focused on the diagnosis and treatment of cats with hyperthyroidism.

There are several aspects to the diagnosis of hyperthyroidism. These include the presence of a palpable thyroid nodule; classical signs of thyroid disease (polyphagia, weight loss, increased vocalization, pu/pd, etc), and elevated serum total thyroxine (TT4)

Hyperthyroid cats will present with some combination of these findings. The consensus statement uses these to divide cats into 6 categories for the purposes of diagnosis, and recommends next steps:

- Classic disease: Elevated TT4 and consistent clinical signs
  - Treat hyperthyroidism
- Possible hyperthyroidism with probable non-thyroidal illness: Clinically hyperthyroid with normal T4
  - Check T4 and free-T4 2-4w later, evaluate and treat non-thyroidal illnesses, consider T3 suppression or scintigraphy
- Enlarged thyroid without clinical hyperthyroidism: No clinical signs, normal T4, but an enlarged thyroid gland
  - Monitor clinical signs and repeat T4 in 6m
- Subclinical hyperthyroidism: No overt signs, but exam suggestive of hyperthyroidism, elevated T4
  - Repeat T4 in 2w, if elevated, treat, if normal recheck in 6m,
- Clinical hyperthyroidism with confirmed non thyroidal illness: Clinically hyperthyroid, elevated T4, one or more other illnesses
  - Treat hyperthyroidism and appropriately manage other conditions
- Clinically normal: No clinical signs or palpable nodule but elevated T4
  - Confirm T4 and lack of clinical signs, recheck in 6m, if still elevated, treat

When managing hyperthyroid cats that are also azotemic, there is no justification to keep cats “a little” hyperthyroid, and in fact this is detrimental. The panel recommends treatment of hyperthyroidism regardless of comorbid conditions.

The treatment options for hyperthyroidism are methimazole, surgical thyroidectomy, dietary therapy, and radioiodine. Each of these may be considered acceptable for a given cat.

### **Antimicrobial use Guidelines for Treatment of Respiratory Tract Disease (ISCAID)<sup>2</sup>**

Respiratory infections in cats are a common occurrence, and one of the most common reasons for presentation to a veterinary hospital. A wide range of treatment options are available for respiratory diseases, leading to a diversity of care. These guidelines cover upper and lower respiratory infections in cats, as well as pyothorax. Our discussion will focus on the more common upper respiratory tract infection.

The panel defines an acute bacterial upper respiratory infection as clinical signs of a respiratory infection less than 10 days duration involving purulent or mucopurulent nasal discharge. If these are not present, the infection is considered viral and treatment is not recommended. Culture and cytology of discharges is not recommended. The only diagnostic recommended at this point is retroviral testing. Infections greater than 10 days duration should be considered chronic, and may receive more intensive workup.

If the cat experiences fever, lethargy, or anorexia in the first 10 days, therapy is recommended. If these are not present, observation is recommended until either resolution, the above clinical signs develop, or the infection lasts 10 days.

The recommended first line therapy is oral doxycycline, as it is well tolerated and treats *Bordetella*, chlamydia, and mycoplasma. Amoxicillin is an alternative first line option if chlamydia and mycoplasma are deemed clinically unlikely. Treatment duration should be 7-10 days. Cefovecin is not recommended at this time.

If the antimicrobial is ineffective, further workup is recommended. This should include a detailed oronasal exam. Nasal lavage or brushings with cytology, culture, and PCR, nasal biopsies, CT, and rhinoscopy may be required.

### **Support for Rational Administration of Gastrointestinal Protectants (ACVIM)<sup>3</sup>**

Gastroprotectants are some of the most commonly used medications in veterinary medicine. While they are generally well tolerated, side effects are not unheard of, and they are often overutilized in many situations. This consensus statement discusses the preferred gastroprotectants and the situations in which they should be used.

In virtually all cases where gastroprotection is indicated, a proton-pump inhibitor (PPI) is the preferred choice (ie omeprazole, pantoprazole). There is no evidence to suggest one PPI is superior to any other. PPIs are in all cases superior to anti-histamines (ie famotidine, ranitidine), and there is no data to suggest combination therapy is better than a PPI alone. Misoprostol may be indicated in cases of NSAID induced ulceration/erosion. Sucralfate may have efficacy in esophageal disease and in managing ulcer induced pain, but is not as effective as a PPI in treating ulcers and there is no evidence that combination therapy is superior to a PPI alone.

There are several situations where the use of gastroprotectants is indicated in cats. The most commonly encountered situation is gastroduodenal ulceration and erosion (GUE). Note that this is limited to cases of confirmed or strongly suspected GUE and does not apply to all anorexic or



vomiting cats, the majority of whom have no evidence of this. Cats with nonerosive gastritis should not receive therapies with gastroprotectants. Reflux esophagitis is the other indication for PPI use.

There is weak evidence for using gastroprotectants in cats with hepatic disease without GI bleeding. There is no evidence for the use of gastroprotectants in cats with renal disease, pancreatitis, non- *H. pylori* helicobacter infection, thrombocytopenia, critical illness, or disk surgery. They should not be used in these patients.

The main “take-away” message of this consensus is that gastroprotectants should only be used when truly indicated (ie GUE or reflux esophagitis), and if therapy is indicated, PPIs should be the drug of choice.

### **Consensus on the Rational Use of Antithrombotics (VECCS)<sup>4</sup>**

Feline Aortic Thromboembolism (FATE) is a complication of cardiac disease that leads to significant morbidity and mortality. It is the most common reason for anticoagulation in feline medicine. Cats with a history of FATE, left atrial dilation, spontaneous echo contrast, or reduced flow in the left auricular appendage are at an increased risk for FATE. This consensus statement recommends the use of antithrombotic therapy for cats with identified cardiomyopathy, especially if any of the above criteria are met.

The antithrombotic of choice for prevention of FATE is clopidogrel. It is recommended that it be used instead of aspirin in cats due to better efficacy. Other antiplatelet agents and Xa inhibitors may have efficacy, however insufficient data is available to recommend their use. Combination antiplatelet and anticoagulant therapy may be indicated in cats at high risk for thromboembolism, in which case low-molecular weight heparin is the proffered anticoagulant.

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## MINIMALLY INVASIVE SURGERY IS BETTER THAN TRADITIONAL OPEN SURGERY: WHAT IS THE EVIDENCE?

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Minimally invasive surgery (MIS) was first described in veterinary patients in the mid-1980's at a similar time to its initial development in humans. A series of patients undergoing laparoscopic renal biopsies was described in 1983. In 1985 another group of early adopters used laparoscopic uterine horn occlusion on 6 bitches and 3 queens in an attempt to describe an alternative method for mass sterilization of small animal patients.<sup>1</sup>

Over the last 15 years, despite the lack of a broad-based adoption of MIS alternatives to open surgery by veterinary surgeons, a slow but steady evolution and refinement of laparoscopic and thoracoscopic techniques in small and large animal practice has taken place. Rawlings amongst others was an early pioneer of many laparoscopic-assisted and laparoscopic techniques that are user friendly and can often be performed using only basic laparoscopic instrumentation. These techniques include laparoscopic-assisted ovariohysterectomy, ovariectomy, gastropexy, cystotomy, cryptorchidectomy and a variety of laparoscopic organ biopsy techniques.<sup>3-6</sup> They have allowed many veterinarians with limited MIS experience to start performing MIS procedures in referral as well as general practice. A natural progression to more complex techniques has occurred more recently with laparoscopic adrenalectomy, cholecystectomy and thoracoscopic lung lobectomy being performed in some referral centers.<sup>7-10</sup> Other trends in the development of veterinary MIS include the movement towards fully laparoscopic versions of previously described laparoscopic-assisted techniques. These "second generation" techniques are aimed at minimizing incision size and therefore invasiveness even further.<sup>11</sup> Similarly, reducing port size and number, a concept that is gaining great popularity in human medicine, is now well under way in veterinary MIS and is also aimed at reducing the invasiveness of certain procedures.

Despite all of the new procedures and refinements to existing techniques that have been made, the evidence base to suggest that MIS has advantages over traditional surgery remains weak in veterinary medicine. Most authors have suggested that advantages may exist in minimizing pain and improving return to function, decreasing risk of surgical site infection (SSI) and reducing various morbidities when patients undergo a laparoscopic or thoracoscopic approach compared to a celiotomy or thoracotomy. While we would like to think this is true and we are quick to "borrow" evidence from human medicine it is imperative that veterinarians demonstrate these advantages with rigorous scientific evaluation of the techniques.

There is now a steady trickle of evidence to suggest that many of the advantages that humans have enjoyed since the paradigm shift to MIS may also be afforded to our small animal patients. Reliable outcome measures are a challenge in veterinary medicine but most investigations have employed either defineable outcomes such as surgical time and complication rates or parameters of post-surgical pain or stress such as serum cortisol and glucose measurement as well as a variety of visual analogue scales.<sup>12,13</sup> In

Devitt's paper, one of the earliest to compare a population of healthy animals undergoing either open or laparoscopic ovariohysterectomy, the MIS group was found to have lower pain scores for 24 hours post-operatively whereas indirect measures of surgical stress, cortisol and glucose, were significantly increased in the open group up to 2 and 6 hours respectively compared to baseline, which was not the case for the MIS group.<sup>13</sup> Surgical time has been compared between open and MIS approaches in a number of studies. Surgical time needs to be interpreted with caution in these studies as many represent the early part of a center's learning curve in comparison to that of an open procedure that the surgeon is presumably, in most cases, experienced with. However, several studies have documented longer surgical times associated with an MIS procedure compared to the traditional open procedure.<sup>10,14,15</sup> As more experience is gained with newer techniques however we may find that there is a time advantage to some procedures that are performed using an MIS technique as has been shown in one study of laparoscopic adrenalectomy.<sup>16</sup> Other studies have evaluated the return to normal function using an objective measure of activity. Accelerometry has been validated for use in both dogs and cats and was used to compare open to laparoscopic OVE in cohorts of small dogs.<sup>13</sup> A detectable difference was found between groups with activity counts in the 48 hours post-operatively being 25% and 62% below baseline activity in the laparoscopic and open groups respectively.<sup>13</sup> In another study using accelerometry devices the authors compared a laparoscopic-assisted gastropexy to a "next generation" technique performed entirely laparoscopically using intracorporeal suturing.<sup>11</sup> Accelerometry revealed activity counts that were 44% and 11-19% decreased compared to pre-operatively in the laparoscopic-assisted and total laparoscopic groups respectively in the 7 days post-operatively a difference that was statistically significant and was attributed to the avoidance of the deep paramedian incision performed for the "assisted" technique. The duration of this effect appeared to be somewhere in the region of 4-5 days post-operatively.<sup>11</sup> More recently other studies have concentrated not only on improvements in post-operative discomfort but in the effect on morbidity of MIS approaches. In a study comparing surgical site infection (SSI) rates between open and minimally invasive surgery, the authors found that on univariate analysis surgical approach (MIS versus open) had a beneficial effect on SSI rate post-operatively.<sup>17</sup> The SSI rate for the open group was 5.5% compared to an SSI rate of 1.7% in the MIS group. However, it should be noted that on multivariate analysis, this difference was at least in part driven by other potential confounders. Further studies will be required to confirm this hypothesis. In thoracic surgery few studies have been pursued evaluating the difference between open and MIS approaches. One study evaluated the difference between an open and a VATS approach in a canine pericardectomy model.<sup>12</sup> In this report the VATS approach was associated with lower post-operative pain scores in the post-operative period as well as higher blood glucose and cortisol concentrations in the thoracotomy group. Rescue analgesics were used with greater frequency in the thoracotomy group and fewer complications were observed in the VATS group.<sup>12</sup> A recent clinical study has documented the results of VATS lung lobectomy in 22 canine patients with primary lung lobe tumors compared to a population that underwent thoracotomy for the same reason.<sup>10</sup> The authors were able to demonstrate that the VATS approach was feasible and not associated with significantly greater morbidity but were not able to demonstrate

apparent advantages in the length of hospital stay, ICU time or indwelling thoracic drain time advantages which have all been documented in humans after VATS lobectomy.<sup>18,19</sup> In this study no attempt was made to evaluate post-operative pain, discomfort or activity between groups. Additionally, outcome measures were not indexed to any clinical benchmarks and significant confounders caused by the decisions of different managing clinicians may have influenced outcomes. Future studies are required in this area to investigate in a prospective fashion the effects of these interventions versus their traditional open counterparts.

In conclusion, much research remains to be done in establishing which procedures will lend themselves well to an MIS approach and in which cases a traditional open approach might remain the wiser choice. We must also continue to strive to critically evaluate the procedures we perform to ensure that our MIS procedures are really delivering the advantages that we hope they will.

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## Canine Rehabilitation Outcome Assessment Tools: Using Goniometry and Girthometry in Clinical Practice

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Objective outcome assessment tools in canine rehabilitation, orthopedic, and neurologic patients are vital to determine dysfunction, treatment success, and/or progression of disease. Although the physical examination and gait assessment are an important part of the assessment, objective measurements can be improved by using tools such as goniometry and girthometry. These tools are easy to learn and perform and can help the veterinarian understand joint range of motion and muscle strength, thus guiding appropriate intervention.

Goniometry has been used for many decades for human physiotherapy patients and can be easily modified for the canine patient. With the patient laying in lateral recumbency, a special tool called a goniometer is used to measure joint angles. These values can then be compared to a set of normal published values and they can be compared from limb to limb. Goniometry can highlight abnormalities in joint range of motion and can help the veterinarian determine appropriate management modalities. Measurements can vary slightly from evaluator to evaluator, however, with practice and when used properly, discrepancies can be minimized.

Girth measurements can be performed on large muscle groups such as the thigh and forearm using a special spring-tension tape measure called a Gulick. A regular tape measure can be used; however, the measurements tend to be less accurate and repeatable. Values can be compared from the left limb to the right limb and can be evaluated at pre-set time intervals. The results can indicate an indirect assessment of muscle strength. Atrophy or and muscle development can therefore be monitored, and interventions applied as needed.

Objective tools for assessing patients must be easy, accessible, inexpensive, and reliable in order to help the veterinarian assess and monitor the canine rehabilitation, orthopedic, and neurologic patient. Goniometry and girth measurements are two such tools that can be implemented in a general practice setting.



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## ADVANCED GASTROINTESTINAL SURGERY

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Gastrointestinal (GI) surgery can vary from very simple to highly complex depending on the state of the patient, the disease process being treated and the expertise of the surgeon. It is critical to understand the general principles of anatomy and physiology in order to achieve good surgical outcomes when intervening in the GI tract.

In general, vascular supply to bowel is still evaluated using very simple clinical parameters as more objective methods have generally failed to translate into practical and reliable “in the clinic” assessment tools. Color, consistency, motility and bleeding/perfusion are still the four principal methods used to assess the vascular integrity of GI tissue. Knowledge of the blood supply to different parts of bowel is important to plan enteric incisions and anastomoses. The jejunum has generally obvious vascular arcades that lend themselves easily to planned ligation. The duodenum receives shared blood supply from the cranial and caudal pancreaticoduodenal arteries, branches of the celiac and cranial mesenteric arteries respectively as well as the gastroduodenal and right gastroepiploic in its most proximal aspect. When the descending portion of the duodenum requires resection it is usually best to seal the duodenal blood supply directly at the antimesenteric margin in order to avoid damage to the pancreatic ductal system and blood supply. If a more extensive disease process dictates the resection of part of the pancreas, consideration should be given to making sure pancreatic tissue is resected in a way that avoids leaving areas of pancreas that are isolated from their ductal drainage system and therefore exocrine drainage mechanism. Care should also be taken in this area to make sure that the common bile duct is not involved in the disease process or is not impacted by the proposed resection. The area around the ileocecolic junction can also be challenging as it receives a mixed blood supply from the colic and ileocolic arteries. In this area, extensive collateral circulation appears to exist but direct visualization can be obscured by extensive fat deposition and the lymph nodes present within the mesenteric root. Much like in the duodenum, the safest course of action when performing an ileocolic resection is to take down the blood supply close to the mesenteric margin. The large intestine receives its blood supply from anastomosing branches of the colic arteries that arise from the cranial and caudal mesenteric arteries. These arteries, however, are not intimately associated with the mesenteric wall of the large intestine. In contrast, they give off vasa recta which are short branches that emanate from the arteries and provide a segmental supply of blood along the length of the large intestine. In the case of large bowel resections these vasa recta are individually sealed by ligation or use of a vessel-sealing device between the colic arteries and the intestinal wall thus preserving optimal blood supply from the colic arteries. Care should be taken if resection of the distal descending colon is planned to try and preserve as much of the cranial rectal artery, a

branch of the caudal mesenteric which provides the principal arterial blood supply to this area of colon.

Many principles of bowel closure are common to all areas of the GI tract. When hand-sutured enterotomy closure or resection and anastomosis is performed, simple appositional suture patterns are usually preferred with the use of monofilament suture. Simple continuous and simple interrupted have been shown both in cadaver studies<sup>1</sup> and in vivo<sup>2</sup> to be largely equivalent in effectiveness and safety. More recently barbed suture has been shown to be safe for use in enteric closure although its widespread adoption has not yet occurred possibly due to current cost concerns.<sup>3</sup> Although skin staples have been used for enteric closure in clinical studies in both dogs and cats<sup>4,5</sup> some concerns have been raised as to their ability to counteract physiological pressures during peristalsis in cadaveric models.<sup>1</sup> No matter which suture technique is used the critical component of any enteric closure pattern is that the submucosa, the holding layer of the gastrointestinal tract, be incorporated in the closure. For small intestinal resection specifically, new data has recently been published documenting improved outcomes with surgical stapling compared to hand-suturing in certain cohorts of patients.<sup>6,7</sup> These multi-institutional studies have shown statistically using much larger case cohorts that dehiscence rates may be decreased if surgical stapling is used especially in the presence of septic peritonitis.<sup>7</sup> Generally a functional end-to-end anastomosis is created using a Gastro-intestinal anastomosis (GIA) stapler. The end of the two stapled segments of small intestine are then sealed with either a Thoracoabdominal (TA) stapler or a second GIA cartridge. These anastomoses are very rapid to perform but do add significant cost over hand-sutured techniques. However, in the subgroup of dogs requiring GI resection in the face of peritonitis this cost appears to be warranted. Surgical stapling however is not the only modality a surgeon can rely on as it really is only practical for GI resection in the jejunum and ascending duodenum as the large ends of the GIA forks need to be able to be passed through the lumen of adjacent segments of intestine. This requires significant mobility of the bowel segments involved and makes it impossible in the descending duodenum, around the ileocecal valve and in the large intestine. It is also not practical in smaller breeds of dogs and cats using the most commonly used human GIA staplers (e.g. GIA stapler, Medtronic, Salem, MA).

The descending duodenum is an unusual site for surgical lesions to occur with the possible exception of ulcers associated with NSAID and/or steroid use, renal disease or other conditions. In these dogs, a predilection site for the upper descending duodenum appears to be present although these lesions seem to be getting less commonplace with a better understanding by veterinarians and owners on the use of sensible prescribing habits and the avoidance of co-administration of these different groups of drugs. In the case of a perforating ulcer in the proximal descending duodenum a local resection of the ulcer bed can be performed with a transverse closure in order to minimize the risk of luminal narrowing if the lesion is modestly-sized. With more extensive ulcers or masses in this area care should be taken to visualize the common bile duct as if resection of this structure or the major duodenal papilla is deemed necessary biliary rerouting will need to be performed.



Knowledge of factors that adversely affect healing of the large intestine should be considered prior to undertaking large intestinal resections. The large intestine has a much greater anaerobic bacterial load compared to the small intestine. The large bowel heals more slowly and may in the case of large resections (such as those performed during subtotal colectomy for feline megacolon) be exposed to significant tension. Additionally, the blood supply to the lower colon may not be as robust as that of other areas of the bowel making preservation of the caudal rectal artery important when performing resections in this area. Indications for large intestinal resection are principally for management of megacolon, resection of neoplastic lesions and rarely mesenteric volvulus involving the large intestine. Colotomy for foreign body removal is generally not indicated and neither are full thickness biopsies of the colon as colonoscopic biopsies usually suffice for diagnosis of inflammatory conditions of the large intestine. Large intestinal closure is performed by this author in the same way as for small intestine with a single layer appositional suture pattern although some surgeons prefer a two-layer closure for large intestine especially in large breed dogs.

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## BACK TO BASICS: SECURE KNOTS, BEAUTIFULLY CLOSED SKIN & SEROMA PREVENTION

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Performing secure vascular ligations are a critical aspect of any surgical procedure. The challenge in large vascular pedicles (e.g. obese, large breed dog ovarian pedicle) is that the initial throw can loosen as a result of elastic recoil resulting in an inefficient (loose) knot. This can result in devastating hemorrhage complications and, indeed, hemorrhage is the most common complication following ovariohysterectomy. Most practitioners are obviously well adept to tying knots, however, knot loosening can occur with large vascular pedicles filled with fat. Friction knots (e.g. surgeon's, Millers, strangle) will maintain the tension placed on the first throw and WILL NOT loosen even in the face of uneven tension or elastic recoil from thick vascular pedicles. Friction knots will be demonstrated by video in the lecture.

The choices that veterinarians make everyday with regard to suture materials, needle choices and how to optimize their use in closure of all kinds of tissues tend to be automated and are generally given little consideration. Most veterinarian's busy clinical lives leave little time for consideration of these more mundane-seeming points but these decisions can have profound effects on surgical outcomes including surgical site infections (SSI) and wound dehiscence. These complications can not only lead to a longer treatment course for the patient and increased costs for owners can even precipitate life-threatening or fatal results when procedures involve luminal organs of the gastro-intestinal or urinary tract. Over the last few years much research in this field has emerged and medical device companies have introduced many new products in the wound closure space.

Needle selection in small animal surgery can be mind-boggling as a huge variety of choices that are on offer to the human medical world are also available to veterinarians. Needle point type is one important choice to make. Most commonly either taper point or cutting needles are used. Taper point are preferred for luminal organs, vascular surgery and subcutaneous closure. Taper point needles will not cut through delicate tissues and tend to reduce the size of the hole created in the tissue. A variety of cutting needles exist that allow passage of the needle through fibrous or dense tissue such as fascia and the dermis/epidermis. Reverse cutting needles are often the preferred cutting needle type in order to prevent widening of the suture holes as the needle is drawn through the tissues. Regardless of needle type it is essential to remember that the way a needle is passed through tissue has a major effect on the tissue track that a needle creates. Surgeons should always use a rotating wrist action to allow the curvature of the needle to pass through the tissue rather than pushing the needle through which tends to result in larger needle holes.

Suture should ideally only persist in tissue for as long as it is required and no longer. Suture materials are generally categorized according to whether they are monofilament, multifilament, absorbable or non-absorbable. Monofilament sutures are generally preferred as they have less tissue drag and are less likely to harbor bacteria although there are also coated multifilaments that minimize the risk of bacterial colonization and improve handling. Multifilaments have the one distinct advantage of having less memory and therefore better handling properties. Absorbability occurs due a variety of mechanisms including proteolytic enzyme breakdown (chromic gut) and hydrolysis (polydioxanone, poliglecaprone 25, polyglactin 910). The rate of absorption is important to understand as well as the fact that absorption can be markedly affected in the face of different tissues as well as different environments such as infection. In healthy tissue loss of 50% of normal tensile strength for commonly used suture materials including Poliglecaprone 25 (e.g. Monocryl), Polyglactin (e.g Vicryl), and polydioxanone (PDS) occurs at 1-2 weeks, 2-3 weeks and 5-6 weeks respectively with complete absorption occurring at 119 days, 56-70 days and around 180 days respectively. However, an example of the effect of tissue environment on suture absorption is urinary tract infection. Data from experimental studies where commonly used suture materials were bathed in urine containing bacteria commonly implicated in urinary tract infections showed profound effects in some cases.<sup>1</sup>In this study soaking of tested sutures in urine accelerated degraded of all suture types tested and Proteus infected urine caused poliglecaprone 25 to retain only 11-14% of tensile strength by day 14.<sup>1</sup>As a result, the authors suggested that poliglecaprone 25 may not be an appropriate suture type for use in animals that might be harboring such an infection. Data such as this should help inform surgeons suture choices and is the reason the author prefers longer lasting sutures such as polydioxanone in the urinary tract and why if possible an effort should be made to minimize exposure of suture material to urine when these cases are being operated. The gastro-intestinal tract environment can also have potential effects on the degradation of certain suture materials. One study evaluated the effect of pH on polydioxanone degradation and found that in acidic environments such as the stomach tensile strength degraded rapidly after 2 weeks immersion in a solution with a pH of 1.0 at which time there was no measureable tensile strength remaining.<sup>2</sup>

Other important considerations when choosing sutures are suture sizes and knot security. The weakest point of any continuous closure is the knot and so in these situations knot security is paramount. It is well known that extra throws should be placed on the ends of continuous closures and it is generally recommended that one extra throw should be placed at the beginning and 2-3 extra throws should be placed at the end of a continuous line.<sup>3</sup> We also know that suture size is an important variable in knot size and secondarily tissue reactivity to the knot. For every suture size increase knot volume increases by a factor of 4-6 with a consequent increase in tissue reactivity of 2-3 fold.<sup>4</sup> Use of the smallest sized suture that is strong enough for any given indication is therefore encouraged.

As it is well recognized that there is an inverse relationship between the volume of suture material in a wound and the number of bacteria needed for a SSI to develop, considerable interest in the role of antibacterial sutures has developed. Most

antibacterial sutures use a coating of Triclosan as their active agent which has been shown to have in vitro activity against *Staphylococcus aureus* and *epidermidis*, methicillin-resistant *staphylococcus aureus*, *enterococcus sp.*, *pseudomonas sp.*, and *Escherichia Coli*.<sup>5</sup> While several large studies have struggled to demonstrate wholesale improvements in SSI or other wound complication rates both in veterinary<sup>6,7</sup> and human studies<sup>8</sup>, other studies have shown interesting findings in certain procedure types, notably in gastrointestinal applications, where inflammatory and wound healing parameters were improved with the use of triclosan-coated antibacterial suture materials.<sup>9</sup> Further larger studies in veterinary species will be required to fully elucidate the quantitative benefit if any in our small animal species.

One new and exciting development in the suture space recently has been the availability of barbed sutures designed to facilitate knotless continuous suturing. While primarily developed to facilitate intracorporeal suturing where knot tying is a significant challenge, they are also being used extensively in open surgical techniques. Barbs cut into the body of the suture create friction as they pass through tissues thereby maintaining tension and negating the need for knots to be tied at the end of the continuous line. At the start of a suture line barbed sutures either incorporate a loop (VLOC, Medtronic Inc, Stratafix, Ethicon Inc) through which the suture is passed after the first bite has been thrown or a fixation tab (Stratafix, Ethicon Inc) which will anchor the suture end as it will not easily pass through the tissue after the first bite has been taken. These sutures have been used extensively in minimally invasive procedures such as intracorporeal gastropexy<sup>10</sup> but also have been described for open gastrointestinal suturing as even tendon repair.

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## Canine Cruciate Rupture: Conservative Treatment vs Surgical Treatment?

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### *Introduction*

Cranial cruciate ligament rupture is the most frequent cause of lameness in dogs with \$1.32 billion spent by owners in the U.S. in 2003<sup>1</sup>. Instability of the canine stifle leads to progressive osteoarthritis and possible damage to the medial meniscus. This largely degenerative process affects both stifles within a year of the initial injury in up to 40% of dogs<sup>2</sup>. The decision to treat conservatively with medical management or surgically remains an area of controversy. Conservative management is advocated by some with success rates ranging from 84-90% in dogs <15 kg but poor results if dogs are >15kg<sup>3</sup>. In most cases, surgical intervention is recommended. The intent of surgical intervention is to re-establish joint stability, slow the progression of secondary degenerative joint disease, address concurrent and prevent late meniscal injuries and to return the dog to a functional state.

### *Conservative management*

Conservative management includes cage rest with short controlled leash walks, NSAIDs, weight management, analgesics such as gabapentin, amantadine, chondromodulating agents and dietary supplements.<sup>4</sup> Other multimodal components of conservative management that have been suggested include rehabilitation, acupuncture and regenerative medicine.<sup>4,5</sup> It has often been suggested that small breed dogs with a body weight less than 10 kg can be managed conservatively. This information is largely based on a retrospective study published in 1984 where it was reported that 85% of small dogs were considered to be normal or improved with nonsurgical management. It was also reported that recovery was prolonged with a mean of 4 months. This study was retrospective and outcome measures were based on veterinarian evaluation with no objective outcome measures. Additionally, 43% still had a positive cranial drawer, 67% had increased medial buttress, 19% of dogs with apparent resolution of lameness had clinically evident muscle atrophy and 100% had evidence of radiographic progression of degenerative joint disease (DJD). The remaining 15% of dogs that did not respond to conservative treatment underwent surgical stabilization and medial meniscectomy.<sup>6</sup> Conservative management of small breed dogs is still widely recommended. A recent survey of UK veterinarians indicated that immediate surgical management was performed in only 16% of small breed dogs present with ccl rupture.<sup>7</sup> This study also reported that the decision for conservative versus surgical management depended on a variety of factors such as age, body weight, severity and duration of lameness, and degree of instability. Surgical management consisted of extracapsular stabilization (ECS) (63%), corrective osteotomies (33%) and intra-articular methods (7%). Witte et al reported that none of the small breed dogs in their study responded to conservative management of mean duration of 8 weeks.<sup>8</sup>

One method of conservative management that is commonly proposed is the use of a brace. This is a controversial topic among surgeons and rehabilitation physicians in both the human and veterinary medical fields. A recent study by Hart et al. compared dogs

treated with a custom made stifle joint brace and dogs undergoing the TPLO procedure. They found that the proportion of owners who reported that their dogs had mild or no lameness and rated the intervention as excellent, very good, or good was significantly greater for the TPLO group than for the orthosis group. However,  $\geq 85\%$  of respondents in both groups reported that they would choose the selected treatment again. Of 151 respondents from the orthosis group, 70 (46%) reported skin lesions associated with the device, 16 (11%) reported that the dog subsequently underwent surgery, and 10 (7%) reported that the dog never tolerated the device. Owner satisfaction was found to be high in both groups. Results indicated high owner satisfaction rates for both interventions. When considering nonsurgical management with an orthosis, owners should be advised about potential complications such as persistent lameness, skin lesions, patient intolerance of the device, and the need for subsequent surgery.<sup>9</sup>

One factor that must be considered when debating conservative versus surgical management is the medial meniscus. Meniscal tears at the time of surgery are reported to be between 30 and 80% in CCL deficient stifle joints. The more widespread use of arthroscopy and probing of the meniscus have led to a higher sensitivity in detecting meniscal tears in our patients. Regardless of the choice between conservative or surgical management, our patients will remain lame if meniscal pathology is not properly diagnosed and addressed initially or our treatment choices do not adequately stabilize the joint resulting in late meniscal tears.

#### *Is There a Superior Surgical Method?*

The three main categories of surgical intervention for cranial cruciate ligament rupture in dogs are extracapsular techniques, intra-articular reconstruction and osteotomy procedures. Surgical techniques can also be classified as passive or dynamic stabilizing techniques. Those techniques imparting passive stability utilize autogenous, allogenic or synthetic materials placed within or about the joint. Those providing dynamic stability do so by modifying joint biomechanics.

#### *Passive Stability Techniques*

The lateral fabelloibial suture (LFTS) extracapsular repair has been reported to result in 82 to 85% good to excellent function. The complication rate reported is 17.4% with second surgeries required reported to be 7.2 to 13.8%. Case selection is important with higher complication rates reported in dogs with increasing body weight and young age<sup>10</sup>. The Arthrex Tightrope procedure has a 95.2% success rate with 43.4% of these cases being described as excellent and 51.8% of these cases good. These results are reported in an Arthrex brochure and utilized data from 479 cases with a weight range of 2 to 93 kg. Overall, the veterinary literature reports that these methods good to excellent limb function in most cases with 90-95% owner satisfaction. These techniques are relatively simple to perform. Most act as an 'internal splint' and rely on joint fibrosis to provide stabilization of the joint. Sub optimal outcomes are usually the result of failure to obtain adequate stability at the time of surgery, failure to identify and address meniscal injury, premature suture breakage, failure to maintain long term stability, failure to stop the progression of osteoarthritis and failure to prevent future meniscal injuries.

#### *Dynamic Stability Techniques*

The majority of veterinary surgeons performing orthopaedic surgery routinely perform one of the many dynamic stabilizing techniques. These techniques alter stifle biomechanics using some form of osteotomy. The most common of these surgical methods are the tibial plateau levelling osteotomy (TPLO) and the Tibial Tuberosity Advancement (TTA) technique. Slocum originally reported subjective faster return to function and outcome of 73% excellent, 21% good and 3% fair<sup>11</sup>. There have been many scientific studies reporting the outcome and complications following TPLO surgery. Most of the published studies have reported success rates and owner satisfaction in excess of 90%. Similar results have been reported following TTA. Good to excellent function in 90 % of cases, complication rates of 20 to 59% and 11 to 14% requiring additional surgery. Owner satisfaction approaches 95%<sup>12</sup>.

### *Comparison of Surgical Methods*

The veterinary literature has many published accounts of comparisons of current cruciate repair techniques. A summary of the methods, the outcomes and the quality of these reports is beyond the scope of this presentation. There have been several systematic reviews published most concluding that there is not enough quality evidence to support one single surgical method that can consistently return dogs to normal function after CCL injury<sup>13</sup>. Most recently a study was published that looked 444 studies on cruciate disease and dogs determining that 34 studies met the evidence criteria for inclusion. The most common procedures evaluated included the tibial plateau leveling osteotomy, lateral extracapsular suture, and tibial tuberosity advancement. The evidence most strongly supports the ability of the TPLO to result in dogs returning to normal function. There was also strong support that functional recovery in the intermediate postoperative time period was superior following TPLO compared to lateral suture. Unfortunately, there was insufficient data to adequately evaluate other surgical procedures<sup>14</sup>. A recent study compared long term function of the TTA to the long term function of dogs undergoing TPLO or extracapsular stabilization (ECS) for treatment of a ruptured cranial cruciate ligament. They concluded that at the walk, TTA achieves normal function by 12 months. However, at the trot TTA is indistinguishable from ECS. TPLO resulted in operated limb function that was similar to the control population by 6–12 months postoperatively at the walk and the trot.<sup>15</sup>

### *Additional Food for Thought*

Some interesting information has recently come to light as researchers further explore canine cruciate ligament rupture and treatment. One such study has looked at real time kinematics of the cruciate deficient stifle both before and after surgery. This study has changed the way we think of the biomechanics of the stifle joint when the cruciate ruptures and may make us scrutinize our current methods of repair. This study investigated TPLO, TTA and extracapsular stabilization and reported that in vivo stifle kinematics questioned our ability to achieve stability of the stifle following these procedures with  $\geq 50\%$  of stifles remaining unstable at surgical follow up. TPLO stifles with a post-operative tibial plateau angle of  $\leq 5^\circ$  were stable. TTA stifles remained unstable regardless of the patellar tendon angle<sup>16, 17</sup>. This is contrary to reported favorable outcomes following TTA and TPLO and suggests that there is a component to biomechanics of the cranial cruciate ligament deficient stifle that remains to be fully understood.

### *How Do We Choose?*



For the most part surgeon discretion and case selection drive selection of our surgical method and we base this mostly on anecdotal evidence and personal experience. The learning curve, expertise and experience, equipment, dog size and economics are all important considerations for many of us. Interestingly, a survey of ACVS Diplomate Surgeons revealed that they performed TPLO (63%), followed by extracapsular suture (16%), TTA (10%), non-surgical treatment (5%), and finally TR (2%) when they treated their own pet or the pet of a close friend/family. TPLO was the most commonly performed surgical procedure for cranial cruciate ligament rupture in dogs amongst ACVS Diplomates<sup>18</sup>.

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## Rehabilitation Modalities in the Management of Osteoarthritis

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### ***Introduction***

Rehabilitation is a relatively new pursuit in veterinary medicine with the first interest gaining momentum in the late 1980's through to the present. Many of us have experienced first hand the benefits of physiotherapy following injury and/or surgery and thus it would seem logical that our veterinary patients would experience the same benefits. That being said, there is a paucity of quality publications in the literature that provide strong evidence that rehabilitation is beneficial. With increasing client interest in veterinary rehabilitation, the availability of training courses for veterinarians and veterinary technicians and the recent formation of the American College of Veterinary Sports Medicine (ACVMSR), hopefully we see strong evidence supporting this practice.

Currently established physiotherapy techniques that are used to manage canine patients that have OA have the following perceived benefits:

- reduce pain
- resolving inflammation
- improve strength and balance
- increase range of motion
- prevent muscle spasms
- help to restore more normal joint function
- preventing or minimizing muscle atrophy
- preventing periarticular contraction
- increasing blood and lymph flow through the affected area
- providing positive psychologic effects for the patient and owner

The ultimate goal for any rehabilitation protocol would be to restore function to as close to normal as possible. In many cases, physiotherapy also helps to reduce the dose of analgesics necessary to maintain patient comfort.

### ***Benefits of Rehabilitation***

It is well established that joint dysfunction that arises from osteoarthritis can range from minor discomfort to complete debilitation. In veterinary practice we see patients all along this spectrum. In many cases OA is advanced and progressing before owners report clinical signs and many pathological changes have already occurred in both the joint and the periarticular structures such as tendons, ligaments and the joint capsule. An obvious example of this is the 'medial buttress' seen on the medial aspect of the canine stifle with cranial cruciate ligament rupture and subsequent instability and advancement of osteoarthritis. With this fibrosis and scarring we see a reduction in range of motion both from physical restriction but also from the discomfort associated with movement of the joint. This vicious spiral leads to disuse, muscle atrophy, further loss of joint support and further deterioration in the range of motion and quality of movement.

Therefore the goal of any therapy should be to reduce discomfort, improve range of motion and thus quality of movement minimizing the negative effects of loss of use. It is important to realize that these periarticular structures are well innervated and must be considered a source of discomfort that are major contributors to the pain associated with OA. Anyone that has had a joint immobilized in a cast or joint surgery can attest to the discomfort associated with a joint with a reduced range of motion. This is especially apparent when the well-meaning physiotherapist uses manual stretching to help restore normal range of motion!

### ***Rehabilitation Techniques and Modalities***

#### ***Cryotherapy***

When tissues are inflamed, pain management and rehabilitation starts with cryotherapy. Cryotherapy is an inexpensive and readily available modality that is effective for reducing swelling and inflammation for tissues that are chronically inflamed, recently injured or post operatively. It can consist of ice packs, ice wraps, and cold compression wraps and can be as simple as a bag of frozen peas a Ziplock™ bag with two parts water and one part alcohol or as complicated as a Game Ready™ cold compressive therapy unit. Using compression such as an elastic wrap can further decrease the temperature of the deeper tissues.

Cryotherapy is most effective when inflammation is present and some of the perceived benefits of cryotherapy include:

- Promotion of vasoconstriction and skeletal muscle relaxation and decreases nerve conduction
- vasoconstriction limits blood flow into the area, thereby reducing edema
- muscle relaxation can decrease edema formation by improving venous return and by preventing endothelial damage caused by local acidosis
- decreased nerve conduction produces mild analgesia

### **Moist Heat**

Moist heat can be applied using warmed oat bags in a moistened towel, using commercial, microwaveable moist heat packs or using moist heat bags from a hydrocollator commonly found in physiotherapy facilities. It is best used after acute inflammation has resolved. It is very useful when applied before stretching, massage therapy, passive range-of-motion (PROM) exercises, or active exercise. The benefits of moist heat include:

- A reduction in muscle spasms and increase in blood flow to the treatment region
- Penetration to a tissue depth of 1 to 2 cm
- Causes vasodilation, mild sedation, relief of muscular pain, resorption of extravasated fluids, and increased local circulation
- Enhances local metabolism and improves the delivery of nutrients
- Increases the compliance of joint capsules, tendons, and scar tissue and reduces joint stiffness, thereby countering much of the stimulus for pain

### **Passive Range of Motion Exercises (PROM)**

The purpose of passive range of motion activities is to advance the joint through a comfortable range of motion. This is not considered stretching and is not intended to exceed the limit of comfortable joint movement or the 'end point' as it is called. Common questions that arise related to PROM activities include use of sedation or muzzles during this activity. In the majority of cases neither is required. Animals with temperaments such that a muzzle is required may not be good candidates for this type of manipulation. PROM is intended to:

- maintain normal range of motion in joints
- prevent contracture
- improve blood and lymphatic circulation
- stimulate sensory awareness
- reduce the catabolic effects of immobility on articular cartilage

### **Stretching**

When additional pressure is applied at the end points of the ROM then it becomes stretching. The goal of stretching is to increase tissue extensibility. These activities are ideally performed several times daily after the application of moist heat or therapeutic ultrasound therapy. Trained individuals can perform both passive ROM and stretching. Caution should be exercised when instructing owners to perform stretching exercises, as there may be some discomfort associated with manipulating a joint past its end point if limitations in joint range of motion are present.

### **Massage**

Massage techniques are adjunct therapy that may have direct and indirect effects on pain sensation. These techniques do not have any direct on muscle mass, strength or rate of muscle atrophy but when used in conjunction with pain management modalities and exercise will increase mobility and improve function.

Direct effects on pain include:

- Stimulation of sensory afferents
- Counterirritant theory
- Psychological effects

Indirect effects on pain include:

- Increasing extensibility of tight muscles, scar tissue, joint capsule, tendons, ligaments
- Assisting venous and lymphatic flow

**Electrical Stimulation (EStim)**

Electrical stimulation (EStim) is commonly used in human physiotherapy to increase muscle strength, improve joint range of motion, re-educate muscles, and decrease edema and pain. There are both pain management and muscle stimulation modes for this modality. Transcutaneous electrical nerve stimulation (TENS) is commonly used to treat a specific area of pain or to stimulate a particular muscle in order to combat muscle atrophy. These TENS units are readily available, battery powered and inexpensive.

**Hydrotherapy**

Hydrotherapy in the form of the underwater treadmill is one of the most effective methods of providing controlled and targeted therapy for our patients. It's benefits in pain relief in postoperative, neurological, and chronic OA patients are a result of the effects of buoyancy, hydrostatic pressure and temperature. It provides safe, controlled, supportive and non explosive activity that is ideal for weight loss, hip dysplasia, FHO patients. The one unfortunate drawback of underwater treadmills is the expense, space requirement and maintenance of the equipment.

**Therapeutic Exercises**

The true gains made in any rehabilitation protocol are made through exercise. Most of the modalities mentioned previously are intended to provide better quality and more comfortable movement allowing our patients to exercise to regain strength, range of motion and muscle mass whose loss is associated with injury, disuse or chronic conditions. Unlike the underwater treadmill, these activities can be done with little financial investment with a bit of ingenuity and creativity. Activities as simple as walking and trotting over different inclines and terrain, walking over cavaletti rails, walking with resistance provided by water, elastic bands, sand, snow and sit to stand exercises are all exercises that can be incorporated in to a dry land rehab program. Many of these activities are essential to a well-directed home exercise program. Stairs, exercise balls and peanuts, orange safety cones and broom sticks can all be modified and used inexpensively to set up a dry rehabilitation area.

**Therapeutic Ultrasound (TUS)**

Therapeutic ultrasound has been used widely in human rehabilitation as being an effective treatment modality for rehabilitating musculoskeletal conditions such as restricted range of motion (ROM) resulting from joint contracture, pain and muscle spasm, and wound healing.<sup>2</sup> Many protocols for the administration of US are based on tradition or extrapolated from basic science research and remain to be tested in controlled clinical trials.<sup>3</sup>

**Proposed Mechanism of Action**

Energy within a sound beam decreases as it travels through tissue, because of scatter and absorption. Scattering is the deflection of sound out of the beam when it strikes a reflecting surface. The transfer of energy from the sound beam to the tissues is through absorption. Absorption is higher in tissues with high protein content and relatively low in fatty tissue. The creation of a thermal effect is a major indication for the use therapeutic US. Increasing tissue temperature may increase collagen extensibility, blood flow, pain threshold, and enzyme activity, as well as mild inflammatory reactions, and changes in nerve conduction velocity. Treatment with US for 10 to 20 minutes at high intensities, skeletal muscle temperature and blood flow increase.

**Proposed Indications for Therapeutic Ultrasound**

Thermal effects of TUS can be effective in addressing scar tissue, joint restriction associated with periarticular structures, muscle spasm, and nonacute soft tissue injuries. Nonthermal effects of TUS can facilitate healing of acute soft tissue injuries and peripheral nerve injuries.

**Treatment Variables**

The following list contains treatment variables that should be considered when designing the TUS protocol. The details of treatment variables should be documented in the patient record.

1. Frequency
2. Intensity
3. Duty cycle
4. Treatment area
5. Treatment duration

6. Speed of the sound head
7. Treatment schedule

The frequency of the soundwave is the variable that determines the depth of penetration. Most commonly, a frequency of 1 MHz is utilized because it provides adequate depth of penetration and adequate heating in most situations. A 1 MHz frequency heats at depths between 2 and 5 cm. Increasing frequency decreases depth of penetration. The other commonly used frequency of 3.3 MHz (commonly referred to as 3 MHz) heats at depths between 0.5 and 3 cm. Increasing intensity results in faster heating and higher temperatures. Generally intensities required to increase tissue temperature 2° C or more vary from 1 to 2 W/cm<sup>2</sup> continuous wave US for 5 to 10 minutes. Duty cycle refers to the fraction of time that the US is emitted from the head compared to the length of time the head is in contact with the skin. This changes when pulsed ultrasound protocols are used. The treatment area should be two to four times the size of the effective radiating area of the transducer head. If a larger area requires treatment then it should be divided. If the total treatment area is expanded beyond the recommended area, the dosage and the heating effect will be decreased. Duration of 5 to 10 minutes has been shown to produce adequate tissue heating in an area equivalent to two to three times the diameter of the sound head. The speed at which the sound head is moved over the skin is approximately 4 cm per second to achieve uniform distribution of energy to the target tissues. Treatment schedules may include daily treatment initially, followed by less frequent sessions as the condition improves. It has been recommended that daily treatments should not exceed 10 consecutive days however the scientific basis of these recommendations is not clear.

Advantages of TUS	Disadvantages of TUS
Local heating of tissue	Dosage is difficult to monitor
Short treatment time	Hair clipping required
	Transducer contact may aggravate irritated tissues

### **Low Level Laser Therapy (LLLT)**

Over the past 6 or 7 years this modality has been gaining popularity for treatment of a variety of conditions in veterinary medicine. In 2015, it was estimated that close to 20% of veterinary hospitals in North America were using a therapeutic laser in their practice. This is likely due to an increased awareness and deployment of veterinary rehabilitation services, availability of educational resources on therapy lasers, and the development of products and protocols that have resulted in more consistent clinical outcomes. Laser therapy is considered a noninvasive, drug-free treatment option, providing clients with a nonpharmacologic treatment option. Quality research in the area of photobiomodulation in veterinary medicine is scarce. Much of the information advocating use of lasers is extrapolated from *in vitro* studies or from studies performed in other species. Published, well-designed studies are for the most part not available in veterinary species.

### **Proposed Mechanism of Action**

LASER is an acronym for “light amplification by stimulated emission of radiation”. A laser produces electromagnetic radiation that is monochromatic, coherent, and collimated allowing laser light to penetrate tissues. Power and wavelength are two parameters important when using laser therapy. Power, measured in watts (joules/second), is the rate of energy production. Laser dosage is determined by multiplying power by time. Energy provided can then be measured in power density (W/cm<sup>2</sup>) or energy density (J/cm<sup>2</sup>). Laser light wavelength is the parameter that determines depth of penetration. The wavelength of laser light determines the depth of penetration. Longer wavelengths are more resistant to scatter and thus tend to penetrate tissues better. Lasers are also categorized into different classes based on the potential for tissue damage. Class 1 lasers are used in audio-visual players are very mild. Laser pointers are Class 2 lasers (<1 mW), and emit light in the visible spectrum and pose little threat of eye damage. Therapy lasers begin at Class 3A lasers (1–5 mW) emitting visible light. Class 3B lasers (5–500 mW) are also used in rehabilitation and produce nonvisible light but can still result in eye injury. Class 4 lasers (>500 mW) are both therapy and surgical lasers. Class 4 lasers have potential for eye damage as well as causing tissue burns. Most lasers used in rehabilitation are low power (or cold) lasers and typically have a power of 500 mW or less.

It is proposed that LLLT modulates cellular functions by a process known as photobiostimulation. Therapy lasers induce a nonthermal interaction of monochromatic radiation with the tissues requiring treatment. The physiologic effect of this type of energy application on tissue is still not completely understood. LLLT has been reported to modulate various biologic processes, such as mitochondrial respiration and adenosine

triphosphate (ATP) synthesis, to accelerate wound and joint healing, and to promote muscle regeneration. Acute and chronic pain control has been reported using this type of low-energy photon therapy. Treatment of chronic and acute edema, neurologic conditions, and postoperative care are some other popular conditions treated with laser therapy.

#### *Indications for use of LLLT*

The efficacy of LLLT remains controversial in veterinary medicine. Some veterinary studies have shown some promise for use of LLLT for preservation of cartilage properties, improvement in peripheral nerve injuries, and as a possible adjunct to managing pain in patients with osteoarthritis. Laser therapy may have some benefit in early wound healing.

#### **Extracorporeal shock wave therapy (ESWT)**

Extracorporeal shock wave therapy (ESWT) was initially introduced in human medicine in the early 1980s as a noninvasive method for reducing the size of nephroliths. Increasingly ESWT is being suggested as treatment for certain musculoskeletal conditions in humans and veterinary patients. Reported benefits include pain relief, antibacterial properties and improved wound, bone, tendon, and ligament healing.

#### *Proposed Mechanism of Action*

The exact mechanism of action of ESWT is not well understood. One theory proposes that mechanical stimulation from soundwaves results in the expression of growth factors and cytokines involved in the healing process. ESWT applied to chronically injured tissues may restart the inflammatory process and facilitate healing by causing the release of inflammatory mediators. The proposed mechanism believed to be responsible for pain relief is related to increased serotonin activity in the dorsal horn, and descending inhibition of pain signals

#### *Indications for use of ESWT*

ESWT has been reported to be beneficial as an ancillary treatment in cases of osteoarthritis. One study reported improved weight bearing and passive range of motion are similar to results expected with NSAID treatment. On occasions when NSAIDs cannot be prescribed, extracorporeal shockwaves therapy may provide an alternative for treatment of osteoarthritic conditions. Anecdotal reports indicate that conditions affecting the elbow, hip, or back treatment of conditions may be more responsive to ESTW than other joints. Other reported indications for ESWT include delayed or nonunion fractures, wound management, tendinopathies and ligament injuries.

#### **Suggested Readings**

- 1) Marcellin-Little DJ, Levine D and Millis D. *Veterinary Clinics of North America: Small Animal Practice: Veterinary Rehabilitation and Physical Therapy*, Vet Clin Small Anim 45 (2015)
- 2) Millis D and Levine D. *Canine Rehabilitation and Physical Therapy*. Second Edition, Elsevier, 2014
- 3) Zink MK and VanDyke JB. *Canine Sports Medicine and Rehabilitation*. First edition, Wiley-Blackwell, 2013
- 4) Kieves NR, MacKay CS, Adducci S et al. *High energy focused shock wave therapy accelerates bone healing. A blinded, prospective, randomized canine clinical trial*. Vet Comp Orthop Traumatol 2015; 28: 425–432
- 5) Leeman JJ, Shaw KK, Mison MB et al. *Extracorporeal shockwave therapy and therapeutic exercise for supraspinatus and biceps tendinopathies in 29 dogs*. Veterinary Record, 2016
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**SPAY/NEUTER CONTROVERSIES**

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Although there are strong arguments for the current standard of sterilization of companion animals, which is typically at 6 months and in some instances earlier, there is growing evidence that in large breed dogs, later sterilization *may* be protective against some conditions. However, much of this data is only evaluating specific breeds, and some is contradictory. It is known that sterilized dogs live longer than intact dogs and in some cases this may account for the increased incidence of certain conditions such as neoplasia.

This session will evaluate the current literature surrounding timing of spay/neuter in dogs and cats. In addition, a variety of techniques for sterilization will be discussed along with risks and benefits of each technique.

**Male and female cat**

There is good evidence to support spaying cats prior to their first estrus, and similar support for neutering cats at a similar age. Waiting until 6 months can allow a cat to experience their first estrus (first heat cycle). In fact, cats can be spayed and neutered much earlier than the routine age of 6 months. There have been numerous studies evaluating early spay/neuter programs in cats, particularly focusing on possible increased risk of anesthesia, alteration in growth, and the behavioural effect of early spay/neuter.

Some concerns exist of an apparent increased risk of capital physeal fractures in adult castrated male cats and its possible relationship to castration. Delayed physeal closure in cats (and dogs) that are gonadectomized early in life has been suggested as a factor for the increased risk in these cats. In the largest series of cases reported, 14 of 16 cats for which the age at castration was known, were castrated before 6 months of age. Body weight at the time of initial exam was also significantly greater in the affected cats suggesting that an abnormally high body weight was a risk factor for a capital physeal fracture, as was neuter status, age, and delayed physeal closure. Client education is necessary, particularly with male cats castrated before a year of age, to prevent these cats from becoming overweight. Another alternative is to wait until after a year of age to castrate male cats but many male cats will develop undesirable behaviours if castrated beyond puberty making this approach less ideal.

**Male dog**

Male dogs have an increased lifespan if they are neutered.(add ref?) Neutering dramatically reduces the risk of certain prostatic diseases, such as bacterial prostatitis, benign prostatic hyperplasia and paraprostatic cysts. Neutering will prevent testicular cancer, although most testicular cancers in the dog are benign. Eliminating testosterone will also resolve most perianal gland adenomas, and largely eliminates the risk of development of perineal hernia, which is primarily a disease of intact male dogs. Perineal hernia is a very challenging disease to treat surgically and is associated with a high complication and recurrence rate. Regarding neoplasia, most studies do not show a risk with castration of male dogs on the development of



hemangiosarcoma or mast cell tumour. However, depending on the study and breed, an association has been reported.

Controversy remains regarding timing of gonadectomy and increases in the risk of hip, stifle and elbow disorders. Hip dysplasia is a multifactorial disease that is influenced by environment, genetics, diet, and many other factors. A study of 759 golden retriever dogs reported males castrated before 1 year of age had a higher risk (10.2%) of hip dysplasia than intact dogs (5.1%) or those castrated after 1 year of age (3.1%). Another study of 1,500 Labrador retrievers reported no difference in the risk of hip dysplasia in males at any neuter period compared to intact dogs. A study in 1500 Labrador retrievers found that males castrated before 6 months of age had a higher risk (7.6%) of developing cranial cruciate ligament rupture compared to intact males (2.3%). This study did examine body-condition score (BCS). A mean BCS of both castrated and intact males with cranial cruciate ligament rupture was 6 compared to a BCS of 5 in the castrated and intact males without rupture. Elbow dysplasia in male Labrador retrievers is seen more frequently in males castrated at 6 months (4.2%) and between 2 and 8 years (2.2%) compared to intact males (0.6%).

The recommending for neutering small breed dogs remains 6 months since they are at reduced risk of many of the oncological and orthopedic diseases discussed. Large- and giant-breed dogs should be neutered at

#### Female dog

Like their male counterparts, female dogs have an increased overall lifespan if spayed, however, an increase in obesity and sedentary lifestyle are seen with spaying. OVH will eliminate the development of pyometra, other than cases of stump pyometra which is generally a result of ovarian remnant syndrome. OVH should prevent ovarian cancer, and timing of OVH will dramatically reduce the incidence of mammary tumours.

In one study of 759 golden retriever dogs, ovariectomy or the timing of the procedure did not influence the risk of hip dysplasia in females. Another study of 1,500 Labrador retrievers reported that in females, the risk of developing hip dysplasia was higher for those spayed at 6 months (5.4%), 6–11 months (5.1%), and 12–23 months (4.3%) compared to intact females (1.7%). The same study reported no differences among female dogs with regard to the risk of cranial cruciate ligament rupture and timing of spaying compared to intact females. No differences in the occurrence of elbow dysplasia were seen in females at any spaying age interval compared to intact dogs.

The recommendation to spay small breed female dogs remains 6 months. For large- and giant breed dogs, a discussion should be made with the owner to discuss the risks and benefits of spaying along with the orthopedic consequences of spaying. A blanket statement of not spaying any large- or giant-breed female dog prior to 1 year may not be ideal for all situations. Furthermore, consideration should be given to the fact that spaying a large- or giant-breed dog when they are >1 yr will increase technical challenges.

#### SURGICAL PROCEDURES

In North America, ovariectomy (OVH) is the most commonly performed surgical procedure for sterilization of female dogs and cats. Following a 3-5 cm incision originating at the umbilicus, both ovarian pedicles and uterine body are ligated allowing for removal of the entire

reproductive tract. Complications associated with OVH include hemorrhage from the ovarian pedicle, ovarian remnant syndrome and ureteral ligation. These complications may be a result of reduced visualization of the ovarian pedicle (particularly the more cranially based right ovarian pedicle). In several European countries, ovariectomy (OVE) has become the standard technique for sterilization of female dogs and cats. If performing OVE, the incision can be centered on the umbilicus allowing the surgeon improved visualization of both ovarian pedicles compared with the longer, often more caudal incision for OVH. Ovariectomy does not result in increased risk of urethral sphincter mechanism incontinence, obesity and does not alter the risk for neoplasia or orthopedic disease compared to OVH. Another consideration is whether leaving the uterus can result in a greater risk of pyometra and/or neoplasia. Since the ovary has been removed, progesterone cannot be produced which is the hormone responsible for cystic endometrial hyperplasia that results in pyometra. Uterine neoplasia has an exceedingly rare incidence (0.003%) and has not been reported in ovariectomized dogs if the procedure was performed before two years of age.

Experienced practitioners can perform OVH with a low complication rate. However, OVE may be considered for practitioners early in their learning curve that may want to gain increased exposure of the ovarian pedicles allowing for their safe ligation and potentially reduced risk of hemorrhage from a slipped pedicle. To date, both OVH and OVE are considered safe procedures to sterilize female dogs and cats.

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## TOP 5 MISTAKES TO AVOID IN YOUR POISONED PATIENT

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In the veterinary poisoned patient, the goal of decontamination is to “inhibit or minimize further toxicant absorption and to promote excretion or elimination of the toxicant from the body.”<sup>1,2</sup> When treating the poisoned patient, the clinician should have an understanding of the toxic dose (if available), the pharmacokinetics (including absorption, distribution, metabolism, and excretion), the underlying mechanism of action, and the potential clinical signs that can be observed with the toxicant.<sup>2</sup> This will help determine appropriate decontamination and therapy for the patient. If this information is not readily available, the reader is advised to contact the [ASPCA Animal Poison Control Center](https://www.aspca.org/poison-control) (888-426-4435) for life saving, 24/7 advice as needed. For further review on decontamination and specific treatment, attendees are referred to a veterinary toxicology book for more detailed review.

Appropriate decontamination and therapy is indicated to improve the overall prognosis and outcome of the small animal poisoned patient. The use of decontamination, if and when appropriate, should be implemented to help prevent further toxicant absorption. Gastrointestinal (GI) decontamination (including emesis induction and/or administration of activated charcoal with a cathartic) is considered the best method of limiting absorption and preventing continued exposure to potential toxicosis in veterinary medicine. This is particularly beneficial with potentially harmful or life-threatening ingestions. It is imperative, however, to consider whether decontamination is appropriate, as it may be too late or contraindicated (resulting in potentially further harm). Evaluation of the potential risk associated with induction of emesis needs to be considered. Five key mistakes to avoid in the poisoned patient include:

1. Not obtaining an appropriate toxicology history
2. Not triaging the poisoned patient appropriately
3. Not knowing the indications or contraindications for emesis induction
4. Using the wrong emetic agent to induce emesis with
5. Not knowing more about activated charcoal

### NOT OBTAINING AN APPROPRIATE TOXICOLOGY HISTORY

One of the first mistakes made in the field of veterinary toxicology is not taking the time to obtain an appropriate toxicology history. Some key questions to ask prior to consideration for emesis induction include:

- What was the product ingested? Do you know the active ingredient?
- Can you bring me the original box/container/pill vial?
- How many total tablets could have been ingested? What was the minimum and maximum amount that your pet could have been exposed to?
- Was this an extended- or sustained-release product? Was there an extra “letter” behind the brand name (e.g., Claritin vs. Claritin-D)?
- When did your pet get into this?
- Has your pet shown any clinical signs yet?

- Did you give your pet anything at home (e.g., hydrogen peroxide, salt, milk) when you found out he was poisoned?

### **NOT TRIAGING THE POISONED PATIENT APPROPRIATELY**

The second important consideration is to make sure that pet owners are instructed to do the following:

- Safely remove their pet from the area of poisoning so additional ingestion does not occur
- Do *not* give any home remedies found circulating on the Internet (e.g., milk, peanut butter, oil, grease, salt)
- Do not induce emesis without consulting a veterinarian or the ASPCA animal poison control center first.
- Bring the pill vial, bait station, or container in to the veterinarian so they can assess the bottle for verification of the product name and/or active ingredient.
- Have the pet owner call the original pharmacy to find out how many total pills were prescribed, and attempt to back-count how many were taken/ingested.
- Seek immediate veterinary attention.
- Provide adequate ventilation (e.g., rolling down the windows, turning on the air conditioner) if emesis occurs with zinc phosphide toxicosis as the phosphine gas is also poisonous to humans.

Once the poisoned patient is presented to the clinic, veterinarians should do the following:

- Re-verify the spelling of the product and confirm the active ingredient (AI).
- Evaluate if the product is a sustained-release (SR), extended-release (XR), or long-acting (LA) product. These initials will follow the name of the drug on the vial.
- Evaluate whether the patient should have emesis induced (see “Not knowing the indicators or contraindications for emesis induction”).
- Stabilize the patient based on triage and physical examination findings (e.g., temperature, heart rate, pulse rate, pulse quality).
- Call for medical assistance and toxicology advice if needed.

### **NOT KNOWING THE INDICATIONS OR CONTRAINDICATIONS FOR EMESIS INDUCTION**

The goal of decontamination is to inhibit or minimize further toxicant absorption and to promote excretion or elimination of the toxicant from the body. Decontamination can only be performed within a narrow window of time for most substances; therefore, it is important to obtain a thorough history and time since exposure to identify whether decontamination is safe for the patient or if it will actually be beneficial for the patient. Decontamination categories may include ocular, dermal, inhalation, injection, GI, forced diuresis, and surgical removal to prevent absorption or enhance elimination of the toxicant.

One of the primary ways of decontaminating veterinary patients is via emesis induction. While gastric lavage is often more effective at removing gastric contents, it is less often performed in veterinary medicine as it requires intravenous (IV) catheter placement, sedation, intubation with an appropriately inflated endotracheal tube (ETT), and appropriate gavage technique. Veterinarians should be aware of which circumstances are appropriate for emesis induction versus gastric lavage, and be aware of contraindications for emesis induction.

### **Inappropriate Timing of Decontamination (See Table 1)**

Emesis induction should only be performed with recent ingestion of a toxicant or unknown time of ingestion in an *asymptomatic* patient. The more rapidly emesis is induced post ingestion, the greater yield of recovery of gastric contents. Studies have shown that gastric recovery within 1 hour after toxin ingestion was approximately 17% to 62%. When emesis was induced within an even shorter time span (within 30 minutes), mean recovery of gastric contents was approximately 49% (range 9–75%). If several hours have elapsed since ingestion, the contents have likely moved out of the stomach and emesis will no longer be of benefit.<sup>1,2</sup> While delayed emesis may still sometimes be successful, the amount of gastric recovery significantly decreases as time passes. That said, induction of emesis can be performed in *asymptomatic* patients up to 4 hours post ingestion, particularly with certain toxicants.<sup>1,2</sup>

In certain circumstances, delayed emesis induction can be performed within 4 to 6 hours of ingestion provided the patient remains *asymptomatic* with the following circumstances: when certain toxins that delay gastric emptying are ingested (e.g., salicylates, opioids, anticholinergics, tricyclic antidepressants) or if the toxin is known to physically stay in the stomach for a longer duration of time or form a large bezoar or concretion (e.g., iron tablets, a large amount of chewable multivitamins, bone or blood meal). Additional examples include:

- Large wads of xylitol gum
- Large amounts of chocolate
- Grapes and raisins
- Foreign material (e.g., sawdust/wax, kitty litter, bone meal)

### **Not Knowing the Contraindications for Emesis Induction**

Certain animals with underlying medical concerns should not have emesis induced (particularly at home by the pet owner) due to a higher risk of aspiration pneumonia or secondary complications. Examples include a prior history of laryngeal paralysis, megaesophagus, aspiration pneumonia, and upper airway disease. Likewise, certain species and breeds may limit our ability to perform emesis induction. Most dogs, cats, ferrets, and potbelly pigs can be safely induced to vomit.<sup>3</sup> Certain breeds (e.g., pug, English bulldog, Shih-Tzu) with brachycephalic syndrome (e.g., elongated soft palate, stenotic nares, everted sacculles, and a hypoplastic trachea) may be better candidates for sedation and gastric lavage rather than emesis induction due to the risks of aspiration pneumonia.<sup>1</sup> Rabbits, ruminants (e.g., sheep, cattle, llamas, and goats), horses, birds, and rodents (e.g., chinchillas, rats, gerbils) cannot safely have emesis induced or may not anatomically be able to vomit.<sup>3</sup>

Likewise, there are certain toxic ingestions where emesis should never be induced. Emesis should not be performed when agents such as caustic or corrosive substances (e.g., undiluted drain cleaners, toilet bowl cleaners, hydrochloric acid, concentrated sodium hypochlorite, lye products) are ingested. These agents can result in further burns and corrosive injury to the stomach, esophagus, and mouth when vomiting occurs after ingestion. In addition, if hydrocarbons and petroleum distillates (e.g., gasoline, mineral spirits, fuel, kerosene, furniture polish oils) are ingested, emesis should never be induced. These low viscosity liquids are very easy to aspirate when the patient vomits; therefore, emesis is contraindicated due to the high risk of aspiration.

### Induction of Emesis in the Symptomatic Patient

Patients that are already symptomatic for the toxicosis should never have emesis induced. Certain toxicoses may result in severe sedation, a decreased gag reflex, or reduce the seizure threshold, increasing the risk for aspiration pneumonia during emesis induction. Patients with a lowered seizure threshold have the potential to develop seizures during emesis induction. As the patient is already symptomatic, the toxin has likely been already absorbed, and emesis induction is typically unrewarding.

### USING THE WRONG EMETIC AGENT TO INDUCE EMESIS WITH

Emetic agents work by causing local gastric irritation, stimulating the central nervous system (CNS) chemoreceptor trigger zone (CRTZ), or a combination of gastric irritation and CNS stimulation.<sup>1,2</sup> Considerations in choosing an emetic agent are broad and varied. Many home or Internet remedies are used without success and have the potential of causing further harm. Emetic agents are not effective if an antiemetic such as ondansetron or maropitant has been previously administered. Currently, the only home recommendation for dog owners is hydrogen peroxide, while veterinary-prescribed emetic agents include apomorphine hydrochloride (dog) and xylazine hydrochloride (cat).<sup>1,2</sup>

Hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) works by local irritation of the oropharynx and gastric lining, which results in a gag reflex. It is usually recommended for oral administration by the dog owner when transportation to a veterinary clinic is delayed. Only a 3% hydrogen peroxide solution should be used, as higher concentrations can potentially be corrosive to the GI mucosa. Adverse effects associated with use of H<sub>2</sub>O<sub>2</sub> as an emetic agent include irritation to the GI tract, gastroduodenal lesions, gastric dilatation and/or volvulus (dogs), and potential for aspiration pneumonia.<sup>1,2,4</sup> When using hydrogen peroxide as an emetic agent in dogs, the administration of sucralfate and antacids (e.g., proton-pump inhibitors or H<sub>2</sub> blockers) should be considered. Hydrogen peroxide is not a reliable emetic in cats and its use generally is NOT recommended in this species. In addition, cats can develop profound clinical signs from the administration of H<sub>2</sub>O<sub>2</sub>, including profuse foaming from the mouth and severe hemorrhagic gastritis.

Apomorphine hydrochloride is a centrally acting emetic agent. Administration results in stimulation of the CRTZ, quickly followed by emesis. Adverse effects associated with apomorphine administration are prolonged emesis and ocular irritation when administered subconjunctivally.<sup>1,2</sup> While apomorphine is listed as an emetic agent in cats, it is generally not considered to be effective. Apomorphine should not be used when there has been ingestion of medications that result in compounding of symptoms (e.g., respiratory or CNS depression) or with antidopaminergic drugs (e.g., metoclopramide) that prevent emesis from occurring.

Dexmedetomidine and xylazine hydrochloride, alpha adrenergic agonists, are centrally-acting emetic agents that are used as emetic agents in cats. The use of apomorphine and hydrogen peroxide are *not* recommended for cats, as they are ineffective or can result in severe adverse effects (e.g., hemorrhagic gastritis), respectively. Xylazine does not reliably produce an emetic response in dogs, and thus is not recommended in dogs as an emetic agent. Adverse effects associated with alpha-adrenergic drugs include bradycardia, sedation, tremors, and respiratory depression.<sup>1,2</sup> Thawley and Drobatz found that dexmedetomidine (7 mcg/kg, IM) resulted in emesis approximately 80% of the time in cats, as compared to only about 44% of the time in

cats with xylazine.<sup>5</sup> A similar study by Willey et al supported this.<sup>6</sup> Alpha adrenergic agonists should not be used in cats that have ingested medications (e.g., other alpha-adrenergic agonist drugs) or products that may result in compounding of bradycardia, respiratory depression, sedation, or CNS depression symptoms.<sup>1,2</sup>

Methods that are not recommended for emesis induction include digital induction of emesis, syrup of ipecac, liquid soaps, dry mustard powders, and salt. Digital induction of emesis often results in physical injury to the pet owner (dog bite), or injury to the pet's throat and soft palate. Syrup of ipecac has historically been recommended to induce emesis, but is no longer the standard of care. Its cardiotoxic potential and tendency to result in prolonged vomiting, lethargy, and diarrhea have caused it to fall out of favor in both human and veterinary medicine.<sup>1,2</sup> Soaps, mustard powders, and table salt are not reliable as induction agents and may be detrimental (e.g., resulting in further complications such as hypernatremia of the patient).

### **NOT KNOWING MORE ABOUT ACTIVATED CHARCOAL**

After an appropriate history, triage, physical exam, and initial decontamination procedures have been performed in the poisoned pet, the next step is the administration of activated charcoal (AC), if appropriate. Activated charcoal should not be given to the poisoned patient when the toxicant does not reliably bind to AC (see below) or when it is contraindicated to administer AC (e.g., salt toxicity, poor gag reflex). In addition, symptomatic patients who are at risk for aspiration pneumonia should not be administered AC orally. Finally, the administration of AC with a cathartic should be cautiously used in dehydrated patients due to the potential (albeit rare) risks for hypernatremia secondary to free water loss in the GI tract.

When administering AC, it should ideally be given within  $\leq 5$  minutes of ingestion to be most effective. In veterinary medicine, this is almost impossible due to driving time (to the clinic), lapsed time since ingestion, time to triage, and the amount of time it takes to physically deliver AC (e.g., syringe feeding, orogastric tube). As a result, administration of AC is often delayed for up to an hour or more. As time since ingestion is often unknown (e.g., pet owner coming home from work to find their pet poisoned), decontamination (including emesis and administration of AC) is often a relatively benign course of action, provided the patient is not already symptomatic. As always, when administering *any* drug, it is important that benefits outweigh the risks, and that complications be prevented when possible. In veterinary medicine, administration of AC with a cathartic as long as 6 hours out may still be beneficial with certain types of toxicosis, particularly if the product has delayed release [e.g., extended release (XR) or sustained release (SR)] or undergoes enterohepatic recirculation (see multi-dose AC below). While human medicine has moved away from administration of AC with poisoned patients, the aggressive use of AC in veterinary medicine is still warranted, as this is often our last line of defense when it comes to adequately decontaminating our patients. Certain modalities of therapy—e.g., antidotes [such as fomepizole, pralidoxime chloride (2-PAM), digoxin-specific antibody fragments], plasmapheresis, hemodialysis, mechanical ventilation—along with financial limitations of pet owners, limit our ability to treat poisoned pets aggressively as compared to human medicine. As a result, the continued use of AC in veterinary medicine is still warranted as a first line of defense therapy. Current recommended dosing for single dose AC is 1–5 g of AC/kg with a cathartic (e.g., sorbitol) to promote transit time through the GI tract.



### **Administration of Activated Charcoal When the Toxicant May Not Bind Appropriately**

Before administering AC and a cathartic, it is imperative to consider whether or not the patient has a contraindication for its administration. Contraindications for AC administration include severe sedation, decreased gag reflex, or intestinal obstruction. Likewise, if the toxicant does not physically bind to AC, it is contraindicated to administer AC. Examples of toxicants that do not absorb reliably to AC include ethylene glycol, alcohol, xylitol, and heavy metals. Contraindications for cathartic administration include hypernatremia, dehydration, and salt toxicosis (e.g., salt, ice melters, homemade play dough), as fluid loss through the intestinal tract can result in excessive free water loss and severe, secondary hypernatremia.

### **Multi-dose Activated Charcoal**

Human studies have found that multi-dose AC significantly decreases the serum half-life of certain drugs, including antidepressants, theophylline, digitoxin, and phenobarbital. While veterinary studies are lacking, there is likely an added benefit from using multi-dose AC, provided the patient is well hydrated and monitored appropriately. Certain situations or toxicities, including drugs that undergo enterohepatic recirculation; drugs that diffuse from the systemic circulation back into the intestinal tract down the concentration gradient; or ingestion of SR, XR, or long-acting (LA) release products will require multi-dose administration of AC. Keep in mind that when administering multiple doses of AC to a patient, the additional doses ideally should *not* contain a cathartic (e.g., sorbitol), due to increased risks for dehydration and secondary hypernatremia. Current recommended dosing for multiple doses of AC is 1–2 g of AC *without a cathartic* /kg of body weight, PO q 4–6 hours for 24 hours.

### **Contraindications of Activated Charcoal**

Contraindications for AC include endoscopy (which would obscure visualization), abdominal surgery of the GI tract, gastric or intestinal obstruction, gastrointestinal hemorrhage or perforation (due to pathology, caustic injury, etc.), recent surgery, late-stage presentation with clinical signs already present, dehydration, lack of bowel sounds, ileus, hypernatremia, hypovolemic shock, compromised airway (risk for aspiration pneumonia), and ingestion of a caustic substance or hydrocarbon (due to increased risk for aspiration pneumonia). In patients that have an unprotected airway that are at risk for aspiration pneumonia (e.g., a depressed state of consciousness, excessive sedation), the use of AC is contraindicated without ETT intubation (to protect the airway during gastric lavage and AC administration).

### **CONCLUSION**

The appropriate and careful use of decontamination of the poisoned patient should be considered. Thorough history taking and physical examination of the patient is imperative prior to emesis induction. Recognizing contraindications for emesis induction, or which emetic to use for emesis induction, is imperative. With careful and thorough evaluation of the poisoned patient, proper decontamination can be performed confidently with safety and efficacy to aid in ensuring a positive outcome.

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NOTE: When in doubt, all drug dosages should be confirmed and cross-referenced with a reference guide such as *Plumb's Veterinary Drug Handbook*.

**Table 1. Emesis Induction: Indications and Contraindications[1,2]\***

<b>WHEN EMESIS SHOULD BE PERFORMED</b>	<b>WHEN EMESIS SHOULD <u>NOT</u> BE PERFORMED:</b>
With recent ingestion (<1-2 hours) in an asymptomatic patient	With caustic or corrosive toxicant ingestion (e.g., batteries, ultra-bleach, lye, oven cleaning chemicals), where emesis induction may result in further injury to the oropharynx, esophagus, and GIT when these agents are expelled.
With unknown time of ingestion in an asymptomatic patient	When petroleum distillates or hydrocarbons are ingested (e.g., kerosene, gasoline, motor oil, transmission fluid, etc.); these toxicants can be easily aspirated into the respiratory system and result in severe aspiration pneumonitis.
When ingestion of a product known to stay in the stomach for a long time is ingested in an asymptomatic patient (e.g., bezoar, massive ingestions, grapes/raisins, chocolate, wads of xylitol gum, FBO, etc.)	In symptomatic patients that have a decreased gag reflex (e.g., sedation, coma, hypoglycemia, etc.) or a lowered seizure threshold (e.g., tremoring, seizing, etc.) that may be unable to protect their airway, resulting in aspiration pneumonitis.
	In patients with underlying medical conditions that may predispose them towards aspiration pneumonitis or complications associated with emesis induction (e.g., megaesophagus, history of aspiration pneumonia, upper airway disease, laryngeal paralysis). Brachycephalic breeds (e.g., English bulldog, pug, Shih-Tzu) with an elongated soft palate, everted sacculles, a hypoplastic trachea, or stenotic nares may be better candidates for sedation, intubation, and gastric lavage rather than emesis induction due to the risks of aspiration.
	Species that anatomically cannot vomit or cannot safely have emesis induced such as birds, rabbits, ruminants (e.g., sheep, cattle, llamas, and goats), horses, and rodents (e.g., chinchillas, rats, gerbils)

\* From Lee JA, Decontamination of the poisoned patient, in the *Textbook of Small Animal Emergency Medicine* (Eds: Drobatz et al).

## TOP 10 HUMAN FOOD TOXINS POISONOUS TO DOGS AND CATS

Justine A. Lee, DVM, DACVECC, DABT, CEO, VETgirl

### INTRODUCTION

Each year, the [ASPCA Animal Poison Control Center](#) (APCC) manages hundreds of thousands of pet poisoning calls due to common food items found in the kitchen. This lecture will review kitchen dangers poisonous to dogs and cats, including mechanism of action (if known), clinical signs, and overall treatment.

### GRAPES, RAISINS, AND CURRANTS

Grapes and raisins (*Vitis* spp) have been associated with the development of acute kidney injury (AKI) in dogs since 2001. All types have been implicated with toxicosis, including organic grapes, commercial grapes, homegrown grapes, and seedless or seeded grapes. While the mechanism of toxicosis is unknown, there are several suspected hypotheses, including individual inability to metabolize certain components of the fruit (e.g., tannins, high monosaccharide content),<sup>1</sup> the presence of mycotoxins or pesticide residues on the fruit,<sup>1</sup> or salicylate-like (e.g., aspirin-like) chemicals within the grape or raisin. Common kitchen items also contain raisins in their active ingredient, including raisin bread, trail mix, chocolate-covered raisins, cereal with raisins, etc. Currently, grapeseed extract has not been associated with nephrotoxicity.<sup>1</sup> Treatment for grape and raisin ingestion includes aggressive decontamination as the first-line of therapy. Grapes and raisins seem to stay in the stomach for a prolonged period of time, and are not rapidly broken down or absorbed from the gastrointestinal (GI) tract; hence, delayed emesis induction even several hours post-ingestion can still be initiated to maximize decontamination methods. One dose of activated charcoal can also be administered to prevent absorption of the unknown nephrotoxin. In general, all ingestions should be treated as potentially idiosyncratic and be appropriately decontaminated and treated. Initially, vomiting may be observed within the first 24 hours of ingestion.<sup>1</sup> Within the next 12-24 hours, clinical signs of lethargy, dehydration, vomiting, diarrhea, anorexia, abdominal pain, uremic breath, and diarrhea may be seen.<sup>1</sup> Azotemia may develop within 24 hours, with hypercalcemia and hyperphosphatemia occurring first.<sup>1</sup> Oliguria and anuria may develop 48-72 hours post-ingestion,<sup>1</sup> at which point the prognosis is poorer. Treatment includes decontamination, aggressive intravenous (IV) fluid therapy, anti-emetics, blood pressure and urine output monitoring, and serial blood work monitoring (q. 12-24 hours for several days). In severe cases, hemodialysis or peritoneal dialysis may be necessary. Asymptomatic patients that have been adequately decontaminated and survive to discharge should have a renal panel and electrolytes monitored 48-72 hours post-ingestion. Overall, the prognosis varies from good to poor, depending on time to decontamination, response to therapy, and prevalence of oliguria or anuria. While 50% of dogs that ingest grapes and raisins never develop clinical signs or azotemia, aggressive treatment is still warranted.<sup>1</sup>

### XYLITOL

Xylitol is a natural sweetener found in small quantities in certain fruit. Xylitol has gained recent popularity because it is sugar-free, and is often found in diabetic snacks, foods, baked foods, mouthwashes, toothpastes, chewing gum, mints, candies, chewable multivitamins, and less popular brands of peanut butter.<sup>2</sup> Sugarless products, particularly those with xylitol listed within the first 3 to 5 active ingredients, can result in severe toxicosis within 15-30 minutes of ingestion. Ingestion of xylitol results in an insulin spike in non-primate species, resulting in severe hypoglycemia. Many pieces of candy and gum (e.g., Orbit™, Trident™, Ice Breakers™)

contain various amounts of xylitol ranging, on average, from 2 mgs to 1.0 grams/piece. Unfortunately, not all sources are disclosed by the company (e.g., how many grams of xylitol may be in each piece of gum) due to a proprietary nature. With xylitol toxicosis, it is imperative to calculate whether a toxic dose has been ingested. Doses > 0.1 g/kg are considered toxic and result in profound, sudden hypoglycemia from insulin stimulation.<sup>2</sup> Higher doses (> 0.5 g/kg) of xylitol have been associated with acute hepatic necrosis. Clinical signs of xylitol toxicosis include lethargy, weakness, vomiting, collapse, anorexia, generalized malaise, tremors, and seizures (from hypoglycemia). When hepatotoxic doses are ingested, clinical signs and clinicopathologic findings may include melena, icterus, increased liver enzymes, diarrhea, hypoglycemia, hypocholesterolemia, decreased BUN, hypoalbuminemia, etc.

When presented a patient that has ingested a toxic amount of xylitol, a blood glucose should be checked immediately upon presentation *prior* to emesis induction; if hypoglycemic, a bolus of 1 ml/kg of 50% dextrose, diluted with an additional amount of 0.9% NaCl (in a 1:3 ratio) should be given IV over 1-2 minutes. Emesis induction should only be performed once the patient is euglycemic. Keep in mind that activated charcoal does *not* reliably bind to xylitol, and is not routinely recommended for xylitol toxicosis. Hypoglycemic patients should be hospitalized for IV fluid therapy [supplemented with dextrose (2.5 to 5% dextrose, CRI, IV)] for approximately 12-24 hours, and frequent blood glucose monitoring should be performed every 1-4 hours. For patients ingesting a hepatotoxic amount of xylitol, the use of hepatoprotectants (e.g., SAME, n-acetylcysteine), anti-emetics, and supportive care (including frequent liver enzyme monitoring) are warranted.

### CHOCOLATE (THEOBROMINE/CAFFINE)

Chocolate is one of the most well-known toxic foods that pet owners are aware of. Chocolate contains methylxanthines such as theobromine and caffeine (More information on caffeine specifically can be found below in the next section). Methylxanthines antagonize adenosine receptors and inhibits cellular phosphodiesterases, causing an increase in cAMP.

Methylxanthines also stimulate release of catecholamines (e.g., norepinephrine) and cause an increase of calcium entry into cardiac and skeletal muscle, resulting in central nervous system (CNS) stimulation, diuresis, and myocardial contraction. When ingested in toxic doses, clinical signs may include agitation, vomiting, diarrhea, panting, tachycardia, polyuria, hyperthermia, muscle tremors, and seizures. Clinical signs of theobromine toxicosis can be seen at within a few hours, up to 10-12 hours out (as the absorption time is slow). As theobromine has a very long half-life (e.g., 17 hours), treatment may be necessary for 72-96 hours.<sup>3</sup> Toxic doses of theobromine can be seen at:

- > 20 mg/kg: mild signs of agitation and gastrointestinal distress (e.g., vomiting, diarrhea, abdominal pain)
- > 40 mg/kg: moderate signs of cardiotoxicosis can be seen in addition to aforementioned signs (e.g., tachycardia, hypertension)
- > 60 mg/kg: severe signs of neurotoxicosis can be seen in addition to aforementioned signs (e.g., tremors, seizures)
- 250-500 mg/kg: LD<sub>50</sub> (for dogs)<sup>3</sup>
- 200 mg/kg: LD<sub>50</sub> (for cats)<sup>3</sup>

Rarer secondary complications may also be seen from chocolate toxicosis, including pancreatitis and secondary aspiration pneumonia. In general, the darker and more bitter the

chocolate, the higher the concentration of methylxanthines in the product. For example, a 20-kg dog would need to ingest approximately 14 oz. of milk chocolate, or 4.5 oz. of semi-sweet, or 2 oz. of unsweetened chocolate to cause moderate signs of toxicity (e.g., agitation, tachycardia). As chocolate tends to stay in the stomach for a prolonged period of time, delayed emesis induction (e.g., even several hours after ingestion) - provided the patient is asymptomatic – may help decontaminate the patient, as chocolate tends to remain in the stomach for quite some time. Further decontamination includes the administration of multiple doses of activated charcoal (1-2 g/kg every 6 hours X 4 doses), as methylxanthines undergo enterohepatic recirculation. Treatment includes gastrointestinal support (e.g., anti-emetics), supportive care, IV fluid therapy, frequent walks (to prevent reabsorption of methylxanthines from the urine across the bladder wall), sedatives for agitation (e.g., acepromazine, butorphanol), beta-blockers for persistent tachycardia or hypertension (e.g., propranolol), methocarbamol for tremors, and anticonvulsants for seizures, as needed.

## CAFFEINE

Caffeine poses a significant risk to pets, and is one of the few toxicants that I have observed to result in fatalities. While a small amount of caffeine is found in chocolate sources (see above), other sources of caffeine may be more concentrated, resulting in more profound signs. Caffeine is often found in coffee bean sources (e.g., coffee, chocolate-covered espresso beans, etc.), tea, diet pills, herbal products containing guarana, caffeine stimulant tablets (e.g., NoDoz®, Vivarin®), caffeine stimulant drinks (e.g., Red Bull®, Monster®, 5-Hour Energy Drink shots, etc.), and even gum (e.g., Rockstar, Amp Energy, Alert Energy, etc.). Clinical signs are similar to that seen with theobromine. Caffeine toxic doses are:

- > 15 mg/kg: Signs of agitation
- > 25 mg/kg: Moderate signs
- > 50 mg/kg: Cardiotoxic signs
- 140 mg/kg: LD<sub>50</sub> (for dogs)<sup>3</sup>
- 80-150 mg/kg: LD<sub>50</sub> (for cats)<sup>3</sup>

Caffeine has a short half-life (4.5 hours),<sup>3</sup> and clinical signs can be seen within 30 minutes to an hour. Clinical signs and treatment are similar to theobromine (see above), although signs may resolve within 12-36 hours.<sup>3</sup>

## UNBAKED BREAD DOUGH AND ETHANOL

Unbaked bread dough that contains yeast (including pizza dough, roll products, sourdough “starters,” etc.) can result in toxicosis when ingested.<sup>4</sup> Bread dough toxicosis most commonly occurs during the Easter and Christmas holidays,<sup>4</sup> when the prevalence of baking increases. While most pet owners may notice the bread dough missing (e.g., witnessed ingestion by their dog), pet owners are often not cognizant of the severity of the toxicosis that can occur with this ingestion. When the bread dough hits the warm, moist environment of the stomach (which acts as an “oven”),<sup>4</sup> it causes the yeast to ferment and produces ethanol gas. This can result in gastric bloat or worse, gastric dilatation-volvulus (GDV), which can be life-threatening. Clinical signs of bread dough toxicosis include a distended abdomen, attempting to retch, unproductive vomit, sprung ribs, abdominal pain, agitation, tachycardia, shock, and collapse. In addition, the ethanol results in secondary alcohol toxicity, which may mask some of the signs of bloat/GDV. Clinical signs of ethanol toxicosis include hypoglycemia, weakness, sedation, bradycardia, vocalization, behavioral changes, blindness, drunkenness/ataxia, and a severe metabolic acidosis. Treatment includes decontamination, gastric lavage with cold water (e.g., to stop the

fermentation process, remove the presence of ethanol gas and bread dough, and to minimize the gastric distension of the bloat/GDV), glucose monitoring, IV fluid therapy, anti-emetics, prokinetics (e.g., metoclopramide), symptomatic supportive care, thermoregulation, dextrose supplementation, and rarely, surgical fixation of the bloat/GDV.

### **FOOD OXIDIZER PACKS**

Food oxidizer packs are often found in beef jerky (for human consumption), cookie containers (e.g., Kashi®) or rawhide bags and may contain iron. Small ingestions are less likely to result in toxicity. When ingested in large amounts, however, these packs can potentially result in iron toxicosis. The powder within these oxygen absorbers is often black in color and magnetic. Treatment for iron toxicosis includes antacid therapy (e.g., milk of magnesia), symptomatic supportive care, monitoring blood iron levels, and potential chelation (in severe cases). The use of activated charcoal is not warranted with iron toxicosis, as it does not reliably bind to heavy metals.

### **MOLDY FOOD (E.G., MOLDY WALNUTS, COMPOST, CHEESE)**

Accidental poisoning can occur when compost or moldy food (from a garbage can) is ingested, due to the presence of tremorgenic mycotoxins.<sup>5</sup> The toxins most commonly associated with tremorgenic mycotoxins are penitrem A and roquefortine, and are thought to interfere with the release of neurotransmitter amino acids.<sup>5</sup> Common food sources include moldy nuts (e.g., walnuts), starch sources (e.g., pasta, bread), cheese, nuts, or other decaying matter.<sup>5</sup> This is a common toxicant in free-roaming dogs. Clinical signs include gastrointestinal signs (e.g., hypersalivation, vomiting, diarrhea, distended abdomen) and CNS signs (e.g., agitation, hyperesthesia, ataxia, muscle tremors, seizures, and secondary hyperthermia). Metabolic acidosis may occur and disseminated intravascular coagulation (DIC) may be seen due to persistent tremors and severe hyperthermia. Clinical signs can be seen acutely within a few minutes to hours, with most occurring within 2-4 hours of ingestion. Treatment includes decontamination, if appropriate. Ideally, gastric lavage should be performed in symptomatic patients to allow for appropriate decontamination while protecting the airway with an inflated endotracheal tube. A single dose of activated charcoal should be given (ideally via orogastric tube following gavage). Treatment is symptomatic and supportive care including injectable methocarbamol for tremors (22-110 mg/kg, IV, slow to effect), anti-emetics (e.g., maropitant, 1 mg/kg, SQ q 24), anticonvulsants for seizures (e.g., phenobarbital, diazepam), and IV fluids to aid in cooling the patients and protect the kidneys from acute renal failure secondary to myoglobinuria (rare) from severe tremors and seizures.

### **ONIONS/GARLIC/CHIVES (*ALLIUM SP*)**

The plants that belong to the Alliaceae family (e.g., onions, garlic, chives, leeks) contain propyl disulfides and thiosulfates.<sup>6</sup> When metabolized, these toxic compounds cause oxygen free radicals, denatured hemoglobin (e.g., Heinz body anemia), and methemoglobinemia.<sup>6</sup> Multiple factors contribute to *Allium*'s level of toxicity, including its state (e.g., dried, juiced, powdered, fresh, cooked, etc.), species affected, species of plant, time of year, and duration of exposure (e.g., acute versus chronic).<sup>6</sup> Typically, ingestions  $\geq 0.5\%$  of the animal's body weight warrant decontamination.<sup>6</sup> Cats are at highly risk for toxicosis due to their hemoglobin differences (which contain 8 sulfhydryl groups as compared to dogs who have 4).<sup>6</sup> Likewise, certain dog breeds (e.g., Akita, Shiba Inu, Jindo) with reduced potassium and glutathione concentrations are at higher risk for oxidative damage.<sup>6</sup> Clinical signs are often delayed, and may take days to weeks

to unmask (depending on the chronicity of toxicosis). Clinical signs and clinic-pathologic changes include lethargy, tachycardiac, pallor, GI signs (e.g., anorexia, vomiting, diarrhea), Heinz body anemia, pigmenturia, methemoglobinemia, eccentrocytosis, etc. Treatment includes decontamination (e.g., emesis, charcoal X 1), anti-emetics, fluid therapy, gastric protectants, hematology monitoring, and rarely, red blood cell transfusion.

## MACADAMIA NUTS

Macadamia nuts come from the *Macadamia integrifolia* or *Macadamia tetraphylla* tree.<sup>7</sup> Macadamia nuts are 80% oil and 4% sugar.<sup>7</sup> The mechanism of action is unknown but is thought to involve neurotransmitters, motor neurons, neuromuscular junctions, and muscle fibers.<sup>7</sup> When ingested by dogs, CNS signs (e.g., weakness, ataxia, tremoring, recumbency), GI signs (e.g., vomiting, abdominal pain), musculoskeletal signs (e.g., lameness, hind limb weakness, joint pain), and miscellaneous signs (e.g., hyperthermia, pancreatitis) may be seen. Signs are often seen within 12 hours of ingestion, and resolve within 24-48 hours without treatment. As little as 0.7 g/kg can result in clinical signs, although signs are often seen at higher doses > 2 g/kg.<sup>7</sup> Treatment includes decontamination, anti-emetics, and symptomatic supportive care (e.g., nursing care, subcutaneous fluids, thermoregulation, etc.). Overall, the prognosis is excellent.

## CONCLUSION

Pet owners should be appropriately educated on how to pet-proof the house, and be trained on what common household products and kitchen items are poisonous. Pet owners should also be appropriately educated on crate training to help minimize toxin exposure. Once a pet is exposed to a toxicant, it is imperative to determine if emesis is appropriate, and to understand when it may be contraindicated (e.g., symptomatic patient, delayed time since exposure, hydrocarbons, etc.). Knowledge of the underlying mechanism of action, the pharmacokinetics (including absorption, distribution, metabolism, and excretion), and the toxic dose of the toxicant are imperative in determining appropriate decontamination and therapy for the patient.

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NOTE: When in doubt, all drug dosages should be confirmed and cross-referenced with a reference guide such as *Plumb's Veterinary Drug Handbook*.

## TOP 10 HUMAN MEDICATIONS POISONOUS TO DOGS & CATS

Justine A. Lee, DVM, DACVECC, DABT, CEO, VETgirl, LLC.

Each year, the [ASPCA Animal Poison Control Center](#) (APCC) manages hundreds of thousands of poisoning calls. At the ASPCA APCC, an estimated 50% of pet poisonings comprise human over-the-counter (OTC) and prescription medications. In this lecture, we will review the mechanism of toxicosis, clinical signs, and overall treatment of the top 10 most common human medications affecting dogs and cats.

In the veterinary poisoned patient, the goal of decontamination is to “inhibit or minimize further toxicant absorption and to promote excretion or elimination of the toxicant from the body.”<sup>1,2</sup> When treating the poisoned patient, the clinician should have an understanding of the toxic dose (if available), the pharmacokinetics (including absorption, distribution, metabolism, and excretion), the underlying mechanism of action, and the potential clinical signs that can be observed with the toxicant.<sup>2</sup> This will help determine appropriate decontamination and therapy for the patient. If this information is not readily available, the reader is advised to contact the [ASPCA Animal Poison Control Center](#) (888-426-4435) for life saving, 24/7 advice as needed. For further review on decontamination and specific treatment, attendees are referred to a veterinary toxicology book for more detailed review.

### CALCIUM CHANNEL BLOCKERS, BETA-BLOCKERS, ACE-INHIBITORS, STATINS AND DIURETICS

Certain cardiac medications include broad categories such as calcium channel blockers (CCB), beta-blockers (BB), and angiotensin-converting enzyme (or “ACE”) inhibitors. These medications are commonly used in both human and veterinary medicine to treat underlying cardiac disease or hypertension. Each category of cardiac medication has different margins of safety. CCB and BB toxicosis should be treated aggressively, as these two categories of medications have a narrow margin of safety. Toxicosis of these agents can result in myocardial failure, severe bradycardia, and hypotension; untreated, cardiac output becomes reduced, and secondary severe hypoperfusion and acute kidney injury (AKI) can potentially develop.<sup>3-5</sup> With ACE-inhibitors, severe overdoses can cause hypotension, dizziness, weakness, and hypotension. In general, there is a wider margin of safety with ACE-inhibitors, which are typically considered much safer. Pets ingesting small amounts of ACE-inhibitors can potentially be monitored at home, unless they have underlying disease (e.g., kidney failure, cardiac disease, etc.). With ACE-inhibitors, ingestions > 10-20X a therapeutic dose are generally considered toxic, and can result in severe clinical symptoms (e.g., hypotension).<sup>5</sup> Treatment for any cardiac medication includes decontamination (e.g., emesis induction, gastric lavage, activated charcoal (AC) administration), blood pressure monitoring, aggressive IV fluid therapy if hypotension is detected, and blood work monitoring. With severe toxicosis, the use of high-dose insulin therapy or intravenous lipid emulsion may be warranted as a potential antidote for calcium channel blocker toxicosis.<sup>3</sup>

### SELECTIVE SEROTONIN RE-UP TAKE INHIBITORS (SSRI)

Selective serotonin re-uptake inhibitors (SSRIs) are a class of medications that are commonly used in human medicine for depression. Common examples include the following drugs:

- Fluoxetine (Prozac® in human beings; Reconcile™ in veterinary medicine)

- Citalopram (Celexa®)
- Paroxetine (Paxil®)
- Sertraline (Zoloft®)

Other similar drugs include selective norepinephrine re-uptake inhibitors (SNRIs), which include common drugs like duloxetine (Cymbalta®), nefazodone (Serzone®), and venlafaxine (Effexor®). SNRI and SSRI drugs result in similar clinical signs of toxicosis, and therefore are treated the same. In veterinary medicine, SSRIs are used for a wide array of behavioral problems, including feline urine spraying, canine separation anxiety, lick granulomas, etc. These SSRI drugs work by blocking the reuptake of serotonin in the pre-synapse, thereby increasing the levels of serotonin in the pre-synaptic membrane. In small animal patients, common clinical signs from SSRIs include the following:

- Sedation or central nervous system (CNS) stimulation
- Anorexia
- Lethargy
- Serotonin syndrome

Clinical signs of serotonin syndrome include: gastrointestinal (GI) signs (e.g., hypersalivation, vomiting, diarrhea, abdominal pain) and CNS signs (e.g., stimulation, mydriasis, tremors, seizures, hyperthermia secondary to tremoring and seizuring). Treatment for antidepressants includes decontamination (ideally done at a veterinarian, due to the rapid onset of clinical signs), sedation (e.g., with acepromazine or chlorpromazine), intravenous (IV) fluid therapy, blood pressure and electrocardiogram (ECG) monitoring, thermoregulation, muscle relaxants (for tremors; methocarbamol 22-55 mg/kg, IV, PRN), anticonvulsants (e.g., phenobarbital 4-16 mg/kg, IV, PRN; diazepam 0.25-0.5 mg/kg, IV, PRN), serotonin antagonists [e.g., cyproheptadine (1.1 mg/kg for dogs or 2-4 mg *total* per cat) PO or rectally q. 6-8], and supportive and symptomatic care. In general, the prognosis for antidepressant toxicosis is excellent.

## AMPHETAMINES

Amphetamines are used for a variety of medical and illicit reasons. Legal forms include prescription medications for attention-deficit disorder/attention deficit-hyperactivity disorder (ADD/ADHD), weight loss, and narcolepsy. Examples of amphetamines include:

- Dextroamphetamine
- Amphetamine (Adderall®)
- D-amphetamine (Dexedrine®)
- Methamphetamine (Desoxyn®)
- Lisdexamfetamine (Vyvanse®)

Illegal forms of amphetamines include street drugs like methamphetamine, crystal meth, and ecstasy. This class of drugs acts as sympathomimetic agents, meaning they stimulate the sympathetic system. Amphetamines also cause stimulation of  $\alpha$  and  $\beta$ -adrenergic receptors, and stimulate release of serotonin and norepinephrine; this results in increased catecholamine stimulation in the synapse. Amphetamines also increase release of serotonin from the presynaptic membrane, resulting in serotonin syndrome. With amphetamine toxicosis, secondary stimulation of certain body systems can result in significant clinical signs: GI (e.g.,

vomiting, diarrhea, hypersalivating), CNS (e.g., agitation, mydriasis, tremors, seizures), cardiovascular (e.g., tachycardia, hypertension), and respiratory (e.g., panting). Both clinical signs and treatment for amphetamine toxicosis are similar to SSRI toxicosis, and include IV fluids, cooling measures, sedation (e.g., with acepromazine or chlorpromazine), muscle relaxants, anticonvulsants, thermoregulation, blood pressure monitoring, and symptomatic/supportive care.

## SLEEP AIDS

Sleep aids are often benzodiazepines or non-benzodiazepine hypnotics, and include drugs such as zolpidem (Ambien®) and eszopiclone (Lunesta®). These drugs work similarly to benzodiazepines (e.g., diazepam) as they potentiate GABA transmission, increasing frequency of chloride channel opening and resulting in inhibition of neuronal excitation. While these drugs result in sedation in humans, up to 40-50% of dogs ingesting toxic doses of sleep aids develop paradoxical CNS stimulation rather than expected depression. Clinical signs include CNS depression (e.g., depression, ataxia, weakness, paresis), CNS stimulation (e.g., hyperactivity, anxiety, agitation, panting, tremors), or other signs like nausea, vomiting, diarrhea, and hyperthermia. Treatment includes decontamination, activated charcoal, and for those patients demonstrating signs of CNS stimulation, the use of sedatives or anxiolytics. In patients exhibiting CNS stimulation, benzodiazepines (e.g., diazepam IV) should *not* be used, as they may worsen the symptoms. Rather, the use of phenothiazines (e.g., acepromazine, chlorpromazine) or barbiturates (e.g., phenobarbital IV) should be used instead. In severe cases of respiratory or cardiac depression, the use of the reversal agent, flumazenil, can be considered.

## NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

NSAIDs are competitive inhibitors of prostaglandin synthesis (cyclooxygenase or “COX” inhibitors) and result in decreased prostaglandin, which is important for normal homeostatic function (including maintaining renal blood flow, maintaining mucous production in the stomach, etc.). Common OTC human NSAIDs include active ingredients such as ibuprofen and naproxen sodium. Examples of human NSAIDs include Advil®, Aleve®, certain types of Motrin®, etc. Common prescription veterinary NSAIDs can also result in toxicosis, particularly when available in the chewable, palatable formulation. Examples of veterinary NSAIDs include carprofen, deracoxib, etogesic, previcoxib, etc. With NSAID toxicosis, the GI tract, kidneys, CNS, and platelets can be affected. Cats and certain breeds of dogs (e.g., German shepherds) seem to be more sensitive to NSAIDs, and should be treated aggressively. With cats, severe acute kidney injury (AKI) is often more clinically seen with NSAID toxicosis at lower doses (as compared to dogs). With dogs, signs secondary to GI ulceration (e.g., vomiting, diarrhea, melena, hematemesis, etc.) are more commonly seen initially, followed by secondary AKI. With NSAID toxicosis, it is important to keep in mind that each NSAID has a different toxic dose, margin of safety, half-life, and route of excretion, and an animal poison control should be contacted to identify what specific NSAID and toxic dose was ingested. For example, in dogs, ibuprofen results in GI signs at doses as low as 16-50 mg/kg, while severe GI signs may be seen at 50-100 mg/kg.<sup>6</sup> Renal compromise may be seen at doses of 100-250 mg/kg (resulting in potential AKI), and fatalities have been reported at doses > 300 mg/kg.<sup>6</sup> This differs tremendously from naproxen sodium (dogs), where severe clinical signs can be seen at doses as low as 5 mg/kg.<sup>6</sup> Clinical signs of NSAID toxicosis include anorexia, vomiting, hematemesis, diarrhea, melena, abdominal pain, lethargy, malaise, uremic halitosis, dehydration, etc. Treatment includes decontamination, the use of activated charcoal (often multiple doses due to enterohepatic recirculation, if appropriate), GI protectants (e.g., H<sub>2</sub> blockers, sucralfate), aggressive IV fluid

therapy (to help maintain renal blood flow), anti-emetic therapy, and symptomatic and supportive care. With high doses, anti-convulsants may also be necessary if CNS signs develop.

## ACETAMINOPHEN

Acetaminophen (N-acetyl-p-aminophenol), a cyclooxygenase (COX)-3 inhibitor, is a popular OTC analgesic and antipyretic medication used frequently in humans. It is not considered a true NSAID as it lacks anti-inflammatory properties. Normally, part of this drug is metabolized into non-toxic conjugates via the metabolic pathways (glucuronidation and sulfation);<sup>7</sup> some is metabolized into the toxic metabolite, N-acetyl-para-benzoquinoneimine [NAPQI] via the cytochrome P-450 enzyme pathway.<sup>7</sup> Typically, NAPQI is detoxified by conjugation with glutathione in the liver.<sup>7</sup> Toxicosis occurs when glucuronidation and sulfation pathways are depleted; this results in toxic metabolites building up and secondary oxidative injury occurring.<sup>7</sup> While this drug is very safe for human use, it has a narrow margin of safety in dogs and cats; the severity of toxicosis and development of clinical signs is species-dependent. Cats have an altered glucuronidation pathway and a decreased ability to metabolize acetaminophen, making them much more susceptible to toxicosis. In cats, red blood cell (RBC) injury is more likely to occur in the form of methemoglobinemia (metHb), and toxicity can develop at doses as low as 10 mg/kg.<sup>7</sup> In cats, lethargy, swelling of the face or paws, respiratory distress, brown mucous membranes, cyanosis, vomiting, and anorexia may be seen secondary to metHb. In dogs, hepatic injury is more likely to occur; acetaminophen toxicosis can occur at doses > 100 mg/kg, while metHb can develop at doses of > 200 mg/kg.<sup>7</sup> Dogs may develop clinical signs of keratoconjunctivitis sicca (dry eye), malaise, anorexia, hepatic encephalopathy, vomiting, melena, and icterus secondary to hepatotoxicity. Treatment includes decontamination, administration of activated charcoal (AC), anti-emetic therapy, IV fluid therapy, treatment for hypoxemia (e.g., oxygen, blood transfusion, etc.), antioxidant therapy (e.g., Vitamin C), provision of a glutathione source (S-adenosyl-methionine or SAME), and the antidote n-acetylcysteine (NAC, ideally IV) to limit formation of the toxic metabolite NAPQI by providing additional glutathione substrate.<sup>7</sup> Baseline blood work and follow-up biochemical panels should be performed to monitor for the presence of metHb, Heinz body anemia, or evidence of hepatotoxicity. Generally, prognosis is fair to excellent with therapy. If clinical signs resolve and liver enzymes are within normal limits after 48 hours of NAC therapy, patients can be discharged with SAME (for 30 days). Those with severe hepatic failure have a poorer prognosis.

## ASTHMA INHALERS (e.g., ALBUTEROL)

Asthma inhalers are often used in both human and veterinary medicine. Various types of medications may be used, including steroids (e.g., fluticasone) or beta agonists (e.g., albuterol, salbutamol, etc.). When beta-agonist inhalers are accidentally chewed and punctured by dogs, they can result in a severe, life-threatening, acute toxicosis. (Inhaled steroids are not a large toxicity issue). Because inhalers often contain approximately 200 metered, concentrated doses, a massive amount of beta-agonist is released with just one puncture. Clinical signs include cardiac (e.g., tachycardiac, a “racing heart rate” per the owner, injected gums, hypotension, hypertension, severe arrhythmias), electrolyte changes (e.g., severe hypokalemia, hyperglycemia), GI (e.g., vomiting), and CNS (e.g., mydriasis, agitation, weakness, collapse, death). Treatment includes stat electrolyte monitoring, IV fluids, potassium supplementation, blood pressure and ECG monitoring, sedation/anxiolytics (if the patient is agitated, hypertensive, and tachycardiac), anti-arrhythmics such as beta-blockers (e.g., propranolol, esmolol, etc.), and symptomatic supportive care. Treatment for 24-36 hours is typically necessary, until clinical signs resolve.

## DECONGESTANTS

Cold and flu medications (e.g., “Claritin-D”) often carry decongestants such as pseudoephedrine (PSE) and phenylephrine (PE). The exact mechanism of how these drugs work is unknown but thought to stimulate alpha and beta-adrenergic receptors by releasing norepinephrine.

Phenylephrine is typically considered to be less toxic than PSE as it is less bioavailable with oral ingestion. Clinical signs seen with decongestant ingestion include cardiac (e.g., tachycardia, hypertension, reflex bradycardia), CNS (e.g., mydriasis, agitation, trembling, seizures), and various miscellaneous signs (e.g., hyperthermia). With PSE, moderate to severe clinical signs can be seen at 5-6 mg/kg, while death has been reported at 10-12 mg/kg. With phenylephrine, similar clinical signs can be seen, although GI signs such as vomiting are the most common sign observed. Treatment includes decontamination (if appropriate), administration of one dose of charcoal with a cathartic, IV fluid therapy (to enhance urinary elimination), blood pressure monitoring, anti-emetics, sedatives/anxiolytics (e.g., acepromazine), muscle relaxants for trembling (e.g., methocarbamol 22-100 mg/kg, IV PRN), anticonvulsants (e.g., phenobarbital 4-6 mg/kg, IV, PRN), and rarely, anti-hypertensives (e.g., hydralazine).

## ISONIAZID

Isoniazid (commonly known as INH) is a human medication used for tuberculosis. While it is used in veterinary medicine to treat *Mycobacterium* or *Actinomyces*, it has a narrow margin of safety in dogs and cats. This drug works by blocking the synthesis of mycolic acid. INH depletes the CNS of pyridoxine and also decreases levels of GABA within the brain. Many assume that since this is an “antibiotic” that it is safe; however, when accidentally ingested in dogs (and rarely, cats), it can result in severe CNS signs (e.g., tremors, refractory seizures, coma, death). The LD<sub>50</sub> in dogs is estimated to be as low as 50 mg/kg; at this same dose, seizures can be seen. One 300 mg tablet can result in severe poisoning in a 10-pound dog. Other clinical signs include GI signs (e.g., hypersalivating, vomiting, diarrhea), acid-base disturbances (e.g., metabolic acidosis), hyperthermia (secondary to tremors or seizures) and organ injury (e.g., hepatic injury, acute kidney injury, etc.). Due to the rapid onset of clinical signs, it is often too late to decontaminate the patient. Gastric lavage under anesthesia may be necessary. Treatment also includes IV fluids, anti-emetics, anticonvulsants, muscle relaxants, supportive care, and the antidote pyridoxine hydrochloride (typically available as 100 mg/ML) (Dose: suggested dose of 71 mg/kg IV, diluted to 5-10%, slow over 30-60 minutes). Clinicopathologic monitoring should include a biochemistry panel and recheck hepatic panel (3-5 days later).

## 5-FLUOROURACIL (5-FU)

The most life-threatening topical toxin to dogs and cats is 5-fluorouracil (5-FU). 5-FU, commonly known by the brand names Efudex®, Carac®, Adrucil®, and Fluoroplex®, is a prescription anti-neoplastic medication that is often used for treatment of actinic keratosis or superficial basal cell carcinoma in humans. It is commonly sold in low concentration products (e.g., 0.5-5%), and works by inhibiting DNA and RNA synthesis and production, resulting in programmed cell death.<sup>8</sup> While IV administration of 5-FU is occasionally used as a chemotherapeutic agent in dogs (e.g., for mammary gland tumor, etc.), it is not recommended for use in cats. Decades ago, topical 5-FU was used in cats for the treatment of squamous cell carcinoma; however, it resulted in severe toxicosis and death due to its narrow margin of safety. Clinical signs of 5-FU toxicosis can often be seen within 30 minutes up to 6 hours; death has been reported as early as 7 hours.<sup>8</sup> Clinical signs include acute GI signs (e.g., hypersalivation, anorexia, vomiting, abdominal pain, diarrhea, bloody diarrhea, etc.), CNS signs (e.g., ataxia, tremors, seizures), and

bone marrow suppression e.g., anemia, leukopenia, thrombocytopenia).<sup>8</sup> The lowest reported toxic (oral) dose in dogs is 6 mg/kg, while the minimal reported lethal dose is 20 mg/kg. One case report did have a dog survive ingestion of 46 mg/kg of 5-FU.<sup>8</sup> That said, the prognosis with 5-FU toxicosis is typically grave in cats and guarded in dogs (with a reported survival in dogs of approximately 25%). Death typically occurs due to secondary complications from the 5-FU such as sepsis (due to leukopenia), increased intracranial pressure (due to persistent seizures), intracranial hemorrhage (due to severe thrombocytopenia), or DIC (due to severe seizures). Unfortunately, most patients present with severe clinical signs, where it is too late to perform decontamination. Therefore, treatment should be aimed at symptomatic supportive care, anti-convulsant therapy, anti-emetics, anti-diarrheals, IV fluids (to help maintain perfusion), thermoregulation, broad-spectrum antibiotics, clinicopathologic monitoring, and symptomatic supportive care. If the patient is able to survive the acute crisis, clinicopathologic monitoring is necessary every 3-4 days thereafter for 2-3 weeks, until bone marrow function returns to normal.<sup>8</sup>

## CONCLUSION

Pet owners should be appropriately educated on how to pet-proof the house, and be trained on what common human medications can be toxic to pets. Pet owners should also be appropriately educated on crate training to help minimize toxin exposure. When in doubt, the [ASPCA Animal Poison Control Center](#) should be consulted for toxic ingestions that veterinarians are unaware of.



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NOTE: When in doubt, all drug dosages should be confirmed and cross-referenced with a reference guide such as *Plumb's Veterinary Drug Handbook*.



## POISONOUS PLANTS AFFECTING DOGS AND CATS

Justine A. Lee, DVM, DACVECC, DABT, CEO, VETgirl

Plant ingestions comprise a significant volume of small animal calls to the [ASPCA Animal Poison Control Center](#) (APCC) and clinical cases presenting to the emergency clinic and general practitioner. While the majority of plant toxicosis typically results in mild gastrointestinal (GI) signs, a few plants can be life threatening. Three particularly dangerous plants include lilies (cats), blue-green algae (dogs), and sago palm (dogs). For this reason, veterinary professionals need to be aware of the range in toxicosis of certain plant toxins. It is also important that veterinary professionals be able to rapidly and accurately identify certain common plants. When in doubt, the plant should be confirmed by a florist, botanist, master gardener (available at the ASPCA APCC), or expert.

### INSOLUBLE CALCIUM OXALATES (DIEFFENBACHIA/PHILODENDRON)

According to the [ASPCA Animal Poison Control Center](#), the most common plant exposure is to the *Araceae* plant family.<sup>1</sup> These plants contain insoluble calcium oxalate crystals, and include the *Dieffenbachia* family of plants. These are common houseplants, as they require little water or light, and can survive in office conditions. Other types of insoluble oxalate containing plants include:<sup>1</sup>

- Arrowhead vine
- Calla lily
- Devil's ivy
- Dumbcane
- Elephant's ear
- Mother-in-law's tongue
- Peace lily
- Philodendron
- Pothos
- Sweetheart vine
- Umbrella plant

The plants contain needle sharp crystals, which are often arranged in bundles called raphides.<sup>1</sup> When dogs or cats bite or chew into the plant, it releases the crystals, resulting in acute, profuse pain to the oropharynx. Clinical signs of insoluble calcium oxalate plant toxicosis includes: hypersalivation, pawing at the mouth or muzzle, anorexia, vomiting, and edema of the lips, tongue, and oropharynx may be seen.<sup>1</sup> Very rarely, dyspnea and upper airway swelling can be seen secondary to severe inflammation and swelling of the laryngeal area. If ocular exposure occurs (rare), severe photophobia, pain, and conjunctival swelling can occur. While clinical signs may appear to be dramatic the pet owner, signs are primarily localized to the oropharynx and generally are self-limiting. Treatment can potentially be done at home by the pet owner, and includes removal of the plant, flushing of the mouth (if possible), and offering small amounts of palatable fluid (e.g., canned tuna water, milk, yogurt, chicken broth, etc.) to flush the crystals from the mouth.<sup>1</sup> For more severe clinical signs that present to the veterinarian, the use of anti-emetics, fluid therapy [e.g., subcutaneous (SQ) or intravenous (IV)], or analgesics may be necessary. Atropine is *not* recommended for the hypersalivation.

## SOLUBLE CALCIUM OXALATES

A similarly sounding plant is the soluble oxalate-containing plant. These plants contain oxalic acid and oxalate salts, and must be differentiated from the plant above. Some examples of soluble calcium oxalate-containing plants include: star fruit, common or garden rhubarb, and then shamrock plant.<sup>2</sup> This plant toxicosis is less commonly seen in small animals, and is generally considered more of a concern in large animals (that are chronically grazing on these plants).<sup>2</sup> That said, if this type of plant is ingested in large enough quantities by small animals, it can result in toxicosis. Soluble calcium oxalates are present in varying degrees in all parts of the plant. For example, rhubarb stems are edible, but the leaves are not.<sup>2</sup> When soluble oxalate salts are absorbed from the gastrointestinal tract (GIT), they bind with systemic calcium, resulting in an acute hypocalcemia.<sup>2</sup> The accumulation of calcium oxalate crystals then potentially can result in nephrosis and acute kidney injury (AKI).<sup>2</sup> While the likelihood of AKI is rare from soluble oxalate-containing plants, there is no known toxic dose reported in small animals. Dehydrated patients or those with underlying renal insufficiency may be more at risk for toxicosis, and should be treated more aggressively.<sup>2</sup> Clinical signs include hypersalivation, anorexia, vomiting, diarrhea, lethargy, weakness, and tetany/tremors (secondary to hypocalcemia).<sup>2</sup> Once AKI has developed, signs of pu/pd, oliguria, oxaluria, hematuria, etc., may be seen 24-36 hours post-ingestion. Treatment for large ingestions includes decontamination (e.g., emesis induction, one dose of activated charcoal), fluid therapy, clinicopathologic monitoring (e.g., for hypocalcemia, oxaluria, azotemia, etc.), anti-emetic therapy, and symptomatic supportive care.

## LILIES

The common “true” Lily (from the *Lilium spp.* and *Heimerocallis spp.*) is often found in gardens, floral arrangements, or as fresh cuttings. These beautiful, fragrant flowers are known as the common Easter, tiger, Japanese show, stargazer, rubrum, and day lily.<sup>3</sup> All parts of the plant, including the pollen and water in the vase, are toxic to cats, and result in severe AKI. As little as 2-3 leaves or petals (even the pollen or water from the vase) can result in AKI, and clinical symptoms are typically seen within hours. Clinical signs include early onset vomiting, depression, and anorexia, which progresses to anuric AKI in 1-3 days.<sup>3</sup> Clinicopathologic testing reveals severe azotemia, epithelial casts (12-18 hrs post-ingestion) on urinalysis, proteinuria, and glucosuria.<sup>3</sup> Treatment includes aggressive decontamination (e.g., emesis induction, administration of one dose of activated charcoal), GI support (e.g., anti-emetics, H<sub>2</sub> blockers, etc.), and IV fluid therapy for approximately 48-72 hours (or until resolution of azotemia). The use of SQ fluid therapy is generally not sufficient for the treatment of lily toxicosis. While rarely performed in veterinary medicine, the use of peritoneal or hemodialysis has been successful in anuric AKI cases. With treatment, the prognosis is good if treatment is initiated early and aggressively. Adequate decontamination is of the utmost importance. If aggressive IV fluid therapy is initiated *within* 18 hours, the overall response to therapy is good. However, if treatment is delayed beyond 18-24 hours, or anuria has already developed, the prognosis is grave.<sup>3</sup>

## BLUE-GREEN ALGAE

Cyanobacteria (also known as blue-green algae) are one of the few toxicants that can result in *sudden* death in several species (e.g., humans, dogs, livestock, etc.). This microscopic bacteria is often found in nutrient-rich freshwater or brackish bodies of water, and grows more readily during hot, humid stagnant weather conditions. While the *majority* types of algae are non-toxic, it is very difficult to physically identify which type is toxin without diagnostic analysis. Blue-green

algae typically appears as floating mats or blooms on the surface of the water. Blue-green algae can produce two toxins:<sup>4</sup>

- Microcystins (Hepatotoxic, can result in acute liver failure along with clinical signs of lethargy, anorexia, vomiting, melena, diarrhea, pallor, hepatic encephalopathy, jaundice, seizures, and shock).
- Anatoxins (Neurotoxicant, can result in SLUDGE-like signs, including salivation, lacrimation, urination, defecation, gastrointestinal signs, tremors, paralysis, seizures, cyanosis, etc.).

As this toxicant has a very narrow margin of safety, even minute ingestions can result in severe toxicosis or even fatal poisonings. Depending on what type of clinical signs are seen (e.g., from either the microcystins or the anatoxins), treatment may include: gastric lavage, IV fluid therapy (e.g., crystalloids, colloids), anti-emetics, blood glucose and clinicopathologic monitoring, glucose supplementation, anti-convulsants, muscle relaxants, antibiotics, atropine (if SLUDGE signs are present), Vitamin K<sub>1</sub> or plasma transfusion administration (if coagulopathic), hepatoprotectants (e.g., SAM-e), oxygen therapy, and symptomatic supportive care. Unfortunately, the prognosis for this particular plant toxicant is poor and requires aggressive, 24/7 care.

### SPRING FLOWERS

Certain spring bulbs (e.g., daffodils, tulips, *Narcissus*, etc.) can result in profuse GI signs, and with large ingestions, cardiotoxicity or neurotoxicity. The most toxic part of these spring plants is the bulb, rather than the greens or flowers. Tulips or hyacinths contain allergenic lactones tuliposides A and B, with tuliposides being most concentrated in the bulbs. Tulip and hyacinth bulbs also contain calcium oxalate crystals (see above). With tulip and hyacinth toxicosis, clinical signs of vomiting, hypersalivation, depression, and diarrhea may be seen. With large ingestions, tachycardia, dyspnea, and skin irritation may be seen (rare). Another common spring bulb is the daffodil (*Narcissus*). With ingestion, GI signs (e.g., hypersalivation, vomiting, diarrhea) may be seen; with large ingestions, hypotension, CNS signs (tremors, seizures), and cardiotoxicity (arrhythmias, tachycardia, etc.) are reported (but rarely seen). In general, treatment for spring bulb toxicosis is symptomatic and supportive and includes decontamination, fluid therapy (e.g., SQ or IV), anti-emetics and possible abdominal radiographs to rule out foreign body obstruction or other underlying disease. In massive or severe cases, the use of blood pressure and electrocardiogram (ECG) monitoring, anticonvulsant therapy, and potentially anti-arrhythmic therapy is warranted (albeit rare).

### CARDIAC GLYCOSIDES (FOXGLOVE, OLEANDER, LILY OF THE VALLEY, KALANCHOE)

Cardiac glycoside-containing plants pose a potential life threatening toxicosis to animals; that said, toxicosis has been reported to be more severe in large animals (who are chronically grazing on plants) as compared to dogs or cats. Based on this author's clinical experience, this type of plant is less commonly seen in small animal medicine, but still poses a potentially significant risk with ingestion. Cardiac glycoside plants contain naturally occurring cardiotoxic cardenolides or bufadienolides, which interfere with the Na-K pump mediated by ATPase. This results in increased intracellular sodium and decreased intracellular potassium.<sup>5</sup> Examples of cardiac glycoside plants include:<sup>5</sup>

- Dogbane
- Foxglove
- Giant milkweed
- Kalanchoe
- Lily of the valley
- Milkweed
- Oleander
- Star of Bethlehem

The toxins within these plants are similar to digitalis, and the degree of toxicity varies with the particular plant, part of the plant, and amount consumed.<sup>5</sup> All parts of the plant are generally considered toxic.<sup>5</sup> GI signs (e.g., nausea, hypersalivation, vomiting), profound cardiovascular signs (e.g., brady- or tachyarrhythmias, AV block, asystole), electrolyte abnormalities (e.g., hyperkalemia), or central nervous system (CNS) signs (e.g., mydriasis, tremors, seizures) may be seen.<sup>5</sup> Treatment includes decontamination, if appropriate, along with ECG and blood pressure monitoring. Clinicopathologic testing should be performed to evaluate for the severity of hyperkalemia and azotemia (which can be seen due to severe bradycardia and decreased cardiac output, albeit rare). The use of IV fluids, anti-emetics, and anti-arrhythmics are warranted. The antidote, digoxin-specific Fab fragments, can be considered in severe, life-threatening cases (rare); however, due to the cost, its use is often precluded.

## MUSHROOMS

While there are thousands of species of mushrooms in North America, less than 100 are poisonous; these are most commonly of the *Amanita* species. Unfortunately, mushrooms are very difficult to identify, and unless you are a mushroom expert/hunter or mycologist, then you should *never* eat a wild mushroom. Mushrooms sold in large-chain grocery store are safe and considered non-toxic to dogs. There are 5 main types of mushrooms that are poisonous, and they all work by different ways.

- The most dangerous type of mushroom contains amanitin toxins, which results in severe gastrointestinal signs (within 6-24 hours), a “false recovery” period (where your dog appears to get better), and then severe liver failure (at 36-48 hours post-mushroom exposure). Kidney failure can also develop in the end stages. Examples of these types of deadly mushrooms include *Amanita*, *Galerina*, *Lepiota*, *A. phalloids* (death cap, death angel), and *A. ocreata*.
- Another type of mushroom contains muscarine and causes profuse SLUDE signs (e.g., salivation, lacrimation, urination, diarrhea) and neurologic signs. They work somewhat similarly to the organophosphate and carbamates chemicals. Examples of these types of mushrooms include *Inocybe spp.* and *Clitocybe dealbata*.
- One type of mushroom contains muscimol and ibotenic acid, and causes profuse signs like ataxia, sedation and even tremors or seizures. Examples of these types of mushrooms include *Amanita muscaria* and *A.pantherina*.
- The false morel (*Gyromitra spp.*) causes profuse vomiting and diarrhea and is generally not fatal. Rarely, it can cause seizures.
- Some types of mushrooms just cause gastrointestinal irritation (e.g., vomiting, diarrhea) and are rarely life threatening when ingested. Signs can be seen in 1-6

hours, and generally resolve after 1-2 days. These types of mushrooms include the following types: *Agaricus*, *Boletus*, *Entoloma*

- Hallucinogenic mushrooms aren't life-threatening and rarely need treatment. That said, signs of ataxia, acting abnormal, howling, nystagmus, and hyperthermia can be seen when dogs ingest them. These types of mushrooms include the following types: *Psilocybe*, *Conocybe*, *Gymnopilus spp.*

As mushrooms are difficult to identify, treatment is based on “worst case scenario” (just in case it is *Amanita* spp.). As a result, treatment includes inducing vomiting (if appropriate), charcoal administration (to bind the poison from the stomach and intestines), anti-vomiting medication, and depending on what type of clinical signs are seen, anti-seizure medication, muscle relaxants, atropine and symptomatic supportive care.

### SAGO/CYCAD PALM

Sago palm, which are naturally found in tropical/subtropical environments (e.g., SE, S, SW United States) are life threatening to dogs and cats when ingested. Unfortunately, toxicosis can now be seen throughout North America; that's because these plants have grown in popularity and are now commonly sold as ornamental Bonsai houseplants. These plants are members of the Order Cycadaceae; genera *Cycads*, *Macrozamia*, and *Zamias*.<sup>6</sup> Examples of the cycad family include:<sup>6</sup>

- Cycad (*Cycas cirinalis*)
- Japanese cycad (*Cycad revolute*)
- Coontie plant (*Zamia pumila*)
- Cardboard palm (*Zamia furfuracea*)

All parts of sago palm are considered poisonous, with the female plant (e.g., seeds) being the most toxic part of the plant.<sup>6</sup> This plant contains cycasin, which is the primary active toxic agent resulting in hepatotoxicity. Ingestion results in acute GI signs (e.g., vomiting, diarrhea, hypersalivation) within 15 minutes to several hours after ingestion. Neurologic signs (e.g., weakness, ataxia, seizures, tremors, etc.) and severe acute hepatic necrosis (AHN) can be seen within 2-3 days post-ingestion. Clinical signs include vomiting, diarrhea, generalized malaise, anorexia, ascites, abdominal pain, icterus, and melena. Aggressive decontamination (if appropriate) and treatment should be initiated. Ideally, baseline blood work and coagulation parameters should be monitored. Treatment includes fluid therapy (e.g., IV crystalloids, colloids), anti-emetics, hepatoprotectants (e.g., SAME), Vitamin K<sub>1</sub> or plasma transfusion (if coagulopathic), anticonvulsants, and broad-spectrum antibiotic therapy (if in fulminant liver failure). The use of N-acetylcysteine (NAC) can also be used as a glutathione source. Unfortunately, the prognosis is grave once clinical signs of liver failure have developed, and long-term outcome is poor as the potential for chronic liver disease and underlying potential other damage exists.

### CONCLUSION

While the majority of plant ingestions in small animals often just result in GI signs, some plant ingestions can result in significant clinical signs and can even be fatal without treatment. As different plants have different mechanisms of action or levels of toxicosis, the [ASPCA Animal](#)

[Poison Control Center](#) should be consulted for plant ingestions that veterinarians are unaware of.



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NOTE: When in doubt, all drug dosages should be confirmed and cross-referenced with a reference guide such as *Plumb's Veterinary Drug Handbook*.

## RODENTICIDE TOXICITY: WHAT'S NEW?

Justine A. Lee, DVM, DACVECC, DABT, CEO, VETgirl

According to the [ASPCA Animal Poison Control Center](#), one of the top 10 toxicants that dogs accidentally ingest each year are rodenticides. Due to the growing prevalence or usage within the household, pets are accidentally getting exposed, particularly during the autumn months. New mandates by the EPA (effective 2011) have resulted in the reduction or elimination of certain anticoagulant rodenticides (ACR); instead, two ingredients – bromethalin and cholecalciferol – are increasing in use (and hence, secondary poisoning). So, before you reach for the antidote, Vitamin K<sub>1</sub>, read on! One of the most common mistakes seen in the field of veterinary toxicology is assuming that every green or blue block of rat or mouse poison is an ACR rodenticide. The active ingredient of a rodenticide *cannot* be identified based on physical appearance (e.g., color, shape, size, etc.). When in doubt, the EPA-Reg. number or active ingredient (and concentration) must be properly identified to ensure appropriate treatment and management of rodenticide toxicoses. Several different classes of rodenticides exist. When in doubt, contact the [ASPCA Animal Poison Control Center](#) for life-saving advice.

### BROMETHALIN

Bromethalin, a neurotoxic rodenticide, is marketed under several common brand names of Assault®, Tomcat Mole Killer®, Talpirid®, Real Kill®, Clout®, Fastrac®, Vengeance®, etc. Bromethalin is *not* an anticoagulant rodenticide and should *not* be treated with Vitamin K<sub>1</sub> as an antidote. Bromethalin works by uncoupling oxidative phosphorylation in the brain and liver mitochondria.<sup>1</sup> This results in decreased ATP production, which affects sodium and potassium pumps; as a result, lipid peroxidation occurs, resulting in sodium accumulation within the cell.<sup>1</sup> Edema of the central nervous system (CNS) may result.<sup>1</sup>

In dogs, the LD<sub>50</sub> of bromethalin is 2.38-3.65 mg/kg, with a minimum lethal dose being 2.5 mg/kg.<sup>1</sup> Cats are more sensitive to the effects of bromethalin, and the LD<sub>50</sub> is significantly lower (0.54 mg/kg).<sup>1</sup> Clinical signs are dose-dependent, and the onset of clinical signs depends on the amount ingested. Typically, with acute ingestion, signs may be seen within 2-24 hours.<sup>1</sup> Clinical signs of CNS stimulation or depression, abnormal behavior, ataxia, hyperesthesia, seizures, and coma may be seen.<sup>1</sup> Other common signs include paresis, hind limb paralysis, anisocoria, nystagmus, changes in the pupillary light reflex, and tremors may also be seen. Treatment includes early decontamination, prevention of cerebral edema, and symptomatic supportive care. With recent ingestion in an asymptomatic patient, the use of decontamination (e.g., emesis induction, activated charcoal) is warranted. As bromethalin undergoes enterohepatic recirculation, the use of multiple doses of activated charcoal (without a cathartic) can be administered q 6 hours for 24 hours. Patients should be monitored for signs of neurotoxicity. The use of IV fluid therapy, oxygen support, head elevation, mannitol (to decrease cerebral edema), anticonvulsant therapy, and thermoregulation is warranted if clinical signs develop. The use of intravenous lipid emulsion (ILE) is not recommended for treatment of this rodenticide. The prognosis for bromethalin toxicosis varies depending on the amount ingested and the severity of clinical signs; however, prognosis is generally fair to excellent with appropriate decontamination and treatment *prior* to development of clinical signs. In a recent IVECCS abstract presentation,<sup>a</sup> the prognosis and outcome was excellent with decontamination and supportive care. If persistent seizures or paralytic syndrome is seen, the prognosis is poorer.

## PHOSPHIDES

Phosphide rodenticides have been used since the 1930's and are still readily available on the market.<sup>2</sup> Aluminum phosphide is a pelleted product used as a fumigant in grain storage silos, while the more common zinc phosphide is labeled for use in control of rats, mice, ground squirrels, prairie dogs, voles, nutria, muskrats, feral rabbits, and gophers.<sup>2</sup> Zinc phosphide, a crystalline, grey powder, is available in 2-10% concentrations as grain or sugar-based baits in a powder, pellet, tablet, or paste formulation.<sup>2</sup> Trade names of some of the commercially available zinc phosphide products include: Gopha-Rid, Gopher Bait II, Rodenticide AG, This is the Way, Prozap, Hopkins, and Sweeney's Poison Peanuts Mole.<sup>2</sup> Formulations of phosphides have a unique, distinctive odor similar to rotten fish, garlic, or acetylene.<sup>2</sup> The toxic dose of zinc phosphide in dogs is approximately 20-40 mg/kg, but up to 300 mg/kg on an empty stomach.<sup>3</sup> With zinc phosphide, the administration of food (e.g., bread, milk, etc.) is contraindicated, as it may potentially release gastric acid, promoting hydrolysis and further production of phosphine gas.<sup>3</sup>

Phosphide rodenticides result in the production of phosphine gas. When zinc phosphide combines with gastric acid or moisture (or the presence of food!), liberated phosphine gas is rapidly absorbed across gastric mucosa and distributed systemically, where it exerts its toxic effect. Phosphine gas is considered a corrosive and a direct irritant to the gastrointestinal tract (GIT). Clinical signs can be seen within 15 minutes to 4 hours; death has been reported within 3-48 hours.<sup>3</sup> Clinical signs include severe gastrointestinal (GI) signs (e.g., vomiting, bloat, abdominal pain, hematemesis, melena, etc.), CNS signs (e.g., tremoring, seizing, death), and rarely, cardiopulmonary signs (e.g., pulmonary edema, tachypnea, pleural effusion, etc.) or organ dysfunction.<sup>3</sup> *This type of rodenticide is potentially poisonous to you, your pet owner, and your staff too!* Zinc phosphide also carries a public health risk. Emesis – whether intentionally induced or occurring due to clinical signs - can result in poisoning to the pet owner or the veterinary professional secondary to exposure of phosphine gas. Clinical signs of nausea and difficulty breathing have been reported in humans exposed. To minimize these risks, emesis induction should always be performed in a well-ventilated area (e.g., opening the car window if the patient vomits or inducing emesis outside or in a well-ventilated area). Pet owners should be appropriately educated on the toxic gas exposure to themselves also. Pet owners should be informed *not* to feed their pet to prevent further production of phosphine gas. In addition, the administration of an antacid (e.g., aluminum hydroxide) prior to emesis induction may help decrease the presence of phosphine gas. With recent ingestion in an asymptomatic patient, the use of emesis induction (following antacid administration) and one dose of activated charcoal with a cathartic is warranted to minimize toxic effects of zinc phosphide. Symptomatic supportive care, including anti-emetic therapy, IV fluid therapy, gastric protectants, and analgesics are warranted. Based on a recent paper by Gray et al,<sup>2</sup> the prognosis is excellent with supportive care.

## CHOLECALCIFEROL

Cholecalciferol, the chemical name for vitamin D<sub>3</sub>, is one of the most deadly– and costly – rodenticides to pets. Ingestion of toxic levels of cholecalciferol can result in severe hypercalcemia and hyperphosphatemia, with secondary acute kidney injury (AKI) developing as a result of dystrophic mineralization to the soft tissue and kidneys. Common sources of Vitamin D<sub>3</sub> include over-the-counter (OTC) or prescription vitamins (typically found in a calcium/Vitamin D<sub>3</sub> combination), psoriasis creams (in the form of calcipotriene), and rodenticides. With



cholecalciferol-containing rodenticides, only a tiny amount of rodenticide needs to be ingested before clinical toxicosis occurs due to a very narrow margin of safety within these products. In dogs, cholecalciferol has an LD<sub>50</sub> of 85 mg/kg (based on the rodenticide concentration of 0.075%).<sup>4</sup> Doses of Vitamin D<sub>3</sub> > 0.1-0.5 mg/kg can result in clinical signs and hypercalcemia, respectively.<sup>4</sup> Typically, clinical signs often do not develop for 1-3 days until the patient has already developed clinical signs of AKI.<sup>4</sup> That said, AKI can occur within 12-36 hours following toxic ingestion. Clinical signs and clinicopathologic findings include increased thirst and urination, weakness, lethargy, anorexia, vomiting, generalized malaise, uremic halitosis, dehydration, hypercalcemia, hyperphosphatemia, azotemia, melena, hemorrhagic diarrhea, and death.<sup>4</sup> Decontamination should include emesis induction, if ingestion was recent and the patient is asymptomatic. As cholecalciferol undergoes enterohepatic recirculation, the administration of multiple doses of activated charcoal (without a cathartic) is warranted q 6 hours X 24 hours; more recently, the **ASPCA APCC** has advocated for the use of cholestyramine, a biliary sequestrant. In the past, aggressive treatment was recommended for treatment of cholecalciferol toxicosis, due to the narrow margin of safety. This included the use of aggressive IV fluid therapy, drugs to promote calciuresis (e.g., steroids, furosemide), and drugs to lower calcium levels (e.g., pamidronate, calcitonin). However, *more recently*, the **ASPCA APCC** has modified therapy to withhold the above aggressive treatment *until the patient becomes hypercalcemic*; this is due to the hypothesis that disruption of calcium homeostasis occurs with aggressive treatment.

If the patient becomes hypercalcemic 24-48 hours post-ingestion, aggressive use of IV fluid therapy to promote calciuresis (e.g., 0.9% NaCl), calcium monitoring, GI support (e.g., anti-emetics, H<sub>2</sub> blockers, sucralfate, phosphate binders, etc.), and the use of medications to increase calciuresis (e.g., prednisone, furosemide) and prevent hypercalcemia (e.g., pamidronate, calcitonin). Once the patient develops hypercalcemia, treatment can be expensive, and requires hospitalization for an extended period of time. Some patients may be continued on oral furosemide and prednisone for weeks, following discharge from the hospital. Frequent monitoring of renal function and electrolytes is imperative. Calcium, phosphorous, BUN, creatinine, and ionized calcium should be evaluated every 12-24 hours while hospitalized, and then every 2-3 days thereafter for the next 2-4 weeks. This will allow one to assess the ability to titrate the prednisone and furosemide therapy, and to ensure that the patient does not develop secondary AKI [or potentially chronic renal failure (CRF)]. Even with aggressive treatment, CRF may be a secondary sequela. When in doubt, the **ASPCA APCC** should be consulted.

### ANTICOAGULANT RODENTICIDES (ACR)

First and second generation ACR anticoagulants result in inhibition of Vitamin K epoxide reductase, resulting in inactivation of clotting factors II, VII, IX, and X. First generation rodenticides (e.g., warfarin, pindone)<sup>5</sup> had been largely replaced by more potent second-generation anticoagulants (e.g., brodifacoum, bromadiolone, diphacinone, chlorophacinone, etc.);<sup>5</sup> however, recent EPA mandates have eliminated many second generation ACRs due to relay toxicosis. Each individual ACR varies in the margin of safety and LD<sub>50</sub>. Some have very narrow margins of safety (e.g., brodifacoum), while some have very wide margins of safety (e.g., bromadiolone). When in doubt, the toxic dose should be calculated, or the **ASPCA APCC** contacted to determine if a toxic dose has been ingested. Finally, keep in mind that species differences exist; cats are much more resistant to the affects of ACR as compared to dogs.

**Canine LD<sub>50</sub>**

Difethialone:	4 mg/kg
Brodifacoum:	0.25-4 mg/kg
Bromadiolone:	11-20 mg/kg
Diphacinone:	3-7.5 mg/kg

**Feline LD<sub>50</sub>**

> 16 mg/kg
25 mg/kg
> 25 mg/kg
> 15 mg/kg

When a toxic ingestion of ACR has occurred, prolongation in coagulation factors [prothrombin (PT) or activated partial thromboplastin time (aPTT)] is not seen for 36-48 hours, as based on the half-life of factor VII. Clinical signs typically do not develop for 3-5 days. Clinical signs are due to clotting factor depletion, resulting in generalized hemorrhage. The most common clinical signs include lethargy, exercise intolerance, inappetence, pallor, dyspnea, coughing, hemoptysis, etc. Hemoabdomen, hemothorax, pericardial effusion may also occur. Rarer clinical signs include gingival bleeding, epistaxis, ecchymosis, petechiae, hematuria, bleeding into the subcutaneous space or joint space, and melena.<sup>5</sup>

Errors are often made by veterinary professionals when it comes to the medical management of ACR rodenticides. While it is often appropriate to decontaminate a patient with emesis induction and activated charcoal administration, with non-toxic ingestions (based on the LD<sub>10</sub>), this is often unnecessary (unless the patient is neonatal, geriatric, has an underlying hepatopathy, or has previously ingested a ACR before). Next, the administration of a “one-time,” parenteral injection of vitamin K<sub>1</sub> at the time of decontamination is unnecessary and potentially detrimental. First, vitamin K<sub>1</sub> is faster absorbed *orally* than parenterally (particularly with a fatty meal). Another reason why the “one-time shot” should be avoided is because it will skew point-of-care, accurate blood results of the PT test. As factor VII has the shortest half-life, PT will be the first blood test to be prolonged with ACR ingestion; however, this prolongation of the PT will not normally occur until approximately 36-48 hours post-ACR ingestion. Testing prior to this time is unnecessary (unless the patient has been chronically ingesting a ACR over several days), as the PT will be normal prior to 36-48 hours. By administering a “one-time shot” of Vitamin K<sub>1</sub> therapy, the patient’s PT will be falsely normal at 48 hours, and instead, the patient will be coagulopathic days later (3-5 days, instead of 2 days). Normally, clinical signs of acute, ACR toxicosis typically occur at 3-5 days post-ingestion. With a “one-time shot,” the patient will bleed out at 5-7 days instead of 3-5 days!

When treating ACR rodenticides, two considerations for treatments should be utilized.

- 1) With an acute, one-time ingestion of a ACR, one can decontaminate and check a PT 48 hours post-initial ingestion. If the PT is prolonged at 48 hours, 3-4 weeks of Vitamin K<sub>1</sub> therapy should be initiated (3-5 mg/kg PO, divided SID-BID X 4 weeks). A recheck PT should be performed 48 hours after the last dose; if prolonged, an additional 2 weeks of therapy is indicated, with another PT performed 48 hours after the last dose OR
- 2) With an acute one-time ingestion of a ACR, one can just prophylactically treat with Vitamin K<sub>1</sub> therapy, particularly if the patient is young, debilitated, geriatric, or has underlying liver pathology. Treatment includes Vitamin K<sub>1</sub> therapy (3-5 mg/kg PO, divided SID-BID X 4 weeks), with a recheck PT being performed 48 hours after the last dose; if prolonged, an additional 2 weeks of therapy is indicated, with another PT performed 48 hours after the last dose.

## CONCLUSION

In general, the prognosis for rodenticide toxicosis depends on time to decontamination, appropriate identification of the active ingredient, and prevention and treatment of clinical signs. Overall, the prognosis is excellent for most rodenticides; however, aggressive therapy is warranted to prevent morbidity.

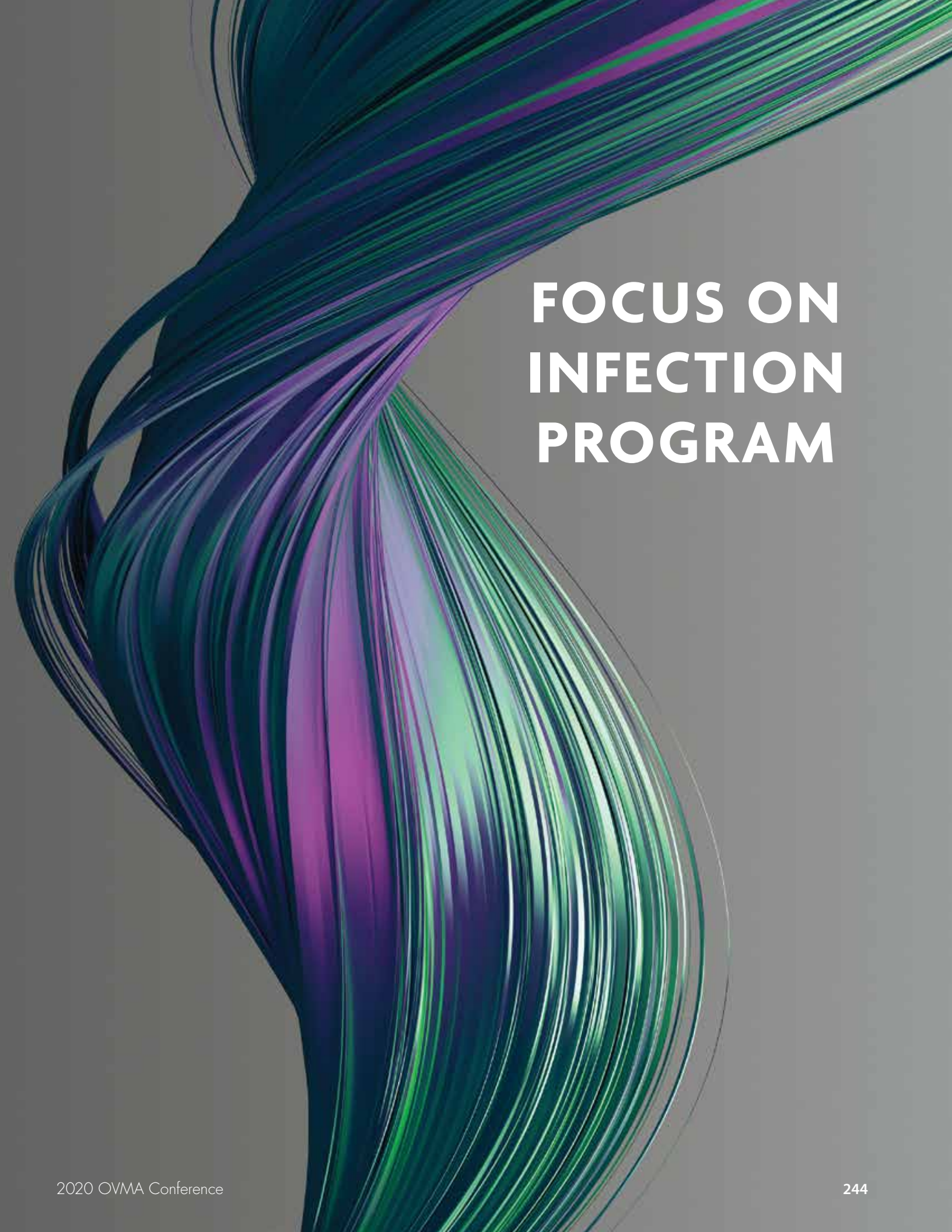
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NOTE: When in doubt, all drug dosages should be confirmed and cross-referenced with a reference guide such as *Plumb's Veterinary Drug Handbook*.



# **FOCUS ON INFECTION PROGRAM**

## Hot topics in Infectious Diseases

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Infectious diseases continue to create challenges in veterinary medicine. A range of issues are present, including ongoing challenges from endemic diseases, changing patterns of endemic diseases, newly recognized diseases and introduction of previously foreign pathogens.

### *Brucella canis*

In the past, *B. canis* has been considered a largely foreign pathogen, most often associated with dogs imported from areas such as Mexico. However, in the past year, two areas of concern have been identified. One is more identification of *B. canis* from imported dogs. In addition to the typical high risk areas (e.g. Mexico), *B. canis* importation has been identified in dogs from various parts of Asia and Eastern Europe, including China, South Korea, Russia and Ukraine. Infected dogs from breeders in the US have also been identified. This has resulted in identification of clinically affected dogs of carriers in households and breeding kennels. Routine testing of all imported dogs should be considered to allow for prompt diagnosis and owner counselling.

An additional (and greater) concern is the recent identification of endemic *B. canis* in commercial puppy breeding operations in southern Ontario. These have been in kennels encountering reproductive losses, as well as kennels with no overt problems. Well over 150 positive breeding dogs have been identified, with that presumably accounting for a distinct minority of cases. Infected puppies have subsequently been identified in households. The zoonotic risks of *B. canis* are not well understood but it is clearly a zoonotic disease, with greatest risk being from contact with fluids and tissues at the time of whelping.

The difficulty in eliminating infection and having confidence that the bacterium is eliminated complicates management of cases and client counselling. The need for spaying or neutering as part of the control strategy has led to widespread culling in affected kennels, but treatment of numerous pet dogs has been attempted. The need for long-term treatment and repeated testing after treatment, with little assurance of permanent resolution, creates many challenges. Because of the spread of this bacterium in commercial breeders, *B. canis* screening should be considered in any dog does not come from a kennel of known negative *B. canis* status (through annual or biannual testing of all breeding dogs).

### Blastomycosis

Blastomycosis, caused by the dimorphic fungus *Blastomyces dermatitidis*, is a regionally important disease in Ontario. Infectious spores live in the soil and inhalation of inoculation can result in infection. Blastomycosis is most common in dogs (and to a lesser degree cats) around Georgian Bay and northwestern Ontario, but sporadic cases can be found throughout the province. Understanding the regional distribution of blastomycosis is important for veterinarians practicing in endemic areas and for querying travel history. Canine blastomycosis is also a relevant One Health issue as dogs and humans are infected from the same source, contaminated environments. Dogs can be sentinels for human exposure risk (and vice versa). Now a reportable disease in people, record numbers of human blastomycosis cases were identified in 2019.

### Leptospirosis

Leptospirosis has been called a 're-emerging' disease for the past 15 years, but it is clear that it should actually be called a widespread endemic disease in Ontario. While the incidence of leptospirosis in dogs varies to some degree across the province, virtually all of the province (except perhaps extreme northern regions) is an endemic area, with the main

reservoirs likely being raccoons (serovar Grippotyphosa) and rodents (serovar Icterohemorrhagiae). Leptospirosis should be considered in dogs with acute renal disease, particularly if there is evidence of concurrent hepatic involvement. A variety of testing options are available, and the relative usefulness of each test varies with factors such as vaccination history and whether antimicrobials have been administered. Leptospirosis vaccination should be considered in virtually all dogs in Ontario, as exposure to contaminated sites from raccoon or rodent urine is difficult to avoid. Leptospirosis was previously considered a disease mainly of large breed dogs in rural areas. However, small breed dogs in urban regions are now the most commonly affected group, likely because of exposure to raccoon urine in urban parks.

#### Antimicrobial Resistance

Antimicrobials have been hailed as one of the greatest (in not the greatest) medical discovery. It should not be surprising, therefore, that antimicrobial resistance has been described as one of the main challenges facing humanity. Any use of antimicrobials creates some potential for resistance, and the massive use of antimicrobials in humans, food animals and companion animals creates a complex epidemiology and ecology of antimicrobial resistance. Resistance in companion animals can be from various sources, including food (e.g. *Salmonella*, multidrug resistant Gram negative bacteria), human contacts (e.g. MRSA), animal contacts (e.g. MRSP), the environment (e.g. resistant Gram negatives, *Pseudomonas*) and mutation of endogenous bacteria during treatment. Antimicrobial resistance will never be eliminated, but its impact can potentially be limited through the use of good antimicrobial stewardship in food animals, humans and companion animals. The emergence and dissemination of multidrug resistant Gram negative pathogens, particularly extended spectrum beta-lactamase (ESBL) producing Enterobacteriaceae (e.g. *E. coli*) is of particular concern given the increasing rates that are seen in companion animals and the limited treatment options that may be present.

#### Tickborne Diseases

Climate change and changes in tick ecology have resulted in continued emergence and spread of some tick species, and their associated pathogens. Of particular concern in Ontario is Lyme disease. As the blacklegged tick expands in Ontario, Lyme disease risk areas expand correspondingly. Understanding regional Lyme disease risk is important for decisions about tick prevention and vaccination, and for consideration of Lyme disease as a differential diagnosis. New initiatives are underway to track ticks from dogs and cats in Ontario, to better define the risk of exposure to ticks and tickborne disease.

## LEPTOSPIROSIS

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### Introduction and Pathophysiology

Leptospirosis is a zoonotic bacterial disease caused by a spirochetal bacterium of the genus *Leptospira*. There are many different types of *Leptospira* organisms that occur worldwide including within Ontario, and only a few of the strains are pathogenic to dogs. Optimal survival conditions for the bacteria include stagnant or slow-moving water, neutral or alkaline pH and ambient temperatures between 0 – 25 degrees Celsius. The bacteria are maintained in the renal tubules of the reservoir host and excreted in the urine. Water contact is the most common means of spread; *Leptospira* organisms invade the host through skin wounds or through intact mucous membranes from the water. Leptospire damage organs by replicating and inducing cytokine production and recruitment of inflammatory cells. Although most cases present with acute clinical illness, there are rare reports of chronic disease due to leptospirosis.

### Clinical Syndromes

The two most common clinical syndromes involve renal or hepatic dysfunction, however leptospirosis patients may also present with conjunctivitis, uveitis, pulmonary hemorrhage, acute febrile illness, pancreatitis and bleeding tendencies. Azotemia (elevated urea and creatinine) is present in greater than 80 – 90% of dogs. This may be accompanied by changes in the urinalysis, which include a decreased urine specific gravity, glucosuria, granular casts and proteinuria. Hepatic dysfunction may be manifested by increases in serum ALT, AST and ALP activities and total bilirubin concentration, which is often in conjunction with azotemia. Electrolyte abnormalities may be a consequence of gastrointestinal or renal fluid losses, resulting in hyponatremia, hypochloridemia, hypokalemia and hyperphosphatemia. Findings on the complete blood cell count (CBC) may include neutrophilia, lymphopenia, non-regenerative anemia and thrombocytopenia. Coagulation parameters, such as the prothrombin time (PT) and partial thromboplastin time (PTT) are often abnormal, and can vary from mild changes to occasional life threatening dysfunction.

When imaging is performed in dogs with leptospirosis, there are no pathognomonic changes noted with any imaging modality. Thoracic radiographs can vary from normal, to nodules and areas of consolidation that can mimic neoplasia or bronchopneumonia. In addition, a generalized bronchointerstitial pattern can be seen, which can mimic chronic bronchitis. Abdominal ultrasound of the liver and kidneys can appear normal in dogs with severely elevated renal and/or hepatic parameter, or non-specific changes can be seen.

### Diagnostic Testing

There are several options available for the diagnosis of leptospirosis, and selection of the appropriate test or tests is not straight-forward. The vaccination history of the dog must be considered, along with recent use of antibiotics (see summary below). Options for testing include polymerase chain reaction (PCR), which detects DNA of the *Leptospira* organism in samples, and antibody tests, which include the microscopic agglutination test (MAT), ELISA antibody test, and the bedside IgM Witness antibody test.

Polymerase chain reaction is a relatively rapid test that detects *Leptospira* nucleic acid in blood, urine, CSF and aqueous humor, although paired blood and urine testing is the most common method of detection. In the first 10 days of infection, organism numbers are highest in the blood. After that time, organisms are present in the highest concentration in the urine. In clinical infections the time of infection is unknown, therefore simultaneous testing of blood and urine is

recommended to increase diagnostic sensitivity. Vaccination should not affect PCR results, however recent antimicrobial therapy can result in false negatives. I would not recommend performing PCR testing if the dog is currently receiving an antimicrobial used for the treatment of leptospirosis, as the result is likely to be negative. Even if a dog has not had recent antimicrobial therapy, a negative result does not rule out leptospirosis because samples may have been obtained when organism numbers in a sample are low. While a positive result confirms infection, a negative test should prompt additional testing to rule out leptospirosis as there is the possibility of a false negative result.

Antibody-based tests (MAT, ELISA and Witness) are not affected by antimicrobial therapy, but are affected by vaccination. The administration of a *Leptospira* vaccine prompts an antibody-based immune response. Therefore, a positive antibody test could be detecting vaccinal antibodies, as opposed to antibodies due to clinical infection (a false positive). However, the duration to which a leptospirosis vaccine affects the outcome of an antibody test is test-dependent. The MAT and ELISA tests are primarily detecting IgG antibodies which persist for months to years, therefore these tests are affected by vaccination for months to years. Use of paired titers 2-4 weeks apart helps to differentiate vaccination from infection in the MAT test. The Witness antibody test detects IgM antibodies, which are relatively short-lived after vaccination. Therefore, most dogs will have a negative Witness test within 2-3 months of vaccination, if not sooner. Both the Witness and ELISA *Leptospira* antibody tests are qualitative (provide only a positive or negative result) and are not serovar-specific, while the MAT provides a titre for each *Leptospira* serovar tested. However, the serovar which has the highest titre with the MAT is often not the actual infecting serovar, therefore serovar information from the MAT test is of reduced benefit. Knowing the infecting serovar does not alter treatment decisions.

The Witness *Leptospira* Antibody Test was introduced in the spring of 2018 in Canada. This test provides a negative or positive result, without information on serovar. This test has been used in Europe for several years, and was recently introduced in the USA. This is a bedside antibody test that detects IgM antibodies. As IgM antibodies are produced early in the course of disease, their production decreases a few weeks after infection. The test is therefore only useful for acute leptospirosis infections, but that comprises almost all cases. The test is not affected by antimicrobial therapy. The Witness test is affected by vaccination (false positive), but only for a few weeks after vaccination. Because IgM levels begin to rise a few days after infection, it is possible to have a negative result early in the course of disease (false negative). If clinical suspicion remains high, a repeat test 2-4 days later is recommended. Due to the low cost of the test, this is more feasible than with some of the other tests. The Witness *Leptospira* Antibody Test is an in clinic test that can be performed within 10-20 minutes, and utilizes whole blood, plasma or serum.

The microscopic agglutination test (MAT) involves reacting serial dilutions of patient serum with several live leptospiral organisms, followed by assessment of organism agglutination. The highest serum dilution causing 50% agglutination is reported. False negative results may occur early in the course of the disease. Although a single positive titer can increase suspicion for the disease, it does not often confirm a diagnosis, particularly if the dog has been vaccinated for leptospirosis at any time in their life. To increase the diagnostic utility of the test, acute and convalescent antibody testing should be performed two to four weeks apart. A four-fold increase in titer supports recent infection; convalescent titers in vaccinated dogs are generally stable or decreased after 2-4 weeks, unless vaccination was very recent.

The *Leptospira* ELISA antibody test is provided at Idexx Canada. This test provides a negative or positive, as seen with the Witness test, without information on infecting serovar. This ELISA



test is not affected by antimicrobial use, but is affected by vaccination. The test will be positive in dogs for months to years after vaccination, therefore may be positive in dogs with up to date vaccination, and also potentially in dogs with out of date vaccination. A negative result is useful in ruling out leptospirosis unless the dog was infected very recently, in which case a false negative is possible. A positive result in a dog confirmed to have *never* received a *Leptospira* vaccine confirms leptospirosis. A positive result in a vaccinated dog indicates that further testing for leptospirosis is needed (PCR +/- Witness or MAT titres if no antibiotics used, Witness or MAT titres if antibiotics used).

Diagnostic testing for leptospirosis cases is not straight-forward. Given the utility of the Witness *Leptospira* antibody test and its low cost, it is worth using as the primary test for leptospirosis in most cases. However, other approaches are needed if the dog has been vaccinated in the previous few weeks.

### Summary of Diagnostic Steps:

Dog that has NOT received antibiotics and is NOT vaccinated:

- Start with Witness *Leptospira* antibody test if you have it in clinic
- Otherwise *Leptospira* spp. Panel (ELISA and PCR)
- If positive on any you have your diagnosis
- If negative and clinical suspicion remains high, repeat testing or do MAT, administer appropriate antibiotics in case of false negative

Dog that has NOT received antibiotics and IS vaccinated in the previous 3 months:

- *Leptospira* spp. PCR
- If positive you have your diagnosis
- If negative and clinical suspicion remains high, do MAT, administer appropriate antibiotics in case of false negative on PCR

Dog that has received antibiotics and is NOT vaccinated:

- Start with Witness *Leptospira* antibody test if you have it in clinic
- Otherwise *Leptospira* spp. ELISA
- If positive on any you have your diagnosis
- If negative and clinical suspicion remains high, repeat testing or do MAT

Dog that has received antibiotics and IS vaccinated in the previous 3 months:

- Acute and convalescent MAT titres

Dog that has received antibiotics and IS vaccinated but not in the previous 3 months:

- Start with Witness *Leptospira* antibody test if you have it in clinic
- Acute and convalescent MAT titres

### Treatment of Leptospirosis

Antimicrobial therapy is essential and should be initiated quickly, prior to confirmation of the diagnosis other than with the bedside Witness *Leptospira* antibody test. The goal of the first stage of treatment is to immediately inhibit multiplication of the organism and rapidly reduce fatal complications of infection. The optimal treatment for Leptospirosis is still unknown, as is the optimal duration of antimicrobial therapy. Doxycycline, at a dosage of 5mg/kg orally q12hr for two weeks, is recommended. Care must be taken to ensure that the doxycycline pill is completely swallowed, as esophageal erosion can occur readily. If vomiting or other adverse reactions preclude doxycycline administration, treatment with ampicillin at 22mg/kg IV q8hr is

recommended (or an oral equivalent). Supportive therapy for animals with Leptospirosis depends on the severity of the clinical signs and whether renal or hepatic dysfunction is present. For stable patients, outpatient treatment with doxycycline can be pursued. Otherwise, patients should be admitted to hospital and medically managed based on their presenting clinical signs and clinicopathological abnormalities. Treatment with ampicillin alone may not clear renal infection or eliminate the carrier state and chronic shedding. The goal of the second stage of treatment, therefore, is to eliminate the carrier state. The recommendation is, either initially or eventually, two weeks total of doxycycline.

When Leptospirosis has been confirmed, all other dogs in the household should be tested, and treated if leptospirosis is confirmed. Subclinical seroconversion has been documented in some dogs living in the same household with dogs with Leptospirosis; this is likely due to exposure to the same environment rather than direct infection from the other dog. The recommended treatment is doxycycline 5mg/kg orally every 12 hours for 14 days. Provided severe respiratory complications are absent from the clinical picture, the prognosis for dogs treated early and aggressively is good. Survival rates of approximately 80% have been reported, both among those dogs treated conservatively and those treated with dialysis.

### Vaccination

Currently, bacterin-based vaccines containing serovars Icterohaemorrhagiae, Canicola, Grippotyphosa and Pomona are available in North America. Vaccines appear to fairly effectively prevent disease from the vaccinated serogroup, and it is possible that there is some cross-reactivity to other serogroups. Some vaccines carry the label claim of the prevention of, or aid in the prevention of, urinary shedding. Vaccines are recommended annually, following a two-injection initial series. As inactivated bacterins, leptospiral vaccines have been thought to be at increased risk of causing allergic reactions. In a study of acute vaccine reactions in dogs utilizing a large database, vaccines containing leptospiral antigen were no more reactive than other vaccines for dogs. Consequently, annual vaccination with the four-serovar vaccine is recommended for at-risk dogs, regardless of breed, with the understanding that the definition of at-risk may vary geographically. Annual vaccination for dogs that have recovered from leptospirosis should be considered because such dogs are at risk of ongoing exposure and life-long immunity may not be provided after natural infection.

Vaccination results in positive results to the MAT. However, the degree of increase in the titre is quite variable. The greatest increase in titre may not be for the serovar in the vaccine. In fact, in some cases no measurable titre is found after vaccination for some of the serovars in the vaccine. Titres immediately after vaccination can be quite high, in some cases up to 1:12,800. There is no cut off above which one can be confident that a titre is due to natural infection rather than vaccination. Typically, titres decline to <1:100 to 1:200 after about 16 weeks, although there are no detailed studies on the increase and decrease seen over time secondary to vaccination. It is not possible to make a rapid definitive diagnosis of clinical leptospirosis in a recently-vaccinated dog. However, evaluation of the convalescent titre should provide a diagnosis; a four-fold increase is expected in natural infection, whereas stable to decreased titres are expected in a vaccinated dog, depending on the timing of vaccination.

### Prevention

Prevention of leptospirosis includes vaccination if indicated, and avoidance of contact with the organism. Knowledge of the environments that support *Leptospira* organisms improves the chance of avoidance. Areas to avoid are damp areas in moderately warm climates, with access by wild animals. This includes standing or slow-moving water, moist ground, and damp foliage. There are known risk factors for the development of clinical leptospirosis, and these include

spending time outdoors, exposure to wild animals which is enhanced by urbanization of the environment, exposure to water especially in areas with flooding, lower socioeconomic areas, living within 2.5 km of a university/college or park/forest, years with high rainfall, housing in kennels or shelters, being of ages 4-10 years old, and lack of vaccination. There is debate as to whether cats are also one of the animals carrying *Leptospira* organisms, with resultant shedding in the environment. The most important aspect of prevention is avoidance of wild animal urine. Routine household disinfectants are effective against *Leptospira* organisms.

### Feline Leptospirosis

Clinical feline leptospirosis is rare; there are sporadic reports in the literature. The rare reports that do exist have renal manifestations of disease, rather than hepatic. Diagnostic tests that are utilized in cats include PCR testing and MAT. There are conflicting reports about the significance of the feline population in carrying the *Leptospira* organism and therefore potentially shedding it into the environment. Many studies have indicated that the importance of the feline population as asymptomatic carriers of the *Leptospira* organism is underestimated, while some studies have indicated a low proportion of carriers. Likely there is geographic variability in the proportion of cats shedding the bacteria.

Treatment of cats proven to carry *Leptospira* is the same as for dogs; doxycycline, at a dosage of 5mg/kg orally q12hr for 14 days. As with dogs, care must be taken to ensure that the doxycycline pill is completely swallowed, as esophageal erosion can occur readily. As there is no vaccine licensed for cats, prevention is solely by reducing exposure to the wild animal population. This is best attained by keeping cats indoors.

### Summary

Leptospirosis is an important disease affecting dogs in Ontario. There does seem to be an increase in clinical cases noted, but vaccination will help to reduce the number of cases. Given the extension of wild animals' habitat into suburban and urban areas, all dogs are at risk for exposure to this bacteria. Testing for leptospirosis can be complex, however there are guidelines available to assist in selection of appropriate tests. Prompt diagnosis and treatment results in an excellent prognosis in most cases. Feline leptospirosis is rare, but the degree to which cats infect the environment is yet to be proven.

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## **ECHINOCOCCUS MULTILOCULARIS: AN EMERGING THREAT TO DOGS AND PEOPLE IN ONTARIO?**

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### **INTRODUCTION**

*Echinococcus multilocularis* is a zoonotic tapeworm that occurs in central Europe, much of northern, central and eastern Eurasia, and parts of North America (Eckert and Deplazes 2004). Adult parasites reside within the small intestine of definitive hosts, which are primarily wild canids (e.g. foxes, coyotes, wolves). However, in some areas, domestic dogs, and to a lesser extent cats, may act as definitive hosts. Eggs shed in the feces of these species are morphologically indistinguishable from *Taenia*-type eggs and are immediately infective for intermediate hosts which include various species of wild rodents. Subsequent to ingestion, a hexacanth embryo is released from the egg, travels to the liver via the hepatic portal circulation and develops into the intermediate, metacestode, stage (Eckert and Deplazes 2004). This larval stage of the parasite is comprised of numerous small vesicles lined with a germinal epithelium from which multiple protoscolices may develop, undergoes exogenous budding, and behaves like an invasive tumour (Eckert and Deplazes 2004). The resultant disease, alveolar echinococcosis (AE), is associated with extensive damage to the liver and occasionally spread to other locations within the intermediate host. When an infected intermediate host is ingested by a definitive host the life cycle is completed; development to the mature tapeworm takes approximately 4-5 weeks (Deplazes et al 2011). Ingestion of eggs by people may also result in AE, a potentially severe, fatal disease that is currently an emerging issue in parts of central Europe (Gottstein et al 2015).

In North America, *E. multilocularis* has historically been considered to occur in two distinct geographic regions: the Northern Tundra Zone that extends from the west coast of Alaska to parts of the Canadian arctic (Eckert et al 2000), and the North Central Region that historically included the southern parts of 3 Canadian provinces (Alberta, Saskatchewan, Manitoba) and 13 neighbouring USA states (North/South Dakota, Iowa, Minnesota, Montana, Wyoming, Nebraska, Illinois, Wisconsin, Indiana, Ohio, Missouri, Michigan) (Eckert et al 2000; Kazacos 2003). Within this latter region, red foxes and coyotes are considered the primary definitive hosts; the most significant intermediate hosts include voles and mice (Eckert and Deplazes 2004; Kapel et al 2006). Strangely, despite this large geographic distribution, there are very few reports of *E. multilocularis* intestinal infections in dogs or cats in either the USA or Canada. Outside Alaska, intestinal infections in dogs appear to have been described only once; using molecular methods, *E. multilocularis* was identified in the feces of 1/218 dogs in 2014 in Alberta (Massolo et al 2014). Similarly, only 5 cats have been reported with intestinal infections; 3 in 1971 in Saskatchewan, and 2 in 1972 in North Dakota (Leiby and Kritsky 1972). Likewise, only 3 cases of alveolar echinococcosis in people are described that appear to have been acquired within the USA or Canada; one in 1937 in Manitoba, one in 1979 in Minnesota, and one in 2014 in Alberta (Massolo et al 2014).

Information concerning dogs as definitive hosts for *E. multilocularis* is contained in veterinary parasitology textbooks. However, what is missing in almost every book is the fact that since the late 1980s, cases of AE, primarily involving the liver, have been described in dogs in Switzerland, Germany, France and Belgium (Deplazes and Eckert 2001). These cases are thought to occur as a result of either ingestion of large numbers of eggs or by autoinfection in association with the presence of adult tapeworms in the small intestine (Corsini et al 2015).

## CASES OF CANINE ALVEOLAR ECHINOCOCCOSIS IN NORTH AMERICA

Prior to 2009, *E. multilocularis* had not been diagnosed in a dog in Canada. However, in that year hepatic AE was diagnosed in a 3-year old dog that had lived permanently in British Columbia; *E. multilocularis* was identified on histology and direct immunofluorescence of hepatic tissue; sequence data for the mitochondrial 12S rRNA gene, and RFLP analysis of the mitochondrial NADH dehydrogenase 1 and 12S rRNA genes, confirmed the diagnosis (Peregrine et al 2012). In 2012, a second case was similarly diagnosed in a 2-year old dog that resided in southern Ontario (Skelding et al 2014). Between 2013 and 2018, five additional cases were diagnosed in southern Ontario. None of the 7 dogs in British Columbia and Ontario were related and none had travelled outside Canada; 6 of the dogs had lived their entire lives in provinces where *E. multilocularis* had not been diagnosed prior to the occurrence of these cases.

## CLINICAL PRESENTATION AND DIAGNOSIS

Corsini and others recently published a retrospective analysis of twenty confirmed (n = 18) or probable (n = 2) cases of canine AE in Europe (Corsini et al 2015). The median age at diagnosis was 3.1 years (range = 1.1-10.7 years) and the most common clinical signs included abdominal distension, lethargy, anorexia and vomiting; less common clinical signs included diarrhea, weight loss, polypnea, fever and polyphagia. Most dogs had lived all their adult lives in areas where foxes occurred and were exercised outdoors.

### Abdominal ultrasound and clinical pathology

In dogs with clinical AE, abdominal ultrasound typically reveals the presence of multiple, large, heterogeneous, poorly limited, cavitated hepatic masses. Usually, there is a hyperechoic thick periphery, an irregular inner surface, and a centrally located cavity filled with corpuscular fluid (Corsini et al 2015). Extension to neighbouring organs is observed in approximately one third of cases; free abdominal fluid is present in a similar proportion (Corsini et al 2015). In many dogs, ultrasound-guided fine-needle aspirates of intralesional or peritoneal fluid generates samples with cytological morphology consistent with AE; calcareous corpuscles and folded membranous structures (Oscos-Snowball et al 2015). While the former indicates the presence of any cestode, the latter has only been described with *E. multilocularis*.

### Histopathology

In dogs with hepatic AE, there is typically extensive involvement of the liver with a multinodular firm pale-tan mass that grossly has the appearance of either a neoplasm or an abscess. Histological examination of hepatic biopsies is extremely helpful as the morphology is characteristic for *E. multilocularis* (Deplazes and Eckert 2001); hepatic architecture is replaced by multi-loculated coalescing cystic structures surrounded by fibrosis. Lining individual cysts is a hyaline membrane ("laminated layer") that stains with Periodic acid-Schiff (PAS) stain. The inner lining of the hyaline membrane typically comprises a basophilic matrix that contains occasional calcareous corpuscles. Intraluminal protoscolices are sometimes observed. A prominent chronic eosinophilic and granulomatous inflammation is also typically present.

### Serology and PCR

Positive serology to the *E. multilocularis* Em2-antigen is observed in most dogs with AE (Staebler et al 2006; Corsini et al 2015). However, at the present time this diagnostic method is only available at the University of Bern, Switzerland. In addition, some dogs will seroconvert, but not develop AE due to abortive infections (Gottstein et al 2014). As a result, examination of intralesional or abdominal fluid, or hepatic tissue, using an *E. multilocularis*-specific PCR provides confirmatory diagnostic information (Trachsel et al 2007).

## MANAGEMENT

Historically, dogs with AE have been managed with surgery and/or treatment with albendazole at 10 mg/kg bodyweight, daily, for life. In the aforementioned case series from Europe, dogs that received any intervention (i.e. only albendazole, or surgery and albendazole combined) were shown to survive significantly longer than dogs with no intervention. However, no significant difference in survival time was observed between these two intervention groups (Corsini et al 2015). While low numbers of dogs limited the statistical power of the study, the authors concluded that there was no evidence that debulking surgery (cytoreduction) followed by treatment with albendazole resulted in a superior outcome compared to treatment with albendazole alone (Corsini et al 2015). As a result, debulking surgery can not be recommended at the present time; as in people, surgery should only be attempted if complete resection is possible (Corsini et al 2015). Thus, ideally, investigation of potential cases requires advanced imaging (CT-Scan) to assess whether surgical excision is possible. Lastly, it has historically been assumed that medical management of dogs with AE is associated with short-term survival. However, 4 of 6 dogs managed with only daily albendazole were alive 0.5, 0.5, 2.6 and 9.5 years after the initial diagnosis and were considered to be in remission (Corsini et al 2015). Medical management of dogs with AE can therefore be associated with long-term survival; however, daily treatment with albendazole is required.

## RISK OF INFECTION IN SOUTHERN ONTARIO

Between 2015 and 2017, rectal fecal samples were collected from 460 wild canids (416 coyotes, 44 foxes) from across southern Ontario during post-mortem examination and analyzed via a PCR method for *E. multilocularis* DNA. Overall, 23% (95% confidence interval: 19-27%) wild canids tested positive. Furthermore, positive animals were detected from the Windsor area to the Quebec boarder. Using a spatial scan test, a significant infection cluster was identified (relative risk=2.26; p=0.002) among 10 contiguous public health units in the western-central region of the province (Brant County, Elgin-St. Thomas, Haldimand-Norfolk, Halton Regional, City of Hamilton, Middlesex-London, Niagara Regional, Oxford County, Perth District, Waterloo); these regions encompass areas of dense human population, suggesting zoonotic transmission is a significant possibility (Kotwa et al 2019).

## PUBLIC HEALTH CONCERNS

The intermediate (larval) stage of *E. multilocularis* in the abdomen of dogs constitutes no risk to public health. However, some dogs with hepatic AE may also have patent intestinal infections and therefore may constitute a zoonotic threat. Thus, as soon as a presumptive diagnosis of hepatic AE is made, dogs should be treated with praziquantel at 5 mg/kg bodyweight to eliminate intestinal *E. multilocularis* infection (Panel on Animal Health and Welfare 2015); treatment should be repeated 24 hours later to ensure the correct dosage is administered.

In areas endemic for *E. multilocularis*, monthly administration of praziquantel at 5 mg/kg bodyweight is required to prevent patent intestinal infections; a risk assessment should be carried out to determine if such preventive treatment is necessary (i.e. does the dog ingest rodents?). Monthly treatment of dogs with praziquantel has minimal impact on the risk of AE in animals that ingest parasite eggs (e.g. in wild canid feces). When recommending monthly treatment with praziquantel, it should be recognised that overuse of praziquantel may lead to the development of resistance to the drug in *E. multilocularis*, as has recently been reported in *Dipylidium caninum* in the USA (Chelladurai et al 2018).

If exposure of people to *E. multilocularis* eggs is a concern, serological testing at 3, 6 and 12 months following exposure using three different ELISAs (EgHF-ELISA, Em2-ELISA and Em18-ELISA) is recommended (Gottstein et al 1993).

## REPORTABILITY IN ONTARIO

As of January 1, 2018, *E. multilocularis* infection was designated a reportable disease in animals in Ontario (Communicable Diseases—General R.R.O. 1990, Reg. 557). This requires veterinarians and diagnostic laboratories to report animal cases directly to the local public health units to minimize potential risks to human health. Furthermore, as of May 1, 2018, *E. multilocularis* infection in humans was designated a disease of public health importance (i.e., a disease that must be reported) in Ontario (Designation of Diseases, O. Reg. 135/18).

## CONCLUSION

In dogs with hepatic masses, travel to areas endemic for *E. multilocularis* should be evaluated. If hepatic lesions are first detected during an exploratory laparotomy, it should be recognised that the gross appearance of hepatic AE in dogs is very similar to that of hepatic neoplasia or abscess. Furthermore, approximately one third of dogs with hepatic AE have patent intestinal infections (i.e. are a public health concern). Thus, histological examination of hepatic biopsies should be carried out to rule this infection in or out, particularly in young dogs. Management of AE involves daily treatment with albendazole for life, with or without surgery; due to the late stage at which infections are diagnosed, the prognosis for long-term survival is often poor.

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## CARE AND MANAGEMENT OF COMMUNITY (UNOWNED, FREE-ROAMING, “FERAL”) CATS AND COLONIES

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### What Are Community Cats?

Domestic cats are classified by ownership status, access to the outdoors and degree of socialization to, and dependence on, humans.<sup>1</sup> “Feral” cats are unowned, not socialized to humans and able to survive independently. “Strays” are free-ranging, previously socialized cats that have been lost or abandoned. They may lose their socialization to humans over time. Cats can move between these sub-populations during their lifetimes. Recognizing this, the term “community cats” is now used as an umbrella term for unowned, free-roaming cats.

Free-roaming cats thrive in many environments, typically close to human habitation, and are found on every continent except Antarctica. Community cats occupy a unique ecological and emotional niche at the interface with humans, domestic cats and other free-roaming animals. Feral cats are genetically and phenotypically indistinguishable from pet cats, and can be socialized to humans within a generation. Individuals who feed and otherwise care for community cats are frequently passionate advocates for these animals and may form strong bonds with individual cats.

### Controversies

Areas of controversy around community cats include public health concerns, transmission of pathogens to pet cats and other species, public nuisance, predation on wildlife (particularly birds), and the welfare of the cats themselves.<sup>2</sup> Strong opinions and diametrically opposing viewpoints may stand in the way of rational policies. Changing attitudes towards cats have informed the approach to population management in many countries.

### Welfare Concerns

Mainstream views, particularly in the animal sheltering world, have embraced the concept that unowned cats that are thriving outdoors should be spayed and neutered and returned to the location where they were found. While some voices advocate strongly against trap-neuter-return (TNR) and return-to-field (RTF) as a management practice,<sup>3</sup> it is difficult to envisage alternative approaches that are concurrently humane, effective and feasible (the goal of non-surgical sterilization continues to be pursued). Given strong recommendations in the US and Canada that pet cats should be kept indoors and the undeniable difficulties that community cats face, a segment of cat advocates are uncomfortable with the idea of any cat living outdoors. This can lead to long-term and inhumane confinement of unsocialized animals in shelters and homes.

The health and welfare of community cats is typically assessed by observation at a distance, examination during TNR programs and, less frequently, attempts to estimate morbidity and mortality in populations. Studies in the US have found that the vast majority of community cats are in good health. This differs from studies in other countries, where many or most cats were considered to be unhealthy, based on criteria such as body condition score, skin lesions, lameness or examination findings at TNR. A basic tenet of TNR is to spay and neuter cats that are healthy, and euthanize those that are considered unlikely to survive or likely to experience poor welfare upon release. Reported euthanasia rates and peri-operative mortality in TNR programs are extremely low.<sup>4,5</sup>



### Infectious Diseases in Community Cats

Numerous difficulties arise when attempting to understand infectious disease dynamics in community cat populations. Most studies use convenience samples taken from anaesthetized cats during TNR programs or from community cats that were euthanized. Pathogen prevalence varies widely between geographic areas and habitat types (e.g. rural or urban). Reported results may reflect previous exposure (e.g. toxoplasmosis seroprevalence) or current infection (e.g. *Bartonella* PCR, feline leukemia virus antigen or parasite counts). Such studies frequently provide little or no information about the clinical impact of the reported pathogens on the cats or, in the case of zoonotic pathogens, on surrounding human populations. Speculation about risks to humans is, however, abundant. Prevalence studies do provide a useful snapshot as to which pathogens are present in a given population or region and how widespread they are. Community cat pathogen surveys may be useful for detection of emerging diseases, which are of particular concern in an era of anthropogenic climate change and habitat fragmentation.

It is reasonable to assume that their lifestyle, sources of nutrition and lack of access to veterinary care would make community cats more susceptible to infectious disease, and this is almost certainly the case. Community kitten mortality has been estimated to be 75%<sup>6</sup> and infectious diseases are likely to be an important contributing factor to this. Antibodies to common feline infections such as calicivirus, herpesvirus, coronavirus and feline panleukopenia virus are absent in many community cats surveyed,<sup>7</sup> indicating that these cats are highly susceptible to infection. This is an interesting observation and begs the question as to why it is so difficult to find any reports of outbreaks of severe or fatal infectious diseases in adult community cats. Possibilities are that outbreaks are uncommon; that animals that succumb are not found or examined; or that these events are not considered noteworthy enough to report in the media or the scientific literature.

Another possibility, which in the author's opinion is the most likely, is that researchers have not conducted field studies and interviews with caregivers and this information has simply not been collected. Anecdotally, upper respiratory infections and feline panleukopenia are relatively common in community kittens that are surrendered to our shelter. In many of these cases, the kittens have been fostered in the homes of colony caregivers prior to surrender and therefore the source of infection is not always clear.

Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) are important pathogens in community cats and many disease surveys have been published. As for other pathogens, prevalence varies widely between geographic locations. In a study of 62,301 cats in the US and Canada, the overall prevalence was 3.1% for FeLV antigen and 3.6% for FIV antibody, with a somewhat higher risk for stray and feral cats compared with owner surrendered cats.<sup>8</sup> For FeLV, stray cats had 3.3% prevalence and feral cats 5.6%. For FIV, strays had 3.7% prevalence and feral cats 11.6%.

A number of studies have compared pathogen prevalence or seroprevalence between community cats and owned pet cats. Significant variability between studies is accounted for by microenvironment, climate, and whether or not pet cats in these populations typically have access to the outdoors. In terms of general trends, pathogen prevalence is not invariably higher in community cats and in fact may be lower than pet cats for certain pathogens.<sup>9</sup> Intestinal parasites are very common in community cats<sup>10</sup> and cestode prevalence, in particular, is typically very high in necropsy studies (as opposed to fecal surveys).

### Zoonotic Disease Risks

Zoonotic disease risks from community cats depend on pathogen prevalence, cat density, presence and abundance of vectors and intermediate hosts, contact with people and the potential for pathogens to persist in the environment. Diseases of concern include rabies, toxoplasmosis, bartonellosis, bite wound infections, toxocariasis and ancylostomiasis. Environmental contamination with *Toxoplasma* oocysts and helminth eggs is frequently high in areas of high outdoor cat density.<sup>11,12</sup> Remediation is difficult to impossible, and prevention of human infection depends on public education and appropriate hygiene.

Cat bites account for 5-25% of reported animal bites. Their epidemiology is strikingly different from that of dog bites.<sup>13</sup> In most cases, cat bites are from community cats and the vast majority are reported as having been provoked. Cat bites carry a high risk of infection because they frequently result in puncture wounds to the extremities, and often transmit the fast-growing bacterium, *Pasteurella multocida*. Given their inciting causes, most cat bites can be avoided through a combination of public education and common sense.

Community cats may transmit rabies, but this is extremely rare in the US and Canada.<sup>14,15</sup> More cats than dogs now test positive in the US (this is not the case for Canada). The relative increase in feline-transmitted rabies in the US (compared with canine) appears to be a product of control of the virus in dogs, rather than an upsurge in feline rabies. The vast majority of rabies worldwide is transmitted by dogs and the vast majority of animals that test positive for rabies in the US and Canada are wildlife species. One presumed and two confirmed cases of feline-transmitted human rabies have been reported in the US since 1960.

People should avoid unnecessary contact with community cats and kittens and use appropriate safety measures (nets, traps, cat gloves, sedation) when this is unavoidable, such as during trapping, TNR programs or in shelters. Gloves should be worn when handling anaesthetized cats during TNR and appropriate infection control measures should be in place during clinics.

### Care and Management of Community Cats

The most devastating “disease” of community cats has been shelter euthanasia. Intake and euthanasia rates have dropped dramatically in the US and Canada in recent years, with the main pillar of the change being the widespread implementation of TNR and RTF.<sup>4,16–18</sup> Sterilization of community cats achieves the goals of both community cat advocates and their opponents: population control, reducing shelter intake and euthanasia, improved welfare, fewer nuisance complaints, decreasing infectious disease risk and reducing predation on wildlife and birds. Sterilization rates need to be high and efforts must be sustained for TNR to be effective. Abandonment and migration can seriously reduce the impact of programs.

TNR goes hand-in-hand with the socialization and adoption of young community kittens, addressing the concerns of those who fear that these vulnerable animals will experience poor welfare and early death. Socialized strays also find their way into TNR programs and frequently enter an adoption stream.

TNR typically provides the only opportunity for a community cat to receive medical care. Cats should at a minimum be given FVRCP and rabies vaccines at the time of surgery. Although rabies boosters should ideally be administered, a single vaccine typically provides long-term or lifelong immunity. A single vaccine at TNR surgery resulted in protective titres against rabies in 98% of cats and protective titres against feline panleukopenia virus, feline herpesvirus and feline calicivirus in the majority.<sup>19</sup> Interestingly, this was the case even for killed vaccines. Retrovirus testing is not recommended for cats in TNR programs, the rationale being that test-and-remove

is ineffective and scarce resources are better utilized by funding more surgeries. Sterilization is an effective strategy for reducing retrovirus transmission because queen-to-kitten transmission is prevented and fighting is reduced, markedly decreasing transmission of both viruses.

Parasite control presents a greater logistical challenge than vaccine-preventable disease, given that the cats will return to an environment where re-infestation is inevitable. Attempting to add anthelmintics to food provided at feeding stations risks underdosing and parasite resistance. A single anthelmintic treatment at TNR is likely to be of benefit to kittens, but for adult cats, in particular, resources are typically better served by being allocated to more surgeries.

Veterinarians play an essential role in the control of community cat populations. High-volume high-quality and pediatric spay-neuter techniques have been widely adopted and training is readily available. The use of mobile clinics extends the reach of spay-neuter services into underserved communities and locations.

Veterinarians may be asked to treat community cats by caregivers who have developed bonds with these cats. Careful consideration must be given to the ability to provide humane care to unsocialized animals, while also ensuring the safety of clinic staff. Surgical procedures such as limb amputation or dental extractions should be discussed with great care, to ensure that the cat will have adequate access to food and shelter if it remains outdoors or will not be confined in a home in which it may live in a state of fear and stress, if it does not. Caregivers are generally able to understand that, despite their appearance, community cats are different from pet cats, and certain levels and types of care cannot be humanely provided. However, it is incumbent on the veterinarian to consider the cat's subsequent care and welfare when undertaking to treat any complex medical conditions.

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## Optimizing Pathogen Detection and Therapy in Granulomatous Colitis

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Granulomatous colitis (GC) is an inflammatory bowel disease (IBD) defined by infiltration of the colonic mucosa with macrophages. Concurrent cellular infiltrates frequently include neutrophils, lymphocytes and plasma cells. GC is often caused by an underlying infection such as bacteria (e.g., *E. coli* in Boxers, French Bulldogs), fungi, algae, or protozoa (see Table 1) in susceptible dogs. Dogs with GC typically have minimal improvement with empirical treatment (e.g., dietary modification, metronidazole), and it is essential these patients are not immunosuppressed until localized and systemic infections have been ruled out. The prognosis for GC can be very good if a treatable infectious agent is detected. Dogs with GC accompanied by disseminated infections or idiopathic GC have a poorer prognosis.

### Diagnostic approach

Clinical signs in dogs with GC broadly parallel those observed in other forms of colitis and include increased frequency of defecation with hematochezia, tenesmus and/or dyschezia. GC is more frequently associated with chronic duration of disease (>2 wks), weight loss, anorexia, and other abnormalities such as uveitis, chorioretinitis, lymphadenopathy, and thickening of the colonic wall as compared to other forms of colitis.

The initial diagnostic approach to dogs with GC presenting with signs of large bowel diarrhea parallels that for other forms of colitis. If the dog is systemically unwell or large bowel diarrhea is severe or chronic, a biochemical profile, urinalysis, and complete blood count are also submitted to screen for evidence of multiorgan involvement. Abdominal radiographs usually yield minimal information about primary colonic disease but can be performed to screen for masses or foreign bodies and to evaluate the relationship of the colon to other viscera and the pelvic canal. Ultrasonography can be useful for detecting ileocecolic lesions and masses, as well as assessing mural thickness and regional lymph nodes. Thoracic radiographs and cytology of a rectal scrape may identify local and disseminated infections such as histoplasmosis. Bacterial cultures (blood, urine, fecal) should be considered, particularly for febrile dogs that are systemically unwell.

The next step in the investigation of chronic and/or severe colitis is endoscopic examination of the rectum, colon, cecum, and terminal ileum. Principal differential diagnoses at this stage are some form of IBD, polyps, and neoplasia. At least 8 to 10 endoscopic biopsies of normal and abnormal mucosa should be acquired, as lesions can be patchy. Where GC is suspected (e.g., susceptible breed, ulcerated and thickened colonic mucosa, evidence of multisystemic infection, geographic risk), biopsies should be obtained for bacterial culture in addition to histopathology. Biopsies may be placed in sterile transport media but must be ground with a sterile mortar and pestle or tissue homogenizer prior to plating. Rigid proctoscopy is an alternative to flexible endoscopy for evaluating and biopsying the distal colon and rectum. This technique is often used to obtain follow-up biopsies in dogs with GC to chart response to therapy and may be performed under heavy sedation.

Histopathologic evidence of GC dramatically raises the likelihood of an underlying infectious etiology, including bacterial, fungal, and algal infections (see Table 1). GC is sub-categorized by the presence or absence of periodic acid-Schiff (PAS) positive material within mucosal macrophages; this is a hallmark of familial *E. coli*-associated GC in Boxers, French Bulldogs, and related breeds. Other special stains (e.g., GMS, Gram, acid-fast) are utilized to help visualize infectious agents in formalin-fixed tissues.

Fluorescence in situ hybridization (FISH) with a probe directed against eubacterial 16S rRNA offers a more sensitive and specific method of detecting bacteria within formalin-fixed tissues (<http://www.vet.cornell.edu/labs/simpson>). In dogs with histopathological evidence of GC, FISH with a eubacterial probe should be performed. The absence of FISH-detectable bacteria in GC should prompt a thorough search for other infectious agents, including special stains of colonic biopsies for FISH-impermeant bacteria (some Gram-positive and acid-fast) and non-bacterial organisms or their eggs (see Table 1). A comprehensive fecal exam for enteropathogens such as *Yersinia*, *Salmonella*, and *Heterobilharzia* (ELISA/IFA/PCR/culture), a fundic examination, and imaging of chest and abdomen

should also be pursued if not already completed. Urine culture can aid in the diagnosis of protothecosis. Other fungal antigen and antibody tests should be considered based on geographic prevalence.

### ***E. coli*-associated Granulomatous Colitis: Boxers, French Bulldogs and Mastiff Breeds**

Granulomatous colitis of Boxer dogs (GCB), historically mischaracterized as histiocytic ulcerative colitis (HUC), is a chronic and severe disease affecting young (<4 years old) Boxer dogs worldwide. Unlike most other forms of chronic colitis, GCB-affected dogs may develop anemia, hypoalbuminemia, colonic thickening, weight loss, and debilitation. These dogs most often present with a lifelong history of diarrhea and/or hematochezia. The classic histopathologic lesion of GCB is mucosal infiltration with large numbers of macrophages staining positively with PAS, typically accompanied by mucosal ulceration and loss of goblet cells.

The initial description of GCB (Van Kruiningen 1965) hinted at an infectious etiology, yet extensive searches for a causative agent were unrewarding. For decades, the disease was considered a severe and unresponsive immune-mediated form of IBD. In the early 2000s, the application of culture-independent molecular microbial methods (DNA sequencing and FISH) to colonic biopsies from Boxers with PAS-positive GC highlighted the presence of *E. coli* within mucosal macrophages (Simpson et al 2006). Subsequent studies have demonstrated that resolution of PAS-positive GC in Boxers correlates with the eradication of intramucosal *E. coli*. Persistence of invasive *E. coli* is linked to treatment failure. A subset of dogs with *E. coli*-associated GC also have ileal intracellular *E. coli*, (Cassmann et al 2016), but does not appear to impact clinical outcome (based on unpublished data from the author's laboratory).

*E. coli* isolated from Boxers with PAS-positive GC typically lack virulence factors harbored by diarrheagenic *E. coli* and closely resemble the adherent and invasive pathotype (AIEC) linked to ileal Crohn's disease in people (Darfeuille-Michaud 1998, Dogan 2014). AIEC are now recognized to be present at low levels in the healthy gut. In both familial *E. coli*-associated GC and Crohn's disease, these bacteria are thought to represent opportunistic pathosymbionts with the ability to persist and replicate in macrophages of susceptible individuals.

While PAS-positive *E. coli*-associated GC is most often reported in Boxers and French Bulldogs (Manchester et al 2013), it is also encountered in American and English Bulldogs, Bull Terriers, Mastiffs, and Alaskan Malamutes. Colonic intracellular *E. coli* were recently described in a cat with PAS-positive GC (Leal et al 2017). It is noteworthy that we have also documented intracellular *E. coli* in PAS-positive macrophages associated with malakoplakia of the bladder and kidneys in Boxers and cats.

A definitive diagnosis of *E. coli*-associated GC is achieved by demonstration of clusters of intracellular *E. coli* within the colonic mucosa using an *E. coli* FISH probe. Because bacterial culture of colonic biopsy specimens often yields *E. coli* in dogs with and without GC, it is not useful, in isolation, for diagnosis. Bacterial culture with antimicrobial susceptibility testing of mucosal *E. coli*, however, enables targeted antimicrobial therapy in dogs with GC.

### **Treatment of *E. coli*-associated Granulomatous Colitis**

Treatment success for dogs with *E. coli*-associated GC hinges upon eradication of intramucosal, intracellular *E. coli*. Achieving this requires an antibiotic effective against *E. coli* that is able to accumulate within macrophages. This has typically been accomplished with 6 to 8 weeks of oral fluoroquinolone administration. Unfortunately, fluoroquinolone resistance is now common among GC isolates. Fluoroquinolone-resistant *E. coli* were isolated from 6/14 GC Boxers (Craven et al 2010) and 15/24 GC Boxers and French Bulldogs (based on unpublished data by Simpson Laboratory) in two recent studies. Fluoroquinolone resistance is often accompanied by resistance to other macrophage-penetrating antimicrobials such as chloramphenicol, doxycycline, rifampicin, and TMS, greatly limiting therapeutic options. As treatment successes are predicated on the judicious selection of appropriate antimicrobial drugs, the authors caution against empirical use of antimicrobial polypharmacy in dogs suspected to have *E. coli*-associated GC.

It is important to impress upon owners that antimicrobials must be continued beyond initial clinical

improvement (which typically occurs within 1 week of appropriate therapy) in order to maximize the chance of lasting clinical remission.

In addition to antimicrobial therapy, adjunctive therapies directed at modifying the luminal environment and colonic epithelium may also help dogs with *E. coli*-associated GC. These include supplemental soluble fiber, dietary modification, and locally acting anti-inflammatories with in vitro efficacy against AIEC, (Zhang et al 2018) as outlined in Table 2. Owners should be cautioned against feeding raw diets as concurrent *Salmonella* infections have been observed in GC dogs consuming these foods.

Probiotics and fecal microbiota transplantation have had minimal efficacy in granulomatous forms of IBD in people. No controlled clinical trials have been completed to evaluate the benefit of any of these adjunctive treatments in GC-affected dogs.

Dogs that achieve clinical remission may experience a clinical cure and live normal lives. Dogs with multidrug resistant (MDR) *E. coli* have a more guarded prognosis, and in vitro susceptibility does not guarantee clinical remission with evidence-based therapy. We have successfully treated GCB dogs with MDR *E. coli* using parenteral meropenem when susceptibility testing suggested there were no other macrophage-penetrating options (based on unpublished data by Alison Manchester, TexasA&M). PAS-positive *E. coli*-associated GC is a familial disease with genetic susceptibility linked to a region encoding the CD48/SLAM family of genes on chromosome. (Hayward et al 2016) .Genes in this region have been implicated in human IBD (Jostins et al 2012) and the sensing and killing of *E. coli* by murine macrophages. Owners should be counseled not to breed dogs affected by this form of GC, or from breeding pairs that have yielded litters with affected dogs.

### ***Prototheca***

*Prototheca* spp. are ubiquitous algae found worldwide. Infection results in disseminated disease in dogs, most commonly affecting the colon, nervous system, and eyes. Boxers and Collies seem to be overrepresented, and a number of patients with FISH-negative GC have ultimately been diagnosed with protothecosis (*P. zopfii*). Urine culture is a reliable means of detecting disseminated protothecosis (Stenner et al 2007). Amphotericin B as well as azole antifungals have been employed, but the optimal treatment regimen is not known. Prognosis is grave for dogs with disseminated disease. This could be related to the late stage of diagnosis in many patients.

## Other Forms of GC

Granulomatous inflammation represents a common host response to various chronic insults. Since many of these are infectious, it is imperative not to immunosuppress patients with granulomatous or neutrophilic intestinal infiltrates until infectious etiologies have been excluded to the best of one's ability. Additional infectious etiologies to consider in canine GC are displayed in Table 1. The prognosis for granulomatous or neutrophilic enteropathies is guarded to poor if an underlying cause is not identified. In rare cases, autoimmune and neoplastic diseases, as well as foreign-body reactions can promote granulomatous enterocolitis.

Bacterial	<i>E. coli</i> , <i>Yersinia</i> , <i>Salmonella</i> , mycobacteria, spiral <i>Helicobacter</i> -like bacteria
Fungal	<i>Histoplasma</i>
Trematode	<i>Heterobilharzia americana</i> (canine schistosomiasis)
Algal	<i>Pythium insidiosum</i> , <i>Prototheca zopfii</i>
Protozoa	<i>Entamoeba histolytica</i> , <i>Cryptosporidium</i> (?)

**Table 1:** Main causes of canine granulomatous colitis

## Primary Therapy

### Antimicrobials\*

Enrofloxacin\*\* is the first-line therapy for biopsy-proven GC [7.5 mg/kg PO q24h for at least 6 weeks]

\*Prescribed based on *E. coli* susceptibility profile. Select an antimicrobial that can penetrate macrophages (e.g., fluoroquinolone, doxycycline, chloramphenicol, TMS).

\*\*Fluoroquinolone-resistant *E. coli* is a growing concern.

## Additional Therapy

### Dietary options

- Highly digestible
- Novel protein
- Hydrolyzed protein

### Fiber supplementation

Unflavored psyllium powder [½ to tbsp small, 2 tbsp medium, 3 tbsp large breed dog, PO q12h]

### Anthelmintics

Fenbendazole [50 mg/kg PO q24h x 3d repeat in 21d]

### Anti-inflammatory anti-*E. coli*

Sulfasalazine [20-30 mg/kg PO q8-12h]

Mesalamine [10-20 mg/kg PO q12h]

**Table 2:** Medical management of *E.coli* associated granulomatous colitis



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# EQUINE PROGRAM

## EQUINE JOINT DISEASE AND THE VALUE OF OBJECTIVE GAIT ANALYSIS

Heidi L. Reesink, VMD, PhD, DACVS-LA

### Abstract

Joint disease is the leading cause of equine wastage. This presentation will discuss common causes, diagnostics, and treatments for equine joint disease. Case studies will be used to highlight the value of objective gait analysis for monitoring response to treatment.

### Diagnosing Equine Joint Disease

The mainstays of diagnosing OA include a thorough history, physical examination, and lameness examination combined with diagnostic analgesia and imaging. Standard radiography is the most common imaging technique used to diagnose OA; however, additional modalities, such as nuclear scintigraphy may be able to provide functional information about whether or not OA is currently active. Ultrasonography can be used to detect traumatic soft tissue injuries, such as meniscal tears or collateral ligament sprains, that may precipitate OA. Computed tomography and MRI can also be useful for identification of joint disease, and MRI is the only modality capable of detecting bone marrow lesions (BMLs), which may be one of the earliest signs of bone injury that may precede the development of OA. Positron emission tomography (PET) may be a viable method for detecting functional bone remodeling in the future<sup>1</sup>.

### Lameness Evaluation and Objective Gait Analysis

Lameness examination in the horse typically involves evaluation at a walk and trot in hand. Baseline lameness is evaluated at a walk and a trot prior to manipulation and may be graded using a 5-point scale (American Association of Equine Practitioners, AAEP) or a 10-point scale, as is more commonly used in Europe. Induced lameness is lameness that becomes apparent as a result of manipulation, such as a flexion test or applied pressure. In cases of subtle lameness, horses are best evaluated under a variety of conditions, including in hand, on soft and firm footing, lungeing in both directions, and under saddle examination performing discipline-specific maneuvers. For the purposes of this session, we will focus on horses with AAEP lameness grades of 2 and 3. In the author's experience, most lameness associated with joint disease evaluated at a referral hospital corresponds to AAEP grade 2 = lameness is difficult to observe at a walk or when trotting in a straight line, but is consistently apparent under certain circumstances or grade 3 = lameness is consistently observable at a trot under all circumstances. One limitation of the 0 to 5 AAEP lameness grading scale is that many horses will be classified as grade 3, but grade 3 lameness can span a broad continuum of lameness severity—ranging from a very mild to a severe grade 3 lameness, without being classified as a grade 2 or 4 lameness.

The continuum of lameness that can be classified as grade 3 on the AAEP lameness scale is one of the reasons that the author has appreciated the ability to quantify lameness more objectively using the Equinosis® Q with Lameness Locator. The Equinosis® Q is not the only objective gait analysis system available; however, the nature of the inertial sensor-based system and laptop offers the advantage of mobile, ambulatory use. Other objective gait analysis systems include the EquiGait® inertial sensor-based system and Qualisys Gait Analysis®, which is an optical-based system for locomotion assessment with high precision and accuracy; however, the optical system is not mobile and only accessible on a referral basis. In addition to being able to quantitate lameness more precisely, objective gait analysis offers the ability to more objectively evaluate response to diagnostic analgesia or, more importantly, the response to treatment over longer time scales. Objective analysis also helps to eliminate bias, conscious or unconscious, by the veterinary practitioner.

### **Diagnosis of Joint Disease in the Racehorse**

Joint disease may affect any joint in the racehorse; however, the metacarpo/metatarsophalangeal joints and carpal joints are over-represented. The most common sites of osteochondral fragmentation in the fetlock are the proximodorsal and proximopalmar/plantar aspects of the first phalanx (P1) and the proximal sesamoid bones (PSBs). The most common sites for osteochondral fragmentation in the carpus are the distal and proximal intermediate carpal bone and distal radial carpal bone. Flexed lateromedial radiographs of the carpus and elevated angle oblique (20 degrees above horizontal and 15-20 degrees dorsal to a standard lateromedial projection) radiographs of the fetlock joints help delineate the sites of osteochondral fragmentation. The tarsus is more commonly affected in Standardbred racehorses due to the trotting or pacing gait, and osteochondrosis dissecans (OCD) of the tarsus and stifle is common in both Thoroughbreds and Standardbreds. In addition to osteochondral fragmentation, osteochondral fracture, soft tissue injuries, subchondral cystic lesions and osteochondrosis can all precipitate joint disease in the racehorse<sup>2</sup>. However, OA of the fetlock in racehorses is common and can be insidious in nature with no known causes. Diagnosis of subtle injuries, especially involving subchondral bone, can be challenging and may require volumetric imaging.

### **Diagnosis of Joint Disease in the Non-Racehorse**

Predispositions for specific joint disease will depend upon breed, conformation and discipline. In general, western performance horses are predisposed to joint disease affecting the tarsus and stifle, while it is common for hunters and showjumpers to have distal interphalangeal (DIP) joint and proximal interphalangeal (PIP) joint disease. Likewise, horses with sickle-hocked conformation will be predisposed to distal tarsal joint disease, while carpal and fetlock angular limb deformities or offset knees can predispose to joint disease secondary to uneven mechanical loading and stresses on these joints. However, although it is helpful for the equine practitioner to be aware of certain breed and discipline predispositions to joint disease, it is also important to keep an open mind. For example, although metacarpal/tarsal condylar fractures are far more common in racehorses, they do occasionally occur in non-racehorses.

### **Treatment of High-motion Joint Disease**

Treatments for high-motion joint disease typically involve pharmaceutical and biological therapies that will be discussed in depth, along with emerging experimental therapies, in a subsequent session, "Frontiers in Management of Joint Disease." Apart from biologic and pharmacologic treatments, mainstays of treating joint disease in high-motion joints are aimed at resolving the inciting cause of joint disease. In young, growing foals, the veterinarian may be able to intervene to help correct angular deformities, flexural deformities or other conformational faults. However, in many cases, we are treating joint disease in adult horses. In adult horses, treatment is aimed at early surgical removal of osteochondral fragments which may be secondary to either osteochondrosis dissecans (OCD) lesions or traumatic osteochondral fragmentation, repair of articular fractures, and/or stabilization of unstable joints secondary to soft tissue injuries.

### **Treatment of Low-motion Joint Disease**

Although low-motion and high-motion joints with early or mild OA are often treated with similar biological or pharmaceutical agents, principles of managing moderate-to-severe OA differ for low- and high-motion joints. An advantage of low-motion joints is that severe OA can be treated with either surgical arthrodesis or facilitated ankylosis techniques to encourage fusion of painful joints with the potential for significantly improving or eliminating lameness without adverse mechanical gait effects. The proximal interphalangeal (PIP) joint, distal tarsal joints and carpometacarpal joints are the low-motion joints most commonly affected by OA in the horse.

### **Proximal Interphalangeal Joint Osteoarthritis: Treatment**

Proximal interphalangeal (PIP) joint arthritis occurs with some frequency in both old and young horses. Indications for joint fusion in young animals include: subchondral bone cysts, trauma (fracture or collateral ligament injury), severe pastern subluxation, or joint sepsis that can result in rapidly progressive PIP joint arthritis. Arthrodesis may allow affected animals to go on to their intended purpose, with a better prognosis for hindlimb pastern arthrodesis than forelimb. Chronic osteoarthritis with more advanced radiographic evidence of PIP joint arthritis is more common in older animals.

Although non-surgical methods for facilitated ankylosis of the pastern joint have been described, non-surgical methods have a lower success rate and typically take longer for the joint to fuse than surgical arthrodesis. For this reason, non-surgical methods should be offered as an alternative option where clients are reluctant to perform surgery and where radiographic evidence of arthritis is already moderately advanced. In a retrospective study on facilitated pastern ankylosis using intra-articular ethanol injections in 34 horses, 50% of horses were sound at 6 months follow-up, 38% of horses were improved but not sound, one horse showed no improvement in lameness, and 3 horses were lost to follow-up<sup>3,4</sup>. The median time to return to work was 8 months (range 0-15 months), and the median age of horses was 13 years (range: 1-24 years)<sup>3</sup>. As such, surgical arthrodesis is the technique of choice to achieve more rapid joint fusion, decrease periosteal callus and improve comfort and return to function. Pastern arthrodesis with a combination of a plate and screws is the most stable fixation<sup>4</sup>, followed by screw fixation with 2-3 parallel screws<sup>5-7</sup>. Many surgeons will also opt to apply cast or bandage cast coaptation for the first few days to weeks post-operatively<sup>5,6,8</sup>. A combination of diode laser-facilitated pastern arthrodesis with parallel screws has been reported to increase fusion and reduce immediate post-operative lameness<sup>5</sup>. Although plate fixation results in the most stable construct, a technique for standing, percutaneous PIP joint arthrodesis with 3 screws has been reported in horses with severe osteoarthritis that avoids the need for general anesthesia and in which cast coaptation was not performed<sup>7</sup>.

### **Distal Tarsal Joint Osteoarthritis, Distal Tarsitis, or Bone Spavin: Treatment**

Horses of many breeds and disciplines are affected by distal hock joint OA. While distal tarsitis tends to progress and become more severe in middle-aged horses or horses engaged in intense athletic endeavors, a severe form of distal hock joint OA is occasionally observed in young horses, referred to as 'juvenile spavin.' Severe radiographic changes indicative of distal hock OA in a young horse (< 3 years old) are typically clinically significant; however, it is important to keep in mind that radiographic changes do not always correlate well with clinical signs, and it is always best to confirm that the distal hock joints are the source of lameness via diagnostic analgesia. It is also important to keep in mind that distal tarsal OA may occur concurrently with proximal suspensory ligament desmopathy.

In mild-to-moderate cases of distal tarsal OA, clinical signs can be managed with intra-articular injections. Of note, a recent contrast radiographic study involving injection of distal tarsal joints in live horses revealed 96% accuracy for injecting the tarsometatarsal (TMT) joint but only a 42% accuracy for injecting the centrodistal (CD) or distal intertarsal joint<sup>9</sup>. The authors concluded that radiographs or ancillary techniques may be needed to ensure appropriate needle placement for CD joint injections to avoid peri-articular medication<sup>9</sup>. In early tarsal arthritis, platelet-rich plasma (PRP) and hyaluronic acid (HA) can be administered. However, corticosteroids are more commonly used to treat distal tarsitis. Proper trimming and shoeing, especially increasing breakover and keeping horses in regular work can also help manage the clinical signs associated with distal tarsal arthritis.

However, if these interventions are not sufficient, either facilitated ankylosis or surgical arthrodesis may be options to treat distal tarsal arthritis. Injection of the TMT joint or both the TMT and CD joint with 70 to 100% ethyl alcohol has been reported to achieve ankylosis in both healthy horses and horses with OA<sup>10-12</sup>. Injections of 3 mL of 70% ethyl alcohol in 20 horses with distal tarsal arthritis resolved lameness in 85% of horses by 3 months post-injection<sup>11</sup>. Lack of complete response was attributed to another source of lameness in the same limb in one horse and collapse of the CD joint in one horse which precluded needle entry<sup>11</sup>. In another study, improvement in lameness was reported in 60% of cases (21/35); however, 4 horses (19%) deteriorated and 2 developed significant complications<sup>12</sup>.

When considering alcohol-facilitated ankylosis, it is imperative that contrast arthrography be performed to confirm absence of communication with the proximal intertarsal (PIT) joint or tarsocrural (TC) joint, which would be a contraindication for this technique. Ethyl alcohol must never be injected into tarsal joints where communication with the PIT or TC joints are present, as this could result in devastating consequences of severe tarsocrural joint OA. Surgical arthrodesis is probably the most reliable and effective method to induce distal hock fusion; however, it is more expensive. Surgical techniques for achieving fusion of the distal tarsal joints include surgical drilling<sup>13</sup>, with or without the use of a diode laser. Diode laser surgery alone, without surgical drilling, has been reported as a successful method for distal tarsal fusion. Laser surgery is reported to be associated with less discomfort immediately post-operatively as compared to surgical drilling but may result in less complete fusion<sup>13</sup>. Surgical drilling in a fan shaped pattern with a 4 mm drill bit has been reported to result in quicker fusion but not necessarily a better long-term result than laser surgery<sup>14</sup>. At the author's referral institution, we have achieved success with both techniques but find surgical drilling to be the most definitive treatment. In some cases, laser surgery alone may be insufficient to achieve joint fusion due to the inability to place needles at an appropriate depth, especially where bone bridging precludes adequate depth of needle penetration in the CD joint. For this reason, if laser surgery is used, it is typically combined with surgical drilling. Typically, drilling is performed bilaterally, unless the distal tarsal arthritis is due to unilateral joint sepsis or trauma. Other surgical techniques are being investigated to perform arthrodesis of the distal tarsal joints; however, these are experimental and not routinely performed in practice<sup>15</sup>.

### **Carpometacarpal Joint Osteoarthritis: Treatment**

Carpometacarpal joint arthritis may occur secondary to traumatic injury in any age and breed of horse, alone or in conjunction with trauma to the high-motion antebrachiocarpal and middle carpal joints. However, moderate-to-severe carpometacarpal arthritis has been reported in older Arabian and Quarter Horses with a much higher frequency than the general equine population<sup>16,17</sup>. One hypothesis for the increased prevalence of this disease in these breeds is that many of these horses have an anatomical variation in the metacarpal 2 (MC2) – metacarpal 3 (MC3) articulation where the MC2-MC3 articulation palmar to the carpometacarpal interosseous ligament is absent<sup>16</sup>. Carpometacarpal arthritis originates at the medial aspect of the joint, can result in severe osteoproliferation and lysis, and tends to lead to progressive collapse of the medial joint space resulting in carpal varus conformation. If left untreated, this progressive disease typically results in carpal instability and/or severe lameness, necessitating euthanasia. However, surgical drilling has been reported to result in marked improvement in 92% of horses at 6 months, with 67% of horses returning to their original activity. However, fusion of the joint is not immediate, and owners should be forewarned that a carpus that is beginning to develop a varus deformity may need to be splinted to prevent further collapse as the joint begins to fuse.

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## FRONTIERS IN MANAGEMENT OF EQUINE JOINT DISEASE

Heidi L. Reesink, VMD, PhD, DACVS-LA

### Abstract

Corticosteroids, non-steroidal anti-inflammatories and hyaluronic acid have been mainstays of equine joint therapy for decades. In this session, emerging therapies for joint disease will be discussed, including commercially available therapeutics and drugs still in development.

### Equine Joint Disease

Joint disease remains the leading cause of equine retirement across all equestrian disciplines. Osteoarthritis (OA), or degenerative joint disease, may develop secondary to many causes, but trauma and excessive wear-and-tear are probably the most common causes of OA in horses. Osteoarthritis that occurs secondary to trauma is referred to as post-traumatic osteoarthritis (PTOA) and is most commonly due to intra-articular fracture or trauma to intra- and peri-articular soft tissues, such as the cruciate ligaments and menisci in the stifle or the collateral ligaments in distal limb joints. Trauma, associated with osteochondral fragmentation or maladaptive bone remodeling, is a common cause of OA in racehorses. OA may also occur as a result of congenital or acquired conformational abnormalities and may be impacted by genetics, age, metabolic status, exercise and wear-and-tear.

### Non-Pharmacological Treatment of Joint Disease

The primary focus of this session will be on pharmacological treatment of joint disease; however, it is important to recognize there are several important non-pharmacological treatments that can help horse owners manage OA. Most horses with OA benefit from a regular exercise program, and trimming/shoeing for proper balance can help improve clinical signs of lameness. In addition, some horses may benefit from physical therapy and rehabilitation programs, including underwater treadmilling, the use of tactile stimulation devices to improve proprioception and/or weights to improve strength, and exercises to improve motor control and joint range of motion, such as cavalettis<sup>1</sup>. More investigation into physical therapy and rehabilitation programs in horses is needed to determine what exercises are most effective. Other modalities that may be useful but have not been studied extensively in the horse include: therapeutic ultrasound, extracorporeal shockwave therapy (ESWT), low-level laser therapy, transcutaneous electrical nerve stimulation (TENS), pulsed electromagnetic field therapy (PEMF), neuromuscular electrical stimulation, vibration therapy, and chiropractic, massage and acupuncture therapy<sup>1</sup>.

### Surgical Treatment of Joint Disease

Surgical arthrodesis of high-motion joints, including the distal interphalangeal (DIP) joint, metacarpo/metatarsophalangeal joint and carpal joints is salvage option for patients with severe joint trauma, joint instability or osteoarthritis that is refractory to other treatments. Unlike humans and small animals, joint replacement is not a viable option for horses, so treatments are needed for both synovitis-to-early OA and moderate-to-severe OA. The goal of therapy for treating synovitis and early OA is to inhibit inflammation and delay or prevent to progression of joint disease. At this time, the goal for treating moderate-to-severe OA in high-motion joints is to relieve pain and discomfort.

### Systemic Pharmacological Treatment of Joint Disease

#### Non-Steroidal Anti-Inflammatory Medications (NSAIDs)

Horses with OA typically benefit from systemic pain relief provided by non-steroidal anti-inflammatory drugs (NSAIDs), the mainstay of analgesia in the horse. While phenylbutazone is still one of the most effective NSAIDs for musculoskeletal pain, it is the least cyclooxygenase-2



(COX-2) specific and therefore associated with more adverse effects, including gastric ulceration, right dorsal colitis and other gastrointestinal disturbances. The COX-2 specific NSAID firocoxib is now licensed in both tablet form and paste form for use in horses in the United States, and is associated with fewer gastrointestinal side effects. However, anecdotally, firocoxib appears to be less effective for musculoskeletal pain than phenylbutazone. Flunixin meglumine is also used to provide analgesia for musculoskeletal disease, as are meloxicam and ketoprofen. A recent study evaluating the prescription of NSAIDs in equids in the United Kingdom, United States and Canada suggested that the majority of practitioners continue to prescribe phenylbutazone and flunixin meglumine and that the use of other NSAIDs remains limited<sup>2</sup>. The prescription of NSAIDs was most common in the USA (42.4%), followed by Canada (34.2%) and the UK (28.6%)<sup>2</sup>.

### **Hyaluronan (HA)**

Sodium hyaluronan is available as an intravenous (IV) formulation (Legend®) to treat osteoarthritis in horses, specifically licensed for non-infectious joint dysfunction in the carpus and fetlocks. Because of the ease and low risk of adverse effects associated with IV administration, Legend® is commonly used in equine practice, both for the treatment of OA and for prevention of joint disease. Intravenous Legend® has been shown to improve clinical lameness, synovial membrane histology and synovial fluid parameters in the carpal osteochondral fragment model of OA (ref) and has been shown to result in a higher average number of starts, more money earned and a longer time before requiring a first intra-articular injection in a 9-month study of racing Quarter Horses that were administered IV Legend® prophylactically<sup>3</sup>.

### **Polysulfated Polysaccharides**

Polysulfated polysaccharides include polysulfated glycosaminoglycan (PSGAG, Adequan®), pentosan polysulfate and chondroitin sulfate. In a 2011 survey on joint therapy in equine practice, PSGAG was selected as the most frequently used disease-modifying OA medication, independent of route of administration<sup>4</sup>. The majority of respondents who used PSGAG chose to administer it intra-muscularly (IM), with common uses including prophylactic treatment, chronic joint maintenance and postoperative administration<sup>4</sup>. Although there is more evidence for a beneficial effect of PSGAG administered intra-articularly as compared to the IM route, many practitioners choose to administer it IM due to safety concerns. In one study, intra-articular PSGAG was shown to potentiate the risk of joint sepsis<sup>5</sup>; therefore, most practitioners who use PSGAG intra-articularly will administer this in combination with an antimicrobial, most commonly amikacin. A hyaluronan, sodium chondroitin sulfate and *N*-acetyl-D-glucosamine combination product (Polyglycan®) has been administered via the IV, IM and IA routes; however, minimal data is available to support the systemic routes of administration whereas IA administration has been shown to have some beneficial disease modifying effects<sup>6</sup>. Pentosan polysulfate (PPS) is licensed for use in horses in Australia and can be administered via IM or subcutaneous routes. Although anecdotal reports suggest value in PPS, data in the equine literature is lacking.

### **Bisphosphonates**

Bisphosphonates, including tiludronate (Tildren®) and clodronate (Osphos®) are licensed for the treatment of navicular syndrome in horses; however, literature suggests that bisphosphonates may also be effective for treating distal tarsitis or bone spavin<sup>7</sup>. While tiludronate and clodronate are known to inhibit osteoclast-mediated bone resorption, they also provide analgesia by an as of yet unidentified mechanism. Anecdotally, bisphosphonates have been reported to improve lameness in horses with distal tarsal OA, bone marrow lesions (BMLs) and other diseases associated with bony remodeling such as impingement of the dorsal spinous

processes or 'kissing spines' and sacroiliac joint arthritis. However, there are no controlled studies yet available on the use of bisphosphonates for OA in sites other than the distal tarsal joints, and it is critical to remember that bisphosphonates are not licensed for use in horses < 4 years of age and may have the potential to impair bone remodeling during fracture healing or bone microdamage repair. More research is needed to evaluate the effect of bisphosphonates for the treatment of joint disease in horses.

### **Intra-articular Pharmacological Treatment for Joint Disease**

#### **Corticosteroids**

Intra-articular administration of corticosteroids remains one of the most effective treatments for synovitis and inflammation-associated musculoskeletal pain in both humans and animals. However, several equine organizations, including racing jurisdictions and equestrian oversight committees, such as the Fédération Equestre Internationale (FEI), responsible for overseeing the welfare of the horse have been more strictly regulating corticosteroid use in racing and competition horses due to concerns about masking pain and risks of catastrophic injury. Therefore, although corticosteroids play an important role in management of joint inflammation and osteoarthritis in horses, it is important for both owners and veterinarians to be aware of competition rules for the use of all medications, but particularly corticosteroids. The most commonly used IA corticosteroids in equine practice include: triamcinolone acetonide (Vetalog® and Kenalog®), methylprednisolone acetate (Depo-Medrol®), and betamethasone sodium phosphate/sodium acetate (Celestone Soluspan®). Methylprednisolone acetate has the longest duration of action but also the longest withdrawal times. In addition, while triamcinolone has been shown to be chondroprotective and betamethasone esters have been shown not to have adverse effects on cartilage, methylprednisolone acetate has been consistently shown to have deleterious effects on cartilage<sup>8</sup>. Therefore, this author typically restricts use of methylprednisolone acetate to peri-articular injections (e.g., 'kissing spines' or sacroiliac joint injections) or injections into low-motion joints with moderate-to-severe OA where continued cartilage degradation is encouraged in order to promote long-term fusion.

#### **Hyaluronan (HA)**

Hyaluronan is the primary viscous lubricant in synovial fluid and functions to provide both lubrication and to reduce white blood cell-mediated inflammation. Hyaluronan formulations for intra-articular (IA) administration have been available to both the equine and human medical professions for decades. While low molecular weight HA has pro-inflammatory effects, medium-to-high molecular weight HA is anti-inflammatory. Hyvisc® and HyCoat® are two of the higher molecular weight HA products currently available to equine practitioners. Numerous clinical reports and systematic reviews in human patients suggest that there is a moderate effect of HA in improving knee pain<sup>9</sup>. Combined use of a corticosteroid and HA is reported 59% of the time in a recent survey of equine practitioners<sup>4</sup>.

#### **Regenerative medicine therapies for intra-articular administration**

Biologics, gene therapy and other regenerative medicine approaches for both joint disease and tendon and ligament disease will be discussed in a subsequent session, "Hitchhiker's Guide to Equine Regenerative Medicine". Therapies include: platelet-rich plasma (PRP), autologous conditioned serum (ACS) or IRAP™ II, Pro-Stride Autologous Protein Solution (APS), bone marrow concentrate and cell-based therapies such as mesenchymal stromal cells (MSCs).

#### **New Frontiers for Management of Equine Joint Disease**

##### **Non-animal stabilized hyaluronic acid (DUROLANE® with NASHA® technology)**

Hyaluronic acid (HA) injections have been used in horses for decades for their lubricating and anti-inflammatory properties; however, a limitation of many HA formulations is the brief intra-

articular residence times post-injection. DUROLANE® is a newer HA product that is stabilized through cross-linking to substantially increase its residence time after intra-articular injection by up to >1 month. NASHA has been shown to be as effective as methylprednisolone for knee OA in humans<sup>10</sup>. In a randomized, double-blinded, placebo-controlled clinical study on intra-articular NASHA treatment in equine metacarpophalangeal joint lameness, a single IA NASHA injection was not better than a single saline injection at reducing lameness; however, flexion test scores improved more in the NASHA group than the saline group<sup>11</sup>.

### **Polyacrylamide hydrogel (PAAG)**

Polyacrylamide hydrogels, including both Noltrex® Vet and Arthramid® Vet are marketed as polymer gel-based medical devices used to treat OA in horses by providing joint lubrication. However, histologic studies in rabbits and horses show evidence of incorporation of hydrogel into the subsynovial lining that can persist up to years<sup>12</sup>, and recent evidence suggests that PAAG may function by increasing elasticity and tensile strength of the joint capsule and synovium, resulting in reduction of synovitis and mechanoreceptor activation<sup>13</sup>. Field studies have shown improvement in joint effusion and lameness in 82.5% of horses with OA treated with a 2.5% cross-linked PAAG (Arthramid® Vet) at 24 months follow-up<sup>14</sup> and an improvement in lameness in 82% of horses with OA treated with a 4% cross-linked PAAG (Noltrex® Vet)<sup>15</sup>; however, a limitation of these studies is that they did not include controls are, therefore, at risk of bias. A recent prospective, longitudinal study showed improvement in lameness grades in 49 flat-racing Thoroughbreds with carpal or metacarpophalangeal joint lameness treated with a 2.5% cross-linked PAAG (Arthramid® Vet) from 1 to 24 weeks post-treatment<sup>16</sup>. Although early results look promising, properly randomized, blinded and controlled studies are needed to evaluate the efficacy of PAAG and have yet to be performed.

### **Therapies Targeting Novel Pain Pathways**

#### **Anti-nerve growth factor (NGF) therapies**

Many new OA therapies for humans are directed towards alleviating pain rather than altering the progression of disease. Many structures within the knee joint, including the joint capsule, ligaments, periosteum, menisci, subchondral bone and synovium are highly innervated with nociceptive nerve fibers; therefore, peripheral nociceptive pathways are an attractive target for novel analgesic agents. Monoclonal antibodies (e.g., tanezumab) have been tested in clinical trials for knee OA in humans, showing superiority to both NSAIDs and oxycodone<sup>9</sup>. Anti-NGF therapies were evaluated in a transient, IL-1 $\beta$ -induced tarsocrural synovitis model in the horse, demonstrating effective suppression of inflammation, pain and catabolic activity after intra-articular administration<sup>17</sup>.

#### **Capsaicin**

Nociceptive fibers express a receptor for capsaicin, transient receptor potential cation channel subfamily V member 1 (TRPV1). Activation of TRPV1 receptors induces desensitization and capsaicin has therefore been an attractive candidate for treating pain, with phase III trials in humans currently underway<sup>9</sup>. While topical perineural capsaicin has been shown to provide measurable pain relief in a reversible model of equine foot lameness<sup>18</sup>; however, to the author's knowledge, intra-articular capsaicin has not specifically been evaluated for OA pain in the horse.

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## ENIGMATIC EQUINE TENDON AND LIGAMENT INJURIES

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### Abstract

Regional anesthetic techniques can localize lameness to a specific region; however, lesion diagnosis is not always straightforward. Strategies for diagnosis of challenging soft tissue lameness will be discussed, including cases where advanced imaging or surgery were required to achieve a diagnosis.

### Common Equine Tendon and Ligament Injuries

Tendonitis, also referred to as a “bowed tendon”, is a common injury in racehorses and sport horses of many disciplines. Tendon bows or tendonitis can affect both the superficial digital flexor and the deep digital flexor tendons. Superficial digital flexor (SDF) tendonitis is one of the most common causes of lameness in racehorses but is not typically a diagnostic challenge as most horses will have swelling, heat, sensitivity to palpation, and often mild to severe lameness associated with the injury. Tendon pathology in the metacarpal and/or metatarsal region is typically diagnosed with routine ultrasonography, as is desmitis of the accessory ligament of the deep digital flexor tendon (ALDDFT) and suspensory ligament desmitis; therefore, these injuries will not be discussed further here.

### Tendon and Ligament Injuries: Challenging Diagnoses

The goal of this session is to discuss tendon and ligament injuries that are not amenable to diagnosis with routine ultrasonography alone, either because the injury is located within a site that is difficult to ultrasound, such as the carpal/tarsal sheath or the foot, or because ultrasound is not a highly sensitive modality for that injury, such as tears of the manica flexoria or marginal tears of the deep digital flexor tendon. Case examples will be presented to highlight specific challenges and to demonstrate how advanced imaging or surgical approaches were able to achieve a definitive diagnosis.

### Diagnosing Tendon and Ligament Pathology within the Foot

#### Deep Digital Flexor Tendonitis

The deep digital flexor tendon (DDFT) is commonly affected by injuries within the pastern and foot and, because of its position within the hoof capsule, visualization of deep digital flexor tendon pathology within the foot is often not possible with ultrasound. With the advent of magnetic resonance imaging (MRI), diagnosis of deep digital flexor tendinopathy is becoming much more common, either alone or in combination with navicular pathology, including navicular bone disease, navicular bursitis and/or impar ligament changes.

Although horses whose lameness improves with a palmar digital (PD) or abaxial nerve block may have bone or joint disease, many horses undergoing bilateral foot MRI have tendon and/or ligament injuries as either a primary or concurrent diagnosis. For horses whose forelimb lameness responds to diagnostic anesthesia with a PD nerve block but where radiographs are unremarkable, MRI is an option to characterize soft tissue lesions within the foot. At Cornell, routine sequences for orthopedic MRI imaging involve proton density weighted (PDW) and STIR sequences in all 3 planes: sagittal, dorsal, and transverse. PDW images have good anatomical detail and emphasize the distribution of fluid with better contrast (i.e., greater grey scale) and Short-T1 Inversion Recovery (STIR) images suppress the fat signal to enable sensitive detection of bone abnormalities, such as bone marrow lesions or bone edema. Forelimbs constitute the majority of foot MRIs performed.

Pathology of the DDFT often involves linear, longitudinal tears affecting either the medial or lateral lobes of the DDFT. Tears may be short or long, and can extend from the level of the middle phalanx to the navicular bone. In conjunction with DDFT tears, it is common to see navicular bursitis—either increased fluid and synovitis or adhesions, adhesions between the DDFT and the flexor cortex of the navicular bone, navicular bone changes—enlarged synovial invaginations, navicular bone edema, navicular bone distal border fragmentation/fractures, and impar ligament desmitis. In fact, sometimes so many abnormalities are detected that it can be difficult to determine which lesion is the primary source of lameness or whether the lameness is the result of a combination of many factors.

The treatment for DDF tendonitis in this region depends upon location, severity and chronicity. In horses with dorsal border longitudinal tears of the DDFT that communicate with the digital flexor tendon sheath or navicular bursa, tenoscopy or bursoscopy can be used to further evaluate and debride the tendon lesion and administer biologics. In one study, horses with dorsal border lesions of the DDFT had a better prognosis for return to athletic activity than horses with complete splits or core lesions of the DDFT within the hoof capsule diagnosed via MRI<sup>1</sup>. Core lesions can be injected with regenerative medicine therapies. Lesions at or distal to the level of the navicular bone are less accessible and are best treated by MRI-guided needle injection in open MRI units<sup>2</sup>. In a study of 97 horses with DDFT injury diagnosed with MRI and treated medically with intrasynovial corticosteroids and sodium hyaluronan, rest and rehabilitation, or both, 61% returned to activity for a mean duration of 22 months, and 26% were still sound at follow-up (median time: 5 years)<sup>3</sup>. Western performance horses returned to use for a longer duration of time than English performance horses, and horses treated with intrasynovial corticosteroids and rest/rehabilitation returned to use for a longer duration than horses treated without rest<sup>3</sup>. Horses presenting with an acute duration of signs typically respond better than horses with chronic lameness.

### **Diagnosing Tendon Pathology within the Digital Flexor Tendon Sheath (DFTS) Manica Flexoria Tears**

The manica flexoria is a sleeve formed by the tendon of the superficial digital flexor that surrounds the tendon of the deep digital flexor at the level of the metacarpo/metatarsophalangeal joints. Injuries to the manica flexoria are reported more frequently in Europe than in North America, possibly due to the over-representation of cobs and ponies in Europe, accounting for 83% of 53 cases in one report from the United Kingdom<sup>4</sup>. Tears of the manica flexoria occur much more frequently in the hindlimbs (85% of cases)<sup>4</sup> and are associated with digital flexor tenosynovitis.

Standard ultrasonography does not have a high sensitivity for the detection of manica flexoria tears, and tenoscopic diagnosis is considered the gold standard for definitive diagnosis. To increase the sensitivity of pre-operative diagnosis, the use of both intrathecal analgesia and contrast radiography have been proposed to evaluate digital flexor tendon sheath pathology pre-operatively<sup>5</sup>. In a UK-based study, contrast radiography predicted manica flexoria tears with a sensitivity of 96% and a specificity of 80%<sup>5</sup>. Some authors have proposed that dynamic flexion/extension and non-weight bearing ultrasonography are helpful for diagnosing manica flexoria tears where findings include: abnormal sliding of the SDFT relative to the DDFT on flexion/extension with medial displacement of the SDFT, appearance of an anechoic gap between flexor tendons, or reduced SDFT sliding<sup>6</sup>.

However, even with contrast radiography and dynamic and non-weight bearing ultrasonography, manica flexoria tears may be challenging to diagnose prior to tenoscopy. In horses that present with hindlimb lameness and persistent, unilateral tenosynovitis, digital sheath tenoscopic

evaluation is recommended to achieve a definitive diagnosis, with tears of the manica flexoria and marginal tears of the DDFT both being differential diagnoses.

### **Deep Digital Flexor Tendonitis**

In addition to tendinopathy within the foot, marginal tears of the DDFT can also occur within the digital flexor tendon sheath, resulting in persistent tenosynovitis. Differentiating manica flexoria tears from marginal DDFT tears within the digital sheath can be challenging. With contrast radiography, marginal tears of the DDFT were predicted with a sensitivity of 57% and a specificity of 84%<sup>5</sup>. Interestingly, DDFT tears were significantly more likely to respond positively to intrathecal diagnostic analgesia than manica flexoria tears<sup>5</sup>. In a study evaluating 76 cases of noninfected tenosynovitis of the digital flexor tendon sheath, marginal tears of the DDFT were associated with post-operative lameness as compared to tears of the manica flexoria, and long DDFT tears were associated with a reduced prognosis as compared to short tears<sup>7</sup>. DDFT tears were approximately twice as common as manica flexoria tears in this U.K. study, and at a minimum of 6 months' follow-up, 68% of animals were sound and 54% had returned to preoperative levels of performance<sup>7</sup>. Although the prognosis for marginal tears of the DDFT is not as optimistic as for manica flexoria tears, tenoscopy can provide the most accurate diagnosis and can guide prognosis and therapeutic decision making.

### **Superficial Digital Flexor Tendinopathy within the Carpal Sheath**

In older horses, spontaneous rupture of the proximal superficial digital flexor tendon at the level of the carpal sheath or proximal metacarpus has been reported<sup>8</sup>, presumably due to stiffening and loss of elasticity with age. Complete SDFT rupture results in overt clinical signs, including visible swelling over the palmar aspect of the carpus or cannon bone, reluctance to straighten the knee and pain upon palpation, and the diagnosis can be confirmed ultrasonographically<sup>9,10</sup>. However, acute SDF tendonitis or degenerative changes within the carpal sheath may also occur which are not as readily detectable on physical or ultrasound examination. Older horses (> 15 years of age) are more likely to show evidence of superficial digital flexor tendonitis within the carpal canal<sup>9,10</sup>. Because the carpal sheath is a difficult area to evaluate ultrasonographically and lesions may be difficult to diagnose in acute stages, magnetic resonance imaging or surgery may be required to achieve a definitive diagnosis. Early literature reported a poor prognosis for spontaneous SDFT rupture in older horses regardless of the method of management; however, a more recent case series suggests that horses could return to light ridden exercise following a rehabilitation program involving box stall rest, non-steroidal inflammatory administration, bandaging and a gradually increasing exercise program over a 6-month period<sup>8</sup>.

### **Conclusions**

Many tendon and ligament injuries are amenable to diagnosis with diagnostic analgesia and ultrasonography, especially with advances in ultrasound technology and techniques. However, ultrasonography is not sufficient to diagnose all tendon and ligament injuries, especially those in difficult-to-image regions such as the hoof or the carpal and tarsal sheaths. In addition, the sensitivity of ultrasonography for lesions in certain locations, such as manica flexoria tears and marginal tears of the deep digital flexor tendon within the digital flexor tendon sheath, is poor. For lameness that has been localized to these regions but where ultrasonography does not yield a diagnosis, advanced imaging (MRI) or surgery may be considered as additional diagnostic options.

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## THE HITCHHIKER'S GUIDE TO EQUINE REGENERATIVE MEDICINE

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### Abstract

The “alphabet soup” of regenerative medicine therapies available to equine veterinarians, ranging from ACS to PRP to MSCs, will be discussed from an evidence-based perspective. Case studies will be used to highlight indications for regenerative medicine approaches.

### Regenerative Medicine

Regenerative medicine broadly refers to the use of agents to help repair, replace or regenerate lost or damaged tissue and organ function. In horses, regenerative medicine is commonly used to treat musculoskeletal injuries affecting the soft tissues, such as tendon and ligament strains, and joint disease. Many of the regenerative therapies currently employed in the field of equine surgery involve the use of biologic agents or stem cells to stimulate the immune system to promote endogenous healing. Regenerative medicine approaches involving tissue engineered constructs or engineered biomaterials have also been applied in the horse for applications such as articular cartilage repair; however, these approaches have been primarily restricted to research studies or small clinical cohorts at academic research hospitals. Regenerative medicine is an active area of ongoing research, and new therapies are emerging on a regular basis. Due to the evolving nature of this field, it is important to stay abreast of the literature as recommendations and regulations governing the use of regenerative medicine approaches continue to change frequently.

### “Alphabet Soup” of Biological Therapies

Most regenerative medicine therapies are considered biologics, which differ from conventional drugs in that most biologics are complex mixtures that are not easily identified or characterized. Biologics can be isolated from a variety of natural sources, and most biologics used in the equine industry are isolated from tissues or body fluids from the animal being treated, including: blood, bone marrow or adipose tissue. Some of the commonly available biologics or regenerative medicine therapies available to equine practitioners will be discussed below.

### Platelet-rich plasma (PRP)

Platelet-rich plasma (PRP) is plasma with a platelet count greater than that of whole blood; however, there is no consensus definition and PRP composition may vary significantly between individuals and between commercial systems or processing techniques used. There are a multitude of studies and systematic reviews on the use of PRP for tendon/ligament and joint disease in humans<sup>1,2</sup> and a systematic review that compares PRP for orthopedic applications in both humans and horses<sup>3</sup>. There is more data available on the use of PRP for equine tendon and ligament injuries than intra-articular injuries. In a recent international survey of rehabilitation modalities offered for horses from the United States, Europe and Canada, the proportion of respondents using PRP (86.5%) was greater than those using IRAP (81.4%), followed by mesenchymal stem cells (62.7%) and adipose stem cells (36.6%)<sup>4</sup>.

PRP is thought to promote healing through the release of growth factors present in the  $\alpha$ -granules of platelets, including: platelet-derived growth factor (PDGF), transforming growth factor- $\beta$  (TGF- $\beta$ ), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1) and bone morphogenetic proteins (BMPs). Because PRP is minimally manipulated and easy to prepare patient-side, there is less regulatory burden associated with the use of PRP as compared to pharmaceuticals. A recent meta-analysis suggested that the use of leukocyte-poor platelet-rich plasma (LP-PRP) may result in superior functional scores in human knee OA as compared to leukocyte-rich platelet-rich plasma (LR-

PRP) or hyaluronic acid (HA)<sup>5</sup>. However, both LP-PRP and LR-PRP were associated with a higher incidence of adverse reactions than HA. Some of the more common commercial PRP systems available to the equine practitioner include:

- Arthrex Angel® PRP System
- Arthrex Autologous Conditioned Plasma (ACP®) Double-Syringe System
- Harvest Technologies Harvest Smart-PRP2®: PRP, BMAC and stromal vascular fraction, SVF
- Medtronic Magellan® Autologous Platelet Separator System
- Pall® V-PET Veterinary Platelet Enhancement Therapy
- Zimmer Biomet® Biologics Gravitational Platelet Separation System (GPS® III)

### **Autologous Conditioned Serum (ACS) or IRAP™ II**

Autologous conditioned serum (ACS) is a blood product containing concentrated amounts of interleukin-1 receptor antagonist protein (IRAP) and is licensed as a medical device. Commercial systems include IRAP™ II, IRAP ProEAS™ (Arthrex® Vet Systems), and Orthokine®/Vet IRAP (Orthogen Veterinary). MediVet ACS (MediVet® Biologics) is also marketed as an ACS product; however, there is no peer-reviewed literature available evaluating this product. ACS is subject to some of the same variability in final product that PRP is, with variation between different patients and even within the same patient during different clinical circumstances. For example, surgical stress associated with elective equine castration has been shown to result in alterations in cytokine content in ACS<sup>6</sup>. Equine studies suggest that there is clinical and histologic improvement following treatment with ACS (Orthokine®) in the carpal osteochondral fragment model of OA<sup>7</sup> and clinical improvement in lameness and ultrasonography in horses with naturally occurring superficial digital flexor tendinopathies<sup>8</sup>; however, carefully designed randomized clinical trials are needed to draw definitive conclusions.

### **Pro-Stride Autologous Protein Solution (APS)**

Pro-Stride APS is a dual-device system that produces a concentrated solution of cells, platelets, growth factors and anti-inflammatory proteins, such as interleukin-1 receptor antagonist protein (IL-1ra), which are obtained from the patient's blood. The "APS" stands for Autologous Protein Solution. There is one study evaluating Pro-Stride APS in horses. This study investigated a single intra-articular injection of APS in 40 client-owned horses with naturally occurring osteoarthritis in a high-motion joint (fetlock, carpus, stifle, tarsocrural) or the proximal intertarsal joint<sup>9</sup>. Horses were randomly assigned to receive an injection of 5 mL of saline or 5 mL of APS and were evaluated on the basis of lameness, kinetic gait analysis, joint circumference and range of motion at 14 days, in addition to client evaluation of lameness prior to treatment and at 12- and 52 weeks post-injection. By 14 days, the APS-treated group had improved lameness grades, asymmetry indices of vertical peak force and range of joint motion as compared to controls. Clients assessed lameness and comfort as improved in APS-treated horses at 12 and 52 weeks; however, there was no placebo-treated group evaluated at these time intervals. Horses were more likely to respond to Pro-Stride APS if they had less severe lameness and less advanced radiographic evidence of OA.

### **BMC**

Bone marrow concentrate (BMC) is typically obtained from either a sternal or tuber coxae bone marrow aspirate in horses and concentrated using a commercial system. Unlike PRP, BMC contains cells, a small subset of which are considered to be mesenchymal stem cells. Most BMC systems are also thought to concentrate growth factors and IRAP. Although a previous study suggested that microfracture augmented with BMC yielded structurally superior cartilage repair as compared to microfracture alone in an equine full-thickness defect cartilage model<sup>10</sup>, a

more recent study suggested that cartilage repair results were similar between direct application of minimally manipulated BMC versus microfracture to equine full-thickness cartilage defects<sup>11</sup>. Although MRI outcomes were better for BMC-treated lesions, the authors attributed this to reduced surgical trauma to the subchondral bone since microfracture was not performed in this group<sup>11</sup>.

### Cell-Based Therapies

“Stemness” is a property that refers to an undifferentiated cell capable of self-renewal, or the ability to give rise to indefinitely more “stem” cells, and from which other specialized cell types arise by differentiation. Mesenchymal stem cells (MSCs) are the most commonly employed cell therapy for equine musculoskeletal disease, as MSCs are multipotent stromal cells that can differentiate into a variety of cell types, including cartilage, bone, muscle, tendon, and adipose tissue. MSCs can be autologous (obtained from the same individual), allogeneic (obtained from a different individual of the same species) and xenogeneic (obtained from a different species). Although allogeneic cells have advantages in terms of characterization and off-the-shelf availability, there is evidence that allogeneic stem cells are not completely “immune privileged”. Therefore, current evidence suggest that autologous stem cells, or MSCs obtained from the same individual to be treated, may be the best source for musculoskeletal tissue healing. However, autologous cells must be culture-expanded to generate a sufficient number of cells for therapeutic applications, and this may delay treatment for 4 to 6 weeks.

Initially, stem cells were thought to repair tissue by engraftment and proliferation to directly replace damaged or lost cells from that tissue to be treated. However, paradigms have shifted over the past decade, and recent evidence suggests that stem cell therapies do not result in cell engraftment into tissue but, rather, stem cells are able to secrete factors that modulate the surrounding environment to promote healing by the body’s own cells. For this reason, new research is focusing on the stem cell “secretome”, or the paracrine (cell-to-cell communication) soluble factors produced by stem cells that promote healing. Stem cells have been shown to secrete exosomes, or extracellular vesicles, that contain many pro-growth and anti-inflammatory factors that have yet to be fully characterized. There is evidence both for and against the use of stem cell therapy for the treatment of tendon/ligament and joint disease in horses. This primary literature is too extensive to summarize here, though several reviews are available on the use of cell-based therapies for joint disease in veterinary medicine<sup>12</sup>, extracellular vesicles in joint disease and therapy<sup>13</sup> and practical considerations for the use of MSCs in horses<sup>14</sup>.

### Gene-Based Therapies

Gene therapy is an experimental technique that involves the delivery of genes (or nucleic acids) into a patient’s cells to treat or prevent disease. Gene therapy is currently being employed to treat medical conditions in humans for which no other effective treatments are available; however, many gene therapy approaches are still experimental and are being investigated in clinical trials. There are no gene therapy approaches currently approved for equine musculoskeletal disease; however, experimental research into gene therapy for joint disease and tendon and ligament injuries is currently underway. Genes being investigated for joint disease in the horse include interleukin-1 receptor antagonist (IL-1ra)<sup>15,16</sup>, and genes being investigated for tendon and ligament injury in the horse include: vascular endothelial growth factor (VEGF164) and fibroblast growth factor 2 (FGF2)<sup>17</sup>.

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## ADVANCED IMAGING OF FATAL MUSCULOSKELETAL INJURIES IN RACEHORSES

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### Abstract

Fatal musculoskeletal injuries (FMI) are of utmost concern to equine veterinarians, racehorse owners/trainers, and the general public. Advanced imaging approaches, including standing CT, MRI and PET imaging, show promise for detecting fetlock pathology prior to catastrophic injury.

### Overview of Fatal Musculoskeletal Injuries (FMI) in North America

Fatal musculoskeletal injuries (FMI) are the leading cause of death in racing Thoroughbreds and Standardbreds, accounting for ~70-80% of all fatalities<sup>1-3</sup>. The majority of musculoskeletal fatalities are localized to the metacarpo- and metatarsophalangeal (fetlock) joints. Catastrophic biaxial proximal sesamoid bone fracture is the most common FMI in North American Thoroughbred racehorses<sup>1,3,4</sup>, accounting for ~35% of fatalities in NY racehorses, followed by metacarpal/tarsal fractures, accounting for ~25% of fatalities<sup>3</sup>.

While veterinarians, horse owners and horse trainers have made strides in reducing the number of pelvic and proximal limb stress fractures (e.g., tibial, humeral, radial and scapular) through improved detection via nuclear scintigraphy, catastrophic fetlock fractures continue to occur at a concerning rate. Proximal limb fractures have been shown to be a result of stress-induced bone injury, and we are more likely to detect proximal limb stress fractures because many horses show evidence of prodromal lameness before the catastrophic fracture occurs. Unfortunately, lameness is often not present or not detected in horses prior to sustaining catastrophic fetlock fractures. This has been documented on NY racetracks where horses are evaluated by racetrack veterinarians and other officials at several times before each race, including when jogged in hand for a pre-race inspection and palpation, in addition to evaluation by regulatory veterinarians when walking in the paddock, when ridden under saddle in the post parade, while warming up at the gallop on the racetrack and again when being led to the starting gate<sup>5</sup>. While one possibility is that these horses have bilateral lameness or a short-strided, choppy gait that is not detected as asymmetry or overt lameness, another possibility is that these horses simply don't manifest clinical signs of lameness. The detection of sub-clinical lameness in racehorses is currently the subject of several ongoing studies using objective gait analysis techniques at racetracks in Singapore and Hong Kong.

A recent meta-analysis of risk factors for FMI in flat racing evaluated 86 evidence-based studies between 1990 and 2017 and identified some risk factors with consistent evidence for increasing risk of FMI while other factors were less certain or contradictory<sup>6</sup>. Horse-related factors with strong evidence included: older age and older age at first start, male sex, higher race class and lower claiming price. Race-related factors included: firm turf-track conditions, wet dirt-track conditions, longer race distance and greater number of starters in a race. Management-related factors included: greater time between starts, greater number of starts, longer racing career, abnormal pre-race examination findings, previous injury and recent administration of medication to horses.

### Volumetric Imaging for Assessment of FMI in Racehorses

In addition to epidemiological studies and studies investigating lameness in racehorses, recent efforts have focused on the application of advanced imaging approaches to detect pathology associated with FMI in racehorses. Traditional radiographs are not sensitive for detecting fetlock pathology or predicting risk of catastrophic fetlock fractures. In an effort to gain more information about the underlying pathophysiology and pathological changes that may occur in

horses sustaining catastrophic PSB and condylar fractures, distal limbs from horses that have sustained FMI have been scanned using computed tomography (CT), micro-CT and magnetic resonance imaging (MRI). In addition, positron emission tomography (PET) has recently been applied, in conjunction with CT imaging, to look for functional changes in the bones of live horses using 18F-sodium fluoride<sup>7</sup>. Whereas CT and PET imaging have historically required general anesthesia for imaging in horses rendering these modalities impractical for screening horses for risk of fracture, advances in medical technology have resulted in the design of CT units for use in standing, sedated horses<sup>8,9</sup> and a PET device that would allow for equine distal limbs data acquisition in the standing horse which is currently in beta testing.

### **MRI Imaging**

A recent study compared metacarpophalangeal joint injury patterns obtained via standing low-field MRI in racing Standardbreds and Thoroughbreds<sup>10</sup>. While Thoroughbreds had a higher rate of stress fractures (40.3% vs.10%), more severe subchondral sclerosis and bone marrow lesions (BMLs) as compared to Standardbreds, Standardbreds had more sites of resorption and subchondral bone defects, in addition to higher synovitis and joint capsule thickening scores.

### **Proximal Sesamoid Bone (PSB) Fracture**

An equine standing MRI system was used to determine associations between catastrophic PSB fracture and bony changes in the metacarpophalangeal joints in 21 Thoroughbred racehorse cadavers and 53 control cadavers from Florida racetracks<sup>11</sup>. Grading scales were created to assess the density of the PSBs and the third metacarpal (MC3) subchondral bone plate thickness. PSB fracture was associated with increased PSB density in the fractured limb, increased MC3 subchondral bone plate thickness in the contralateral, non-fractured limb, and the presence of orthopedic disease in the contralateral, non-fractured limb. According to this study, horses with contralateral MC3 orthopedic disease were 39.0 times as likely to have a PSB fracture as compared to horses without contralateral MC3 orthopedic disease. The authors proposed that horses sustaining PSB fracture have a pre-existing lesion in the contralateral forelimb leading these horses to favor the contralateral limb, thereby leading to the PSB fracture. However, cause-and-effect cannot be determined by case-control study designs.

### **Condylar Fracture**

Studies show potential for MRI to be able to help discriminate between horses at risk of condylar fracture, but more investigation is needed. One overarching challenge with MRI as a screening tool for condylar fracture is the extended time it takes to acquire images. High-field MRI was used to determine whether subchondral bone thickness in the lateral parasagittal groove of the third metacarpal bone could be used to identify horses at risk of catastrophic lateral condylar fracture<sup>12</sup>. This case-control study evaluated 191 third metacarpal bones from U.K. racehorses, revealing distinct patterns of subchondral bone plate thickness between fractured bones, contralateral bones from horses with lateral condylar fractures, and control bones. While this study demonstrated increased depth of dense subchondral/trabecular bone in fractured bones suggesting that MRI could offer some ability to detect horses at risk of condylar fracture, the positive predictive value of the test decreased from 95% to 9.8% when a real-world prevalence of 0.5% was considered. Therefore, the authors concluded that pre-screening tests were required to eliminate many of the true negative horses prior to MRI in order to improve the positive predictive value of MRI.

An equine standing MRI system was used to determine associations between condylar fracture and bony changes in the third metacarpal bone in 26 Thoroughbred racehorse cadavers sustaining condylar fractures and in 88 control cadavers from Florida racetracks<sup>13</sup>. Bone marrow lesions (BMLs), previously referred to as bone marrow edema, were defined as regions

with high intensity on STIR and T2\*W images and low intensity on T1W images. Within cases, 100% of fractured limbs had BMLs, whereas only 27% of non-fractured contralateral limbs had BMLs. BMLs were also significantly more common in fractured limbs (100%) as compared to non-fractured limbs from control horses (7%). The dense bone volume percentage (DBVP) was increased in both medial and lateral condyles of fractured bones as compared to control bones. The authors concluded that the presence of BMLs and increased DBVP may be useful for detecting horses at risk of catastrophic condylar fracture; however, this has not yet been evaluated in a cohort of live racehorses. Receiver operator characteristic (ROC) curves and predictive values were not calculated for this study.

### **CT and Micro-CT Imaging**

#### **Proximal Sesamoid Bone (PSB) Fracture**

CT and micro-CT imaging has recently been employed, primarily in cross-sectional cadaver studies, to evaluate differences in PSB morphometric parameters between horses that have sustained catastrophic PSB fracture and controls that have died due to other causes. In one study, voxel-based morphometry computational techniques were used to evaluate statistical variation in CT-measured bone density in the PSBs from six horses sustaining PSB fracture and six age-matched control specimens<sup>14</sup>. Results demonstrated that bone mineral density in the abaxial regions of both medial and lateral PSBs were ~ 12.7% and 13.5% higher, respectively, than controls. In a similar study from this same group, surface-based morphometry demonstrated that the abaxial margin of the medial PSB base was up to 3.5 mm more prominent in the fracture group as compared to the control group<sup>15</sup>. In a micro-CT study evaluating PSBs from eight horses sustaining PSB fracture and eight controls, bone volume fraction, bone width, trabecular thickness and degree of anisotropy were significantly different between fractures and controls<sup>16</sup>. A combined model incorporating bone volume fraction and width was able to identify fracture from control horses with an area under the curve of 0.938 using receiver operator characteristic (ROC) curves. Future prospective, *in vivo* and longitudinal studies are required to determine the value of CT for detecting prodromal changes associated with catastrophic PSB fracture.

#### **Condylar Fracture**

There are numerous studies using CT to investigate both qualitative and quantitative changes in the metacarpal 3 bone and condyle in racehorses that have sustained fatal condylar fractures. One study suggested that differences in volumetric bone mineral density in the distal epiphysis of the third metacarpal bone are subtle<sup>17</sup>. An investigation using high-resolution peripheral quantitative CT suggested that increased bone volume fraction of the distal metacarpus had some value for identifying horses at risk of any FMI (sensitivity: 82.8%, specificity: 62.5%) but was not able to differentiate between horses with and without metacarpal condylar fractures<sup>18</sup>. However, another study using qualitative assessment of bone density was able to demonstrate significantly higher bone density in both fractured and non-fractured condyles from horses sustaining fatal condylar fracture as compared to control condyles<sup>19</sup>. Future prospective, *in vivo* and longitudinal studies are required to determine the value of CT for detecting prodromal changes associated with catastrophic PSB fracture.

#### **Positron Emission Tomography (PET) Imaging**

Positron emission tomography (PET) is a nuclear medicine functional imaging technique used to observe metabolic processes which is commonly employed in human medicine for cardiac and brain imaging, in addition to cancer diagnostics. PET can be combined with volumetric imaging techniques such as MRI and CT to provide additional anatomical detail. In horses, <sup>18</sup>F-sodium fluoride (<sup>18</sup>F-NaF), a PET bone tracer, has been used to evaluate metabolic bone remodeling in the distal limbs of anesthetized horses<sup>7</sup>. PET imaging has highlighted areas of increased bone



metabolism in the front feet and fetlocks of horses corresponding to regions of increased vascularity and osteoblastic activity<sup>20</sup>. In particular, when comparing <sup>18</sup>F-NaF PET, CT and scintigraphy, PET was particularly useful for detecting focal areas of <sup>18</sup>F-NaF uptake in the PSBs where other imaging modalities did not identify abnormalities<sup>20</sup>. PET appears to be a promising technique for identification of functional bone remodeling, especially when combined with CT.

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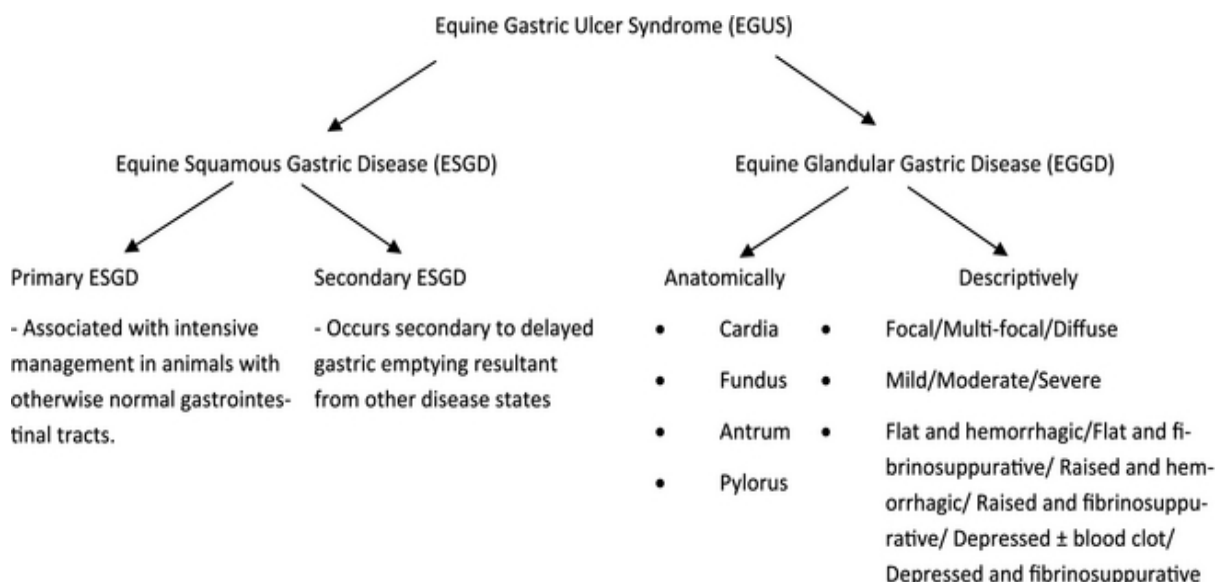
## Gastric Health in Horses: Feeding and Management Tools

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### Introduction

It has been well defined that gastric ulceration in the horse is of extreme significance due to its prevalence (Nadeau et al., 2000) as well as the role that gastric ulcers play in decreasing health parameters and overall equine performance (Bell et al., 2007). Historically, ulcers found in the terminal esophagus, as well as the nonglandular and glandular portions of the equine stomach were associated with a diagnosis of equine gastric ulcer syndrome (EGUS) (Andrews et al., 1999). Recently ulcers associated with the glandular portion of the stomach have been further characterized to be part of a separate diagnosis termed equine glandular gastric disease (EGGD), while ulcers in the nonglandular region have been collectively grouped to a separate diagnosis of equine squamous gastric disease (ESGD) (Sykes et al., 2015) (Figure 1).

Figure 1: Equine Gastric Ulcer Terminology and Definitions (Sykes et al., 2015)



While ulceration in different anatomical regions of the stomach is likely caused by unique factors, the persistent low pH (high acidity) of the equine stomach has been routinely identified as a major causative factor in the development of gastric ulceration (Widenhouse et al., 2002). The most recent consensus statement by the European College of Equine Internal Medicine highlights the control of acid accumulation as critical in the treatment and prevention of gastric ulceration. The statement goes as far as to say, “no acid, no ulcer.” While it is critical that the acidic nature of the stomach be maintained to maximize the digestive processes, prolonged exposure to acidic gastric juices has a profoundly negative effect on the health of the gastric mucosa. As treatment of gastric ulcers via pharmacological intervention is not the focus of this review and is covered in depth in other articles (Sykes et al., 2014a, Sykes et al., 2014b, Doucet et al., 2003), this review will focus on nutritional intervention as well as management strategies that can be utilized to support the health of the equine gastric environment.

## Equine Gastric Ulcer Syndrome Physiology

Comprising only roughly 8% of the equine gastrointestinal tract, the stomach is a critical component responsible for the initiation of digestion of fats, carbohydrates and proteins. A unique feature of the equine stomach is the near continual secretion of gastric acid, mainly HCl, which maintains the stomach in an acidic environment. This low pH is necessary to promote enzyme function as well as begin the breakdown of feedstuffs into absorbable components in the small intestine (Geor et al., 2013). Meant to be grazing animals, horses evolved to consume low quality forages nearly constantly, thus supporting the continual secretion of gastric acid. However, modern management practices typically restrict access to forage sources and promote extended periods of time with little to no gastric fill. At these times, the pH of the gastric environment can fall to dangerously low levels, promoting the formation of gastric ulcers. While a natural rhythm of pH changes does occur in the fasted horse the amount of time that the gastric environment remains below a pH of 4.0 is significantly greater when no feedstuffs are present in the stomach.

The prevalence of EGUS varies in adult horses, but it is thought that all breeds and ages are susceptible to the development of EGUS with thoroughbreds being more prone to ulceration. Horses with warmblood breeding are thought to be more susceptible to EGGD, however this very new classification is not fully understood or described. Numerous studies evaluating the prevalence of EGUS across breeds and disciplines has determined the following rates of EGUS prevalence: Thoroughbred racehorses- 93% (Murray et al., 1996), Standardbred racehorses- 87% (Rabuffo et al., 2002), 3-day event horses- 75% (Michael Murray, Unpublished data), show horses- 58% (McClure et al., 1999), endurance horses- 67% (Nieto et al., 2004) and Western performance horses- 40% (Bertone, 2000). Interestingly leisure horses had a rate of gastric ulceration over 35% in a post mortem study (Murray et al., 1996). Overall, the following risk factors have been determined in the development of gastric ulcers in horses:

- Age
  - Risk increases with age (Rabuffo et al., 2002)
  - Risk is highest under 6 years of age (Chameroy et al., 2006)
- Exercise
  - Increased workload increases risk (White et al., 2007)
  - “Acid-Splashing” Hypothesis (Lorenzo-Figueras & Merrit, 2002)
- Fasting
  - Continuous gastric acid secretion during fasting (Vatistas et al., 1999)
- Starch Intake
  - High starch intake increases risk (Frank et al., 2005)
  - High quantities of starch present in the stomach increase VFA production and may impact gastric integrity (Nadeau et al., 2003)
  - Important to note that an upper limit for starch in concentrates has not been determined as it relates to gastric ulcer formation.
- Pasture Turnout
  - Decreased prevalence in grazing horses (Murray et al., 1989, Hammond et al., 1986)
- Water Intake
  - Increased risk with limited water intake (Lutherson et al., 2009)

- Electrolyte Administration
  - Increased risk when dosed with electrolytes via syringe (Holbrook et al., 2005)
- NSAID Administration
  - Increased risk with NSAID administration (Tomlinson and Blikslager, 2003)
- Travel stress
  - Increased risk of ulceration in horses that travel
- Forage Feeding
  - Increased saliva production with forage feeding (Meyer et al., 1985)
  - Alfalfa hay feeding can increase gastric pH (Lybbert et al., 2007)

### Clinical Signs and Diagnosis of Equine Gastric Ulcer Syndrome

Clinical signs of EGUS can be variable and specific to the behavior of the individual horse. Horses may show relatively limited signs of discomfort but still have severe gastric ulceration when observed via endoscopic evaluation. Typically, as the severity of the ulceration progresses, clinical signs will increase in both number and severity. The following clinical signs are commonly observed in horses with EGUS.

- Changed eating behavior/poor appetite
- Weight loss/difficulty maintaining weight
- Poor hair coat
- Reduced performance/behavioral changes/cribbing
- Abdominal discomfort
- Colic

In order to truly evaluate not only the number, but also location and severity of gastric ulceration, an endoscopic evaluation must be conducted. When an evaluation is performed, typically the number, location and severity of the lesions are scored utilizing the scoring system below.

Table 1: EGUS Scoring System (Andrews et al., 1999)

Score	Appearance of Mucosa
0	Intact epithelium
1	Intact mucosa, evidence of hyperkeratosis or hyperemia
2	Small, single or multifocal lesions
3	Large, single or multifocal lesions or extensive superficial lesions
4	Extensive lesions with areas of apparent deep ulceration

### Nutritional Management of Equine Gastric Ulcer Syndrome

Maximizing pasture turnout to allow grazing is one of the most important management strategies for controlling gastric ulcers in horses. If a horse is stalled for any period of time, continuous access to forage should be allowed. Inclusion of alfalfa hay in the diet, preferably provided at regular 5 – 6-hour intervals, is recommended as it may have a protective buffering effect in the stomach (Nadeau 2000). Feeding a fat- and fiber-added and lower soluble carbohydrate concentrate is recommended if additional calories are needed. Increasing the frequency (3 to 4 meals per day) and decreasing the size of concentrate meals is recommended, especially if the horse is consuming a large amount daily. If a forage-only diet meets caloric requirements, a high-quality ration balancer will provide the protein, vitamin, and minerals lacking in a forage-only diet.

There are currently many supplements on the market claiming to prevent, reduce or eliminate gastric ulcers, but most of these products have not been tested and little scientific evidence exists regarding their efficacy. Many supplements contain varying concentrations and preparations of calcium carbonate, which is the primary component of human antacid preparations. These preparations have been shown to temporarily increase gastric juice pH for 2 hours following administration (Garcia et al. 2005, Reese and Andrews 2009). Because of this short duration effect, frequent feedings would be necessary to elicit any long-term effect or to prevent gastric ulcers. When determining whether a gastric supplement should be incorporated into an equine ration, certain criteria should be met. Firstly, the supplement should have been researched in horses. Additionally, the specific formulation of the supplement that is marketed should be the one that is contained in the supplement. Next, a list of specific ingredients, each with a purpose should be evaluated. Many times, gastric supplements contain an “everything but the kitchen sink” approach. Unfortunately, many of the ingredients in these supplements have not been evaluated in the horse, and in many cases have not been evaluated at all. The final important consideration is the dosage of the active ingredients included in the supplement. Inclusion of the proper dosage of ingredients is critical in evaluating the overall efficacy of the supplement.

Horse owners should be encouraged to work with veterinarians and equine nutritionists to develop a gastric health management plan that can utilize nutritional intervention to facilitate improvements and consistency in gastric health. It is important to understand that while nutritional management can be utilized to mitigate some effects of gastric ulceration, currently pharmaceutical intervention is the only recognized method of treating gastric ulcers in horses.

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## Feeding (Fueling) the Performance Horse

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### Introduction

Equids, and horses in particular display an amazing capacity for exercise, specifically related to speed, endurance, and agility. As this capacity for exercise has been harnessed by the equine industry for performance, research has focused on providing the nutritional substrates necessary to support such athletic endeavors. While all exercise levels will require inputs of additional nutrients, different disciplines may require unique substrates or combinations of substrates to support nutritional needs. However, the main goals of any nutritional program designed for performance horses should focus on 1) providing adequate fuel to support the specific energy expenditure, 2) replenishing nutrients utilized during exercise, and 3) supporting optimal health through a balanced and nutritionally sound diet. This paper will outline specific nutritional requirements related to energy, proteins, vitamins, minerals, and electrolytes. Further it will expand on feeding strategies for performance horses afflicted with a variety of myopathies.

### Energy

Energy for work should be the primary consideration when designing a ration for the performance horse. Providing the fuel necessary to complete the training, performance, or competition is critical to the success of the endeavor. At the most basic level, fueling the system involves providing the substrates necessary for the horse to convert chemical energy into mechanical energy. The equine body has three sources from which it can derive energy. Body stores of fat, glycogen, and protein can all be metabolized to produce adenosine triphosphate (ATP) which fuels muscle cells to contract (Cain and Davies, 1962). ATP is also the source of energy required for muscles to relax via the distribution of calcium ions (Astrand and Rodahl, 1986). While ATP is an important energy substrate in the horse, there is a finite supply stored in the muscle, and muscle reserves can be depleted after only a few seconds of muscle activity. Because of this, prolonged muscle exertion requires the resynthesis of ATP through either aerobic phosphorylation or anaerobic glycolysis.

The primary energy substrates, by far, in the horse are fatty acids and glucose. Fatty acids are released from triglyceride stores in adipose tissue and muscle, while glucose is derived from the breakdown of liver and muscle stores of glycogen. Glucose can also be mobilized via gluconeogenesis occurring in the liver. A typical 1000 lb horse has approximately 3000-4000g of muscle glycogen and 100-200g of liver glycogen. Triglyceride stores are largely derived from 35,000-45,000g stored as adipose triglyceride with a smaller amount stored in muscle (approximately 1400-2800g; Harris, P.A. 1997). While glycogen stores may be exhausted during exercise, it is unlikely that fatty acid shortage will become an issue during exercise (Lacombe et al., 1999).

Data remains limited related to the role of protein as an energy substrate in the horse, however, extrapolation from other species would suggest that proteins, and more specifically amino acids, are not a major source of energy in the exercising horse. Studies in humans have indicated that less than 2% of energy expenditure during exercise is provided by proteins. However, when glycogen stores are inadequate, protein utilization, as an energy source may increase. Utilization of protein as an energy source is metabolically inefficient and expensive. Proteins have much more utility as structural components of bone and muscle, antibodies, enzymes,



hormones, and other functional components. Further, utilization of protein for ATP synthesis produces 3-6 times as much heat as does metabolism of fats and carbohydrates while increasing water and electrolyte loss.

### Energy Utilization

Energy utilization in the muscle of the horse is a product of three energy systems:

1. Intramuscular stores of ATP and creatine phosphate
2. Anaerobic glycolysis
3. Oxidative phosphorylation

While energy utilization is largely characterized as either aerobic or anaerobic, it is unlikely that only one process is occurring as the sole source of energy production. Rather, a combination of processes is necessary to fuel the athletic endeavors of the horse. A brief description of these process follows.

Creatine phosphate and ATP stores can provide energy for only a very short period of time prior to the mobilization of energy via either glycolysis or oxidative phosphorylation. While oxidative phosphorylation is a much more efficient utilization of glucose (producing 36-38 ATP molecules vs 2 molecules), it is a much slower process highlighting the main advantage of anaerobic glycolysis. However, in the production of energy via anaerobic glycolysis, a rapid decline in intracellular pH occurs as lactate and hydrogen ions accumulate resulting in the onset of muscle fatigue and the impairment of muscle contractility. Typically, an increased fitness level in horses results in a slower rise in lactate concentration at lower speeds or intensity levels compared to an unfit animal (Persson and Ulberg, 1974). Interestingly, lactate, once thought to be only a waste product, can be utilized by the liver to produce pyruvate which can be ultimately used via gluconeogenesis to produce glucose.

The contribution of either aerobic or anaerobic metabolism to the energy stores in the body is a function of the type of exercise being conducted as well as the fitness level of the individual animal. As stated previously, a combination of both energy systems largely accounts for energy production. However, certain exercises will call upon a preferred method of energy production. Typically, short term, high intensity exercises will require energy via anaerobic glycolysis, while long term, lower intensity exercises will draw energy predominantly from oxidative phosphorylation. Substrate utilization is also dependent upon the diet which the horse is being fed. Increased levels of fat in the diet compared to non-structural carbohydrates can push the metabolism to utilize fat as an energy source more readily. However, during the first minutes of exercise, carbohydrates are largely used as the main energy substrate. Glycogen depletion and replenishment are critical considerations related to energy utilization. Once glycogen stores have been depleted, the replenishment of these stores is more prolonged in horses than in other species taking on average 72 hours following glycogen depleting exercise. One study found that horses fed a diet high in non-structural carbohydrates compared to a diet higher in fat had quicker glycogen replenishment (Veronique et al., 2004).

Conditioning will also play a role in the metabolic profile of skeletal muscle. Specifically, the density of mitochondria will increase with training, leading to an increased capacity for oxidative phosphorylation. These increases can also result in the mobilization of NEFA's by muscle fibers, resulting in a glycogen sparing effect during low to moderate intensity exercise and the production of large amounts of ATP (146 molecules of ATP).

In summary, energy utilization in horses is a combination of multiple pathways resulting in the production of ATP necessary for muscle contraction and relaxation. Diet and physical conditioning of the animal play a major role in the utilization of energy substrates. A mix of both carbohydrates and fat is metabolized to produce energy during work, and fatigue is a factor of a depletion in muscle glycogen, reduction in circulating glucose, and a decrease in intracellular pH related to an increased production of lactate.

## Energy Requirements

The basic unit of energy is a “calorie.” To describe the large energy requirements of horses, the term kcal or Mcal is typically used with a kcal containing 1000 calories and an Mcal comprising 1,000,000 calories. To determine the energy composition of feeds multiple measurements and values can be ascertained:

- Gross Energy (GE): The heat released from complete combustion of a feedstuff
- Digestible Energy (DE): Energy available to the animal. Calculated as GE- energy contained in feces
- Metabolizable Energy (ME): Energy remaining after removal of urinary energy and gaseous energy
- Net Energy (NE): Energy remaining after heat energy is removed from ME

Equine nutrition typically utilizes DE values when evaluating the energy content of feedstuffs in contrast to other livestock species in which ME and in some cases, NE have been calculated. The DE of a diet is supplied by the starch, sugar, fat, fiber, and protein components of the diet. Digestible energy values for feedstuffs are typically estimates based on the proximate analysis of other components of the diet (digestible protein, crude fiber, nitrogen free extract, and ether extract). Much of the work conducted to determine equine DE values was done with feedstuffs lower in fats and fibers resulting in values that typically underestimate true DE values of currently available commercial diets. With that knowledge, it is important to understand that any ration evaluation in which DE is calculated can be evaluated only as an estimate. The amount of energy available to any given horse will be variable and other tools are necessary to evaluate the calorie content of feeds relative to the DE needs of the horse.

When evaluating the DE requirements of horses, many factors must be taken into account including the age, body weight, body condition, exercise level, pregnancy status, sex, and health conditions of the horse. True energy requirements of the horse may be difficult to ascertain. Rather utilization of a Body Condition Scoring (BCS) system (Henneke et al., 1993) can ascertain whether the energy requirement of the horse is being met. In brief, the BCS evaluates the energy stores of the animal by assigning a score from 1-9 relative to the condition of the animal. A score of 1 indicates a highly starved animal while a score of 9 coincides with a morbidly obese individual. For most horses, a BCS of 5-6 is ideal. Falling below energy requirements results in a negative energy balance and a decrease in BCS, while providing excess calories may result in the deposition of increased adipose tissue and a subsequent increase in BCS. Estimating the energy requirements of the performance horse can be complex. The NRC outlines needs for specific activity levels highlighted in the table below:

Table 1: Energy Needs by Exercise Category (NRC, 2007)

Exercise Category	Description	Examples	Daily Requirement (Mcal)
Light	1-3 hours per week Walk, trot, some canter	Recreational riding Early training Occasional showing	20.0
Moderate	3-5 hours per week Walk, trot, canter Light jumping, cutting, other skill work	School horses Early training program Recreational riding Frequent show horses Polo Ranch Work	23.3
Heavy	4-5 hours per week Walk, trot, canter Gallop, jumping, other skill work	Ranch work Polo Frequent show horses Strenuous events Low-medium level eventing Race training	26.6
Very Heavy	Various 1 hour of speed work Up to 12 hours of slow work	Racing Upper level eventing	34.5

The energy needs of the horse are typically met through carbohydrates and fat incorporated into the ration. Dietary carbohydrates can be classified into two general categories: non-structural and structural carbohydrates. Non- structural carbohydrates (NSC) include the sugars and starches that are digested in the small intestine, while the structural carbohydrates include the indigestible fibers that are fermented in the hindgut (cecum and colon) of the horse. The product of NSC digestion is blood glucose that serves as a readily available substrate for ATP synthesis. Fiber digestion results in the production of volatile fatty acids (VFA). The VFA's produced via microbial fermentation in the hindgut of the horse are used as a source of maintenance energy. It is estimated that 20-30% of maintenance energy requirements are met by the VFA production in the hindgut of the horse (Glinsky et al., 1976). As the end products of NSC digestion are used as primary substrates for ATP synthesis it is critical that they are supplied in the diets of horses. Diets too low in NSC may result in deficiencies in performance relative to energy availability.

Researchers have identified that the capacity of the small intestine to digest and absorb NSC prior to reaching the hindgut to be around 2-4g of starch/kg of BW (Potter et al., 1992, Radicke et al., 1991). Exceeding this limit may result in starch leaking into the hindgut of the horse resulting in digestive upset. It is always recommended to reduce large volume feedings in to smaller feedings multiple times per day. A good rule of thumb is to feed no more than 0.5% of the horse's BW in one meal.

The fat portion of the horse's diet is significantly more concentrated in terms of energy than the carbohydrate contribution. Fat contains on average 2.25 the amount of energy than an equal amount of carbohydrate (Hinchcliff and Geor, 2008). Feeding fat allows for the development of a more energy dense diet and incorporation of certain fatty acids that are vital for cell membranes, skin and coat quality, and hoof health. Fat sources are variable, and the source of the fat dictates the fatty acid profile. Good quality fat sources for horses include vegetable oils,

marine oils, flaxseed, and rice bran. Dietary fat also facilitates the absorption of fat-soluble vitamins that are important to numerous physiological processes. The upper limit of fat inclusion to the diet should be no greater than 20-25% of the total diet (not the individual components).

Considering the type of exercise the horse is performing is important in determining the fueling strategies. During high bouts of intense exercise, almost all the energy is derived from creatine phosphate, glucose, and glycogen via anaerobic respiration (Hinchcliff et al., 2008). As such, providing a diet that contains the proper substrates is important. In general, the faster and shorter the duration of exercise, the more NSC should be provided in the diet of the horse. Conversely, longer and less intense exercise bouts can be fueled by a diet rich in fats.

### **Protein and the Exercising Horse**

As the exercise level of the horse increases as dictated by Table 1, the dietary protein requirements increase as well. However, these needs are typically met as the dry matter intake increases to meet the elevated energy requirements. While protein content is important, protein quality is essential to the functionality of the performance horse. The adage that “not all protein is created equally” holds true for the performance horse diet. While most amino acid requirements for horses are not fully elucidated, there is an established lysine requirement in horses. Certain essential amino acids such as lysine, methionine, and threonine have been identified as major components of muscle protein and are critical for growth, maintenance, repair, and muscle function (NRC, 2007). Typically, commercially available concentrate feeds are fortified appropriately for the classes of horses they are designed to feed relative to the amino acid balance. High quality protein sources for horses include but are not limited to soybean meal, alfalfa, and whey protein, in addition to individual crystalline amino acids.

Performance horses often are fed diets with excess dietary protein due to the goal of meeting the increased energy requirements of the horse. The horse is fairly tolerant of excess protein in the diet with excess amino acids being broken down to nitrogen and ammonia and being excreted in the urine and feces. However, as the protein excess increases, so does the requirement for water. If adequate clean water is not available, the horse can be at risk for dehydration or kidney dysfunction. Further, excreted ammonia can be an irritant to mucus membranes and may aggravate the respiratory tract. To prevent the negative effects of protein excess, total protein in the performance horse’s diet should be kept at approximately 10-16% of the total diet (NRC, 2007).

### **Water and the Performance Horse**

Water is often the most overlooked nutrient regardless of the class of horse for which a diet is being formulated. Horses ingest water either through the consumption of feedstuffs (grains, concentrate, and hay are roughly 10% water, pasture can be as high as 80% water) or through the direct consumption of water. Exercising horses lose water through sweat, urine, and feces. A horse undergoing moderate exercise in temperatures around 68°F will lose up to 1-2 gallons of sweat per hour while horses exercising at higher temperatures can lose 2-4 gallons of sweat per hour at the same workload. Exercising horses should be encouraged to consume 10-20 gallons of fresh, clean water daily. Ensuring that water sources are clean and free of feed, hay, ice, and manure is critical. Horses exercising in cold weather may need to be persuaded to drink water more than horses in warmer climates. Addition of salt to rations can stimulate water intake and prevent dehydration. Much of the research around sweat loss in horses was conducted prior to the 1996 Olympic Games in Atlanta, GA where horses were worked under much warmer temperatures than they were used to. The findings from veterinary studies that occurred prior to

the equestrian competitions provided guidelines to event organizers and are published in multiple journal articles (Saunders et al., 1998).

### **Electrolytes**

Electrolytes, typically Na, Mg, K, and Cl, are not stored in the body and thus must be supplied daily to the horse. A performance horse will lose electrolytes in the same way that water is lost, via sweat, urine, and feces. Equine sweat has a high concentration of sodium and chloride, followed by potassium, and relatively smaller amounts of calcium and magnesium. Maintaining a proper electrolyte balance is critical to ensuring the horse consumes an appropriate amount of water. Electrolytes drive the thirst response in the horse. The quantity of electrolytes lost in 1.5 gallons of sweat is approximately: 16g Na, 30g Cl, and 8g K (NRC, 2007). Replenishing the electrolytes to the horse can typically be achieved by feeding a good quality forage (provided at 1.0-1.5% of BW), providing a good quality concentrate (at or above manufacturer's minimum recommended feeding level), and 1-2 oz of plain white salt daily.

Providing supplemental salt to horses should be done daily. Horses should either have access to a white non-iodized salt block or have white table salt top dressed on to their daily ration. Salt intake is likely to be highly variable between horses, but most horses will consume an adequate amount of salt daily if applied directly to the daily ration. In hot and humid environments, increased salt supplementation is recommended. When selecting an electrolyte supplement, it is important to evaluate the ingredients and guaranteed analysis. Many commercially available electrolytes have large amounts of dextrose and relatively limited levels of electrolytes. Administering electrolytes to an already dehydrated horse is dangerous and may in fact exacerbate dehydration (Holbrook et al., 2005). Properly hydrating a horse prior to electrolyte administration is critical. Further, addition of electrolytes directly to water has been shown to decrease voluntary water intake in horses.

### **Vitamins and Minerals**

Similarly to protein, the increased vitamin and mineral needs of the performance horse are likely to be met by the increased DM intake associated with meeting energy requirements. Commercially available concentrate diets are often fortified appropriately to provide the required levels of vitamins and minerals when fed according to directions. Vitamin E is a fat-soluble vitamin that acts as an important antioxidant to neutralize free radicals produced during exercise. A minimum level of 1000 IU per day of vitamin E should be supplied to the equine athlete to support optimal muscle health (NRC, 2007). For some horses suffering from certain myopathies or neurological abnormalities, up to 5000 IU per day of Vitamin E may be beneficial (Kane et al., 2010, Valberg, 2012).

### **Feeding Horses with Various Muscle Myopathies**

While different muscle myopathies such as recurrent exertional rhabdomyolysis (RER) and polysaccharide storage myopathy (PSSM) are fundamentally different, dietary management can play a critical role in supporting the nutritional needs of these horses. For horses with RER reducing the soluble carbohydrates in the diet is critical. Supplemental energy should be supplied via dietary fat and horses should receive optimal levels of Vitamin E daily. RER is commonly seen in Thoroughbred horses with increased nutritional requirements. Providing these horses with high quality concentrate diets is critical to ensuring optimal performance. PSSM is a blanket name for two separate disorders. PSSM1 and PSSM2 represent different disorders relative to the genetic mutation associated with the diseases. PSSM1 and PSSM2 are

most commonly observed in Quarterhorses, Warmbloods, and Draft Horses though other breeds of horses may be afflicted. Horses with PSSM1 are more sensitive to dietary starches and sugars as they accumulate more muscle glycogen than horses with PSSM2 or typical horses. A mutation in the GYS1 gene has been associated with horses with PSSM1 but not in horses with PSSM2. Horses with PSSM1 store an amylase resistant form of starch in muscles which cannot be used by muscle fibers. Dietary recommendations for horses with PSSM1 revolve around replacing calories from NSC's with calories from fats. Current recommendations for horses with PSSM1:

- Minimum of 1.5% BW of low NSC forage (<12% water soluble carbohydrate + starch)
- Concentrate should be no more than 15% of total DE as NSC
- 10-20% of the total daily energy should come from fat

Horses with PSSM2 do not have a mutation in the GYS1 gene but do have an abnormal muscle histology. Horses with PSSM2 are not sensitive to NSC in their diets in the way that PSSM1 horses are. Supplying optimal levels of Vitamin E and good quality protein has been recommended for horses with PSSM2. For all these horses, conditioning programs and consistent exercise protocols should be followed. Horses with PSSM1 benefit most from consistent exercise programs as it reduces the overall amount of glycogen build up in the muscle fibers.

### **Conclusion**

Feeding the performance horse may at times seem challenging. However, understanding the need for precise energy sources to support the specific activity that the horse is doing can help guide the decision-making process. In general, providing a minimum of 1.2-1.5% BW as good quality forage per day supplemented with a high-quality concentrate feed, should meet the requirements of the horse. Understanding the physiology of exercise and energy utilization can serve as a guide in determining the optimal concentrate diet for the individual horse. When the feeding program is working, it will become apparent in the horse's performance and when it needs to be altered, that can be done relatively simply. Having a nutrition program that complements a training program is critical as these go hand in hand in ensuring the health and performance of the exercising horse. It is important to remember that successful performances and winning is not the result of feeding a single certain supplement or feed. Rather, it is the combination of knowledge of the physiology of the animal with the diet that they are being provided.

### **References Available from the Author Upon Request**

## Feeding for Certain Medical Conditions

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### Introduction

The healthy horse should receive a diet that maximizes high quality forage, typically in the form of pasture or hay, supplemented with a concentrate that meets the specific nutritional needs for that class of horse as outlined by the NRC for protein, vitamins and minerals. However, horses with certain medical conditions may require a unique feeding management protocol. Unfortunately, little published data exists regarding what to feed the “sick” horse, as most studies have focused on meeting the nutritional needs of the “healthy” horse. This paper will serve as a reference for feeding management of horses afflicted with certain clinical cases including: 1) Feeding the starved or severely malnourished horse 2) Feeding horses suffering from chronic colic, and 3) Feeding horses prior to and immediately following surgery. This paper should serve as a starting point when looking for information; however, there are many in-depth references available (Reed et al., 2010, Geor 2009, Lewis 1995, Geor et al., 2013).

### Causes of Extreme Weight Loss or Malnutrition

Extreme weight loss in horses is often highly emotive. However, it is important to consider each case individually. Extreme weight loss, defined as an individual approximately 30% below ideal body weight, may be the result of one or multiple causes. The following list outlines a more comprehensive causative list of emaciation in horses.

- Partial or total deprivation of food (bad teeth, bad feet, bad feed, or bad humans)
- Deprivation of energy or protein, or both (misuse of supplements, underfeeding of horses suffering from DOD)
- Seasonal declines of nutrients in pasture
- Malnutrition
- Malabsorption, chronic diarrhea
- Intestinal parasites; severe lice or ticks
- Cancer
- Chronic liver, kidney, pancreatic, or heart disease
- Chronic infectious disease
- Pregnancy and/or lactation
- Senescence or senility in old age

Because of the multi-factorial nature of malnutrition, it is critical that a complete physical examination of the individual be conducted along with gathering a comprehensive history that includes a time course for the loss of body condition. While the causative factors of emaciation in horses is extensive, typically the pathophysiology of the condition is similar across cases. As the individual horse routinely and consistently experiences nutritional deprivation, body stores of carbohydrates, fat and protein are metabolized and utilized to sustain critical physiological functions. If this process persists, significant stores of adipose tissue and skeletal muscle will be depleted leading to visible muscle wasting as well as harder to detect depletion of cardiac muscle and organ tissue (Witham and Stull, 1998). Deficiencies of other nutrients may be

harder to detect. Dietary insufficiencies of minerals such as calcium and phosphorus may lead to instances of abnormal joint and bone development. Deficiencies of other minerals such as iodine and selenium may cause more noticeable clinical signs including goiter and hair loss respectively. Understanding the unique signs of nutritional insufficiency is important in treating the malnourished horse. This section will focus however, on better understanding the physiology of the starved horse and the unique strategies necessary to successfully refeed the individual.

### **Physiology of Starvation**

Designing and implementing a successful protocol requires an understanding of the unique pathophysiology of the starved horse. Feed deprivation in horses is generally met with a predictable series of metabolic, physiological and behavioral changes. With declining dietary input of critical nutrients comes a reduction in circulating concentrations of these nutrients in the blood. As nutrient levels, specifically glucose, reach critically low levels, preservation of central nervous system (CNS) function becomes a priority and nutrient utilization and mobilization is preferentially shunted toward nervous tissue. In a relatively short period of time, typically less than 24 hours, endocrine function is altered to conserve blood glucose concentrations. At the same time, mobilization of glycogen from skeletal muscle and liver stores occurs as the primary defense mechanism against starvation. However, these reserves are typically depleted in 72 hours (Hoffer, 2006). Once glycogen stores are depleted, acute starvation has developed into chronic starvation with significantly more detrimental health effects both in number and in severity.

Once glycogen stores are depleted, gluconeogenesis is necessary to maintain blood glucose concentrations, and stored adipose and protein are catabolized to fuel the energy intensive gluconeogenic processes. This catabolism of adipose and skeletal muscle results in the drastic appearance of malnourished horses. However, the unseen damage as a result of malnourishment is typically manifested in damage to the nervous system. Neural tissue has an extremely high glucose requirement, accounting for up to 20% of glucose utilized in the system. As glucose availability is diminished, the nervous system utilizes ketones, byproducts of adipose catabolism, as its' primary energy source. The increased catabolism of body stores adipose and protein can lead to conditions such as hyperlipidemia and elevated plasma urea nitrogen respectively. Evaluation of serum triglyceride levels and plasma urea nitrogen are a useful tool in evaluating nutrient deficiency in horses and may in fact be more applicable than measurements of plasma glucose and insulin (Christensen et al. 1997; Sticker et al. 1995; Stull et al. 2003).

As starvation progresses, visible physical changes as well as unseen changes occur throughout the body of the horse. The body condition of the horse will diminish with much of the bony architecture of the animal visible. Additionally, protein catabolism, not restricted to skeletal muscle breakdown, can significantly alter the architecture of the gastrointestinal tract resulting in decreased absorptive capacity, reduced intestinal mobility and volume and delayed gastric emptying. These changes, resulting in diminished immune function may predispose the horse to systemic infections as the damage to the digesta-blood barrier is compromised. All of these issues must be taken into account as a refeeding protocol is designed on an individual basis.

### **Refeeding Syndrome**

First described following the Second World War and the discovery of hundreds of thousands of severely malnourished humans, the aptly named refeeding syndrome is a major factor contributing to the high mortality rates during the rehabilitation of emaciated individuals. Briefly,



under a chronic state of starvation, the body decreases its reliance on glucose as the predominant energy source. Subsequently the body becomes extremely sensitive to the effects of insulin. If a high glycemic feed is abruptly reintroduced into the system, a potentially fatal increase in blood insulin elicited (Tresley and Sheean, 2008). A system that has been metabolizing fat and protein for energy now has a large carbohydrate bolus that it is unprepared to cope with. Coupled with the alterations in the architecture and function of the GI system described previously, the system may go into a state of shock potentially leading to respiratory and cardiac failure leading to death.

The effects of “refeeding syndrome” are typically observed in the horse 3-7 days following the start of a refeeding program. Horses reintroduced to feeds with high levels of non-structural carbohydrates may in fact succumb even quicker (Witham and Stull, 1998). In addition to the effects of a shift towards glucose metabolism described earlier, a rapid influx of electrolytes may further exacerbate health issues as the organ systems are not primed to deal with this. The resulting electrolyte imbalances may lead to organ failure, red blood cell death and hypoxemia as a depletion in phosphorylated metabolites rapidly occur (Witham and Stull, 1998). It is important that during all stages of a refeeding program, but particularly the early days, serum electrolytes, specifically phosphorus and magnesium, be monitored as a measure of progress and to address any deficiencies or imbalances (Hurley, 2005). Monitoring horses’ fluid levels and associated edema is critical during the initial refeeding period as endocrine alterations associated with antidiuretic hormone and aldosterone may lead to reduced sodium and water excretion (Dunkel and Wilkins, 2004; Hurley, 2005, Wilson and Fitzpatrick, 2004). Levels of water-soluble vitamins, specifically thiamin should be monitored due to their important role as co factors in carbohydrate metabolism. Providing the proper levels of vitamins to allow for substrate utilization is critical to the success of a refeeding program (Magdesian, 2003).

### **Developing a Refeeding Plan**

As is the recommendation with any dietary alterations to the equine diet a slow and steady approach is preferred when developing a refeeding program. It is important to understand that the emaciated and malnourished condition that the horse is in did not occur over a short period and the successful rehabilitation may take even longer. Taking care to not overload the damaged digestive system is critical. As part of a successful refeeding program, the initial step should be a comprehensive physical examination to determine any underlying medical conditions that may complicate the success of the plan. Any aberrations in liver, kidney or gastrointestinal function should be treated in conjunction with the proper refeeding management.

Severely malnourished or debilitated horses may no longer be able to support themselves and the use of a sling may be necessary to support the weight of the animal (Lewis, 1995). Especially on the first day, priority should be given to rehydration either by allowing the horse to drink or via nasogastric intubation or intravenous administration. However, IV and parenteral or enteral administration of fluids should be done carefully and should not contain added dextrose or potassium in order to not further the effects of refeeding syndrome (Kronfeld, 1993) The use of dilute salt water (0.5-1.0%) may be helpful in stimulating the horse to drink. Once the horse has regained a healthy hydration level, free-choice water may be offered.

Multiple studies investigating the proper refeeding of horses have evaluated a variety of forages, concentrates, grains and nutrient delivery methods to identify the ideal refeeding protocol (Beckvarova and Thatcher, 2009, Stull et al., 2003, Durham et al., 2004, Poupard, 1993). Currently, in horses that are in such a debilitated state that they will not eat voluntarily, enteral

feeding is necessary to hasten gut integrity, attain normal nutrient absorption and microflora activity (Durham et al., 2004). Enteral diets should contain high quality protein sources as well as highly digestible fibers. Concentrated nutrition is critical in these cases as it is unlikely large volumes of feed will be tolerated by the horse. For the average 500 kg horse, approximately 0.6 kg of leafy alfalfa should be offered every 4 hours for the first 3 days of refeeding (AAEP 2004). The amount of alfalfa can be slowly increased while the number of feedings is decreased from day 4 – 6, so that by day 6, a total of 7.5 kg of hay is being offered in three meals at 8-hour intervals. If diarrhea appears and/or persists, replacement of a portion of the alfalfa with good quality grass hay may be of benefit. After 10 days, the horse should be re-evaluated to determine if weight gain has been established. If the horse has positively responded to the 10-day refeeding protocol, concentrate feedings can be instituted and free-choice access to alfalfa hay may be allowed. Feeds with a good balance of fiber and a low glycemic index can be slowly introduced, and deworming and correction of dental problems can be addressed.

Once the initial refeeding period has proven successful, a long-term plan must be put into place. The refeeding protocol should be dictated by the energy requirement of the horse and the amount of weight that needs to be gained. The NRC should be consulted to determine the daily energy requirements for specific horses taking into account age, activity level, body size and pregnancy status. It takes approximately 20 Mcal above the horse's maintenance requirement to induce 1 kg of weight gain, and 16 – 20 kg of gain is required for an increase of one unit in body condition score (BCS). For every BCS that a horse needs to gain, it can take between 40 – 60 days to accomplish that gain (NRC 2007). For an adult horse, a safe rate of weight gain is estimated to be between 0.2 – 0.5 kg/day, although this may be increased depending on current dry matter intake and other factors. To calculate how many calories above maintenance the horse should consume per day to gain body condition, use the following equations:

- $\text{Kg gain required} = (\text{desired BCS} - \text{current BCS}) * 20$
- $\text{Days to accomplish gain} = (\text{kg gain required}) / (\text{desired rate of gain in kg/day})$
- $\text{Mcal/d above maintenance} = (\text{kg gain required} * 20 \text{ Mcal}) / (\text{days to accomplish gain})$

For example, if a 500 kg horse (ideal body weight) is currently a 3 BCS with a desired BCS of 5.5, then 50 kg of gain would be required over a 125 days period at a desired rate of gain of 0.4 kg/day. Therefore, the horse must be fed a ration providing 8 Mcal/day above the daily maintenance requirement (a total of 26.2 Mcal/day) for 125 days to gain 50 kg and increase from a 3 to a 5.5 BCS.

Once the target daily DE intake has been established, choosing which feeds to provide that requirement depends on several factors. The use of high-quality forages should be maximized whenever possible. Pasture should be introduced slowly and conservatively. For horses with suspected digestive problems, including malabsorption or persistent diarrhea, feeding a highly digestible and well-fortified complete feed will facilitate digestion and absorption and maximize the horse's ability to extract nutrients from the feed. If no underlying renal or liver dysfunction is present, calorie-dense fat-added concentrates can also be used to meet daily energy requirements. As when introducing any horse to a fat-added diet, the inclusion should commence slowly to allow for adequate adaptation. If refeeding a young growing horse, a conservative approach should be taken when bringing the youngster back to a full ration to prevent the occurrence of developmental orthopedic disease that can sometimes be induced by a compensatory growth spurt.

## Nutritional Management of Chronic Colic

While “chronic colic” is not a specific diagnosis or disease, managing a horse which suffers from regular bouts of abdominal pain necessitating medical intervention can be frustrating for an owner. A wide variety of conditions, including gastric ulcers, enteroliths, uroliths and others may result in frequent bouts of colic. Feeding recommendations for this type of horse are straightforward and feeding management practices are just as important as the type of feed offered. In general, a stable diet consisting of high-quality forage balanced for nutrient content by a concentrate should be the hallmark of nutritional management. Stabled horses with reduced access to grazing are 3 times more likely to suffer from colic and maximizing pasture access should be initiated if at all possible (Durham, 2010). Like horses with malabsorption problems, only highly digestible feeds should be utilized, and small, frequent meals should be offered throughout the day. Providing a minimum of 1.5% of a horse’s bodyweight in forage per day is advisable. In addition to grass pasture, good forage options include high quality alfalfa or grass-alfalfa mix hay, soaked alfalfa cubes, and beet pulp. Use of specialized hay nets or hay bags that reduce the rate of intake will help to mimic natural grazing behavior while stalled. Sudden changes in forage source, such as when switching to a new batch of hay, should be avoided. Having hay tested at a forage testing lab is a good idea to ensure that the forage is of acceptable quality, as consumption of mature hay can easily lead to colic in sensitive horses.

In some cases, replacing all or most of the long-stemmed hay with a complete feed will reduce the frequency of colic bouts. Utilizing a complete feed with a highly digestible fiber source, high quality protein, and an energy content suitable for the specific horse is important. Again, small frequent meals should be offered. If high quality hay is well-tolerated, concentrate feeds offered should be higher in digestible fiber with moderate soluble carbohydrate content. As with all dietary modifications, changes should be made slowly and the horse should be monitored for body condition, eating behavior, weight and any health issues that might arise.

## Pre-Surgical Nutritional Management

Much of the information regarding nutritional recommendations for surgical cases come from case studies and studies involving humans. Because of this, little data is available to draw conclusively from and as with all clinical cases, horses should be evaluated on an individual basis. Prior to surgery, and because of general anesthesia usage, horses develop stress that alters endocrine and metabolic function. These changes affect the horse’s ability to maintain certain homeostatic processes related to digestion, absorption and nutrient utilization (Wagner, 2009). Characteristically, perturbations in the adrenocortical system are observed in horses undergoing general anesthesia that result in alterations in blood flow to the gut as well as the mobilization of certain substrates including glucose and free fatty acids to allow for the activation of the immune system (Muir, 1990). Typically, recommendations are to withhold food but not water 6-12 hours prior to surgery. This allows for enough emptying of the gut without a drastic decrease in total gut fill, which could be detrimental to the health of the horse. It is recommended that no significant changes to the diet occur in the days leading up to surgical intervention as these changes may likely aggravate a potentially disturbed gastrointestinal tract that could lead to complications. While pre-operative starvation does induce metabolic changes, these alterations are generally short-lived and the benefits outweigh the potential harmful effects of a full gut under general anesthesia (Reinprecht et al., 2007).

## Post-Surgical Nutritional Management

Major complications related to post-operative gut health are generally related to post-operative ileus and generalized colic (Becht and Richardson, 1981, Adams, 1988, Little et al., 2001 and Senior et al., 2004). While the complete pathophysiology of post-operative ileus is unknown, it is generally believed that intestinal inflammation and distension are likely culprits (Koenig and Cote, 2005). When not related to post-operative ileus, colic following abdominal surgery affects approximately 6% of all horses, typically within 72 hours of surgery (Miricica et al., 2003). In terms of post-operative feeding management, reintroduction of feed should be done on a case-by-case basis. Typically, for those horses that have undergone a non-abdominal surgery, reintroduction of feed should commence at 6-12 hours following recovery from anesthesia (Spier and Meagher, 1989). It is important to understand that healing is a nutrient-intensive process and a negative energy balance or deficiencies in nutrients may diminish the ultimate ability of the horse to heal. Providing proper nutrients in a safe and concentrated way should be a priority. For horses that do not have the ability or desire to eat post-operatively, an enteral diet remains the ideal nutritional choice.

## Nutritional Management for Intestinal Resection

Insight into feeding management of intestinal resection patients is largely garnered from case studies. A thorough understanding of the gastrointestinal physiology of the horse will help in making nutritional recommendations for these unique horses. Simply put, following recovery from intestinal resection surgery, the maintenance diet should consist primarily of higher fiber, easily digestible feedstuffs which are fermented in the hindgut. The duodenum and jejunum are the primary sites for starch, vitamin, and mineral absorption (except phosphorus, which is absorbed in the colon), while the ileum is the primary site for fat and fat-soluble vitamin absorption. Horses with 50% small intestine resection have been successfully maintained on diets containing fermentable fibers and fat from oil and rice bran sources (Geor 2000). Including alfalfa hay into the forage program is recommended. Horses with 70% distal small intestine resection have been successfully maintained on frequent small feedings of complete feeds (Lewis 1995). If >50% of the small intestine has been removed, additional vitamin and mineral supplementation may be necessary, and a high-quality ration balancer may be necessary.

In cases of colon resection, more emphasis should be placed on maximizing small intestinal digestion while still providing some easily digestible fiber to maintain hindgut health and integrity. For the first 30 days following surgery, a low fiber, high protein and phosphorus diet should be provided. Concentrates formulated for growing horses paired with high quality alfalfa or alfalfa-mix hay, work well during this time. For horses with extensive colon resections (>90%), this diet should be continued, and B-complex and K vitamin supplementation may be required due to a compromised ability to produce these vitamins (Lewis 1995). However, digestive ability may return to normal in horses with resection of only the left colon or cecum.

## Conclusion

Nutritional management of clinical cases should be of utmost importance. Maintaining a working understanding of the anatomy and physiology of the equine gastrointestinal tract will help when developing feeding management plans. Much of the information regarding feeding for specific clinical cases originates from case studies, and the nutrient requirements of horses with specific medical conditions are largely unknown. Although scientific research to support recommendations for feeding sick horses is limited, general guidelines are beginning to be

established and field experience gives equine nutritionists a basis for making sound recommendations. Treating each ill horse individually, while utilizing common sense as it relates to nutrition and physiology can help many of these animals return to health. Future research will assist in further developing feeds and feeding guidelines for medical conditions, leading to the improved health and well-being of the horse.

**References Available from the Author Upon Request**

## Current Status of Infectious Disease in Ontario

Luis G. Arroyo, Lic. Med Vet. DVSc., PhD.

Several diseases of infectious origin are a common occurrence in horse in Ontario. Some diseases are seasonal, and their occurrence is largely dictated by the nature of the vector or intermediate host's life cycle and others are endemic in the horse population. Equine practitioners in Ontario are faced with infectious diseases in horses on a daily basis. The most common infectious agents encountered and tested for include *Salmonella* spp., *Neorickettsia risticii* (Potomac Horse Fever), *Clostridioides difficile*, *Lawsonia intracellularis*, Strangles (*Streptococcus equi sub. equi*), equine herpesvirus-1, Eastern Equine Encephalitis, West Nile virus encephalitis, Rotavirus, Influenza A, *Rhodococcus equi*, and *Borrelia burgdorferi* (Lyme disease). There is also distinct seasonal presentation for some of these pathogens, which are largely affected by environmental variables, complex life cycles of intermediate hosts and vector dynamics.

Upper respiratory tract infections continue to be one of the most diagnosed condition in Ontario horses with viral infections thought to be the most common. They have a significant health and economic impact on equine athletes. When outbreaks occur, the most common pathogens isolated are equine rhinitis virus A, influenza and *Streptococcus equi sub. equi*.

Viral outbreaks tend to occur in the Fall coinciding with racehorse yearling sales and Fall shows. Sporadic cases or isolated outbreaks of strangles cases are regularly reported by practitioners.

Strangles cases can occur anytime of the year but generally an increase occurs over the Spring to Summer months. Biosecurity awareness and implementation are critical to manage and prevent the further spread of this organism to other horses.

In foals, *Rhodococcus equi* is sporadically identified in 3-4 month old foals with respiratory signs. *R. equi* is an individual farm problem. The number of positive cases is likely not reflected by testing as many breeding farms treat based on other parameters (clinical signs, physical examination, CBC/chemistry and ultrasound evaluation). The impression through the Ontario Animal Health Network is that the number of foals with *R. equi* infection is decreasing although there has also been a significant decrease in foal numbers and commercial breeding operations.

Equine neurological diseases occur throughout the year but have different risk factors. Equine herpes myeloencephalopathy can occur at any time of the year but is generally diagnosed in the Fall through to early Summer. Sometimes, cases of EHM are correlated to EHV-1 abortion on the property. Other times cases or outbreaks are related to stressors such as transportation, co-mingling and possibly other environmental factors.

Equine protozoal myelitis continues to be diagnosed with frequency in the province. Positive tests occur mainly in the south-western part of the province. The protozoa must **cycle** of the between the opossum and an intermediate host to complete its **life cycle** and is and is transmitted by opossums through fecal contamination of feed and hay. There is a cyclical nature to the number of positive tests due to the prevalence of the opossum. Winters with a lot of snow are harsh on them as they do not hibernate and need to forage for food during the Winter. Their coats are not suitable for the very cold. When the snow is high they cannot get out of their holes to forage and many will die from starvation.

Vector--borne neurological diseases have a seasonal component. The two most commonly diagnosed ones in Ontario are Eastern equine encephalitis and West Nile encephalitis.

EEE virus is transmitted in Ontario predominantly by the mosquito *Culiseta melinura*. This mosquito breeds in hardwood swamps delineating their location in the province. The third generation has the most prolific viral load (?) therefore we see our first cases at the end of July to early August. The eastern and central parts of the province are considered endemic for the disease with sporadic cases occurring annually to biannually. Outbreaks occur in other parts of the province making predictions difficult. Vaccination against the virus is the best strategy. West Nile virus is transmitted in Ontario by the mosquito, *Culex pipiens*. This mosquito breeds in stagnant water in rural and urban communities. Equine cases occur annually in the southwestern part of the province.

Rabies horses continue to be tested in the province but no horses have been diagnosed with rabies infection for a number of years.

In recent years, there has been an increase in the number of PHF cases, although a great deal of yearly and geographical variation should be considered in Southern Ontario. Currently, PHF is possibly the most important known cause of equine colitis in Southern Ontario, at least during the summer months. *Salmonella spp* and *Clostridium difficile* are uncommon causes of colitis in horses in Ontario.

*Lawsonia intracellularis*, the cause of equine proliferative enteropathy in young foals, however in recent years has been sporadically diagnosed in horses older than a year of age. These horses have presented with severe hypoproteinemia presumably due to protein losing enteropathy and have tested positive for this organism in fecal PCR and serology.

EHV-1 abortion occurs during the last trimester of gestation and we will start to see them anywhere from November through to March. Generally, these cases are sporadic but abortion storms do occur occasionally.

Horses exposed to *Borrelia burgdorferi*, the causative agent of Lyme disease, have been identified across the province with a higher prevalence in eastern

Ontario. In recent years, *Anaplasma phagocytophilum*, had been suspected in some part of Southern Ontario but unconfirmed by laboratory testing.

This presentation will focus on the epidemiology of common infectious diseases in Ontario and their diagnostic approach, management and prevention.

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## New drug regulations and veterinary medicine

Melanie K. Barham, DVM, PMP, MBA (c)

### INTRODUCTION

Over the past 12 months, the veterinary industry in Canada has seen significant changes to access and responsibilities surrounding veterinary drugs. In addition, practitioners are called upon to stay abreast of rapidly evolving national and international regulations with respect to performance horses. Technology to detect substances in the performance world is evolving, as are rules surrounding welfare and modalities used. As always, veterinarians are called upon to take a leadership role, and be a source of knowledge for clients and the equine industry. This lecture will provide a current “roundup” of new regulations, as well as a discussion on opportunities for practitioners to take the lead with respect to antimicrobials, medications, and treatment of horses.

The information provided within the lecture and ensuing discussion will be updated immediately prior to the conference due to rapidly changing drug regulations for horse shows and racing. Rather, general resources are listed below.

### HORSE SHOWING

Equestrian Canada Equestre (ECE) Medications Regulations 2019

[https://www.equestrian.ca/cdn/storage/resources\\_v2/i94QevrCm9pdig9Bm/original/i94QevrCm9pdig9Bm.pdf](https://www.equestrian.ca/cdn/storage/resources_v2/i94QevrCm9pdig9Bm/original/i94QevrCm9pdig9Bm.pdf)

ECE Rules: <https://www.equestrian.ca/programs-services/rules>

ECE veterinary email list for news and alerts (free): email [khouse@equestrian.ca](mailto:khouse@equestrian.ca)

Federation Equestre Internationale (FEI) Medications Guidelines

<https://inside.fei.org/content/anti-doping-rules>

FEI Veterinary Regulations <http://www.fei.org/fei/regulations/veterinary>

United States Equestrian Federation (USEF) Medications Guide

<https://www.usef.org/compete/resources-forms/rules-regulations/drugs-medications>

### HORSE RACING

Canadian Pari-Mutual Agency (CPMA) Regulations <http://www.agr.gc.ca/eng/about-us/partners-and-agencies/canadian-pari-mutuel-agency/canadian-pari-mutuel-agency-equine-drug-control-program/?id=1204670391600>

Subscribe for email updates to CPMA regulations (free): <http://www.agr.gc.ca/ESS-SAC/sub-abon.do?lang=eng&id=1207588534717>

## ANTIMICROBIAL REGULATIONS

The Veterinary Drug Directorate (VDD), as a branch of Health Canada, has taken the lead on changing the access to antimicrobials in the veterinary sphere in Canada. The change has been two-fold and came into effect late 2018:

- Antimicrobials deemed medically important antimicrobials (MIA)s for animal use in Canada can only be obtained through a veterinarian by prescription.
- The “own use loophole” whereby animal owners could import medications from another country, typically the United States, for their own use only, has now been restricted.

Veterinary Drug Directorate information on antimicrobials: <https://www.canada.ca/en/health-canada/services/drugs-health-products/veterinary-drugs/antimicrobial-resistance.html>



# PRACTICE MANAGEMENT PROGRAM

**VETERINARY DISRUPTORS – Part I**

Dr. Loise Langlais - Staged Dental Procedures  
Darren Osborne, MA

After decades of promoting veterinary dentistry to pet owners, it seems that veterinarians are finally gaining traction. The 2017 Ontario Survey of Pet Owners shows that 33% of pet owners want to discuss oral health with their veterinarian, and that one in ten pet owners report going to their veterinarian for regular dental care. To process the increased demand for dentistry, the modern veterinary hospital often includes a dental suite, and in some hospitals, the dental suite is used more often than the surgical suite.

More dentistry is better for pets and for clients, but some hospitals are struggling to keep up with the workload. One problem is the nature of dental surgery; it is very difficult to assess exactly how extensive a pet's dental disease is during a routine physical examination. Many aspects of veterinary medicine are predictable enough to present a treatment plan and estimate, but a dental procedure can vary widely in both time and cost, and the veterinarian doesn't always know where it will land until they have examined the dog under anesthesia.

Invariably, a veterinarian will schedule one hour for dental surgery and it will last two hours, or they will schedule two hours and will finish the procedure in under an hour. In both cases, examinations suffer. In the first case, clients are kept waiting an hour or more, while in the second case, one hour of examination revenue is lost. A solution to this is the staging of dental procedures.

Staged dentistry involves splitting the dental procedure into various stages. The first stage is the prophylaxis, the second stage (if required) is oral surgery. If the oral surgery lasts longer than two hours, it can also be broken into stages.

One of the benefits of staging include more accurate estimates for the client. When a dental procedure is staged, the veterinarian can provide a firm quote for the first stage – the prophylaxis, dental examination, and dental radiographs, for example. If the veterinarian determines, from this first stage, that subsequent surgery is required, they can develop a treatment plan and provide a client a firm quote for the second stage.

Dr. Loise Langlais, a veterinarian at Hespler Animal Hospital in Cambridge has been staging her dental procedures for several years. “We book the second stage when we present the client with the bill for the prophylaxis. When we give them a bill that is exactly what we said it was going to be, it instills confidence.”

Dr. Langlais provides x-rays and pictures to show the client why their pet requires oral surgery. She adds, “when we ask them to bring the pet back in a week for the surgery, that gives the client time to come to terms with the procedure, and if needed, time to find the funds to pay for the surgery.” Dr. Langlais assures the client that they would not have to pay any more for two procedures than they would if it was all done at one time. To harmonize the fee for staged dentistry, Dr. Langlais does not charge the client for a second anesthetic induction or IV set up fee. An example of how Dr. Langlais charges staged dental procedures can be found in the sample invoices section of the OVMA Suggested Fee Guide.

The cost of staging dental procedures is the loss of revenue from the complimentary anesthetic induction fee and IV set up with the surgical stage of the treatment. According to the 2018 OVMA Suggested Fee Guide, the cost is \$287.80. Even though the time spent performing the prophylaxis and surgery would be roughly the same whether the procedure was staged or not, breaking the procedure into stages does require additional cost to rebook, admit and discharge the animal the second time.

Dr. Ron Mergl, of Niagara Falls Animal Medical Centre, is convinced that the increased compliance from staged dental procedures offsets these additional costs. For many pet owners, dentistry comes as a bolt from the blue; when they are presented with an estimate that ranges from \$500 to \$3,000, many will go into fight or flight mode, and contemplate the worst-case scenario.

“When we tell the client they can come back in a week for the surgery, you can see the relief on their faces. They are not under pressure to make a now or never decision right then and there.” Explains Dr. Mergl.

In addition to increased compliance, staging dental surgery allows for more productive scheduling for dental cleanings, oral surgery, and exam room appointments. Without staging, the time required for the dental procedure is typically a best guess scenario, that may work out just fine, but often ends up missing the mark, as the dentistry turns out to be more extensive than expected.

Unless there is someone else there to lend a hand, the veterinarian now has the additional stress of calling the client to explain that they underestimated the surgical time, as well as telling all the clients waiting for their appointments that they will be delayed. Hospitals that stage their dental procedures have a better idea of how long the oral surgery will take, so they can more effectively schedule everything else in their busy days.

Clients’ fear of having their pets under anesthesia is the main reason a lot of hospitals avoid staged dentals. They parrot the pet owner’s concern that two anesthetics means twice the risk for their pet. Dr. Tania Burrows offers that it is all in the way it is presented to clients. When she frames staged dentistry to her clients at Big Bay Animal Hospital in Barrie, it comes across as the safer option. “I explain to clients that we only anesthetise up to a maximum of two hours. I tell them, if your pet needs surgery beyond two hours, we will stage it to minimize the risk. Safety is not optional.”

**VETERINARY DISRUPTERS – Part II**

Dr. R. Reed Stevens – Operating a Low Fee Clinic and a High Fee Hospital in the Same Neighborhood  
Darren Osborne, MA

Five years ago, Dr. R. Reed Stevens uncovered a disturbing client spending pattern in his Buffalo, New York veterinary practice. He was going through his client transaction data at Ellicott Small Animal Hospital and discovered he had two distinct sets of clients – one group was paying an average of \$250 per transaction and a second group was paying an average of \$75 per transaction. The split was roughly 50/50. As a native to Buffalo, Dr. Stevens was aware of the unique issues Buffalo had with poverty (third highest in the country) and now saw how it was directly affecting his practice. He was keeping his fees low to cater to his lower income clients and was struggling to maintain the high standard of care his higher income clients expected.

Most veterinary practices have a unique personality and they draw clients that fit their personality. High service / higher fee practices draw clients that want to spend more time with their veterinarian and seek the best possible care for their pets. Higher volume / lower fee practices tend to draw price conscious clients who want the best for their pets but have limits on what they can or will afford. Both types of practice can be successful if they stick to their personality. A high-volume practice succeeds with several clients per hour to offset the lower revenue per client and a high service hospital succeeds with higher revenue per client and services fewer clients. Dr. Stevens was struggling because he was trying to run two different types of practice at the same time.

“I would present a new client with an estimate for \$250 and they would say, “well I only have \$75”, explains Dr. Stevens. “Then I would think to myself, that only covers the cost of an exam and half a rabies vaccine.” Dr. Stevens was stuck. He didn’t want to turn his back on the lower income pet owners in his community, but he could not survive on \$75 per 30 minutes. The solution came to him when he was challenged with helping revitalise the West End community of Buffalo. He would open a limited service / low fee clinic in his neighborhood to service his lower income clients.

In 2014, along with Dr. Susan Sickels, Dr. Stevens opened West Side Pet Clinic, a low-cost, limited service veterinary hospital four kilometers from Ellicott Small Animal Hospital. The new hospital focused exclusively on examinations, vaccines, and common health problems like ear infections, fleas and worms. Pets requiring advanced care (eg. Radiology, surgery or hospitalization) were referred to a full-service veterinary hospital.

Dr. Stevens is passionate about helping the lower income pet owners in his community. “Lower income people deserve respect,” Dr. Stevens states. “In some cases. they have less free time than higher income individuals, so they need access to appointments and walk ins.”

Dr. Stevens is also passionate about business. Before his career in veterinary medicine, he was an international brand manager with Nestle Purina and he drew on his marketing and management skills to differentiate the branding and management of his new hospital.

In his first hospital, Ellicott Small Animal Hospital, Dr. Stevens focused on good medicine with high service standards; at West Side Pet Clinic, the focus was on good medicine presented in a different form. Client service was still important, but productivity was as important if he was going to be able to deliver low cost medicine and pay the bills. At West Side Pet Clinic, Dr. Stevens worked at increasing

productivity at the reception desk, improving client flow through the exam room and keeping the appointment schedule full.

Reception area productivity was increased using cutting edge technology alongside old school branding. To accommodate a high volume of walk-in clients, Dr. Reed set up a live “Lobby Cam” with the approximate wait time printed on the screen. Instead of calling to find out the wait time, clients could log into the West Side Pet Clinic website, click on the Lobby Cam button and see how many people are in the waiting room. The staff update the approximate wait time as it changes throughout the day. To save reception time going over the estimate or final bill, all available services with their fees are presented on a large menu board right above the receptionist. “Ninety percent of what we do is on the board” says Dr. Stevens. The idea for the menu board came to Dr. Stevens during a business meeting at a neighborhood restaurant. For over 50 years, this family owned Italian restaurant has had a huge menu board above the bar you see as soon as you walk in. When Dr. Stevens saw the menu board he immediately saw how the concept would work in his new hospital.

Client flow is quick and steady at West Side Pet Hospital using a circular traffic pattern. The client and pet enter through the “In” door and are greeted by the receptionist one side of her two sided desk. The client and pet are seated in the lobby to wait for their exam. When ready, they are taken into an exam room adjacent to the lobby, and at the end of their appointment they are exited out the other side of the hospital and settle with the receptionist on the other side of her desk. The circular flow ensures everyone goes past the desk on their way in and out and keeping everyone moving in the same direction prevents two potentially unruly dogs from meeting one another as one is leaving and one is arriving.

Appointment productivity is maintained using a team medicine approach with lots of technicians and tech assistants. Delegating services to technicians and tech assistants allows West Side Pet Clinic to see more clients than the average hospital. At the time of the interview for this article, Dr. Stevens and his associate had just finished seeing 49 appointments in 7 hours. Appointments are 10 to 15 minutes and effective utilization of technicians in the exam room and in the treatment area means the veterinarians rarely fall behind. The appointment starts with the veterinarian getting a history and examining the animal. If there is still time, the vaccines and treatment is done in the exam room. If the appointment reaches 10 minutes, the technician takes the animal into the treatment area to finish vaccines and treatment leaving the exam room available for the next appointment. When appointment is complete the technician takes the client around to the exit desk where the payment is processed.

Many veterinarians struggle to keep up with follow up phone calls between appointments and often fall behind in both their appointments and their phone calls. At West Side Pet Clinic, the technicians follow up with all clients within 24 hours of their appointment by phone.

While many hospitals are unable to find staff, Dr. Stevens says staff seek out a job at West Side Pet Clinic. “Young people want to work here (West Side Pet Clinic) because its more than just a job to them; they feel they are doing something rewarding for animals and for pet owners in their community.”

When asked how he feels about high income clients using a hospital designed for lower income pet owners, Dr. Stevens explains how the wait time is a means test. “Out wait time is one to two hours and people who can afford not to, generally will not wait 2 hours to see a veterinarian.” If a higher income client books an appointment, Dr. Steven honors the appointment but politely informs them that they

are taking an appointment slot from someone who might need it more. Dr. Stevens and his staff take advantage of having both hospitals to direct pet owners to the hospitals that best suits them. Clients who struggle to afford the care at Ellicott Small Animal Hospital are directed to West Side Pet Hospital and in the last year 10% of revenue in Ellicott Small Animal Hospital came from West Side Pet Hospital in the form of dentistry, surgery and hospitalization.

West Side Pet Clinic has been a big hit with pet owners and a remarkable success for Dr. Stevens and Dr. Sickels. The popularity of West Side Pet Clinic has made it easier for Dr. Stevens to manage Ellicott Small Animal Hospital because he and his staff can focus on their high touch clients which have grown from half to two thirds of total clients. In their fifth year at West Side Pet Clinic, their low fee approach is receiving rave review from low income pet owners and Dr. Stevens' productivity strategies has made their new hospital a profitable business.



## VETERINARY INNOVATORS

Dr. Nigel Gumley - Team Medicine

Darren Osborne

Team medicine was first envisioned by Dr. Gumley when he was an associate in one of the biggest multi-doctor hospitals in Canada. Like most veterinarians, he was frustrated when he could not find a technician. Even though there were several technicians on shift when he was working, he spent way too much time hunting down a piece of equipment, a file or performing technical tasks while a client was kept waiting. He developed a model where each veterinarian would be assigned their own technician who would report only to them, follow them around all day and help them do their job better and faster. Each day, the veterinarian would get to work with the same technician, so they could get to know each other's style of work and over time, work better together.

Under Dr. Gumley's model, the technician would see the client first, perform a TPR, take the history and ferret out issues with the pet. The veterinarian would come in after, confirm the technician's findings, and perform their examination and any required clinical pathology. While the veterinarian was doing their job in the examination, the technician would be typing in the notes for the veterinarian, retrieving instruments and performing any other delegated tasks. After the examination, the technician would take responsibility for the patient invoice, subsequent diagnostics, and follow up with the client.

Dr. Gumley showed the partners that by using a team medicine approach, clients would get better, seamless service. They would always speak to their veterinarian or their technician minimizing communication problems and enhancing client loyalty. With team medicine, Dr. Gumley said he could save time delegating

- TPR
- History
- Record keeping
- Invoicing
- Follow-up (unless required by the veterinarian)

Outside the exam room, there could also be countless hours saved delegating procedures, hunting for files, instruments and technicians. The time saved delegating to the team technician would open up more appointment slots. Dr. Gumley assured his partners that he would earn more revenue by providing more services to existing client and seeing more clients. His plan was rejected by the partners.

Unfortunately, Dr. Gumley's partners thought team medicine was too radical; they were concerned about needlessly taking on increased staff and could not make the connection between increased costs and increased revenue. Dr. Gumley persisted and even offered to pay for his technician out of his own earnings. His partners relented and agreed to a trial run.

Team medicine was an instant success. The number of appointments, revenue per appointment, and doctor revenue all went up immediately. Client feedback was very positive and the first measure of team medicine showed Dr. Gumley with his team technician was the highest revenue generator in the practice.

Today, Dr. Nigel Gumley is the owner Cedarview Animal Hospital, a three doctor hospital in the suburbs of Ottawa Ontario. He is still passionate about team medicine and passes on his team mentorship to his

associates. Compared to the rest of the province, Cedarview Animal Hospital stands out with significantly higher production per client, more clients per veterinarian and top scores in both revenue and expense management. Cedarview is a financial powerhouse.

### Appointment Schedule

A typical day at Cedarview Animal Hospital starts at 8:00 am. Veterinarians are scheduled for six or seven hours and their technicians are scheduled for eight. Appointments run every thirty minutes with an hour for second opinion appointments and new pet examinations. Most days are booked solid.

The team technician starts each appointment and takes 10 to 15 minutes for the TPR and history. After completing the initial assessment, the technician goes over her findings with the team veterinarian (away from the client) and the team veterinarian steps in to complete appointment. While the veterinarian is examining the patient, they are dictating their findings to their team technician who is typing up the client records. During the appointment, the veterinarian may ask the technician to step out to get an instrument or medication but most of the time, the team is together in the exam room. When the veterinarian completes the appointment, they leave the patient and client with the technician who completes the records, creates the invoice, books the next appointment and exits the client.

Before the next appointment starts, the team veterinarian has a few minutes usually spent going over diagnostic reports, making phone calls or checking on admitted patients.

One of the big benefits to team medicine is that everything gets done during the appointment so there no extra time spent at the end of the day writing records, calling client. Most of the time, the veterinarians leave at the end of their shift. Their team technician has one or two more hours on their schedule which is spent wrapping up client files and completing technical tasks delegated throughout the day.

Outside of the exam room appointments, technicians retrieve lab results from the central email server, do required call-backs for the veterinarian, develop estimates, and perform follow-up care for patients.

At Cedarview Animal Hospital, the veterinarians have a layer of protection with their team technician. Clients are trained to contact the technician first and even when the client asks for the veterinarian, they get to talk to the technician first. If a client insists on speaking with the veterinarian, the staff are trained to find out the nature of the inquiry and most of the time, they assure the client that their team technician can take the call.

Technicians are encouraged to take the same time off as their team veterinarian, but this is not enforced. If the team technician wants to work while the veterinarian is on holiday, they can act as a float for other teams and remain the first point of contact for their patients and clients.

Team medicine empowers staff to take ownership of the treatment, the case, the patient and even the client. When Dr. Gumley and his team technician see a client with their pet, either one or both might be following up with the client after the appointment. For example, if a pet is sick and diagnostic tests are required, the technician may follow up with the results saving Dr. Gumley a phone call. This responsibility requires committing to active participation for both veterinarian and technician. If the technician gaps out during the part of the appointment when Dr. Gumley was explaining why they were

running a certain test, they would not be able to answer the client's question about why they needed to run that specific test.

All the veterinarians and technicians at Cedarview Animal Hospital are encouraged to enhance their training in at least one area of veterinary medicine. For example, if a veterinarian / technician team wanted to enhance their dental skills, both would attend dental continuing education courses to ensure they were both able to provide enhanced care. This requires planning and accommodating to match not only conference schedules but also specific course schedules. would not work if the veterinarian on team spend all year in dental labs while her team technician spent all year in dermatology lectures. One expert in dentistry alongside one expert in dermatology is not as useful as an expert dental team.

Once a year, Dr. Gumley reassigns veterinarians and technicians. This helps ensure teams continue to build off each others expertise. For example, a technician might explain to her team veterinarian an alternate way to perform a procedure that she learned on her last team rotation. Capitalizing on the shared knowledge between the teams elevates the knowledge of the hospital.

When you ask Dr. Gumley for the biggest advantage to team medicine he will tell you the patient is the one who benefits the most. With team medicine, the patient and client get two people who know what is going on with their pet – two heads are better than one. For the veterinarian, the ability to delegate more with team medicine leaves more time to focus on what you love, the medicine.

## BEST PRACTICES NOT USED IN VETERINARY MEDICINE

Expanding into Real Estate

Darren Osborne, MA

Many veterinarians feel the need to own their own building for one reason - they have a guaranteed tenant. In your heart, owning versus renting seems like the right thing to do, and for veterinarians, it can provide an opportunity to shore up a considerable retirement nest egg. In other industries, owning your own real estate is the cornerstone of the business model. McDonalds "restaurant" chain is actually a real estate empire run by a clown flipping burgers.

### Veterinarians Get Preferred Rates

If a construction contractor was to walk into a bank and ask to borrow one million dollars to buy the land that held their shop, the bank would ask for 25% down payment, 10 year amortization and an interest rate well over prime. Monthly payments would be over \$8,000. If a veterinarian walked into the same bank and asked to borrow one million dollars to buy the land that held their veterinary hospital, they would be offered the entire amount without any down payment, 25 years amortization and prime. The monthly payments would be half as much.

### The Math

First off, let's get away from the percentage trap. Just because the average veterinarian in Ontario pays out 6% of gross revenue in rent, that does not mean you set your budget at 6%. In many cases, veterinarians can get a better deal on rent and pay a lot less than 6% of gross revenue and in rare cases, veterinarians have to pay more than 6%. Newer practices that have not grown into their building generally pay more than 6% of gross revenue to rent and mature practices in a high rent neighborhood may pay higher than 6% over the life of the practice. Don't calculate your rental target based on your revenue, calculate based on the market conditions. Sometimes you have to play the hand you're dealt.

An even simpler calculation you can rely on is whether or not the cost of borrowing for the land and building is cheaper than the rent. This depends on the rent (duh), interest rates and the amortization period. When doing this calculation, the amortization period factors heavily into the decision. The monthly payments are a lot smaller when you have 25 years to pay off your mortgage compared to 10 years. If you are looking at a \$500,000 building, amortized over 25 years, your monthly payments (principal and interest) would only be \$2,550. The same loan, amortized over 10 years would have monthly payments of \$4980.

### 25 Year Commercial Mortgage

Clearly, the 25 year option has lower monthly payments but until recently, a 25 year commercial mortgage was not available. For the longest time, the best a veterinarian could get for a commercial mortgage was a 10 year amortization period. With only 10 years to pay, it was dicey whether you were better off renting or buying. Buying usually cost more but after you factored in the cost of borrowing against having a real estate investment it sometimes worked. Sometimes it didn't. All that changes with a 25 year commercial mortgage.

In almost every case, if a veterinarian buys the building from their landlord with a 25 year commercial mortgage, they will have lower monthly expenses. Usually, a veterinarian renting a building that is

worth \$500,000 will pay upwards of \$5000 per month. If that same veterinarian could buy the building, they would pay half as much with a mortgage. Plus, they are slowly acquiring an asset. Plus, they can put the building in their spouse's name, pay rent to their spouse and save some tax income splitting. Plus, the mortgage payments stay the same each year while revenues increase with inflation – over time, the mortgage payments get relatively smaller.

Susan Shulist, Senior Manager with Scotia bank, says the bank is now offering commercial mortgages up to 25 years to veterinarians at prime. “This is a game changer for most practices,” Ms. Shulist offers. For most veterinarians, that means buying will be cheaper than renting.” Ms. Shulist qualified her statement that the veterinarian has to qualify for the loan.

#### Retirement Planning

One downside to owning your own building shows when it is time to sell the practice. If the land and building are included in the price of the practice, the total price may be beyond what a lot of potential candidates can afford. If the person buying the practice does not want to buy the land and building you are stuck being a landlord into your retirement.

One way to avoid the pitfall of owning is to keep the land and building in a separate company and have the veterinary hospital pay rent to the separate company. When it is time to sell, the practice can be sold separately if required and the land and building can be held or sold to a third party.

## JUST THE NUMBERS

Darren Osborne, MA

How do you measure success in a veterinary hospital? Many veterinarians are scientists and require an objective measure. Success for a veterinarian means higher than average, more than before, or any measurable gain. The problem with this perspective is that few veterinarians take the time to learn the importance or unimportance of management metrics and can waste a lot of time worrying about the wrong numbers and not enough time focussing on the important numbers.

I fell into a metric last year when I focussed too much attention on parasite revenue. I calculated that half the increase in revenue from 2018 came from an increase in parasite treatment sales. I falsely concluded that veterinarians in Ontario were doing a great job with parasite treatment marketing, sales and compliance. Then, I saw a metric that showed over the same time period, unit sales of parasite treatment only increased 1.5%. This meant that the increase in revenue came from selling the same people higher priced products. This could have been avoidable if I spend more time looking at the unit sales. If I had monthly metrics on unit sales, I would have seen stagnant sales figures early and taken steps to increase compliance. Instead I fell into a false sense of security and let a year go by before I did anything.

Veterinary metrics can be arranged into three different groups requiring different levels of attention. The first group of metrics only need to be looked at once a year. If there is a problem, fix it, but if you are at your target, forget it until next year. An example of this is your accounting charges. This figure should be under \$4,000 for the average size practice. If you're below, move on. If you are above, you need to find out why? Maybe your accountant created some tax savings that cost \$2,000 to set up but saved you \$20,000. Maybe you are spending too much for accounting.

The second group of metrics need to be checked every month. These metrics involve processes that can run away from you quite quickly and need to be held in check. The monthly metrics can be found on the OVMA Practice Dashboard and the VP Animalytix Dashboard Report. The OVMA metrics give you top line revenue and client figures while the VP Dashboard provides metrics on unit sales in the hospital. Both reports are free and both are critical to manage your hospital.

The OVMA report focusses on rolling 12 month revenue, active clients (last 12 months), and monthly revenue, clients, invoices and revenue per invoice. For each metric, a comparison to your figures last year and the average for hospitals in the province. This measure offers the answers most veterinarians seek, and I growing and how do I compare to the average. In some months, provincial growth was low so its ok to low. Without these reports there could be some fretting about the future, but misery loves company. "I thought one percent growth is horrible until I got my report and saw the average was zero."

The VP Vetalytix Marketplace Dashboard report focuses on rolling 12 month unit sales for vaccines, parasite treatment and surgeries, and a dollar consumption index that measures overall activity. Like the OVMA Dashboard, it compares hospitals to themselves in the same month last year and the average hospital in their area.

The third group of metrics are daily metrics. Daily metrics focus on client bookings, appointments and utilization rates. Without these numbers, veterinarians rely on the receptionist to fill the appointment

schedule. When receptionists are asked about their compliance rate, their fill rate or their call rate most look at you like you are from another planet and say, "I just answer the phone..."

Fortunately, there are management apps that measure all these metrics and only require someone to track and manage the figures. Client communication applications work with your practice management software and can measure how many clients needed to be contacted for their appointment, how many were contacted, how many booked their appointment and how many showed up.

## EXAM ROOM COMMUNICATION SUCCESS

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### Rocking and Rolling: USING YOUR TEAM TO COMMUNICATE VALUE

#### Communication Starts With Your WHY

Does your team know why they come to work each day? Do they know the core values of your hospital? Can they share them with a client? How is your team organized to communicate with clients? Are you client centered or vet centric? Is your process clear and transparent for the client? Are they engaged during a visit or often left wondering when someone will remember they are there? To serve the most clients, you need to know what gets you talked about, what makes you different. Look at the example of McDonald's and Leroy Burgers. McDonald's, everybody knows. They know about the clean bathrooms, the friendliness, and the kid meals. But Leroy Burgers is unknown. There are a lot of intangibles. Any business has tangibles and intangibles; what you have to do is differentiate those so your clients know them and choose you.

Once you know what defines your practice, then you have to cross off everything that makes us a "me too". Everything on your list that can be done by the hospital down the street doesn't differentiate your practice. When you know what makes your business special, then you can move forward and grow it into a mission statement.

#### Core values

What are the core values of your organization? Core values are the beliefs and values your organization holds dear. These values represent the core priorities in the organization's culture, including what drives members' priorities and how they truly act in the organization. Ideally, you will want to work with your team to develop your core values. Why do they come to work every day? What does your hospital represent to them? Some examples of core values are:

- Compassion
- Family oriented
- Responsibility
- Respect
- Honesty
- Trust
- Kindness
- Fairness
- Continuous Improvement and the Pursuit of Excellence
- Respect and Invest
- Rational Workplace
- Learning and Self-Improvement
- Credibility and Integrity

#### Vision and mission

What is the vision of your hospital? The vision should enable people to imagine what the organization *will be like* in the future - not a strategy of *how* to get there. What is your mission? The vision is what an organization aims to *become* or *be like*, 'mission' is what an organization must concentrate *on doing* to meet major objectives (probably related directly or indirectly to its vision). To some extent, a vision



may never actually be realized. However, a mission is practical - it's the major activity that the organization must start doing now to move forward.

### Points of differentiation

Think about what makes your practice specific and how your team can convey this hospital message. I call it the "hospital story". The hospital does not have to have 10 different strategies to define it, it just needs 2 to 3 well-defined thoughts or themes to tell in your story. The story can be told over and over again, between the hospital, the client and the health care team, to help differentiate your practice from other veterinary hospitals. The themes could be based on people, or other sources. Focus on the benefits of your hospital, not the features. Your benefits may include the partnership clients have with your hospital, that you provide continuous care, peace-of-mind, at-home services, or hands-on care.

What defines or differentiates your hospital? What is experienced when:

- A client views your ads
- A client talks to other clients
- A client calls
- A client passes by your practice
- A client parks and enters
- A client talks to staff
- A client is waiting
- A patient is examined
- A patient is released
- A client gets the bill

What are your touch points?

- External (outside the hospital)
- Hospital (during visits)
- Post treatment/purchase (after clients leave)

Are your touch points adding value?

- What do you want clients to think and feel?
- What do you want them to do?
- Do they reflect mission and values?

Some examples of strategies / touch points to add differentiation

- Specialization/Certification: Animals, Behavior, Nutrition, Cardiology, etc.
- Specialty Animal Programs/Plans
- Drive-up Service/Drop off-Pick up
- Spanish/Sign Language
- VIP Boarding/Grooming
- Relocation for terminally ill clients
- "We Care" - (familiar object with patients)
- Home Euthanasia
- Child-Pet Programs
- Hospital Tours (photographic)
- Literature/Pet Library
- Touch screen client education support

## Communication and Trust

### Building trust

Communication is the creation of shared understanding or meaning through interaction between two or more parties. **Communication is the foundation of your practice.** Through communication you relay the values and processes of the hospital to the health care team, your clients and the community. Through communication you build trust which is the lynchpin of the success of your business. There are four components to trust building communication:

1. Consistency and predictability
  - a. Dependability of events, responses, behaviors

- b. Congruity of verbal and non-verbal messages
  - c. Avoid mixed messages
  - d. Avoiding capriciousness or the appearance of favoritism
  - e. The sense of familiarity, that people will be able to fairly accurately anticipate events, outcomes, responses
2. Integrity
    - a. Doing what you say you're going to do
    - b. Following through on commitments and promises
  3. Respect for confidentiality
  4. Commitment to shared cause and goals , behaviors
    - a. demonstrating concern for the needs of others and the shared cause
    - b. Make sure the goals are clear to everyone.
    - c. Check with people frequently to see if they have what they need to fulfill their commitments
    - d. Strive to create an atmosphere where it is OK for people to ask for help
    - e. Sharing the credit
  5. Examining mistakes - and problem-solving - as a team, not assigning blame

Be aware that trust can be undermined quickly. Trust breakers include:

- failing to deliver on commitments
- gossiping or disregarding confidentiality
- ignoring problems when they occur
- not communicating clearly

### **Communication Skills**

The first communication with clients often starts on the phone. A well-trained front office team can enhance the success of your practice by using communication skills that attract new clients and bond them to your practice.

### **Telephone Skills That Work**

Developing outstanding phone skills is extremely valuable since it is often the first impression clients have regarding the practice. Clients begin to make assessments about the practice based on their interaction with staff on the phone. Communicating effectively with clients on the phone presents challenges since neither person on the phone can rely on visual cues to enhance communication efforts. Here are examples of phone skills and best practices for the phone that will improve client communications:

- Always answer the phone by the 3<sup>rd</sup> ring. When the phone rings longer than 3 rings, clients become irritated and feel the practice doesn't value the importance of providing exceptional client service
- Don't quickly rattle off a greeting that the client cannot easily understand. Identify the name of the practice, your name and ask how you can help the client. This greeting should be articulated clearly and concisely.
- Use a friendly, relaxed and upbeat tone of voice when answering and speaking on the phone. The person on the other end of the line should immediately feel like they are talking to someone who is warm and interested in helping them. Verbalize the same enthusiasm to clients you don't know as you do with clients who are your favorite or best clients.

- Ask if you may place someone on hold and do not put clients on hold until you have heard them verbalize “yes”!!
- If you know that it may take some time to gather the information that a client wants, always ask if they would rather be on hold or have you call them back.
- Remember that clients on the phone cannot see the reception area and have no idea how busy you are. And frankly, they don’t always care—they want your undivided attention. Bear in mind that clients standing in front of you can see that you are busy on the phone and realize that you will be with them once you are off the phone. You can also use visual signals to clients in front of you that you will be right with them. People absolutely hate being placed on hold for any significant length of time. One minute on hold seems like an eternity to most clients.
- Remember to apologize if you have to place someone on hold for any significant length of time. People are less agitated by being on hold if you say “I’m sorry for keeping you on hold” or “I’m so sorry you had to wait on hold. I didn’t forget about you”.
- Offer assurances to clients on the phone. For example, this may be an assurance that you will give a message to the doctor or an assurance that you will check on when their pet can be discharged and then call them back.

### Handling cost inquiries

Don’t make the mistake of simply telling pet owners, “We can’t diagnose over the phone. We have to see your pet and that will cost \$45.” What the caller really wants is meaningful information and empathy. Ask questions about the pet and their symptoms which demonstrate your concern for the pet. Then follow up with empathy phrases. Your end of the dialogue might sound something like this: “Mrs. Humphrey, how long has Chloe been vomiting and how has her appetite been this week? I am so sorry to hear she isn’t feeling well and like you, I know I’d be concerned, too. It’s impossible to say for certain what’s causing her illness. I wish I could tell you something over the phone but really the best option is to have Dr. Taylor check her out. After examining Chloe, she can tell you what she thinks is going on with her and we can certainly let you know any costs involved before proceeding with tests or treatment. Our examination and consultation fee is \$45.”

At this point, pause to let Mrs. Humphrey speak. If she doesn’t indicate a desire to schedule an appointment, further express that she will have peace of mind once she and Chloe see Dr. Taylor and let her know what time she can bring Chloe in or drop her off to be seen.

### Responding to “Phone Shoppers”

It’s a rare client service representative that gets excited about handling phone shopper calls. So, begin by thinking of these as Phone Inquiry calls instead of Phone Shopper calls which carries a negative connotation. Bear in mind that many pet owners are cost conscious in light of the slow economy and it may be your existing clients who are calling about fees.

Follow these tips to have a better chance of converting calls to appointments:

- Start the conversation with a positive comment such as “I’d be happy to help you. Let me get some more information so I can be sure to give you accurate information.”
- Always ask “Have we seen your pet (dog, cat) before?” to determine if the caller is an existing client or has never been in before.
- Try to engage the caller by asking specific questions about their pet or their situation. For example, inquire as to the pet’s name, whether the pet is having any health problems, are they new to the area, how did they hear about the practice, etc.

- Demonstrate warmth and enthusiasm with voice tone and friendly comments such as “Oh, I love Papillons, they are so cute” or “What a cute name.”
- Quote fees as appropriate.
- Ask for the appointment and offer specific times.
- Close by letting the caller know the practice is very interested in seeing their pet. If it is an existing client, phrases such as “We’d love to see Chloe again. Just call me back when you are ready to schedule an appointment.” For new clients, use phrases such as “We welcome the opportunity to care for Chloe and would love to have you as a new client. We’re proud of the quality of medical care and service we offer. And I know you will like Dr. Smith-she is so compassionate and knowledgeable.”

### **Non-verbal communication**

Non-verbal communication can be just as important if not more powerful than verbal communication. Regardless of what we say, our body language also tells a story. It’s imperative that team members be mindful of the message received by clients as a result of non-verbal communication. For example, folded arms, a frustrated sigh, or frowning may indicate impatience and frustration with the client or pet. On the other hand, smiling, nodding of the head, and leaning in toward the client demonstrate interest and patience when the client is talking.

Eye-contact is one of the most significant non-verbal communications. Communications can become impersonal and clients won’t think you’re very interested if you don’t make eye-contact with them. Be sure to establish eye-contact with clients when they arrive at the practice, when you ask them to follow you to exam rooms, when you greet them in exam rooms, when you ask clients questions and when you say good-bye.

Try to sit down next to clients during important discussions. This helps make clients feel like they are a partner in the care of their pets and facilitates easier dialogue without distractions. When you stand while clients sit, clients may feel intimidated and be less likely to ask questions. In addition, it is easier for team members to focus on the client when sitting down to talk.

In addition to your own non-verbal communication, observe the non-verbal communication of clients which will give you clues about their feelings and what actions you may need to take to improve communication. For example, glancing at a cell-phone or watch, pacing, folded-arms, hands on the hip, standing instead of sitting in the exam room, standing near the door, and frowning can all indicate the client is in a hurry or unhappy about the wait time. Clients who are afraid or uncomfortable for some reason may display nervous behaviors such as clutching their pet, looking down, reluctance to talk, or fidgeting in their chair. Once you become more observant of client’s non-verbal communication, you can take action to respond to their body language.

### **Open Ended Questions**

To determine what your client’s needs and wants are, ask questions. How does your client value their pet? Find out what activities they do together. What is the pet’s lifestyle: indoor, outdoor, hunting, community service? Questions can assist and guide the owner to see and understand the medical concerns. Through understanding the medical concerns, clients can better value the comfort and quality added to their pet’s life delivered by the treatment. By asking questions and listening to the client, a team earns the client’s trust and commitment. Then the visit and the treatment become “the clients” idea and vision for a healthy pet and the team the partner that assists them.

There are two types of questions that to gain trust and valuable information so we may know our client's expectations and create compliance.

**Open Questions:** The question process is like a **funnel**. The beginning of the process is very open and broad. It is here that we use questions beginning with How? What? Where? These are called open questions. They are designed to get opinions, attitudes, and beliefs about the pet and owners needs. Let's look at examples of open questions about dentistry for Marty (the cat) and Ms Vickers (his owner). They progress from general to more specific.

1. What type of food does Marty like to eat?
2. How would you describe Marty's chewing and general grooming?
3. Have you noticed any changes to Marty's movie star smile?
4. How are you currently caring for Marty's Teeth?

From asking open questions you tap into a client's insights about the health of their pet. This allows the veterinarian to see gaps in the client's understanding of a disease process, such as dental disease, and the pet's current health status. Or stated another way, where does the client see their pet's health vs. where does the veterinarian see the pet's health. By carefully listening to our clients we can give pet owners information and ask questions to close gaps in health care understanding.

**Closed Questions:** How do we close these gaps? There are closed questions. These are yes or no questions that determine facts and specific information. Here are some examples of closed question on dentistry for Marty and Ms Vickers:

1. Have you noticed the brown discoloration on Marty's teeth? If not show her
2. What about Marty's breath? Does Marty sleep with you? Does he have a different odor?
3. There is a chatter of pain when I touch this tooth. Have you seen this while he is eating?
4. Has anyone ever talked with you about cleaning Marty's teeth?

**Closed questions following open questions** allow the owner to track with the doctor step by step through the disease process. Some short explanations with the questions are helpful however explanations are best understood if accompanied by a visual (such as a cat dental model or a picture of the cat's mouth before and after cleaning). The goal is a shared understanding of the disease with the client as well as a shared vision of their pet disease free. How much should the veterinarian be talking vs. the pet owner? The rule of thumb is 70% of the time the client is the person talking and sharing. The remaining 30% of time are yours to question, explain and reinforce the health care vision.

## Listening

Your secret communication weapon is listening. According to businessman Ken Johnson, who is quoted on the International Listening Association Web site, "The contrast between hearing and really listening can be as different as night and day. And in a business environment, not listening effectively to customers, employees, and peers can mean the difference between success and failure." Most of us take good listening for granted and don't work very hard at improving. But listening is a complex activity. Listening requires an active response, not a passive one. Effective listening doesn't just happen; it takes thought—and thinking can be hard work. But there is no other way to become an effective listener. Think about the complexities of listening, and work to understand them.

When the client responds to your questions, it is critical that you LISTEN to their words and to their non-verbal cues. The goal is to listen for understanding. The process is crucial for building the relationship that will grow the client's confidence to trust and follow your recommendations for their pet. When you listen for understanding rather than listen reactively, you will gain a greater understanding of the client's needs. Your active listening may encourage the client to "open up" and provide more complete information. Also, your willingness to take the time to listen and respond often results in improved client listening and ultimately in compliance.

What does empathetic listening look like in the questioning process? The listener is focused on the words, inflection, facial expressions and body postures of the client. The listener gives verbal and non-verbal feedback to communicate understanding, clarify information or to encourage the client to continue.

Effective listening is challenging. There are many pitfalls poised to push you off track. Examples of obstacles to effective listening include:

- Distractions from thoughts outside the exam room – to listen effectively and completely, you must put aside the other business of the day and focus on the here and now.
- Preparing your response while the client is still talking – if you are busy formulating your answer or follow-up while the client is still talking, you are not fully listening.
- Preconceived judgments of the client –
- Noise, activity – acknowledge the disturbance and if possible, isolate your conversation from the commotion and invite the client to continue.

### **Empathy statements**

While veterinary teams generally do an excellent job of showing compassion to grieving clients and are routinely praised for being kind, many team members miss out on opportunities every day to convey empathy to pet owners. It isn't that doctors and staff don't want to let clients know they are empathetic; rather it is that teams often don't know what to say and when to use empathy statements.

Let's begin by defining empathy statements. These statements convey to the client that you understand their perspective and feelings. Empathy statements are an acknowledgement of the client's emotions or their position. Here are some examples of empathy statements:

- "I can understand that this is a difficult time for you."
- "I appreciate that you were not expecting these expenses for Scooter's care today."
- "I bet it was frustrating to go through that experience."
- "That must have been very upsetting. I know I would be scared too."

Empathy statements don't have to be confined to discussions about the pet. You can express empathy about anything a client may tell you including family illness, job situations, personal problems, minor frustrations, etc. People appreciate affirmations and concern about what they are going through.

### **Team-Based Client Education**

Strive to define clear job roles and responsibilities for all team members to create the best client experience that will also result in pets getting the care they deserve. For this to happen, client engagement and education needs to occur before clients are given recommendations they aren't prepared to accept. Consider that when you see the client, you are following a systematic approach to build trust and relationship.

**1. Identify client concerns/preparation (this happens mostly before the client arrival):**

- Consider: how is this client different, what are the pet's needs
- Think about how to develop rapport and personalize the visit for this client
- Meet as a team to discuss the client and pet before the appointment, define each team member's role
- Color code charts, review medical records before appointment
- Print a list of appointments for the day w/ notes
- Here's an example for new client program. A potential client calls the practice. The receptionist asks questions about the pet - age, breed, and needs. The receptionist integrates the benefits of the well check program and the values of the hospital in the conversation, sets up the appointment, and sends a targeted mailer appointment reminder to the prospect ("We are looking forward to meeting you and Fluffy on the date.")

**2. Client engagement/Needs assessment (getting clients involved in process):**

- Consider the client vs. team member perception
- Client engagement very important
- Develop scripts for needs assessment process and visual tools to help client with descriptions of concerns or questions.
- Continuing with our example, the client enters the practice; the receptionist reviews the client information, and in conversation asks other questions: family, hobbies, activities with pet, etc. A technician takes the client through a needs assessment of the pet. Then the client could be asked questions about diet, favorite foods, exercise, health, history, behavior, grooming, fleas, boarding, etc.

**3. Solve problem/ Make recommendations / Client education (focus on what client needs and wants)**

- Gap analysis: ask open-ended questions, listen, solicit primary concerns at beginning of exam,
- Perform physical exam: determine what pet needs, assess clients' understanding, what does client need to know to change behavior, use core communication skills. Ask questions when doing PE-have they noticed.....rather than beginning lecture on findings
- Don't tell client before they are ready to hear information.
- Focus exam on showing vs telling:
  - Doctors and staff members need to be sure all aspects of the physical exam and procedures are thoroughly explained. While conversing with the client is desirable and necessary, don't make the mistake of having the pet owner completely miss out on the value of the exam because they didn't even realize the pet was being examined. The client should be informed of normal and abnormal findings and the reason for each part of the exam. Make sure clients know you palpated for lymph nodes and what you can feel when you palpate the pet's abdomen.
  - Sometimes veterinarians start making recommendations for services before the physical exam is completed. This is a common scenario with a head to tail process. Periodontal disease may be noted and immediately a discussion of dental recommendations starts. When this happens the pet owner doesn't appreciate the rest of the physical exam which doctors often complete while talking about the dentistry procedures. Moreover, the client

may feel like all you care about is scheduling a dental cleaning rather than discussing the overall health of their pet.

- Even if you take the pet to the treatment room for procedures, take the opportunity to show clients some of the equipment used. For example, show clients the snap test when it is completed and the tonopen or Doppler.
- Educate client using support materials, literature, models, computer educational programs and posters to illustrate and educate on the main points. Use visual aids or models to reinforce verbal messages when possible. For example, use the body conditioning score chart to let clients see why you want to talk about weight loss for their pet. If you don't have client education brochures with pictures or anatomical drawings, look into obtaining these visual aids.
- If information can be emailed to the client, this is even of greater benefit.
- Provide the client a report card of findings
- Present treatment plans: formulate plan with owner, partner with owner
- Strive to build trust
- **Check for understanding/overcome objections:**
  - Use communication skills, talk about money with confidence

#### 4. Commitment (want client to take action) and Satisfaction

- The staff reinforces the DVMs recommendation, provides further information and support so client feels assured in the decision.
- When the client commits to the recommendation, it is written down and prioritized and
- The client is taught how to perform the treatment plan needed.

#### 5. Reinforce messages/gain commitment (want client to take action):

- Use consistent messages by team
- Keep in touch with clients with progress phone calls
- Schedule rechecks at time of first appointment, ,
- Give CE handouts
- Take advantage of online resources and your website to give clients
- In our example, the client receives a folder with Fluffy's medical record in it. The folder has the practice name on the cover and has other pertinent information: emergency numbers, medical information, product coupons, etc. The receptionist makes the next appointment for vaccinations, dentistry, lab, etc. A summary of the finding is then sent to the client with a personalized thank you note attached. One to three days later, the client is called to see if they have any questions or concerns.

#### Check your mindset - Stop selling and start educating

If you want to increase service utilization and compliance for wellness care services at your practice, then start educating pet owners rather than just making recommendations or "selling". Clients feel like you are selling if you immediately tell them what you recommend for their pet before even asking questions, taking a thorough history or performing a physical exam. Pet owners may feel like their pet is just a number to the practice and receives the same recommendations as every other pet that walks through the door. Here are some tips on how to take steps to educate pet owners and inform them about the value and benefits of services:



- Don't assume clients are knowledgeable. Ask if they have questions about heartworm disease and let them know which common parasites are being looked for when they bring in a stool sample.
- Ask open-ended questions about pets and engage clients in a dialogue before immediately launching into what services you recommend. Ask questions such as "what problems is Sophie having?" or "Tell me what concerns you have today about Max?"
- When team members make recommendations for wellness care prior to the veterinarian doing a physical exam and consultation, be sure to let client's know that the doctor will do a full evaluation of their pet's health and answer any questions they may have.
- Give clients sufficient information. For example, after recommending wellness care such as diagnostic testing, give the client more detailed information about what tests are included and what they will reveal about the pet's health.
- Don't just make recommendation-focus on need recognition and the value of the services. Tell the client why the pet needs the tests. Use phrases such as "the senior testing will determine if Jake is healthy or if he has any early indications of illness." And finally, tell the client the value of the services by using phrases such as "We want to catch any abnormalities early so that we can help Jake live a long life"
- To effectively communicate the value of a veterinary service or product to clients, make sure everyone on the team understands and agrees with the value of the hospital's services and products. When gaps in knowledge are identified or employees demonstrate discomfort associated with certain client interactions, focus training in these areas.
- Staff meetings are an excellent time to discuss the value of veterinary services. Train team members so they can easily describe services or products to clients in lay terms and convey to clients the benefits for each service.
- Be sure to give clients consistent messages about the value of routine preventative healthcare services and products.
- Remember to always highlight the benefits of services to clients even when the client has purchased similar services in the past.

### **Summary: Measuring Results, Fostering On-Going Relationships/Client Loyalty**

When the whole team focuses on enhancing client communications, you will improve client engagement and trust which leads to greater client loyalty and client compliance with treatment recommendations.

Remember to select the core messages you want to communicate throughout your operation. Multiple communication channels can and should be widely used to reinforce and support your core messages. Develop highly visible scoreboards, bulletin boards, or announcements of progress toward team and organization goals and priorities. Establish an internal "best practices and good tries" communication system. A free flow of information and active communications is the lifeblood of a learning organization.

## ENHANCING THE EXAM ROOM EXPERIENCE

*Key to your success*

*Communicate,  
Communicate,  
Communicate*

### COMMUNICATION MODEL

#### 1. **Preparation**

- + 1 minute of preparation **saves 3** minutes in the exam room
- + **Review** the client history and **ask** Technician or Assistant for bullet points from history and prescreen
- + Set specific objectives for the visit -. Identify the **3-5** concerns. How will you confirm or raise awareness of these? List them on the record before you walk in
- + Develop a plan of action
- + **SMART** Objectives
  - Specific
  - Measurable
  - Action Oriented (client's actions)
  - Realistic
  - Time Bound

#### 2. **Approach**

- + ☺ "Hello, I am Dr. \_\_\_\_\_"
- + **Welcome** everyone to the exam room – pet owner, pet, children
- + **Attitude** is everything
- + **The Four R's**

#### ☐ ■ **Rapport**

- ♦ Eye Contact
- ♦ Body Posture
- ♦ Voice Tone and level
- ♦ Use owner and pet's names
- ♦ Touch the pet

#### ☐ ■ **Reason**

- ♦ Restate or re-ask the reason for the client's visit
- ♦ Ask for the client's main concern

#### ◀ ■ **Response**

- ♦ Bridge to what you can do to satisfy the client's concern or need.
- ♦ Ask, "...how does that sound?"

#### ▶ ■ **Recruit**

- ♦ Involve the client in the process
- ♦ Give the client a job

#### 3. **Diagnosis**

- + Give a **through exam** Head to Tail
- + Use all your **tools** – stethoscope, otoscope and ophthalmoscope
- + At this stage, **effective questioning and active listening** is vital to help you know how much the pet owner understands about their pet's needs and to help focus the pet owner on your area of concern.
- + Effective Question is like a **FUNNEL**
- + Types of **Effective Questions**
  1. **Open Questions**
    - ♦ Determine thoughts, feelings, attitudes of clients
    - ♦ How, what, Tell me more
  2. **Closed Questions**
    - ♦ Confirm information or direct conversation
    - ♦ Yes or no answers
    - ♦ Brief response
- + **Listening Effectively:**
  - ♦ Improves understanding of needs
  - ♦ Helps to empathize
  - ♦ Encourages clients to "open up"
  - ♦ Makes others more willing to listen

#### 4. **Recommendation: Compliance**

- + This is the step when you take the pet owner's concerns and **connect** them to a product, service or program that answers their concerns uncovered with your open questions.

- + Use the exam room **report card** to list your recommendations. Also, provide clients with a **timeline** for when services are to be performed. Use mind maps to simplify complicated treatments and diagnostic plans.
- + **Pictures** are worth a thousand words, so **never tell what you can show**. People remember less than 10% of what they hear, but **90%** of what they see, hear and do themselves
- + **Features & Benefits**
  - ♦ Features – Products, Programs & Services
  - ♦ Benefits – the SO WHAT'S – How does it solve the client's concern?

*Remember*

*Clients do things for THEIR reasons not OURS*

#### 5. **Addressing concerns-**

- + The **5 step** approach
  1. Acknowledge
  2. Clarify
  3. Answer
  4. Verify
  5. Close

#### 6. **Commitment & Follow-up**

- + When to **complete the visit**
  - ♦ Receiving positive responses
  - ♦ Time is running out
  - ♦ Client Closes
- + In completing, **always**
  - ♦ **Summarize** the key points
  - ♦ Request their **commitment**
  - ♦ Make sure a plan is created and placed in the computer. **Complete** your record.
  - ♦ Make sure you give them a **timeline** so they know when they are to return.
- + **First visit** = Treatment.
- + **Second visit** = Prevention plan.
- + Reminders, Recheck, Recall (**R<sup>3</sup>**)

**Thank them for choosing the hospital and you.**

## MONEY TALKS THE EASY WAY: DEFINING AND ASSIGNING VALUE PART ONE AND TWO

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People do not like to talk about money. Why? Culture! In the United States, money, is a symbol of worth, competence, freedom, prestige, masculinity, control, and security, all of which can become areas of conflict.” (Turkel, Ruth Ann. 1988. “Money as a mirror of marriage.” *Journal of the American Academy of Psychoanalysis*, 16: 525-535

- Money holds deep cultural taboo in conversation
- Money is a central motivation for many in our society.
- Money = power

Current charging Veterinary realities require us to address cost issues with clients more than ever. Virtually anything a medical doctor can do for a human patient, a veterinarian can do for an animal. The strengthening of the human–animal bond is an even greater factor. Diagnostics are more sophisticated and comprehensive and so are treatments. These advances have made it possible for many animals to live well into old age where they then require care from their owners and their veterinary teams and specialists.

While many pet owners plan for routine care, they rarely budget for unexpected veterinary care. In addition *people are often insulated from the costs of their own medical care by insurance*. Consequently, they are shocked by the costs of the care their animal receives compared to the much smaller co-pay or no cost to them for the same procedure.

Dependent on each person’s experience and expertise, perceptions about money differ from individual to individual. Parents from the depression may teach their children different money values vs. parents from the “yuppie” generation. The first tends to be very frugal while the latter more often is of the mind to spend it now while you can enjoy it. These beliefs can potentially affect the veterinarian-client relationship. Associates, technicians and staff who did not set the fees may feel prices are too high, especially if they were not included in the decisions and reasons behind the fee structure.

- We all fear being judged as “money grubbing”, uncaring, and only in this profession for profit. Until we can be comfortable with what we charge and why, this will fuel the discomfort.
- Time: we may think that there’s not enough time to truly explain the value of our treatment plan so it’s avoided. Making sure that a client is on board with the recommendation and costs will save tremendous time in the long run, and angst trying to play catch up later on if there is a disconnect. Even if it takes 20 minutes, 30 minutes, an hour—we need to make the time. In reality, it usually only takes an extra few minutes coupled with good communication skills.

A 2003 study looking at patient-physician communication about out-of-pocket expenses found that even though both patients and physicians believed that discussion of out-of-pocket costs were important, these discussions were uncommon. Barriers to discussion that both physicians and patients voiced included: *Discomfort discussing financial issues, insufficient time, and belief that there were not viable solutions.* The difference between what physicians reported they should do- what they knew would be helpful to the client and what they actually did in conversation was striking.

Why do we charge fees? Practices need income to hire good people, give benefits, raises and bonuses, and offer continuing education. This allows for people to be the most up-to-date with medicine/surgery, as well as ensuring good quality employees who will offer the best to the clients. Without a healthy profit, clinics would be unable to purchase or even upgrade equipment. Digital radiographs vs. replacing the air conditioner or remodeling—which is better? CAT scans, MRI machines, laser, ultrasound, etc all take money for both upkeep and knowledge. How about having clean, new and modern facilities?

So why avoid the discussion? Clients are legitimately interested in the options available for medical care, and understanding these alternatives and associated fees is a vital component of good decision making. In the veterinary setting, the client is purchasing our time, knowledge, and expertise. Clients need to trust the doctor and medical team and **want a clear understanding of why they need to do something**, what they are getting for their money, when they need to take action, and how the various options minimize whatever risks or discomforts they perceive.

However, it is important to note that your own feelings about finances influence your comfort in talking money. A field known as "behavioral finance" or "behavioral economics: has evolved. Behavioral economics combines the twin disciplines of psychology and economics to explain why and how people make seemingly irrational or illogical decisions when they spend, invest, save, and borrow money.' Also, how we can project our own financial situation onto our clients assuming it's the same.

#### **Price is an issue in the absence of value:**

Value can be defined in a number of ways. In relation to veterinary services it is more than just the price of something.  $\text{Value} = \text{Perceived Benefits} \div \text{costs}$ .

Customer value can be increased by

1. increasing the perception of the total benefits a customer receives,
2. decreasing the cost to the customer, or
3. by providing a combination of the two

Ron Wanek, Ashley Furniture's chairman, says that if consumers are unable to determine any differences between two comparable products, furniture becomes a commodity and they'll choose the one with the cheapest price tag. "When people can compare apples with apples," he insists, "Ashley comes out on top every time because consumers buy furniture based on its design, quality, *and* price. Price will be the tiebreaker only when they can't see any other reasons to buy. But when they can

compare not only price tags but design and quality, their buying decision is based on the combination of these three considerations.

So, what adds to your value?

In 2007, a focus group study of veterinarians' and pet owners' perceptions of the monetary aspects of veterinary care was published in the JAVMA (Coe and Adams). Six key issues were identified:

### 1. **Care of the animal should take precedence over monetary aspects**

Whether pet owners perceived their veterinarian as having an interest in the care and well-being of the pet versus making a profit appeared to have an influence on the pet owners' experiences. As a corollary, there was an expectation among some participants that out of a shared interest for the pet, the veterinarian would work with the client to find a solution if the client could not immediately afford veterinary care.

Participating pet owners consistently discussed compassion and caring in terms of the veterinarian going beyond their expectations, stating that "It makes you feel good because it's not the money issue. It's like 'I'm concerned about you and I'm concerned about your animal.'"

### 2. **Discussion of costs should be initiated up front**

Across the pet owner focus groups, participants expressed the idea that they expected veterinarians to discuss the costs of veterinary care upfront. However, two different perspectives on this issue emerged.

The first reflected the opinions of experienced veterinary clients who were comfortable not discussing the costs associated with routine care because they were familiar with them and knew what to expect on the basis of their previous experiences

The second perspective reflected the feelings of clients who were relatively new to pet ownership and who, as a result, had less experience with veterinary care. Their expectation was that veterinarians would be upfront with respect to all costs

A key point made during the pet owner focus groups is that failure to discuss costs upfront contributed to clients' suspicion and mistrust of the veterinary profession.

### 3. **Costs of veterinary care should be placed in a meaningful context**

In examining the manner in which pet owners and veterinarians referred to the discussion of costs, it became apparent that the two groups often approached these discussions from different contexts. The veterinarians tended to focus on the value of their services in terms of tangibles such as their time and service. In contrast, pet owners focused on what their money was providing in terms of outcome and wellbeing for their pet.

Estimates or Medical Care Plans can be powerful messages and are best organized by grouping expenses into categories rather than detailing each item or service and associated fee. Do not try to accomplish everything with one plan if there are too many

variables. Use Medical Care Plans to consistently communication value to outline costs associated with:

- Preventative plan
- Treatment Plan
- Diagnostic Plan

What about the challenge that “[Veterinarians] view Medical Care Plans as estimates and clients view them as quotes, and a quote tends to be, if you said it was \$662, it should be \$662, not \$685.” To help address this type of concern, Use the reveal technique to review the Medical Care Plans with clients. To use the reveal technique, place a blank piece of paper over the estimate lines and reveal them one at a time as you highlight the service, describe it to the client as the value to the pet, and indicate where some variation in cost may arise.

#### **4. Client suspicion should be addressed**

The issues arising from the conflict between the idea of veterinary medicine as a health-care profession versus a business were complicated because pet owners often expressed conflicting expectations of veterinarians depending on the context of the discussion. For instance, when pet owners were considering the health and well-being of their own pets, emotions often appeared to drive their decisions, with monetary considerations put on hold. In contrast, when the emotional concern for their own pet’s health and well-being was not at the forefront, participating pet owners appeared to approach their decisions in a manner similar to their approach to other consumer purchases, taking into consideration the financial aspects of their decisions. As stated by one pet owner, “There should be more comparison shopping available for people.” These conflicting expectations may contribute to veterinarians’ feelings that their services are undervalued

#### **5. Financial limitations of clients should be considered**

We can’t know there are financial constraints unless we ask. Clients may not volunteer this information until it’s too late to adapt our treatment plan.

A number of participating pet owners indicated that they expected veterinarians to provide some type of payment plan for expensive procedures. Many participating pet owners also indicated that they had received little information about pet insurance in terms of a possible solution to the costs of veterinary care, although they were curious about the topic. However, one pet owner acknowledged that it may not be feasible for veterinary practices to offer this service to every client because as small businesses, they would have limited financial resources of their own

#### **6. Veterinarians feel their services are undervalued**

Several veterinarians believed clients had a poor understanding of health-care costs because a large portion of their clients’ own health-care costs were not paid out-of-pocket. Therefore, the client had a naive perspective on the cost of health care (e.g., Human Radiograph (\$20) vs Veterinary Radiograph (\$100)).

Some veterinarians were of the opinion that “the value that people place on their pets” was a contributing factor, in that “for some people, pets are a disposable commodity” with a result that they place a low value on the services veterinarians have to offer.

Finally, many veterinarians believed clients held expectations of them that were greater than the expectations they had of other healthcare professionals. As one veterinarian put it, “It sort of irks me, because you guys expect so much from me; look at the service you get on the human side.” (e.g., Blood Work Results – 1 week human, 24 hours veterinary)

### **How Much, Doc?**

“How much?” It’s a normal question, so how can you feel uncomfortable when your patients ask it of you. Remember, they are not challenging your clinical opinion or being difficult; they are trying to understand and make a good decision. They may not know a better question to ask.

A veterinarian’s job is to give clients a honest, accurate answer and let them decide for themselves how much cost will be a factor in their choice of care. You can give better care, and suggest alternatives. If you have taken the time to partner and list to the client, empathize with their decision and concerns and suggest care their pet needs. If more questions, remember it is normal and your comfort in sharing the value of veterinary series make the the difference in a clients perception of service or commodity.,

### **How do Pet Owners prefer to get information?**

- Information up front
- Provided in a number of forms (pictures, reference books, diagnostic test)
- Discussion of all options – regardless of cost
- Respect and Partnership

### **How to discuss finances:**

- Warmth, caring, respectful, Language
- Language: simple, careful word choice, direct, no euphemisms or technical diagnostic terminology, avoid medical jargon
- Allow time to digest and understand
- Check in with reflective questions
- Not at the front desk



# PLENARY SESSIONS



## INFECTIOUS DISEASE ROUNDUP 2019

Maureen E.C. Anderson, DVM, DVSc, PhD, Dip. ACVIM

J. Scott Weese, DVM, DVSc, Dip. ACVIM

### ***Brucella canis* in Ontario breeding kennels and imports**

In late 2018 and early 2019, *Brucella canis* was diagnosed in a number of breeding and rescue dogs in Ontario. This led to a project to look more closely at the prevalence for *B. canis* in commercial dog breeding operations in southwestern Ontario, funded in part by the Ontario Animal Health Network (OAHN). The results showed a highly variable prevalence of infection in individual kennels, many of which are linked by movement of breeding animals. Many subsequently undertook control and eradication efforts, but it is clear that there is a significant risk of *B. canis* infection in dogs from some of these facilities.

Infection typically causes reproductive problems in male and female dogs, but the bacteria sometimes infect other tissues as well. Infection can also be spread to people, particularly through contact with canine placental tissues and fluids. Signs in people are often non-specific, but more severe infections can occur in a small percentage of cases. Treatment can be very challenging. Because many veterinarians, breeders and dog owners have little experience with *B. canis*, here are some useful resources:

- [OAHN \*Brucella canis\* factsheet](#) on clinical aspects, diagnostics and recommendations for infected and at-risk dogs.
- [USDA Best practices for \*Brucella canis\* prevention and control in dog breeding facilities](#)
- [Brucellosis in dogs and public health risk](#) (Hensel et al. Emerg Infect Dis. 2018;24(8):1401-6)
- [Animal Health Laboratory \(AHL\) LabNote 61](#): *Brucella canis* resources and information for veterinarians
- [Brucella canis on Worms & Germs Blog](#): Additional information for veterinarians and the public, including outbreaks outside of Ontario.

### **Infection Prevention and Control Best Practices for Small Animal Clinic – 2019 Update**

In 2008, the Canadian Committee on Antibiotic Resistance (CCAR) sponsored the development of guidelines for Infection Prevention and Control Best Practices for Small Animal Veterinary Clinics. The goal was to provide veterinary personnel with a succinct guide that included basic information needed to develop and establish a clinic infection control program, with emphasis on critical aspects such as hand hygiene, cleaning and disinfection. Although the general principles of infection control remain the same, the practice of veterinary medicine has continued to evolve and expand, and so the guidelines are now being updated, with the new edition sponsored by the Ontario Animal Health Network (OAHN). Significant additions have been made to existing chapters, including hand hygiene, cleaning and disinfection, surveillance, non-patient animals, safety of clinic personnel, patient care and handling. New sections have been added for:

- Management of specific HAIs and infectious syndromes
- Antimicrobial stewardship programs

- Rehabilitation programs
- Blood donation programs

The revised chapters will be completed and made available through the Ontario Animal Health Network website ([www.oahn.ca](http://www.oahn.ca)) and Worms & Germs Blog ([www.wormsandgermsblog.ca](http://www.wormsandgermsblog.ca)) in late 2019.

### Antimicrobial stewardship resources

Antimicrobial stewardship - in all species, including humans - is becoming ever more important as resistant bacterial infections become increasingly common. The Ontario Animal Health Network (OAHN) has produced a series of infographics to help highlight published antimicrobial use guidelines for feline and canine respiratory, urinary and skin infections. Veterinary staff can access these tools by signing up for OAHN and logging in to the [Resources page on the OAHN website](#).

In 2018, the OVMA launched farmed animal antimicrobial stewardship (FAAST), an open-access website which hosts a plethora of news, interactive tools and practical resources for veterinarians and farm animal owners to help curb antimicrobial resistance. In addition to general information on stewardship, in 2019 they also began launching species-specific learning modules (called FAAST Reviews) for the beef and veal industries, with more to come!

OAHN Infographics (sign in to view):

- [If it's just a sneeze: Feline upper respiratory disease and antibiotics](#)
- [Itchy dogs: Topical treatments & culture-critical cases](#)
- [Treat me right: Bacterial cystitis in cats vs dogs](#)
- (Coming soon) Treat me right: Canine infectious respiratory disease complex (CIRDC)
- [Using the best medicine and reducing antibiotic use](#) (open access)
- [Help reduce antibiotic use in horses](#) (open access)

Farmed animal antimicrobial stewardship (FAAST): [www.amstewardship.ca](http://www.amstewardship.ca)

- FAAST Review: [Antimicrobial stewardship in the Ontario beef industry](#)
- FAAST Review: [Antimicrobial stewardship in the Ontario veal industry](#)

### Canine importation checklist

Thousands of dogs are imported into Canada every year, and while most uneventfully find good homes, there are a number of risks. Importation of pathogens is of particular concern, and a range of important animal and zoonotic pathogens have been imported into Canada with dogs. There is little regulation of canine importation, so development and implementation of best practices to reduce the risk of pathogen transmission is important. The [Canadian Veterinary Medical Association \(CVMA\)](#) has produced a [helpful checklist of items for veterinarians to consider discussing with clients before and after importing a dog](#). The checklist is available in both [English](#) and [French](#).

### Rabid dog in Niagara

In February 2019, [raccoon-variant rabies was diagnosed in a domestic dog](#) in Ontario for the first time during the current outbreak. The dog from Wainfleet had prior exposure to wildlife and was not currently vaccinated for rabies. Post-exposure prophylaxis was recommended for individuals who were in contact with the dog, and vaccination and a precautionary confinement period for other pets in the household.

Overall the number of cases of raccoon-variant rabies in Ontario continues to decline, while no cases of fox-variant rabies were reported in the first 9 months of 2019. The number of bat rabies cases remains fairly stable.

Also remember that as of March 31, 2019, killed rabies vaccines with a 1-year duration of immunity claim are [no longer offered for sale in Canada](#).

- OMAFRA Rabies website (for public and vets)  
[www.omafra.gov.on.ca/english/food/inspection/ahw/rabies.htm](http://www.omafra.gov.on.ca/english/food/inspection/ahw/rabies.htm)
- Latest rabies surveillance maps  
<http://www.omafra.gov.on.ca/english/food/inspection/ahw/rabieszone.htm>

### 2019 tick submissions – Pet Tick Tracker

The distribution and incidence of ticks and tickborne pathogens continues to increase in Ontario. Understanding tick patterns is important to understand the risks of tickborne disease, for consideration of tickborne diseases as differential diagnoses and for client counselling regarding tickborne diseases and tick prevention. A variety of resources are available for tick tracking and education.

- Evidence-based information on ticks and tick-borne disease of relevance to Canadian companion animals: [www.petsandticks.com](http://www.petsandticks.com)
- Submit ticks or photos of ticks found on pets in Canada: [Pet Tick Tracker](#)
- OAHN Infographic: [Ticks and Lyme Disease in Ontario: What's the real risk? UPDATED 2019](#)

### Raw diets linked to multidrug-resistant bacteria

While the link between raw pet diets and enteropathogens such as *Salmonella* has been understood for some time, there is increasing concern about other risks. In particular, recent evidence has linked raw meat feeding to increased risk of fecal shedding of multidrug resistant Gram-negative bacteria such as *E. coli*. This raises concern because of the potentially increasing role of these bacteria in diseases such as urinary tract infections. Owners and veterinarians should be aware of the potential for a greater risk of multidrug resistant infection in raw fed dogs and cats.

- [Raw pet food as a risk factor for shedding of extended-spectrum beta-lactamase-producing \*Enterobacteriaceae\* in household cats](#) (Baede et al. PLoS One. 2017;12(11):e0187239)

# 2020 OVMA CONFERENCE SPEAKER BIOS

## SMALL ANIMAL PROGRAM:

**Sarah Boston, DVM, DVSc, DACVS**

***Surgical Oncologist, VCA Canada, 404 Veterinary Emergency & Referral***

Sarah graduated from the Western College of Veterinary Medicine in Saskatoon, Saskatchewan, Canada in 1996. She completed a rotating internship at the University of Guelph the following year. She then returned to Western Canada for 3 years of general practice before going to the University of Guelph for a residency and DVSc in small animal surgery. She became board-certified with the American College of Veterinary Surgeons in 2004. Sarah then completed a Fellowship in Surgical Oncology in 2005. She is an ACVS Founding Fellow of both Surgical Oncology and Oral & Maxillofacial Surgery.

Sarah was on faculty at the University of Guelph for 5 years before moving south to the University of Florida where she was an Associate Professor of Surgical Oncology for 5 years. Sarah returned to Canada and started working for VCA Canada in 2018, where she started the Surgical Oncology Service at 404 Veterinary Emergency & Referral in Newmarket. She is Adjunct Faculty at the University of Guelph.

Sarah is Past-President of Veterinary Society of Surgical Oncology and has authored numerous journal articles and textbook chapters on surgical oncology, some of them good. Sarah is also a published author and cancer survivor. Her first book *Lucky Dog: How Being a Veterinarian Saved my Life*, was published by the House of Anansi Press in 2014. She is also one of the founders of *The Cageliner*, a satirical newspaper for the veterinary industry and her new hobby is stand-up comedy.

**Tiffany Durzi, DVM, DVA, CCRT, CVPP**

***Chief of Service, OVC Fitness and Rehabilitation Service, Ontario Veterinary College, University of Guelph***

Dr. Tiffany Durzi graduated from the Ontario Veterinary College in 2000 and returned in 2010 as a primary care veterinary educator at the OVC Smith Lane Animal Hospital located in the Hill's Pet Nutrition Primary Healthcare Centre. Dr. Durzi, is also the Chief of Veterinarian at the OVC Fitness and Rehabilitation Service, established in 2013. She has a special interest in integrative medicine and pain management. She is a Certified Veterinary Acupuncturist (CVA) through the International Veterinary Acupuncture Society (IVAS), a Certified Canine Rehabilitation Therapist (CCRT) through the Canine Rehabilitation Institute (CRI), and a Certified Veterinary Pain Practitioner (CVPP) through the International Academy of Pain Management (IVAPM). She is currently pursuing her board certification in canine/feline medicine through the American Board of Veterinary Practitioners (ABVP). Dr. Durzi is the recipient of the prestigious 2016 Merial Award of Excellence in Clinical Teaching.

**Thomas Gibson, BSc, BEd, DVM, DVSc, DACVS, DACVSMR**

***Associate Professor, Small Animal Surgery, Ontario Veterinary College, University of Guelph***

Tom Gibson graduated from the Ontario Agricultural College at the University of Guelph in 1986 with a BSc in Agriculture. He then graduated from the University of Windsor's teacher's college and pursued a career in teaching in York Region for three years. Tom then returned to Guelph and graduated from the Ontario Veterinary College in 1995. After 6 years in small animal general practice, he returned to OVC to complete a small animal rotating internship and surgical residency, completing a DVSc and becoming board certified with the American College of Veterinary Surgeons (ACVS) in 2006. After almost two years in private referral practice, Tom returned to OVC as an Associate Professor in Small Animal Surgery in 2007 to combine passions for surgery and teaching. Currently he is an orthopaedic surgeon with an interest in rehabilitation after completing rehabilitation training at the University of Tennessee in 2010. Dr. Gibson achieved board certification with the American College of Sports Medicine and Rehabilitation (ACVSMR) in 2018. He lectures regularly on orthopaedic disease and has presented lectures on the use of rehabilitation methods for treatment of orthopaedic disease and pain management, an area of particular clinical and research interest.

**Barden A. Greenfield, DVM, FAVD, DAVDC**

**Owner, MidSouth Veterinary Dental Referrals**

Barden Greenfield is a graduate of Mississippi State University College of Veterinary Medicine in 1985. He practiced small animal medicine for 24 years before entering a non-conforming dental residency. He became a Diplomate of the AVDC in 2011. Dr. Greenfield is currently the Past-President of the AVDC and also serves on the Board of Directors of the Foundation for Veterinary Dentistry, which is the educational and fundraising branch of veterinary dentistry in the USA. He has a dental specialty practice in Memphis and Little Rock. In addition to his specialty practice, Dr. Greenfield founded and runs the Mississippi Valley Veterinary Dental Educational Center in Memphis, TN. This center trains DVM's and technicians in veterinary dental techniques and procedures. Dr. Greenfield has published in peer-review journals and has spoken on the national and international level.

**Ashley Elizabeth Jones, BHSc, DVM, Diplomate ACVIM (Cardiology)**

**Staff Cardiologist, Veterinary Specialty Center, Buffalo Grove, IL**

Dr. Jones grew up in the Niagara region and is a graduate of the Ontario Veterinary College. Following graduation, she remained at OVC to complete a rotating internship and then moved to Gainesville, FL to complete her cardiology residency at the University of Florida. Her residency research project described a novel technique for atrial pacemaker implantation in dogs. Given her research experience and training at the University of Florida, she has particular interest in congenital heart disease and interventional cardiac procedures. Following completion of her residency and board certification exams, Dr. Jones moved to Boston to work at Angell Animal Medical Center with the goal of growing their interventional cardiology service. In 2016, she moved to Chicago to start a cardiology service at Veterinary Specialty Centre in the northern suburbs of Illinois. Dr. Jones has authored and co-authored several peer-reviewed articles and book chapters throughout her career and thoroughly enjoys the variety of challenges she is presented with each day when managing cardiovascular disease.

**Matthew Kornya, DVM, Resident ABVP (Feline)**

**Associate, The Cat Clinic, Hamilton, ON**

Dr. Kornya is a veterinarian from The Cat Clinic in Hamilton, who has just finished his feline residency. He also spends his time working at emergency clinics around Southern Ontario. His interests lie in the area of feline immunology and retroviruses, and he has published papers in the area of feline retrovirology and veterinary immunology. He is currently a review for the Journal of Feline Medicine and Surgery, a writer for the Winn Feline Foundation, and has presented at several national and international conferences discussing topics surrounding feline medicine. Dr. Kornya lives with his five cats and cockatiel.

**Justine Lee, DVM, DACVECC, DABT, CEO, VETgirl, LLC, Saint Paul, MN**

Dr. Justine Lee is a board-certified veterinary specialist in both emergency critical care (DACVECC) and toxicology (DABT). Dr. Lee attended veterinary school at Cornell University and completed her internship at Angell (Boston, MA). She completed her fellowship and residency in emergency and critical care at University of Pennsylvania. Previously, she was on faculty at University of Minnesota (2003-2008) and the head of an animal poison control center (2008-2013). She is the founder and CEO of VETgirl, a subscription-based podcast and webinar service offering RACE-approved, online veterinary continuing education. More information can be found at [www.drjustinelee.com](http://www.drjustinelee.com) and [www.vetgirlontherun.com](http://www.vetgirlontherun.com).

**Douglas Mader, MS, DVM, DABVP (C/F), DABVP (R/A), DECZM (Herpetology), FRSM**

**Veterinarian, Marathon Veterinary Hospital**

Dr. Mader received his DVM from the University of California, Davis in 1986. In addition, he completed a residency in primate and zoo animal medicine. He works at the Marathon Veterinary Hospital, a 24-hour emergency/referral hospital in the Conch Republic. Dr. Mader is the consulting veterinarian for the Monroe County Sheriff's Zoo, the Key West Aquarium, Dynasty Marine, Everglades Alligator Farm and the Theatre of the Sea. He is an internationally acclaimed lecturer and is on the review boards of several scientific journals. Dr. Mader has published numerous articles in scientific and veterinary journals, national magazines, and is the author/editor and co-editor of three textbooks on Reptile Medicine and Surgery.

**Kenneth W. Simpson, BVM&S, PhD, DipACVIM, DipECVIM-CA**

**Professor of Medicine, College of Veterinary Medicine, Cornell University**

Kenny Simpson graduated from Edinburgh in 1984, and gained a PhD in gastroenterology at the University of Leicester in 1988. Internship at the University of Pennsylvania, (1989) and a medicine residency at THE Ohio State University (1991). Hopped back across the Atlantic as a lecturer at the other Royal Veterinary College until 1995 when he joined the faculty at Cornell University, Ithaca, NY. He is a Diplomate of the American and European Colleges of Veterinary Internal Medicine. He is a recipient of the National Phi Zeta and Pfizer awards for research, the BSAVA Bourgelat Award for outstanding contributions to the field of small animal practice and the AVMF/AKC Career Achievement Award in Canine Research. He is a past-president of the comparative gastroenterology society. His research interests are centered below the diaphragm, with a focus on inflammatory diseases of the GI tract (including the pancreas and liver), host bacterial interactions in health and disease, and culture independent bacteriology.

**Ameet Singh, DVM, DVSc, DACVS**

**Associate Professor, Ontario Veterinary College, University of Guelph**

Ameet is a graduate of the Atlantic Veterinary College and has been a faculty member in the Department of Clinical Sciences and the University of Guelph since 2010. His clinical and research interests include minimally invasive surgery and surgical site infections.

**Lauren Trepanier, DVM, PhD, DACVIM, DACVCP**

**Professor and Assistant Dean of Clinical and Translational Research, University of Wisconsin-Madison**

Dr. Trepanier obtained her DVM from Cornell University, and completed an internship and residency in small animal internal medicine at the Animal Medical Center in New York. She then earned a PhD in Pharmacology, also at Cornell. She is a Professor of Internal Medicine and Assistant Dean for Clinical and Translational Research at the University of Wisconsin-Madison School of Veterinary Medicine. Dr. Trepanier manages internal medicine patients, trains students, interns and residents, and conducts research on the genetic and metabolic bases of drug toxicity and cancer risk. Dr. Trepanier is board certified in both Internal Medicine and Veterinary Clinical Pharmacology.

**Joe Wolfer, DVM, DACVO**

**Ophthalmologist, Toronto Animal Eye Clinic, Toronto, ON**

Joe Wolfer graduated from the OVC in 1988 with his DVM. This was followed by an internship at the WCVM and then a residency in ophthalmology at the OVC. Dr. Wolfer has been in private practice since 1992. He became a Diplomate of the ACVO in 1994 and member of the American Society of Retina Specialists in 2004. He currently works at the Toronto Eye Clinic in Toronto Ontario, and is an adjunct Professor at the Ontario Veterinary College.

**J. Paul Woods, DVM, MS, DACVIM (Internal Medicine, Oncology)**

**Professor of Internal Medicine & Oncology, Ontario Veterinary College, University of Guelph**

Paul Woods is Professor of Oncology in the Department of Clinical Studies at the Ontario Veterinary College and Co-Director of the University of Guelph Institute for Comparative Cancer Investigation (ICCI). Dr. Woods is a graduate of the Ontario Veterinary College. He practiced in Owen Sound, Ontario and then completed a residency in Small Internal Medicine and a Master of Science (investigating hyperthermia as a cancer treatment). At the University of Wisconsin-Madison. Dr. Woods completed a Medical Oncology Fellowship at Colorado State University. He was formerly on the faculty at Oklahoma State University. Dr. Woods is board certified in the American College of Veterinary Internal Medicine (ACVIM) in Internal Medicine and Oncology. His research employs novel therapeutic and diagnostic agents and techniques in clinical trials with veterinary cancer patients.

## FOCUS ON INFECTION:

**Maureen Anderson, DVM, DVSc, PhD, DACVIM**

**Lead Veterinarian, Animal Health & Welfare, OMAFRA**

Maureen Anderson is a 2003 graduate of the Ontario Veterinary College and is ACVIM Board-certified in large animal internal medicine. Her graduate research focused on MRSA in horses and equine personnel, as well as hand hygiene and infection control measures used in small animal clinics. She is currently Lead Veterinarian, Animal Health and Welfare at the Ontario Ministry of Agriculture, Food and Rural Affairs, where she continues to work in areas bridging animal and public health, including infection control.

**Linda Jacobson, BVSc, MMedVet(Med), PhD**

**Senior Manager, Shelter Medicine Advancement, Toronto Humane Society**

Dr. Jacobson received her veterinary degree in Pretoria, South Africa in 1986. She subsequently completed a small animal internal medicine residency and a PhD on the pathophysiology of virulent canine babesiosis. Her clinical experience includes ten years at a veterinary academic teaching hospital, as part of a multi-disciplinary team, and ten years as a shelter veterinarian. Dr. Jacobson joined the Toronto Humane Society in 2010 and is currently Senior Manager for Shelter Medicine Advancement. She completed the University of Florida Online Graduate Certificate in Shelter Medicine in 2015. She is co-founder and President of the Ontario Shelter Medicine Association. She has published 38 articles in peer-reviewed journals, most recently a retrospective study of medical conditions in hoarded cats. Dr. Jacobson's passions and interests include shelter medicine, humane sheltering, infectious diseases, animal hoarding and evidence-based medicine.

**Andrew Seaton Peregrine, BVMS, PhD, DVM, DipEVPC, DipACVM**

**Associate Professor, Ontario Veterinary College, University of Guelph**

Andrew Peregrine obtained his DVM and PhD from the University of Glasgow, Scotland. He then worked for 9 years as a research scientist at the International Laboratory for Research on Animal Diseases, Nairobi, Kenya, where he carried out research to improve control of tropical parasites of cattle. Since 1997 he has been an Associate Professor in clinical parasitology at the Ontario Veterinary College, University of Guelph, where he teaches DVM students in all years of the program. In addition, his research interests currently include emerging zoonotic parasite infections of companion animals, and drug resistance in parasites of dogs and sheep. He is a diplomate of the European Veterinary Parasitology College and the American College of Veterinary Microbiologists.

**Jinelle A. Webb, DVM, MSc, DVSc, DACVIM (Small Animal Internal Medicine)**

**Medical Director, Mississauga-Oakville Veterinary Emergency Hospital**

Dr. Jinelle Webb received her DVM in 2001 from the Ontario Veterinary College. An interest in small animal internal medicine led to the Ontario Veterinary College's DVSc program in Internal Medicine in 2002. She completed her DVSc in 2005, and obtained board certification with the American College of Veterinary Internal Medicine that year. In 2006, Dr. Webb joined the Mississauga-Oakville Veterinary Emergency Hospital to start its' internal medicine service, where she remains today as Medical Director. Dr. Webb has lead the MOVEH rotating internship and Internal Medicine residency programs, and is an Adjunct Professor at the OVC. A published author and speaker, Dr Webb's main research interests include investigating the use of laboratory testing and imaging modalities in the detection of occult disease; development novel approaches to internal medicine procedures, and investigating ways to reduce the invasiveness of procedures.

**Scott Weese, DVM, DVSc, DACVIM**

**Professor, Ontario Veterinary College, University of Guelph**

Dr. Weese is a veterinary internist with a focus on infectious diseases, particularly emerging diseases, antimicrobial resistance and zoonotic diseases. He is a Professor at the Ontario Veterinary College, Chief of Infection Control at the OVC Health Sciences Centre and Director of the University of Guelph's Centre for Public Health and Zoonoses.

## EQUINE:

**Luis G. Arroyo, Lic. Vet Med, DVSc, PhD**

**Associate Professor, Ontario Veterinary College, University of Guelph**

Luis trained as a veterinarian at the Universidad Nacional-Heredia, Costa Rica. After graduation, he practiced in rural Costa Rica for a few years and in 2000 he moved to Guelph to enroll in the large animal medicine Doctor of Veterinary Science (DVSc) program in the Department of Clinical Studies at the Ontario Veterinary College, University of Guelph. He later completed a PhD in the Department of Pathobiology at the same institution and joined the Department of Clinical Studies where he is an associate professor. Dr. Arroyo is board certified in large animal medicine with the American College of Veterinary Internal Medicine. His research interest focus is in large animal gastrointestinal disorders, infectious diseases and arteriosclerosis of the pulmonary artery of racehorses.

**Melanie Barham, DVM, PMP**

***Project Management Professional, Animal Health Laboratory, University of Guelph***

Dr. Melanie Barham graduated from the Ontario Veterinary College, and spent 8 years in practice in the US and Canada focusing on sports medicine, including an internship in Southern California. She is an FEI veterinary delegate, and FEI drug testing veterinarian. She served as the medications control veterinarian for the FEI at the 2015 Pan American Games and the Royal Winter Fair, and as a regulatory veterinarian for AGCO. In 2014, Melanie joined the Animal Health Laboratory in Guelph to coordinate the newly formed Ontario Animal Health Network. In this role, Melanie interacts with all agricultural sectors on the species health networks, where animal health and welfare issues are discussed. Additionally, Melanie connects nationally with the national surveillance groups, and creates podcasts, social media, and other materials in conjunction with the expert networks to keep practitioners up to date on health issues in each sector. Melanie also instructs a course for students within the Bachelor of Bio-Resource Management (Equine) program at the University of Guelph.

Dr. Barham is the past president of the Ontario Association of Equine Practitioners (OAEP) and was the Co-Chair of Equestrian Canada's Health and Welfare Committee for 5 years (2015-2019). She also has her Project Management Professional (PMP) designation, and is currently working on a Master's of Business Administration (MBA) in Sustainable Commerce.

**Robert D. Jacobs, BS, MS, PhD**

***Equine Technical Innovation Manager, Land O Lakes Purina Animal Nutrition***

Dr. Robert Jacobs is the Equine Technical Innovation Manager for Purina Animal Nutrition. Robert received his BS in Animal Sciences with a focus in Pre-Veterinary Medicine from the University of Florida in 2010. He received his MS in Animal Sciences with a focus on equine reproductive physiology from the University of Florida in 2012. His masters research investigated the effects of arginine supplementation to mares during the estrous cycle on uterine fluid clearance and blood flow. He completed his PhD at Virginia Tech in 2015 in Animal Science with a focus on equine nutrition and reproductive physiology. While at Virginia Tech, his research evaluated the effect of DHA supplementation to obese metabolically compromised mares on uterine gene expression and health and subsequent conceptus gene expression. Robert also conducted studies related to exercise physiology and metabolism while at Virginia Tech. In his current role at Purina Animal Nutrition, Robert develops and conducts research related to various areas of equine physiology. He leads a team that conducts an average of 15 research projects yearly utilizing a research herd of 80 horses. Robert is actively involved in the scientific community with peer reviewed publications in the Journal of Equine Veterinary Medicine and the Journal of General and Comparative Endocrinology along with multiple popular press articles. Robert routinely presents research at scientific meetings including the American Society of Animal Science Meetings and the Equine Science Symposium. Robert has a passion for breeding horses and working with broodmares and young growing horses. Robert was born in Fort Lauderdale, Florida and currently lives in St. Louis, Missouri with his wife and daughter.

**Heidi L. Reesink, VMD, PhD, DACVLSA**

***Assistant Professor of Large Animal Surgery, Harry M. Zweig Assistant Professor in Equine, Cornell University***

Dr. Heidi Reesink is a board-certified large animal surgeon with clinical interests in equine orthopedic surgery and sports medicine. She received her veterinary degree from the University of Pennsylvania, followed by residency and PhD training at Cornell University.

Dr. Reesink's laboratory is actively investigating how synovial fluid glycan and glycoproteins, including lubricin and hyaluronic acid (HA), are altered in osteoarthritis (OA) and traumatic joint injury. The aim of this work is to understand how lubricin and HA synergistically enhance joint lubrication, mitigate inflammation and promote cartilage health, with the ultimate goal of developing novel therapeutic strategies for OA. A second major focus is deciphering how bone morphology and bone quality relate to catastrophic fracture in racehorses. Ongoing efforts include developing clinically relevant methods for assessing fracture risk and identifying epidemiologic factors associated with fracture risk in racehorses.

## PRACTICE MANAGEMENT:

**Colleen Best, DVM, PhD, CCFP**

***Principal, BestVet Coaching and Consulting***

Dr. Colleen Best graduated from the Ontario Veterinary College in 2009. She then completed an equine internship in ambulatory medicine and surgery, after which she practiced equine ambulatory medicine in Ontario. Dr. Best returned to OVC to complete her PhD in interpersonal relationships in equine practice in 2015, using both qualitative and quantitative methodologies. Most recently, she has taught and researched nontechnical competencies, including veterinarian-client communication, wellness and resilience, at the Ontario Veterinary College. Dr. Best has presented at a number of international conferences about her research, veterinarian-client and collegial communication, and veterinarian wellness and resilience. She is a member of the board of the Ontario Veterinary Medical Association, a certified compassion fatigue professional, and trained in mental health first aid and suicide intervention.



**Sarah Bernardi, RSW, MSW*****Veterinary Social Worker, Veterinary Emergency Clinic and Referral Centre***

Sarah is part of Toronto's Veterinary Emergency Clinic and Referral Centre's (VEC) professional team. As their first Social Worker on staff, she strives to connect her knowledge of the Social Work profession with the specialty services offered at VEC. Sarah is originally from Northern Ontario where she has grown up a variety of animals, including several rescue dogs. She is passionate about helping all diverse populations facing adversity and is currently volunteering with Link Coalition Toronto, a Not-For-Profit addressing the link between domestic violence, child abuse and elder abuse in the GTA. Sarah holds her Masters of Social Work Degree, with Distinction in Gerontology from the Factor-Inwentash Faculty of Social Work, University of Toronto.

**Shawn G. McVey, MA, MSW*****Co-founder and Chief Culture Officer, Pathway Veterinary Alliance***

Shawn is the Co-founder of Pathway Veterinary Alliance, which holds 225 practices across the US. He served as CEO of Eyecare for Animals, is the founder of Veterinary Specialists in Private Practices and the co-founder of Veterinary Growth Partners, an MSO that serves 7000 clinics. Shawn was also the first non-DVM to hold a board position on the American Animal Hospital Association.

Shawn enjoys staying active with cycling and hiking or combining those activities with a little travel. While at home, his golden retriever, Auggie has provided him with plenty of entertainment for the past 10 years.

**Darren Osborne, MA*****Director of Economic Research, Ontario Veterinary Medical Association***

Darren Osborne is the Director of Economic Research for the Ontario VMA and Economic Consultant for the Canadian VMA, Veterinary Hospital Managers Association, several State VMAs and veterinary study groups across North America. Darren attended York University and completed his Master's Degree in Economics in 1992. When he is not crunching numbers, you can find Darren playing a guitar, running, swimming or cycling.

**Mary Ann Vande Linde, DVM*****Owner, Vande Linde & Associates, Brunswick, GA***

Dr. Mary Ann Vande Linde is a 1985 graduate of the University of Georgia's College of Veterinary Medicine. In addition to private practice experience, her career background includes teaching at various veterinary schools and colleges, technician schools, and veterinary conferences, consulting on practice management issues, developing mentoring and coaching retreats for women practice owners as well as working with the management teams at such corporations as Hill's Pet Nutrition, IDEXX Laboratories, Pet Health Network, Blue Buffalo, Zoetis, BI, Novartis Animal Health US and CAPC.

Dr. Vande Linde is nationally recognized as a leader in the field of veterinary communications. She is widely respected for her ability to inspire others through her guidance in interactive training programs, strategic planning, problem solving, and marketing programs and services. Her concentration on excellent preventative care and good communication between pet parent and doctor are contributing factors to her growing reputation as a voice for total pet wellness and quality of life.

In 2008, Dr. Vande Linde founded Vande Linde & Associates to focus on all aspects of Exam Room Communication Excellence. She shares her time with an energetic border terrier, Mr. Darcy.