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CARDIOLOGY

## Approach to Refractory Heart Failure

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**F**urosemide, a loop diuretic, is the most common diuretic used to treat veterinary patients with congestive heart failure (CHF). Furosemide is prescribed as the mainstay of CHF treatment alongside other vital medications (pimobendan, ACE inhibitors, +/- spironolactone); the combination of these is often referred to as “triple therapy” or “quad therapy.” Management of CHF necessitates close monitoring of renal status in conjunction with at-home monitoring (owners counting resting respiratory rates, for example) and in-clinic diagnostic testing (thoracic radiography, ultrasound assessment of effusions) for recurrence

of CHF symptoms. Many patients respond favorably to standard starting doses of furosemide (~2mg/kg orally twice daily) for multiple months or even years without recurring CHF. However, some patients have frequent relapses and require escalation of CHF therapies due to progression of their heart disease and the development of diuretic resistance. Diuretic resistance may result from nephron hypertrophy, poor oral bioavailability, poor renal perfusion, and renin-angiotensin-aldosterone system (RAAS) activation.

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ANESTHESIA

## Use of Gabapentin in Veterinary Medicine

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**Gabapentin Prescribing Practices**

**G**abapentin is an anti-epileptic and analgesic drug originally intended to be a centrally acting gamma-aminobutyric acid (GABA)-receptor agonist.<sup>1</sup> Gabapentin is currently labeled by the FDA for use in humans as an anticonvulsant and for treating pain associated with spinal cord injuries, fibromyalgia, post-herpetic neuralgia,

and neuropathic pain associated with diabetes.<sup>2</sup> Despite this narrow indication for use, gabapentin is one of the top 10 most frequently prescribed medications in the United States, with over 80% of prescriptions for extra-label use.<sup>3,4</sup>

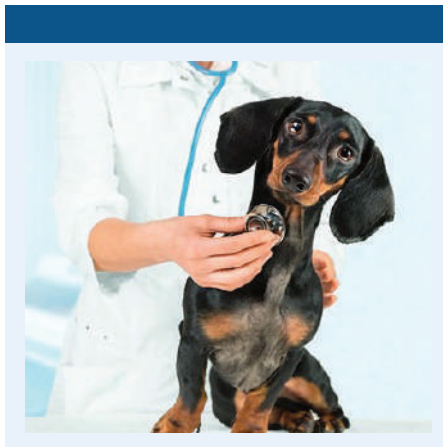
Veterinary use of gabapentin has also increased dramatically over the past several years, likely due to the desire to have an

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## CARDIOLOGY

## Approach to Refractory Heart Failure

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### When standard therapy is not enough

When patients have a recurrence of CHF, we typically recommend increasing the furosemide dose by 25 to 50%, up to a max of ~ 8 to 12 mg/kg/day. If we rapidly escalate the furosemide dose early in CHF management OR once we reach that upper dosing range, we will be more creative with therapies.

### Pimobendan

One relatively simple adjustment is to increase the pimobendan dose. Pimobendan is an “inodilator,” providing beneficial dual properties of positive inotropy and vasodilation. While off-label at doses above 0.3mg/kg twice daily, this medication has been shown to be safe up to 0.4mg/kg orally three times per day, even in cats! Anecdotal reports indicate that doses up to 1mg/kg orally three times per day have been well tolerated in dogs and may allow clinicians to administer lower doses of diuretic therapy.

### Torsemide

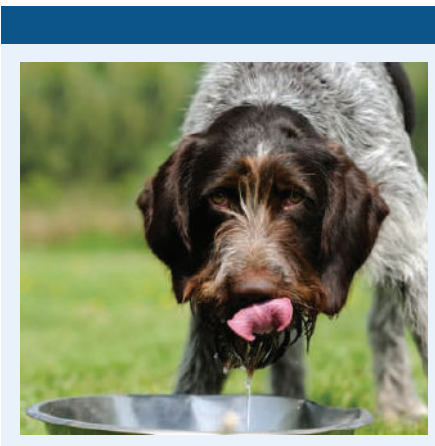
Torsemide is a loop diuretic, similar to furosemide. It has improved bioavailability, a longer half-life, and a longer duration of action than furosemide. Torsemide is also suspected of having aldosterone antagonism properties, which can result in anti-fibrotic effects on the myocardium and reduce diuretic resistance. Studies have determined that torsemide may have 10 to 20x more potency as a diuretic than furosemide. This may also increase the risk of azotemia or electrolyte imbalance; caution should be taken when initiating torsemide in patients with evidence of azotemia already. We typically start the torsemide dose at ~ 1/10 the patient’s current furosemide dose. For example, if a dog is receiving furosemide 12.5mg orally twice daily and we are switching to torsemide, we may recommend 1.25 to 1.5mg orally twice daily.

### Hydrochlorothiazide

Hydrochlorothiazide (HCTZ) is a thiazide diuretic that reduces membrane permeability to Na<sup>+</sup> and Cl<sup>-</sup> in the distal convoluted tubule, leading to increased Na<sup>+</sup>, Cl<sup>-</sup>, and water delivery into the collecting duct. HCTZ has good oral absorption, works within 1 to 2 hours, and has a longer half-life (6 to 12 hours) than furosemide. One significant benefit to adding HCTZ is that this medication can synergistically be used with loop diuretics due to sequential nephron blockade. It also is beneficial in reducing diuretic resistance by blocking sodium reabsorption at the distal convoluted tubule where loop-associated hypertrophy occurs. Given its potential for causing significant electrolyte disturbances or nephrotoxicity, especially in combination with other diuretics, low doses are typically started (e.g., 6.25 mg orally every 72 hours in cats; 0.5 to 1 mg/kg orally once daily in dogs) and titrated based on response. We recommend closely monitoring renal values and electrolytes once this medication is started, typically rechecking lab work after the fourth dose of medication, then every few weeks until trends are established.

### Afterload reduction

In addition to more commonly administered vasodilators (ACE inhibitors, pimobendan), arteriolar dilators can be utilized for afterload reduction. These allow for increased forward blood flow, especially in patients with severe mitral regurgitation. During the acute CHF setting, IV arteriodilators (nitroprusside, hydralazine) can be beneficial in combination with standard therapy. For long-term management of refractory heart failure, oral options such as amlodipine have successfully reduced afterload. Amlodipine, a dihydropyridine calcium channel blocker, helps to relax systemic arteriolar smooth muscle. This medication can be a beneficial addition in chronic



heart failure management in dogs who are normotensive or hypertensive. We recommend monitoring blood pressure before initiation and within 2 to 4 weeks after starting.

### Conclusion

Ultimately, each patient diagnosed with CHF will respond differently to prescribed medications. Beyond standard “triple” or “quad therapy,” there are other strategies for managing CHF. The Angell Cardiology team is always willing to consult and assist in managing any of your more challenging CHF patients!

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## ANESTHESIA

## Use of Gabapentin in Veterinary Medicine

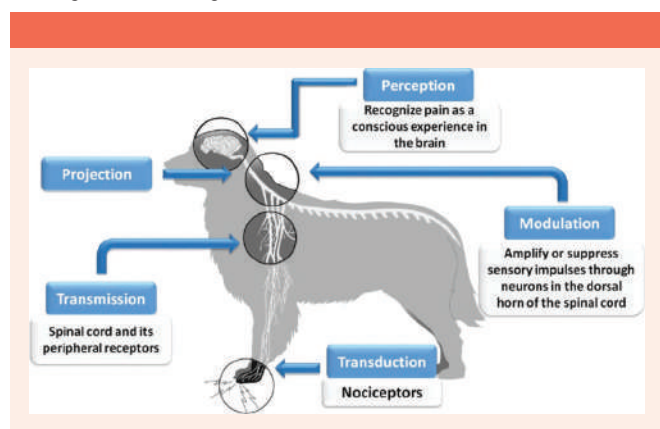
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oral analgesic alternative to non-steroidal anti-inflammatory drugs (NSAIDs). A recent survey of veterinarians found that 69% of respondents prescribe gabapentin daily or weekly, most commonly for acute and chronic pain.<sup>5</sup> Despite this popularity, gabapentin has a similarly narrow indication for use in veterinary medicine, and current prescribing practices warrant further scrutiny.

### Mechanism of Action

Understanding the mechanism of action of gabapentin is critical when evaluating the role that gabapentin may have as an analgesic for veterinary patients. As mentioned, gabapentin was initially intended to be a centrally acting agonist at the GABA receptor. However, while structurally similar to the GABA molecule, gabapentin does not bind to the GABA receptor or influence the action or metabolism of the GABA molecule.<sup>1</sup> Instead, gabapentin is believed to bind to receptors on calcium channels on the presynaptic neurons in the central nervous system. The binding of gabapentin to these receptors blocks the influx of calcium into the presynaptic nerve terminal, decreasing the release of excitatory neurotransmitters.<sup>1</sup>

Mammalian pain transmission involves the conversion of a noxious stimulus to an electrical signal, which is then transmitted by peripheral sensory fibers to the dorsal horn of the spinal cord.<sup>6</sup> Pain signals are either amplified or suppressed by endogenous neurotransmitters or analgesic drugs in the dorsal horn and then progress to the brain, where the signal is consciously perceived.<sup>6</sup> Left untreated amplification of pain signals in the dorsal horn can lead to maladaptive or chronic pain states.<sup>6</sup>

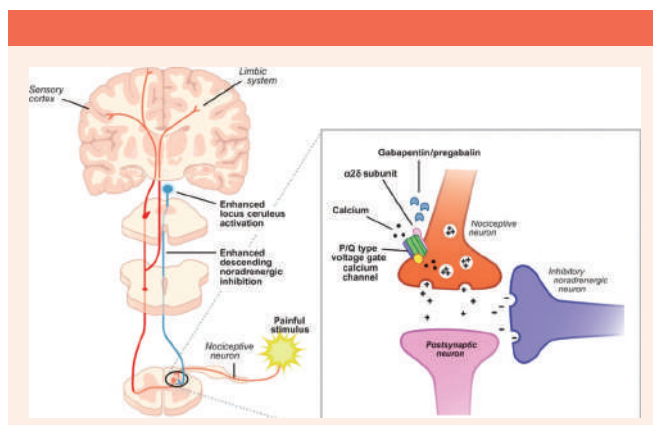


Analgesic properties of gabapentin are believed to be due to the blockade of calcium channels on presynaptic nerve terminals in the dorsal horn of the spinal cord, which decreases the release of excitatory neurotransmitters (e.g., substance P, glutamate, glycine) that would otherwise amplify pain signals. Accordingly, in most circumstances, gabapentin is best thought of as a modulator of pain; administration may decrease the transmission of pain signals but is unlikely to stop pain signals completely.

### Targeted Use of Gabapentin

One of the most commonly cited uses of gabapentin in veterinary medicine is for treating acute post-operative pain.<sup>5</sup> Considering the mechanism of action of gabapentin and its impact on pain signaling, it is unlikely that gabapentin will be an effective analgesic in this context. Inflammation is the most common component of acute post-operative pain, and while gabapentin modulates pain signals from the periphery, it does not treat inflammation directly. As a result, gabapentin may reduce pain signaling associated with inflammatory pain, but it will not address the source of pain directly.

Gabapentin administration is better applied in treating neuropathic pain and complex pain states requiring a multi-modal approach to achieve sufficient analgesia. A primary central or peripheral nervous system lesion, such as intervertebral disc herniation, plexus avulsions, and nerve root impingement, causes neuropathic pain.<sup>6,7</sup> Imbalances between excitatory and inhibitory pain signaling contribute to the development of neuropathic pain,<sup>7</sup> and administration of gabapentin may help reduce the amount of excitatory pain signals generated and subsequently transmitted to the cerebral cortex.



Gabapentin may also be added to an analgesic regimen to manage heightened pain states if first-line analgesics are insufficient. Examples of heightened pain states include polytrauma, pathologic fractures, cancer pain, thrombosis, or conditions associated with extensive inflammation, such as peritonitis and fasciitis. Again, gabapentin's inhibition of presynaptic calcium channels reduces excitatory pain signaling, improving analgesia. Gabapentin may also act synergistically in combination with other analgesics, reducing required doses and minimizing adverse effects (e.g., dysphoria, sedation).

### Dosing and Administration

Gabapentin is rapidly absorbed and eliminated in both canine and feline patients.<sup>8</sup> Frequent administration is needed to maintain minimum target plasma concentrations.<sup>8</sup> Pharmacokinetic data suggest that gabapentin should be dosed at 10 mg/kg every 8 hours in dogs, 8 and 8 mg/kg every 6 hours in cats.<sup>9</sup> Administration of gabapentin on an as-needed basis or at intervals less frequent than indicated may result in insufficient plasma concentrations and lack of efficacy.

Gabapentin is typically considered a safe alternative to other medications, but its administration is not entirely without side effects. Sedation is a common adverse effect of gabapentin, particularly with administration at high doses.<sup>10,11</sup> Ataxia is another common adverse effect of gabapentin,<sup>11</sup> and administration in patients with pelvic-end weakness may exacerbate signs and decrease the ability to ambulate without assistance. Finally, gabapentin is removed from the body via the kidneys and should be used cautiously in patients with renal insufficiency, as increased adverse effects (e.g., sedation, hypotension) are possible.<sup>12-14</sup>

### Why Prescribing Practices Matter

Gabapentin has recently become a popular street drug, with recreational users taking large doses to get high.<sup>15</sup> The prevalence of abuse within the general population remains low, but it increases dramatically for people with a history of opioid abuse.<sup>15</sup> Emergency departments (ED) are reporting a dramatic increase in the presence of gabapentin in the toxicology screens of individuals presenting to the ED for a drug overdose.<sup>16</sup> Most concerning, patients who present to the ED following an overdose are significantly more likely to end

## ANESTHESIA

## Use of Gabapentin in Veterinary Medicine

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up on a ventilator or have a fatal overdose if they have combined an illicit opioid with gabapentin.<sup>16,17</sup>

### Conclusion

The use of gabapentin in veterinary medicine has increased dramatically in the last several years. Despite its popularity, there is a narrow indication of its use in veterinary patients. There is also growing evidence that gabapentin is being diverted for recreational drug use, sometimes with fatal consequences. As a result, the veterinary community should closely scrutinize where gabapentin fits into our “analgesic toolbox,” gabapentin should not be prescribed for conditions where it is unlikely to be effective. Additionally, veterinary practitioners should consider limiting the number of drugs dispensed and placing restrictions on refill authorizations.

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# A Step-by-Step Description of Feline Perineal Urethrostomy

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## Indications for Performing a Perineal Urethrostomy

**A** “urethrostomy” refers to creating a new, permanent opening in the urethra. The perineal area is the most common location chosen for urethrostomy in cats because it allows for urination from a normal anatomic region and facilitates the creation of a comparatively larger stoma in relation to the diameter of the natural urethral orifice. Alternative urethrostomy locations include (modified<sup>1</sup>) prepubic, subpubic, and transpelvic locations; however, these procedures are reserved for urethral lesions located cranial to the bulbourethral glands. All feline urethrostomies are performed at, or cranial to, the level of the bulbourethral glands because the feline urethra gradually tapers in diameter in a cranial to caudal direction with an average internal diameter of 2 mm at the pre- and immediate post-prostatic urethra, 1.3 mm at the level of the bulbourethral glands, and 0.7 mm at the terminal portion of the urethra.<sup>2</sup> A perineal urethrostomy is most commonly performed as a component of management for Feline Lower Urinary Tract Disease (FLUTD) but can also be utilized to treat distal urethral trauma, stricture, neoplasia, or congenital anomalies. Cats with FLUTD are considered candidates for a perineal urethrostomy when other urethral obstruction causes have been ruled out, and cats have continued to develop recurrent urethral obstructions despite appropriate medical management.

## Procedure Description

Perineal urethrostomies can be performed in both dorsal and sternal recumbency. Regardless of the positioning, the patient is placed with the head towards the anesthesia machine and the perineal area at the opposite end of the table to minimize the table distance between the patient and surgeon. An anal purse-string suture should be placed to minimize intra-operative fecal contamination. Patients positioned in dorsal recumbency should have their legs gently positioned cranially and laterally to expose the perineal area (Figure 1) maximally. Patients in sternal recumbency are positioned with the pelvic limbs hanging off the end of the table and the tail gently positioned over the dorsum to maximize exposure (Figure 2).<sup>2</sup>

Figure 1



Additional padding can be placed under the lumbar area (when in dorsal recumbency) or the caudoventral abdomen (when in sternal recumbency) to support the patient and further elevate the perineal area.

Although dorsal recumbency has been advocated in patients requiring a concurrent cystostomy to avoid the need for repositioning between procedures, there is no significant difference in complication rates or the duration of surgery or anesthesia between

Figure 2



positions.<sup>3</sup> A decreased briskness of the perineal reflex and an increased occurrence of spinal pain have been seen in patients 24 hours following surgery; however, there was no difference in the rate of occurrence between patients positioned in dorsal or sternal recumbency.<sup>4</sup>

The perineal area is fully clipped and aseptically prepped for surgery. If a cystostomy is planned under the same anesthesia, the patient can be positioned in dorsal recumbency, and the ventral abdomen can be prepped and draped into the same operating field to avoid the need for repositioning between procedures. If possible, a urethral catheter should be placed before initiating surgery to help facilitate identification and dissection. A blade creates an elliptical incision around the scrotum and prepuce. Intact males are routinely neutered. The distal tip of the penis and/or prepuce can be grasped and manipulated with Allis tissue forceps to ease dissection. The penis is isolated and circumferentially dissected to the level of insertion of the ischiocavernosus muscles on the penis using a combination of sharp and blunt dissection. Monopolar and/or bipolar electrocautery can help minimize bleeding during dissection (Figure 3). The bilateral ischiocavernosus muscles are completely elevated from their origin on the ischium. Electrocautery or a blade can initiate the elevation, which is completed using a freer periosteal elevator to minimize the risk of hemorrhage from the muscle. Releasing the ischiocavernosus muscles allows exposure of the ventral penile ligament, which is sharply transected at the insertion on the ventral and central portion of the penis. Circumferential dissection of the penis from the subcutaneous tissue is continued, and the retractor penis muscle is

Figure 3



## SURGERY

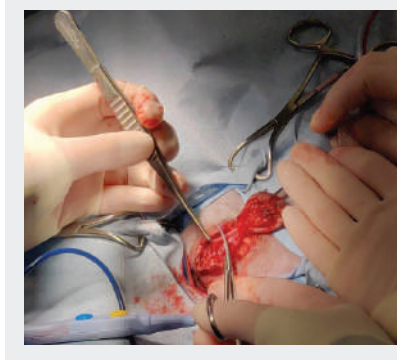
## A Step-by-Step Description of Feline Perineal Urethrostomy

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sharply transected from the dorsal aspect of the penis (Figure 4). Circumferential dissection is continued until the surgeon has exposed the bulbourethral glands. These are best seen and palpated on the dorsal aspect of the penis and are located just cranial to the transected ischioavernosus muscles.

Once the penis has been adequately dissected, a blade or fine tenotomy scissors are used to incise the penile urethra from its distal tip cranially to the level of the bulbourethral glands. Failure to incise the

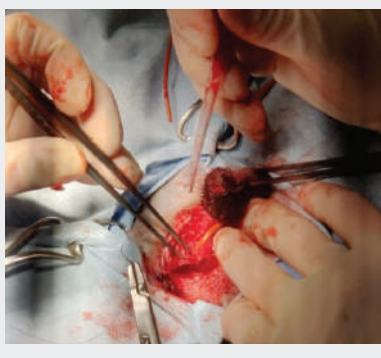
Figure 4



urethra far enough cranially limits the size of the urethrostomy site and increases the risk for stricture formation. If a urethral catheter cannot be placed pre-operatively due to obstruction, a catheter should be placed following the urethral incision to help guide the creation of an appropriate urethrostomy. The post-operative urethrostomy luminal diameter has been shown to decrease by an average of  $0.15 \pm 0.09$  mm<sup>2</sup> by 12 days post-operatively, so the urethrostomy site should be large enough to tolerate this anticipated stricturing that occurs as a natural part of healing.<sup>5</sup> A stoma that can easily accommodate a 10Fr red rubber catheter at the time of surgery has a 6% chance of developing an obstructive stricture, while stomas that can maximally accept an 8Fr or 6Fr catheter have a 44% and 100% chance of developing obstructive strictures respectively.<sup>5</sup>

The urethrostomy is formed by suturing the urethral mucosa to the surrounding skin. Any tension on the site should be avoided to minimize the risk of dehiscence and excessive stricturing of the site. While non-absorbable (e.g., Nylon) and slowly absorbable (e.g., polydioxanone) sutures can be used, rapidly absorbable sutures (e.g., poliglecaprone 25) have been shown to be safe and eliminate the need for suture removal.<sup>6</sup> A simple interrupted or horizontal mattress suture is placed at the dorsal extent, or 12 o'clock position, of the urethrostomy site to maintain appropriate orientation and avoid malpositioning of the urethra. Simple interrupted sutures are placed on either side

Figure 5



of the urethrostomy to gradually create the opening and avoid tension between the two sides. A 10Fr urethral catheter can be left in place during the creation of the stoma to ensure adequate size (Figure 5). Alternately, based on surgeon preference, the catheter can be placed intermittently during the creation of the stoma to confirm the appropriate diameter. A “washboard” can be created using an approximately 1cm long segment of the remaining penile urethra. This 1cm strip of penile mucosa is sutured to the surrounding skin using either simple interrupted or simple continuous sutures. It serves to minimize tension on the site and minimize urine scald. Any penile tissue that remains following the creation of the “washboard” is ligated with a circumferential or transfixing ligature and then amputated. Final sutures are placed in either corner of the distal extent of the “washboard,” the remainder of the skin is routinely closed using a two-layer closure (subcutaneous tissue and skin).

### Outcome

Although good to excellent outcomes have been reported long-term in 81.8 to 100% of cases, it is important to remember that a perineal urethrostomy is a salvage procedure.<sup>7,8</sup> Owners should understand that a perineal urethrostomy can be used to manage FLUTD but is not a cure for the disease. Approximately 54% of cats develop short-term complications, and urinary obstruction and urethrostomy site stricture have been reported in up to 20% of patients at an average of  $92 \pm 25$  days post-operatively.<sup>5,9</sup> Sterile cystitis and urinary tract infections are the most common short- and long-term complications; however, other less common short-term complications reported include urinary incontinence, recurrent obstructions, strictures, urine extravasation into the perineal subcutaneous tissues, and regional dermatitis.<sup>9</sup> Minor long-term complications are less common; however, 13.5% to 39% of patients report recurrent bouts of sterile cystitis and/or urinary tract infections consistent with FLUTD.<sup>6,9</sup> Although subclinical in some

patients, bacteriuria was seen in 77.2% of all cats 12 to 24 months following a perineal urethrostomy.<sup>8</sup>

In summary, perineal urethrostomies are commonly performed procedures utilized as a component of FLUTD management in cats. Although the procedure is associated with a fairly high rate of short-term complications, it has a high long-term success rate. It has been consistently shown to improve the quality of life in affected cats.<sup>7,8</sup>

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# Emergency Handling of, Stabilization of, and Diagnosing the Dyspneic Patient

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## Triage

**D**yspneic patients should be identified immediately upon presentation. Front office staff and triage nurses are on the front lines to identify this type of emergency. It is essential to minimize additional stress on these animals to prevent worsening the clinical condition. Diagnosis and therapy may need to be performed stepwise to allow the patient breaks in between stressful events.

Signalment and presenting complaints are some of the first clues to diagnosing a dyspneic patient. For example, an older chihuahua might place congestive heart failure higher on the differential list, while a young dog presenting for trauma might put pneumothorax or pulmonary contusions higher on the list. Increased respiratory rate in a young cat who presented with an unrelated problem may place stress higher on the list. In this case the veterinarian should confirm with the owner if the cat was breathing normally at home.

## Physical Exam

On the initial physical exam, the emergency veterinarian should evaluate for any external wounds and note the patient's breathing pattern. Stertor and stridor are associated with brachycephalic airway syndrome, laryngeal paralysis, or other upper airway disease such as an obstructive mass. On auscultation, the veterinarian should evaluate for crackles, wheezes, decreased lung sounds, or muffled heart sounds. Crackles are associated with congestive heart failure, pneumonia, or other pulmonary parenchymal disease. Wheezes are associated with lower airway disease, including feline asthma or chronic lower airway disease. Decreased lung sounds may clue the veterinarian into pleural effusion, while muffled heart sounds may help diagnose pericardial effusion.

## Initial Diagnostics

Initial diagnostics performed on triage may include a FAST scan (focused assessment with sonography for trauma) of the chest and abdomen. B-lines are artifacts on ultrasound caused by pulmonary edema, which help diagnose

› Cages that are used to provide oxygen support.



congestive heart failure or pneumonia. A thoracic glide sign, commonly visualized as “ants marching in a line,” is caused by lung visceral pleura sliding along the parietal pleura during respiration. The absence of a glide sign helps diagnose pleural disease such as a pneumothorax, pleural effusion, or other space-occupying pleural lesions. The veterinarian may view the right parasternal short axis of the heart base during FAST scan to evaluate the left atrial-to-aortic (La:Ao) ratio. Generally speaking, a normal La:Ao ratio is considered less than 1.6. An increased La:Ao ratio in combination with b-lines suggests congestive heart failure.

Minimum database bloodwork that includes electrolytes and acid-base status is useful to diagnose causes of dyspnea. In emergency scenarios, a venous blood gas is often most easily obtained, allowing the veterinarian to distinguish between primary or secondary respiratory acidosis or alkalosis. Hypoxemia can be identified if an arterial blood gas can be obtained. Causes of hypoxemia include hypoventilation, alveolar disease, blood shunting, V/Q (ventilation-perfusion) mismatch, or decreased amount of inspired oxygen.

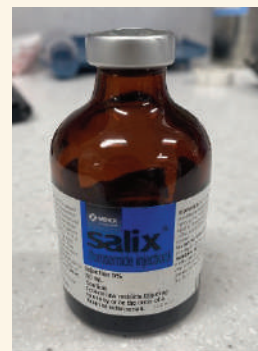
## Initial Treatments

While not all dyspneic animals benefit from oxygen therapy, it is often one of the first and relatively benign therapies that may be

administered on triage. Oxygen therapy may be delivered via flow by or an oxygen cage with FiO<sub>2</sub> 40 to 60%. Anxiolytics and mild sedatives are also mainstay initial therapies, especially in patients whose cause of dyspnea is unknown. More specifically, they are particularly useful for treating upper respiratory disease, lower airway disease, or stress. Butorphanol 0.1 to 0.3 mg/kg IM, SQ, or IV is frequently used. This agonist-antagonist opioid has sedative, antitussive, and mild analgesic properties and minimal respiratory depressive effects. Butorphanol can be partially reversed if needed. Acepromazine, a phenothiazine, is also commonly used for sedation at 0.01 to 0.02 mg/kg IM, SQ, or IV, and it has minimal respiratory depressive effects. However, acepromazine should be used cautiously as it causes hypotension, decreases seizure threshold, and is irreversible.

Moreover, pain should always be considered a possible contributing factor to dyspnea. At Angell Animal Medical Center, if a patient's presenting complaint or apparent clinical condition may be painful, methadone 0.1 to 0.3 mg/kg IM, SQ, or IV is commonly administered on triage. This is a full mu opiate receptor agonist that has minimal respiratory depressive effects, less emetic effects than hydromorphone, and it is reversible.

› Injectable furosemide which is used to treat congestive heart failure.



Further therapies to stabilize the dyspneic patient are more specific. For example, inhalant albuterol in conjunction with butorphanol may be successful

## EMERGENCY &amp; CRITICAL CARE

## Emergency Handling of, Stabilization of, and Diagnosing the Dyspneic Patient

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if feline asthma is suspected. If additional therapy is needed, dexamethasone sodium phosphate may be administered IM or IV on triage. Additional injectable bronchodilators may be administered, such as terbutaline or theophyllines. However, the use of steroids should be cautioned before obtaining a more definitive diagnosis.

If congestive heart failure is suspected, then furosemide, a diuretic, should be administered at a starting dose of 2 mg/kg in dogs and 1 to 2 mg/kg in cats IM or IV. If a patient already takes oral furosemide, it should be administered at a starting dose that is 25 to 50% greater than a patient's current dose at home. Another common cause of dyspnea is pneumonia, and IV antibiotic therapy should be initiated as soon as possible if this disease is suspected. Moreover, if upper airway swelling is suspected, then dexamethasone sodium phosphate 0.1 to 0.2 mg/kg IV may help decrease inflammation. If pleural space disease is identified, an emergent thoracocentesis may be indicated for diagnostic and therapeutic purposes. If pericardial tamponade is identified, then an emergent pericardiocentesis is indicated.

Intubation may be required if the dyspneic patient cannot be stabilized with initial therapy. If there is an upper airway obstruction and intubation is unsuccessful or not an option, an emergent temporary tracheostomy may be required.

### Workup

Additional treatment of the dyspneic animal may require further workup. Thoracic radiographs are often the first diagnostic test; others may include an echocardiogram, computerized tomography, infectious disease panels, or bronchoalveolar lavage.

The dyspneic patient is one of the most stressful presentations to any veterinary clinic. With the right tools and practice, veterinary staff can successfully handle, stabilize, and diagnose the dyspneic patient.

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## Small Intestinal Disease on Ultrasound

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A common presenting complaint to the emergency room and during primary care appointments is vomiting and inappetence in small animals. Abdominal radiographs are commonly initially performed to rule out a gastrointestinal mechanical obstruction, gastrointestinal foreign body, or abdominal mass. If a clear cause is not determined, additional diagnostic tests are pursued that include abdominal ultrasound and blood work. This article will discuss some of the more common small intestinal diseases of dogs and cats on ultrasound.

Small intestinal abnormalities on ultrasound can be broken into two main categories: focal and diffuse disease. Focal small intestinal lesions include mechanical obstruction caused by foreign material, intussusception, or a mass. Masses are described as circumferential, asymmetrically circumferential, or eccentric (Figures 1a-1c). In dogs, one study noted that 99% of dogs with intestinal neoplasia have a loss of wall layering; unfortunately, there can be some overlap between benign and malignant masses on ultrasound. The more common intestinal mass neoplasms include adenocarcinoma, lymphoma, gastrointestinal stromal tumor, leiomyosarcoma, leiomyoma, and mast cell tumor. In cats, the most common intestinal masses are lymphoma or adenocarcinoma, followed by mast cell tumors. Lymphoma can present as solitary or multiple masses or a diffuse altered wall layering. Carcinomas most often are transmural lesions with loss of wall layering and can result in the narrowing of the lumen and secondary mechanical ileus. Mast cell tumors most commonly present as a focal mass that is hypoechoic and either eccentric or asymmetrically circumferential, similar to other intestinal neoplasms, and is rarely reported as a diffuse intestinal wall thickening. An interesting point documented in cats is that mast cell tumors in the intestine can often alter but not completely

disrupt the wall layering. In dogs, it has been reported that there are no ultrasonographic signs to help differentiate between gastrointestinal spindle cell tumor types as they most often are seen as eccentric and bulging out of the serosa; however, gastrointestinal stromal tumors were more commonly seen in the cecum and large intestine.

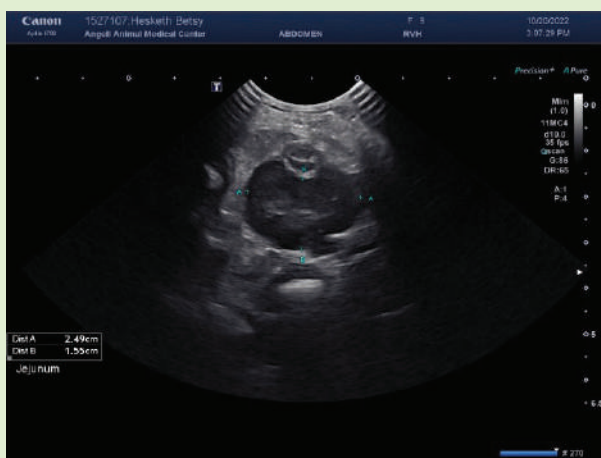
**Figure 1B**

Example of a circumferential small intestinal mural mass diagnosed as lymphoma.



**Figure 1A**

Example of an eccentric small intestinal mural mass as seen with leiomyoma and leiomyosarcoma.



**Figure 1C**

Example of an asymmetric, circumferential small intestinal mural mass diagnosed as lymphoma.



DIAGNOSTIC IMAGING

Small Intestinal Disease on Ultrasound

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Figure 2A

> Schematic of a normal small intestinal wall layering.

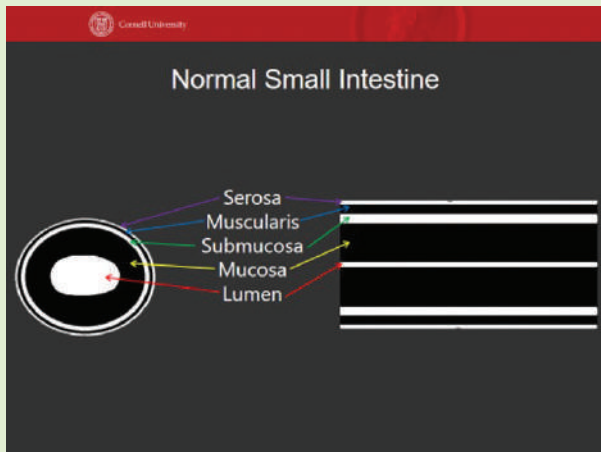


Figure 2B

> Example of a normal small intestinal wall on ultrasound.

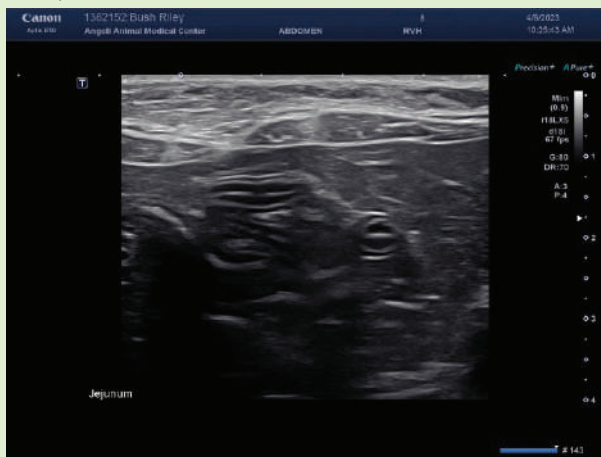


Figure 2C

> Example of a thick muscularis layer of the small intestinal wall as seen with inflammatory bowel disease and lymphoma.



Benign small intestinal mass lesions include granulomas, inflammatory polyps (most commonly seen in the duodenum), and inflammatory masses. Feline gastrointestinal eosinophilic sclerosing fibroplasia (FGESF) is a nodular, non-neoplastic inflammatory lesion that can result in a discrete small intestinal mass with loss of wall layering and ulceration with the same ultrasonographic appearance as neoplastic lesions. These lesions are often seen with mild regional lymphadenopathy and have been associated with intracellular bacteria within the lesions in 56% of cats. Adenomatous polyps are most commonly seen as small, homogenous nodules arising from the mucosa that projects into the lumen with the preservation of wall layering. Certain infectious causes can result in small intestinal lesions that mimic neoplastic lesions, such as feline infectious peritonitis and pythiosis.

Examples of diffuse small intestinal diseases include non-specific enteritis, inflammatory bowel disease, or infiltrative neoplasia such as lymphoma. Both inflammatory bowel disease and lymphoma can have a normal appearance of the small intestine on ultrasound or demonstrate a thick muscularis layer described as muscularis to submucosa ratio of greater than one (Figure 2a-2c). Cats with lymphoma are more likely to present with a thick muscularis layer, while approximately 20% of dogs with lymphoma can have a normal small intestinal wall on ultrasound. In dogs, inflammatory bowel disease can be seen as segmental or diffuse muscularis thickening. Enlarged, rounded, hypoechoic lymph nodes are more often present with lymphoma. They can be a way to obtain a diagnosis via fine needle aspiration without requiring a small intestine biopsy. If the cytology does not clearly indicate round cell neoplasia or the lymph nodes are only mildly enlarged or normal, a biopsy of the small intestine (via endoscopy or exploratory laparotomy) would be required for a definitive diagnosis due to the large overlap in the appearance between the two diseases.

An additional differential diagnosis for a diffusely thick muscularis layer is muscularis hypertrophy. This author has seen this occur secondary to more chronic small intestinal foreign body obstructions and intestinal parasitic infections. This is suspected to be due to hypertrophy of the small intestinal muscle layer against some resistance, similar to building muscles from lifting weights.

Occasionally, inflammatory bowel disease, specifically protein-losing enteropathy in dogs, can present on ultrasound as linear hyperechoic striations within the mucosal layer (Figure 3). These hyperechoic striations have been determined to be dilated lacteals associated with lymphangiectasia.

Figure 3

> Example of hyperechoic striations within the mucosal layer due to dilated lacteals in the small intestinal wall as seen with lymphangiectasia.



## DIAGNOSTIC IMAGING

## Small Intestinal Disease on Ultrasound

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One complicating factor is that the lacteals will dilate normally after a recent meal ingestion; thus, one of many reasons fasting before ultrasound is required. With protein-losing enteropathy, abdominal effusion may also be present secondary to hypoproteinemia.

An additional differential diagnosis for altered small intestinal wall layering is gastrointestinal histoplasmosis infection. In these cases, the submucosal layer was thickened +/- a muscularis thickening. The small intestinal changes were variable, with diffuse circumferential thickening of the colonic wall most commonly seen. Consider this differential if the animal is from or visited endemic areas, and diagnosis can be obtained with rectal scrape cytology, histopathology, fungal culture, or antigen testing.

Abdominal ultrasonography is an invaluable tool when evaluating gastrointestinal illnesses. Differentiating diffuse from focal disease, the appearance of the lesion, and even location can help prioritize and rule out various small intestinal diseases; however, due to the large overlap between the various diseases, cytology or biopsy is often required for a definitive diagnosis.

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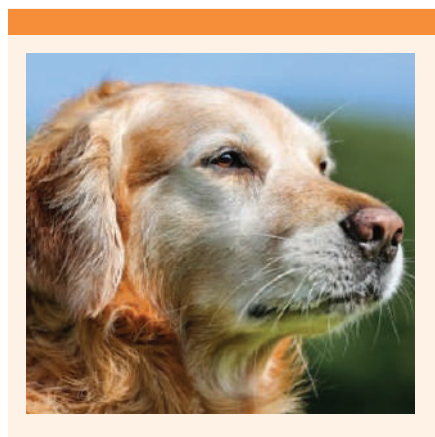


## Trilostane Dosing and Monitoring in Dogs

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**C**anine hyperadrenocorticism (Cushing's disease) is one of the most common endocrine disorders that veterinarians treat. For many years, trilostane has been the treatment of choice for most veterinarians' medical management of the condition. Trilostane is a competitive inhibitor of 3 $\beta$ -hydroxysteroid dehydrogenase, the enzyme required to synthesize cortisol. This inhibition blocks the conversion of pregnenolone to progesterone, which inhibits the production of glucocorticoids and, to some extent, mineralocorticoids and sex hormones. As an aside, it is not uncommon for dogs receiving trilostane to be mild to moderately hyperkalemic due to these effects on mineralocorticoids.

Trilostane has an extensive dose range, and the starting doses can vary significantly. The manufacturer's (Dechra) recommendation is a starting dose of 2.2 to 6.7 mg/kg once daily. Recent studies have shown, however, that lower initial doses are equally effective and may be safer. Generally speaking, the Angell Animal Medical Center Internal Medicine service uses starting doses of 1 to 2 mg/kg twice daily (usually closer to 1mg/kg twice daily). Larger dogs generally require a lower mg/kg dose than smaller dogs. Although trilostane may be given either once or twice a day, twice-a-day treatment is preferred by most clinicians due to the short half-life of the drug and a more consistent clinical response. Trilostane should always be given with food to improve absorption.



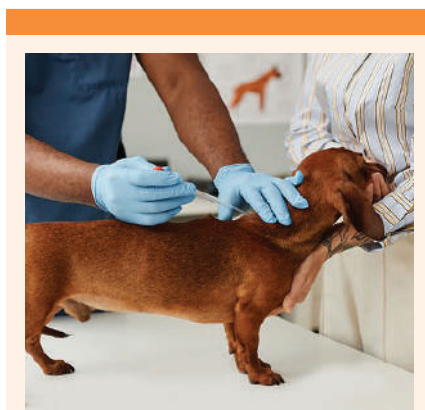
Historically, monitoring treatment includes assessing response to therapy with improvement of clinical signs and an ACTH stimulation test. In recent years, synthetic ACTH shortages and increasing prices have made it more challenging to routinely do the ACTH stimulation test. Additionally, the test requires two blood samples taken an hour apart, resulting in more clinical space and staff utilization. Due to the increased price and time needed for this test, other monitoring diagnostics have been proposed.

Most recently, monitoring Cushing's just based on a "pre-trilostane" (just before the morning dose was to be given) baseline cortisol level alone has been proposed. If used appropriately, this can be a much more practical and less labor intense method of monitoring the response to trilostane. Initial studies at the University of Glasgow showed that the pre-trilostane cortisol levels correlated better with clinical signs than the two-hour post-cortisol level with classical ACTH stimulation testing.

The ACTH stimulation test still has an appropriate place in monitoring. Deciding which test to use is the key to proper assessment and is based on the clinical condition of each patient. Pre-trilostane basal cortisol monitoring should be reserved for dogs clinically doing well. For a dog on trilostane that is feeling well or even still showing signs of Cushing's disease (PU, PD, PP, etc.), it is very reasonable to do a pre-trilostane cortisol level rather than a full stimulation test.

A single cortisol level in dogs feeling ill would probably not be the best choice. For these cases, an ACTH stimulation should always be done. A sick dog's cortisol level may be low but raised to adequate levels with the stimulation test. If just the single cortisol level was used for evaluation, the wrong diagnosis of a cortisol deficiency might be made. The dog may be ill due to a different condition. Dogs not doing well on trilostane therapy should always have an ACTH stimulation test, a more comprehensive evaluation, and possibly additional labwork or diagnostics.

When evaluating the results of a single basal cortisol level in a dog on trilostane, the most important diagnostic criteria, once again, are



clinical signs. Is the dog feeling well? Does the dog still have clinical signs of Cushing's? Is the dog showing any new symptoms? What is considered "normal" cortisol levels in a dog on trilostane therapy are controversial, and the values must be considered in relation to clinical signs? If a specific trilostane dose controls a dog's clinical signs and his cortisol levels are above the normal range, keeping the dog on that same trilostane dose is reasonable.

Conversely, if the dog's clinical signs have not improved significantly, and the cortisol levels are within the normal range, increasing the trilostane dose should be considered. Dosage adjustments should always be made based on the dog's clinical signs (particularly resolution of polyuria/polydipsia, polyphagia, etc.) and the cortisol blood levels. It should be noted that if the clinical signs of Cushing's have not improved within a couple of weeks of an increased trilostane dose, it may also



## INTERNAL MEDICINE

## Trilostane Dosing and Monitoring in Dogs

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be prudent to wait a couple more weeks before increasing the amount of medication as the effects of the given dose of trilostane can often continue to increase even after the first two weeks of therapy. Thus if a 14-day cortisol level is 9 mg/dl, two weeks later, it could be 5 mg/dl.

As a general guideline for using single pre-trilostane cortisol levels in dogs that are not ill:

If **pre-trilostane cortisol levels are < 1.5 mg/dl**, then: 1) consider a lower dose, especially if the dose was just increased; 2) If no clinical signs of Cushing's, then consider continuing the same dose. 3) If clinical signs of Cushing's persist, consider increasing to twice daily treatment (if given once daily at the time of testing), or increase the total trilostane dose if already given twice daily. An ACTH stimulation test should be considered if the dosage is to be increased.

If **pre-trilostane cortisol levels are 1.5 mg/dl to 6 mg/dl**, then: 1) if there are no clinical signs of Cushing's, stay on the current dose. 2) If clinical signs of Cushing's, increase the frequency or dosage of trilostane.

If **pre-trilostane cortisol levels are > 6 mg/dl**, then: 1) if there are no clinical signs of Cushing's, stay at the same dose even though the cortisol level is above the normal range. 2) if clinical signs of Cushing's, increase the trilostane dose.

Most all dogs with **cortisol levels above 10 mg/dl** will show clinical signs for Cushing's and need increased trilostane doses.

Generally, the trilostane dose can be increased by 5 to 10 mg (or 10 to 25%) depending on the cortisol levels, clinical signs, and the patient's size.

Eliminating the need for doing an ACTH stimulation test to monitor dogs on trilostane therapy due to Cushing's disease can significantly affect the chronic care of these patients. Clients may be more compliant in treatment due to the decreased cost and time spent at the clinic. The veterinary practice may benefit from the relative ease of performing a single blood test (lower technician time; able to continue caring for these patients instead of having to refer to specialty practices to do an ACTH stimulation test). Finally, when monitoring dogs on trilostane therapy, the decision to do a stimulation test or just a basal cortisol level needs to be based on each patient's clinical signs

and physical exam. The clinical assessment and presence of clinical signs should always be considered when determining if an increase in the trilostane dosage is appropriate, regardless of the monitoring protocol used.

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# Intralymphatic Allergen-specific Immunotherapy for Canine and Feline Atopic Dermatitis

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## Introduction

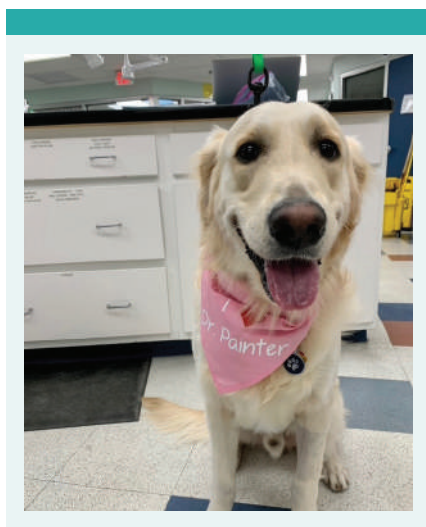
**A**topic dermatitis is a common, inherited, chronic, relapsing inflammatory and pruritic disease involving both skin barrier defects and inflammatory dysfunction. This condition often leads dogs and cats to be presented to the veterinarian for secondary symptoms such as otitis externa, relapsing bacterial infection of the skin, or unmanageable pruritus.

There are several medical management tools available for veterinarians to treat the secondary symptoms of allergy. Examples include medications like Apoquel (oclacitinib), Atopica (cyclosporine, modified), Cytopoint (lokivetmab), antihistamines, or steroids. However, these therapeutics are designed to mask the *symptoms* of the disease. They do not influence the source or pathogenesis directly.

Allergen-specific immunotherapy (ASIT) is the practice of administering gradually increasing quantities of allergen extract to an allergic patient with hopes of reducing the symptoms associated with exposure to causative allergens.<sup>1</sup>

In veterinary medicine, ASIT is a well-established therapy for the management of environmentally driven canine and feline atopic dermatitis. Prescriptions for ASIT are unique to a particular patient and based upon results obtained with intradermal allergy testing (IDAT) and/or *in vitro* allergy testing (IgE serology).

The pathogenesis of atopic dermatitis involves inflammatory dysfunction and cytokine dysregulation generated after exposure to specific allergenic epitopes. Exposure is percutaneous and results in binding of allergens to specific IgE receptors located on the surface of antigen-presenting cells. These cells generate an immune response which leads to effector Th2 cells producing various cytokines such as IL-4, IL-5, IL-6, IL-13, and IL-31. Chronic and acute presentations of allergic skin and ear disease will have different inflammatory profiles which result in various clinical presentations.



However, the hallmark feature of canine and feline atopic dermatitis is the distinct loss of immunologic tolerance. Tolerance is an important feature of the immune system which prevents response against a specific antigen. When tolerance is lost, disorders such as food allergy, auto-immune disease, and atopic dermatitis occur.

This system of tolerance is generally well-orchestrated and straight-forward. Antigen-presenting cells, especially dendritic cells, play an important role in maintaining peripheral tolerance and immunity. Recognition of a given foreign protein (antigen) by an antigen-presenting cell leads to cellular migration to a local lymph node. What happens next is dependent on the environment within the lymph node and the genetic tendency of the individual.

Allergic responses lack tolerance, which results in reduced production of regulatory cytokines and an increased production in inflammatory ones.

## Allergen-specific immunotherapy overview

Allergen-specific immunotherapy (ASIT) has multiple effects on the T-cell-specific response to allergens, the most important of which is to increase production of cytokines with regulatory activity (IL-10, TGF- $\beta$ ). This can lead to an increase in allergen-

specific immunoglobulin (IgG) which can serve as a blocking antibody, outcompeting IgE upon exposure to various allergens.

ASIT remains the only therapeutic for atopic disease which reshapes the immune response. All other therapeutics restrict inflammatory action by way of blocking or neutralizing cytokines. This important difference serves as the main reason why ASIT is recommended for most patients with diagnosed canine or feline atopic dermatitis. This therapy treats the *source*, not just the symptoms.

There are two main types of immunotherapy currently used in veterinary practice.

Subcutaneous immunotherapy (SCIT) has been utilized for many decades in dogs and cats. This involves injecting an aqueous, saline-phenol preserved extract in two or three-vial sets of increasing concentration until a maintenance injection dose and frequency is reached.

Sublingual immunotherapy (SLIT) is an oral modality which harnesses oromucosal dendritic cell potential to induce tolerance. Given their relative abundance in the oral mucosa, and their default nonreactivity to substances placed in the mouth (e.g food), this delivery method is promising for both dogs and cats. A measured drop of glycerinated antigen extract is administered into the oral cavity (cheek pouch) once or twice daily.

There are distinct advantages and disadvantages to each type of ASIT in veterinary medicine. Formal clinical trials are difficult to perform. As a result, published comparisons of clinical outcomes with both SCIT and SLIT are lacking in the veterinary arena.

## Intralymphatic immunotherapy overview

Intralymphatic immunotherapy (ILIT) is an evolving form of allergen-specific immunotherapy involving injection of allergen extract directly into the lymph node.

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## Intralymphatic Allergen-specific Immunotherapy for Canine and Feline Atopic Dermatitis

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This process introduces lower doses of allergen to a large number of highly immunocompetent lymphocytes located with a specific lymph node. In dogs and cats, the popliteal lymph node is selected and identified by either manual or ultrasound identification. As a result of this direct exposure, the probability for tolerance induction is maximized. Cumulative doses are about 1,000 times lower than SCIT doses. Adverse event risk is, therefore, lower.

After patients complete the ILIT induction protocol, they are transitioned to SCIT or SLIT for maintenance.

It remains to be seen if this type of immunotherapy delivery is more efficacious when compared to SCIT and SLIT alone. Larger studies in a clinical context are needed. At this time, only a handful of veterinary dermatology clinics in the United States (including Angell West, Waltham, MA) are utilizing intralymphatic immunotherapy in both canine and feline atopic patients.

The potential for this method of desensitization to be clinically useful, safe, and efficacious for our patients is exciting and pioneering.

### Goals and next steps

The goal with ASIT is to reduce medication dependence and/or symptom severity for patients suffering from canine or feline atopic dermatitis. It is important to recognize that improvement in patients is individualized and often on a spectrum. Some patients have excellent control of their atopic disease and can come off anti-pruritic therapeutics entirely. Other patients have moderate control of their atopic disease and can lessen their medication needs. And, yet, others fail to respond to ASIT entirely.

Given the positive safety margin of ASIT, and potential to produce profound immunologic effects on the atopic individual, this therapeutic modality should be considered for most atopic patients.

It is very important to approach every patient with atopic disease from a multimodal perspective. For example, medical management options provide relief from symptoms and improve life quality. Results are often fast and reliable. We are fortunate to practice in a time when targeted therapeutics are available for our patients with atopic disease.

The value of ASIT from a clinical perspective is potentially massive. If a patient can reduce their medication dependence or symptom severity because of a specific desensitization protocol, the gold standard goal for management of atopic disease has been reached.

It is true, however, that ASIT can take weeks to months to usher clinical improvement. Similarly, schedules and prescriptions are individualized and based on a myriad of factors taken into consideration by veterinary dermatologists with advanced training in ASIT prescribing and maintenance practices.

Referral to a board-certified veterinary dermatologist for allergen-specific immunotherapy remains the standard of care for canine and feline atopy. This ensures the patient is properly diagnosed, medically managed, and started on a targeted ASIT protocol designed specifically for them.

Yet, there is no doubt that management of canine and feline atopic disease is done best when primary and specialty veterinarians work together to advance clinical outcomes and maintain patient life-quality and safety. This is certainly an exciting, collaborative time in veterinary practice – and these advances in immunotherapy showcase some of the value of advanced clinical care for this common disease.

### REFERENCES

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## › Angell Expands Cardiology, Dentistry, and Urgent Care Services



Dr. Michelle Oranges

### Cardiology

**Michelle Oranges, DVM, DACVIM (Cardiology)**

Following the completion of her cardiology residency at Angell and board certification, Dr. Oranges has joined Angell as a full-time staff doctor. Dr. Oranges has particular interests in echocardiography and interventional cardiology; including minimally invasive PDA occlusion, pulmonary balloon valvuloplasty, and permanent transvenous pacemaker implantation.

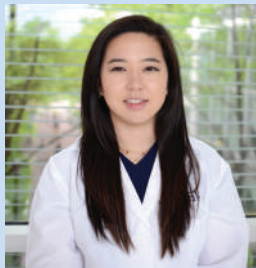


Dr. Terry Huh

**Terry Huh, DVM, DACVIM (Cardiology)**

Dr. Huh studied and trained at Tufts University, Animal Medical Center in NYC, and then the University of Pennsylvania. She has joined Katie Hogan, DVM, DACVIM (Cardiology) and Michelle Oranges, DVM, DACVIM (Cardiology) in Angell's Cardiology service. Dr. Huh has a special interest in interventional procedures and practices at our Boston location.

[angell.org/cardiology](http://angell.org/cardiology)



Dr. Shawna Han

### Dentistry

**Shawna Han, DVM**

We are pleased to welcome Dr. Han to the Angell Dentistry service, where she will join Jessica Riehl, DVM, DAVDC and Joyce Tai, DVM, MS treating patients at our Boston facility.

[angell.org/dentistry](http://angell.org/dentistry)



Dr. Julie Shields

### Urgent Care, Angell West

**Julie Shields, DVM**

Dr. Shields has joined Natasha Pakravan, DVM at Angell West's Urgent Care service in Waltham. She received her veterinary degree from Virginia-Maryland College of Veterinary Medicine and has worked in private practice for 15 years.

Drs. Shields and Pakravan treat animals with conditions that require timely treatment, but are not in need of our Emergency/Critical Care service. Clients can call up to one day in advance to book an appointment. Urgent Care appointments are available 8am–6pm, Monday – Friday.

[angell.org/urgent](http://angell.org/urgent)



Angell Animal Medical Center | 350 S. Huntington Ave, Boston | 617-522-7282  
MSPCA-Angell West | 293 Second Ave, Waltham | 781-902-8400

Angell at Essex | 565 Maple St, Danvers | 978-304-4648

MSPCA-Angell Clinics | Boston, Methuen, Centerville | [angell.org/clinics](http://angell.org/clinics)

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■ We encourage you to contact Angell's specialists with questions.

Main Phone: 617-522-7282 (Boston) | Main Phone: 781-902-8400 (Waltham) | Veterinary Referrals: 617-522-5011  
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\*Boston-based pathologists and radiologists serve both Boston and Waltham locations

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## › Courtesy Shuttle for Patients Needing Further Specialized Care

Angell Animal Medical Center offers the convenience of our MSPCA-Angell West facility in Waltham, MA. The Waltham facility offers Urgent Care and specialized service appointments. If needed, an oxygen-equipped courtesy shuttle can transport animals to Boston for further specialized care and then return them to Waltham. Whether in Boston or in Waltham, our specialists regularly collaborate and plan treatments tailored to our patients' emergency, surgical, and specialty needs.

WE OFFER A BROAD RANGE OF EXPERTISE AND DELIVER THIS CARE WITH THE ONE-ON-ONE COMPASSION THAT OUR CLIENTS AND PATIENTS DESERVE.

We mail one complimentary copy of our newsletter to each of our referring partners. Please circulate this copy within your practice.

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\*Available only in Waltham