



EMERGENCY AND CRITICAL CARE

PAGE 1
Feline Hyperaldosteronism and Hypokalemia

INTERNAL MEDICINE

PAGE 1
Top 10 Endocrine Pearls

OPHTHALMOLOGY

PAGE 8
Approaches to Diagnosing Blindness in Cats

SURGERY

PAGE 11
The Ins and Outs of Chest Tubes

PATHOLOGY

PAGE 14
Color Atlas of Canine & Feline Liver Cytology

INTERNAL MEDICINE

PAGE 19
Treating Hyperlipidemia in Dogs

ANESTHESIA

PAGE 22
Anticholinergics in Dogs and Cats



EMERGENCY AND CRITICAL CARE

Feline Hyperaldosteronism and Hypokalemia

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Feline hyperaldosteronism is likely the most common adrenocortical disease affecting cats. It is rarely identified in dogs, with only a few sporadic case reports testifying its existence in that species. The eponym *Conn's syndrome* is sometimes applied to primary hyperaldosteronism after Jerome Conn, who first identified the issue in humans in 1955.¹ Tumors of the adrenal cortex or adrenal cortical hyperplasia can cause excessive aldosterone secretion. Aldosterone is a hormone that balances sodium and potassium levels. It results in sodium being resorbed in the distal convoluted tubule of the loop of Henle and potassium being

excreted into the urine in the collecting ducts of the distal nephron.

Hyperaldosteronism can be tricky to identify because it is not high on our radar for feline illnesses. It results in a fairly predictable collection of clinical and clinicopathological abnormalities that can strongly suggest hyperaldosteronism as the cause of illness when viewed together.

(CONTINUED ON PAGE 2)



INTERNAL MEDICINE

Top 10 Endocrine Pearls

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There should be no shortcuts when managing patients with chronic health conditions, but the internists at Angell wanted to provide you with a “highlights reel” from the last couple of years. Hopefully, some of these topics pique your interest and provide a jumping-off point to explore deeper.

Special Considerations As You Prepare Your Endocrine Patient for Anesthesia

1. Patients with hyperadrenocorticism: Discontinue veterinary (trilostane) 24 to 48 hours before surgery. Patients need *some* cortisol to help them cope with the stress of hospitalization and surgery. Additionally, these patients often have some degree of hypertension, so our anesthesiologists aim to keep their MAP

(CONTINUED ON PAGE 4)

EMERGENCY AND CRITICAL CARE

Feline Hyperaldosteronism and Hypokalemia

CONTINUED FROM PAGE 1



Profound hypokalemia (<3.0mEq/L) is often the first abnormality identified that triggers suspicion of hyperaldosteronism. Low potassium is seen in 90% of cats with this problem. Interestingly, hypernatremia is not commonly seen since it is usually balanced by water resorbed with excess sodium. Other clin path irregularities include mild azotemia (50% of cases), creatine kinase (CK) elevation (95% of cases), and an elevated aldosterone level seen in about 90% of cases.^{2,3} A serum potassium level of <3.0mEq/L on initial lab work in a patient not taking furosemide is almost always due to either potassium wasting from chronic kidney disease or hyperaldosteronism in our experience.

The clinical or historical signs of hyperaldosteronism are relatively non-specific. These patients generally present with lethargy, weight loss, and historical PU/PD. But if a patient also shows ventral neck flexion due to low potassium or hypertension, which can result in intraocular hemorrhage or retinal detachment - the leap to suspicion of excessive aldosterone secretion is made more easily.

The next diagnostic steps will likely be an abdominal ultrasound and an aldosterone level. But a serum potassium level of <3.0mEq/L often warrants some intervention before those two tests can be accomplished. If the potassium level nears 2.0mEq/L, respiratory muscle weakness and hypoventilation can result.^{5,6} Profoundly weak or azotemic hypokalemic cats should be hospitalized for IV fluid therapy and aggressive IV potassium supplementation. More stable patients can be supplemented with oral potassium gluconate at 2-6mEq/cat BID.^{3,4}

Aldosterone secretion is directly related to the blood potassium level. Aldosterone's primary action is to reduce/excrete potassium. If the blood potassium level is low, then aldosterone secretion should be maximally shut off in the normal patient. Even a hypokalemic patient's aldosterone level

within the normal range would be considered too high and suggestive of aldosterone hypersecretion. If possible, an aldosterone level should be submitted before supplementation with potassium. Either a spun and separated EDTA plasma sample, or a clot tube can be used to evaluate an aldosterone level with a minimal sample requirement of 0.5-1.0ml of plasma or serum. The turnaround time can be up to a week, so prompt submission of this sample is helpful. Consult your lab about specific sample and shipping requirements.

Abdominal ultrasound is the most commonly used imaging modality to identify the source of suspected aldosterone secretion. Single adrenal tumors are the most common finding, often with a small to normal contralateral adrenal gland. Adrenal cortical hyperplasia may manifest itself as bilateral adrenal enlargement. Bilateral adrenal adenomas have even been identified.³ Invasion of the vena cava is uncommon in only about 10% of cases. Caval involvement is more critically evaluated with an abdominal CT scan.²

Cats with concurrent diabetes mellitus or a Cushingoid appearance may also have excessive adrenocortical progesterone secretion. Excessive progesterone has an anti-insulin effect and can be the driving force for the development of diabetes. Progesterone also suppresses the Hypothalamic-Pituitary-Adrenal axis and results in low cortisol secretion. ACTH stimulation tests on these cats may help identify inadequate cortisol secretion. On ultrasound or CT, an atrophic in the inapparent contralateral adrenal gland may suggest adrenocortical insufficiency once the affected adrenal gland is removed. The post-operative management may need to include a tapering dose of steroid and mineralocorticoid to avoid a (mild) Addisonian crisis. Concurrent progesterone secretion/cortisol insufficiency/diabetes mellitus is more commonly seen with adrenocortical carcinomas. Diabetes mellitus can go into remission several months after the affected adrenal gland is removed.⁹ These cats should be rechecked within 1-2 weeks of surgery to assess for biochemical evidence of adrenocortical insufficiency (chemistry panel, +/- ACTH stim test).



Medical treatment should be started once a diagnosis is made or is confidently suspected. The bilateral adrenal disease must be managed medically (no surgical option), and cats with unilateral disease who are contemplating surgical adrenalectomy should be stabilized medically for several weeks before surgery. It can be tough to achieve an adequate potassium level with potassium supplementation alone on an outpatient basis.^{2,3} Spironolactone, an aldosterone antagonist and mild diuretic at 1-2mg/kg BID, should be used in conjunction with potassium supplementation.^{3,4} Although spironolactone has some mild diuretic effect, it is not potent enough to cause the mildly azotemic cat to worsen at home. However, a subcutaneous fluid can easily be added at home to avoid this potential complication. Even when using spironolactone and potassium gluconate together, a normal potassium level is usually difficult to achieve - but *normal* should not be the goal. Try to keep the serum potassium level 3.0-4.0mEq/L, which is usually enough to avoid any complications of hypokalemia. Hypertension (>160mmHg) is best treated with amlodipine at 0.625-1.25mg/cat SID-BID.⁷ If retinal detachment is present, then BID dosing should be considered to control hypertension quickly and maximize the possibility of retinal reattachment.

The prognosis with medical management alone is very good, and survival times can be measured in years.³ Cats on medical management will need to remain on medication lifelong and have occasional BP and renal panel assessment. It is common for azotemia to gradually worsen over months to years due to imperfect control of hypertension and the profibrotic effects of aldosterone, which further damages the kidneys.

Surgical management is often the treatment of choice if a unilateral adrenal mass or enlargement is identified. Left adrenal tumors are easier to access than right-sided masses since the right kidney and adrenal gland are tucked up in the liver's renal fossa, making access challenging. Once the affected adrenal gland is removed, prior hypertension and hypokalemia resolve relatively quickly, and no further medication is needed. The benefit of surgery for a unilateral adrenal disease

EMERGENCY AND CRITICAL CARE

Feline Hyperaldosteronism and Hypokalemia

CONTINUED FROM PAGE 2

is that medications can be stopped, and the gradually detrimental renal effects of excess aldosterone secretion can be avoided. After adrenalectomy, survival times for an adrenal cortical adenoma or an adrenal carcinoma were not significantly different, with a combined median survival time of 1,297 days.² Carcinomas and adenomas are identified with about the same frequency.^{2,3}

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» Emergency & Critical Care Service at Angell West; Urgent Care Available by Appointment

The Emergency and Critical Care service at the MSPCA-Angell West (Waltham, MA) is available 24/7 for clients whose pets need immediate medical care for life-threatening trauma or disease.

Referring veterinarians may alert staff to an incoming case by calling 781-902-8400. Due to expected high case load, there may be times when Angell West diverts cases. Please call to ensure availability.

For more information, please visit angell.org/emergency.

For non-emergent cases, the Urgent Care service at Angell West is available Monday through Thursday for dogs and cats. Exotic mammal Urgent Care appointments are available through the Angell West Avian and Exotics service on some days as well. **Clients can call up to one day in advance to book an Urgent Care appointment; this is not a walk-in service.**

For more information, please visit angell.org/urgentcare.



INTERNAL MEDICINE

Top 10 Endocrine Pearls

CONTINUED FROM PAGE 1

(mean arterial pressures) higher than their normal baselines. These patients may also need more assisted ventilation, especially if they have the classic pendulous abdomen and will be in dorsal recumbency for their procedures.

2. Patients with hypoadrenocorticism: Check when their last dose of mineralocorticoid was given, and try to make sure they aren't at the end of the dosing interval. If they are close, give a dose! Regarding their glucocorticoids, these patients are usually (appropriately) on the lowest physiologic dose of steroid possible, so simply doubling the dose on the day of surgery is often not enough. There's nothing in the literature regarding what dose is appropriate, but our anesthesiologists usually look at what dose they're on and often default to 0.15 mg/kg dex-SP at induction. A telltale sign of an Addisonian crisis under anesthesia is hypotension refractory to traditional interventions (turn down anesthesia, fluid bolus, pressors), and they need more steroids to support them if that is the case.

3. Diabetes mellitus, cat or dog: Yes, please only give ½ dose of insulin in the morning on the day of their planned anesthesia! See how recovery is going in terms of appetite, etc., before making recommendations for post-op insulin. As a rule, our anesthesiologists avoid dexmedetomidine in diabetic dogs and cats because it can further interfere with insulin/glucose ratios. Regarding monitoring, they check a blood glucose (BG) at the time of IV catheter placement and have a cut-off of lower than 350 for anesthesia. Depending on the length of the procedure, recheck BG every 45 to 60 minutes. They occasionally give regular insulin if BG is getting too high, but this is rare. The flip side of this is the RARE situation of supplementing dextrose in the diabetic with low BG when checked. Sadly, literature lacks great evidence-based practices regarding anesthetizing diabetics.

4. Thyroid disease: There has been some recent chatter about prolonged anesthetic recoveries in undiagnosed hypothyroid dogs. Troubleshoot your usual list if you have a patient with a prolonged recovery (reverse what drugs you can, get them moving, address fluid needs, etc.), but in some middle-aged to older dogs without other explanations, consider thyroid testing. Ketamine is

good in hypothyroid dogs, so long as there is no significant concurrent cardiovascular disease, because it provides a boost to their metabolism. Like dogs, screening T4s in cats before anesthesia is a good idea. A thyroid storm/cardiovascular collapse would be the worst complication that could have been prevented in many situations. Otherwise, do your best to have thyroid kitties as well controlled in advance as possible due to the concurrent cardiovascular complications and poor/thin body condition that goes along with hyperthyroidism. Having them as well controlled in advance is ideal, and remember you don't need to wait too long after dose adjustments before checking a T4, so even a little "microregulation" approaching an anesthetic event could work in your favor.

Libre Application and Its Utility for Diabetic Patients

The Freestyle Libre is an invaluable tool to help monitor various diabetic patients, including hospitalized patients with diabetic ketoacidosis, newly diagnosed patients, patients with unstable readings you are trying to stabilize, or periodic monitoring of otherwise stable patients. We recommend that clients purchase a reader rather than use their cell phone for various reasons. If the client wants to track readings on their cell phone, the sensor must be first calibrated with the Libre reader (and then the readings can be uploaded to their cell phone). Unfortunately, you cannot calibrate with a cell phone and then a reader. You may stock sensors and readers at your clinic or provide clients with a prescription to acquire a 14-day reader. In most veterinary patients (60% to 80%), the reader does NOT provide a full 14 days of readings, so try to manage client expectations appropriately and decide as a hospital your protocol for what to do when readers fall off or stop working "early." Lately, we have tried to merely suggest using a Libre as a replacement for a traditional day-long hospitalized BG curve. It's the 14-day label that feels misleading to clients. Tools necessary for application are the Libre sensor/applicator, a reader, clippers, alcohol, a pair of hemostats, tissue glue, and ideally some covering ranging from adhesive covers to a Suitical or ThunderShirt (see Appendix 1 for supplies). Please visit Purdue's website for an easy-to-follow video on application and readings: <https://vet.purdue.edu/vth/small-animal/im-endocrinology.php>

Sensors stay in place for an average of seven days in cats. Resist the temptation to use excessive tissue glue, as adverse skin reactions can and do occur. "SkinTac" wipes may help sensors stick when used before application. "SkinGrip" Freestyle Libre covers or Tegaderm patches may help sensors stay in place. Although the sensor takes readings every minute, the sensor only needs to be scanned by the reader at least once every 8 hours. The reader does

tend to slightly overestimate readings when in the euglycemic or hyperglycemic range and slightly underestimate readings when in the hypoglycemic range. Overall the trends are beneficial when it comes to diabetic management. I suggest using the LibreView site to collect and interpret data from readings. The daily reports are similar to interpreting a traditional BG curve but with an often easier appreciation for the glucose nadir, the duration of the effect of insulin, especially when using long-acting insulin or once-daily insulin administration, and average glucose levels. You are still striving for a glucose nadir of 80 – 150 mg/dL and an average BG of less than 300 mg/dL over 24 hours. Although the reader gives nearly continuous readings, you should still adjust insulin doses only every five to seven days, so if you are lucky, you may be able to get one or two adjustments from one sensor application.

"Rarer" Feline Endocrinopathies

Hyperaldosteronism: We see enough cats at Angell with this condition that it doesn't feel uncommon anymore. If you look for it, you will find it, and it has to be considered in almost every cat with hypokalemia (<3.0mEq/L). Concurrent clin-path abnormalities include mild azotemia and CK elevations. Feline patients with K+ lower than 3.0 mEq/L either have significant renal disease or hyperaldosteronism until proven otherwise (furosemide treatment could cause potassium wasting, but this should be relatively easy to rule out). If the potassium is severely low enough to cause ventral neck flexion or if the patient also has hypertension leading to retinal changes, hyperaldosteronism is also the most likely diagnosis. Cats with K+ serum levels less than 3.0 require treatment. If possible, submit a blood sample for an aldosterone level, then begin IV supplementation if ventral neck flexion or hypoventilation are present. Begin oral supplementation if the patient is stable. Single adrenal tumors are the most likely culprit, and surgical removal may be a worthwhile pursuit. Lifelong treatment is necessary otherwise, and most need more than oral supplementation of K+ (SQF, spironolactone, address hypertension). See



INTERNAL MEDICINE

Top 10 Endocrine Pearls

CONTINUED FROM PAGE 4

Appendix 2 for treatment summary and a helpful article about this condition.

Acromegaly: Acromegaly is the clinical syndrome that develops due to excess growth hormone in cats (hypersomatotropism is most commonly caused by a growth hormone-producing pituitary gland adenoma). These are more often male cats, usually 10 to 11 years old or older, with a normal body condition score (BCS) despite concurrent diabetes mellitus. Often everything is bigger (larger organs on abdominal ultrasound (AUS), larger facial features and interdental space, tongue, ventricles.) Hypersomatotropism is definitely an under-recognized disease in cats. Testing should be considered in patients with difficult-to-regulate diabetes, organomegaly of unknown cause, unexplained weight gain or changes in facial/body features, and neurologic signs. Treatment options for these cats are aggressive insulin treatment for their concurrent diabetes, radiation, hypophysectomy, or pasireotide (Appendix 3; very expensive). Whenever possible, treatment should be considered as many of these cats will do well for a long time!

Hyperadrenocorticism: Hyperadrenocorticism in cats is rare but should be considered in insulin-resistant diabetics or cats with fragile skin syndrome. Other symptoms are similar to those in dogs with Cushing's (PU/PD, symmetric alopecia, infections, and peripheral neuropathy). Low-dose Dexamethasone Suppression (LDDS) is the test of choice, although extreme care must be used if fragile skin syndrome is present (consider urine testing options instead – Appendix 4). A higher dose of dexamethasone (0.1 mg/kg IV) is used than in the dog LDDS. As with dogs, the vast majority of cats with hyperadrenocorticism have the pituitary-dependent form of the disease, while 15% are diagnosed with functional adrenocortical tumors.

Starting Insulin of Choice

Cats: Glargine is our starting insulin of choice in diabetic cats. Glargine combined with a low-carbohydrate diet to minimize prandial increases in blood glucose in cats may result in the highest likelihood of remission. Twice-a-day administration is recommended. The starting dose



for glargine is 0.25 U/kg of ideal body weight if blood glucose concentration is <360 mg/dL or 0.5 U/kg if blood glucose is >360 mg/dL. Lantus Solostar (glargine) 3 mL pens are less expensive options for clients that have allowed us to continue offering glargine as a starting choice despite the recent increase in cost. It is possible to draw insulin out of the top of the pen rather than inject directly with the pen (although some clients like the pens and tiny needles and feel less like they are “giving an injection,” so keep this in mind for fearful owners).

Another option for cats (less \$): Protamine zinc insulin (PZI; ProZinc, Boehringer Ingelheim) is available for use in cats in the US and UK, having been removed from the human market in the 1990s. ProZinc has a concentration of 40 U/mL, and therefore, the use of appropriate insulin syringes must be used. Initial dose recommendations are either 1–3 U/cat (0.22–0.66 units/kg) or 0.25–0.5 units/kg ideal body weight every 12 hours, depending on the severity of clinical signs and hyperglycemia. Study results include a review of 133 diabetic cats treated with PZI (120 newly diagnosed and 13 previously treated with other insulin), showing 85% obtained good control within 45 days, and some cats were able to achieve remission within ~three to four months. (See Appendix 6 for a good 2018 review article on feline diabetes). Maintaining euglycemia as much as possible throughout the day and low-carb diets are some of the more beneficial ways to achieve remission in cats, so we see no reason you could not offer PZI as the first choice. It benefits from being FDA-approved for use in diabetic cats, and many argue that U40 syringes are easier for clients to use.

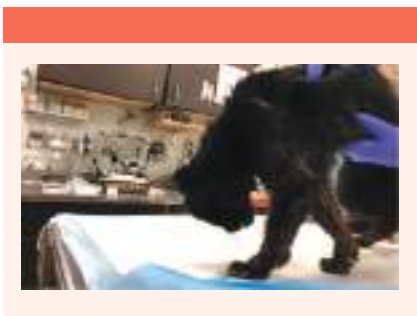
Dogs: Vetsulin vs. Neutral Protamine Hagedorn (NPH). Several Angell clinicians still use NPH to start new diabetic dogs. It has worked well for them historically, and they are most familiar with its use, but it has gotten more expensive. Many start with Vetsulin instead due to its lower cost than NPH and a very user-friendly website we can refer clients (and clinicians!) to familiarize themselves with

diabetes mellitus. Furthermore, Vetsulin, like PZI in cats, uses U40 syringes and is FDA approved for use in dogs, and is also the AAHA Taskforce's recommendation as a starting insulin of choice in dogs. We typically use 0.25 u/kg BID as a starting dose which is comparable to Vetsulin's label recommendation: If twice-daily treatment is initiated, each of the two doses should be 25% less than the once-daily dose of Vetsulin®. Although the Vetsulin label suggests starting dogs at 0.5 u/kg once daily, Angell clinicians typically start twice daily.

Newer Insulins/Formulations

Semglee is a long-acting insulin analog that is the approved biosimilar for insulin glargine (Lantus). It is used to treat human patients with diabetes. Semglee has been proven to be as safe and effective as Lantus and provide the same health outcomes in humans. We expect it will have similar health outcomes in animals, but this has yet to be proven. Anecdotal evidence (very small numbers) suggests it works similarly in cats as our traditional Lantus option for glargine at a lower cost. Studies are in the works in cats. It is available as a pen. Since we have been using Solostar pens successfully in cats, we have had fewer issues with the rising cost of Lantus. See Appendix 8 for a helpful review of the use of pens in veterinary patients.

Toujeo and Tresiba: Insulin glargine 300U/ml (Toujeo®) and insulin degludec (Tresiba®) are synthetic insulin analogs. In people, Toujeo is more predictable and longer-acting compared to glargine 100U/ml (Lantus®); Tresiba is ultra-long acting with a duration of action of over 40 hours that allows a flexible daily schedule of administration. In dogs and cats, very little is known about these formulations. Tresiba has been studied in a small number of healthy cats and seems to have a much shorter duration of action in cats (about 11 hours) compared to people. Toujeo has a longer duration of action in cats (about 16 hours) and a relatively flat time-action profile. Overall, Toujeo seems the best candidate out of the currently available insulin formulation for use as a once-daily injection in both dogs and cats. However, Toujeo is not very



INTERNAL MEDICINE

Top 10 Endocrine Pearls

CONTINUED FROM PAGE 5

potent, and the total daily dose might be high, making it somewhat expensive. For cats, consider 1-2 U/cat once daily to start. For dogs, start with 0.4U/kg once daily (but you might end up much higher than that due to potency issues). I would try PZI in cats before reaching for Toujeo for a number of reasons, even if only once-daily dosing is an option for clients.

What to Feed Diabetic Cats or Dogs?

Cats: I often do not switch cat diets the same visit I start insulin. I worry that this can be too stressful for both the cat and the client. I have had success getting cats off insulin after switching cats to low-carb ($\leq 12\%$ metabolizable energy [ME]) and canned food diets (as supported by literature), so I do think this is a worthwhile venture. You need to use a balanced, low-carbohydrate diet—ideally, one designed for diabetic cats. Canned Purina DM has one of the lowest carbohydrate contents of veterinary diets formulated for diabetes ($<6\%$ ME); highest remission rates are reported using this very low-carb diet and insulin protocols aimed at achieving euglycemia throughout as much of the day as possible. You could try increasing the palatability with gravy or warming or frying if cats aren't initially taking to it. Obesity is the most important acquired risk factor for diabetes, as overweight cats have a 4.6 times greater risk of diabetes than cats in ideal body condition. Longer-term, it is important to coach clients to achieve an ideal body weight for their diabetic cats, but most overweight cats go into remission before substantial weight loss occurs. Weight management is important for maintaining remission in many cats, though. Many low-carbohydrate diets are quite energy-dense, so you need to control the amount being fed. (Encourage clients to invest in a baby scale and give them an exact amount to feed).

Monitor carefully as insulin requirements may decrease as cats convert to low/very low-carb diets. I have also had the experience of cats being hypoglycemic on glargine without apparent clinical signs of hypoglycemia which is both reassuring and disconcerting at the same time. Try the Libre sensor for peace of mind, especially when instituting a diet change or dose adjustment.



Dogs: I am not as picky about what they eat as long as it is consistent and “good food.” If concurrent medical conditions, those nutritional needs dictate those necessitated by their diabetes. Ideally, feed two meals a day, with fewer than 10% of their calories coming through treats the rest of the day, and administer insulin 15 to 60 minutes after eating.

ACTH Stim vs. LDDS

Low-dose dexamethasone suppression tests are the test of choice to diagnose hyperadrenocorticism in dogs at Angell in conjunction with an abdominal ultrasound, although consider cost and patient compliance rather than making this a blanket rule. And honestly, it comes down to what is most practical and appealing for clients and your practice (many prefer a one-hour test!). Choose an adrenocorticotropic hormone (ACTH) stim over LDDS in dogs who will have trouble being at the hospital for the day (i.e., lar par dog, collapsing trachea dog who gets stressed, any super stressed or challenging patient). If cost is a major factor, you may elect an ACTH stim, so you have this test performed before starting a patient on trilostane.

Trilostane Dosing

Starting doses: 1mg/kg BID vs. 2 mg/kg SID. The internists at Angell differ. Some start trilostane at about 1 to 2 mg/kg BID but try to “round down” or go on the lower end of the dose (it all depends on the dog size and what capsule size we have). For the “BID dose preferred” group, they think that given the half-life is so short, BID just makes more sense, and certainly, BID in more serious conditions would be

recommended. All agree that concurrent diabetics try to start BID, for example. The “SID starting dose” group tries 2 mg/kg once daily for six weeks before considering BID dosing.

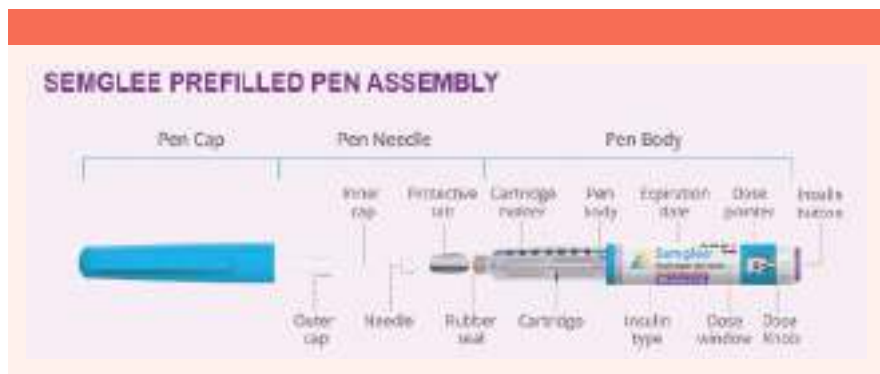
Managing Hyperadrenocorticism

ACTH stim vs. cortisol: For monitoring, many Angell clinicians always start with an ACTH stim, and then if the patient is clinically doing well, it's fine to do a pre-pill cortisol level for further monitoring. Essentially you are making sure this single cortisol level is not too low. If the patients are not doing well, an ACTH stim should be done. Many people still will do ACTH stim for monitoring, but these costs add up for clients, and they truthfully are probably not needed in dogs that are clinically doing well, or at least “not acting Addisonian.” Another common practice for trilostane monitoring is to run serum chemistry and cortisol two to six hours post-trilostane. If this single cortisol comes back <1 , then consider ACTH stim. Universally, everyone's primary focus is on clinical signs, not cortisol values. See Appendix 5 and 6 for two opinions on interpreting “pre-pill” cortisol levels.



Clinical signs: Sadly, few treatments for Cushing's seem really great for controlling proteinuria. Anecdotally, however, these patients don't seem to get progressive renal disease in instances where proteinuria is caused by Cushing's disease. If proteinuria is not “horrible” (in other words, UPC under five or six), some clinicians don't further address the proteinuria. However, if an animal had concurrent hypertension and is still hypertensive after you treat (successfully) for Cushing's, we would definitely recommend treatment for ongoing hypertension.

Clinical sign management is essential, but some ACTH monitoring is still required as a significant percentage of dogs will develop hypoadrenocorticism (estimated cumulative incidence of hypoadrenocorticism in a study of trilostane-treated dogs was 15% by two years and 26% by 4.3 years. Of the dogs that developed hypoadrenocorticism, 74% were transient in nature, and 26% were permanent.) See Appendix 7 for additional clinical sign/clin-path findings when monitoring after starting trilostane.



INTERNAL MEDICINE

Top 10 Endocrine Pearls

CONTINUED FROM PAGE 6

Canine Hypothyroidism

I used to be a big believer in screening only dogs who appeared to have more classic symptoms of hypothyroidism. My justification for screening T4s is that it has a much lower threshold than it used to. I screen all dogs with mild nonregenerative anemia, elevated cholesterol or triglycerides, or mildly elevated ALP/ALT. Whether to add just a TT4 or run a “thyroid panel” (TT4, fT4, TSH) is up to you, ease of running lab tests, and cost to the client. Most hypothyroid dogs have TT4 below your lab’s reference range, but as you know, patients with concurrent illness or exposure to certain medications (glucocorticoids, phenobarb) could have low TT4 and not have true hypothyroidism. NSAIDs do not appear to impact TT4 levels significantly. That being said, a TT4 is an excellent screening test; if the TT4 concentration is well within reference range, it is very likely the dog is euthyroid, and further thyroid testing is not required. A patient with an elevated TSH and low to low normal TT4 and fT4 should be started on levothyroxine. Up to 33% of hypothyroid dogs have normal TSH concentrations, so don’t hold out for an elevated TSH to start treatment.

Although the literature shows evidence that most dogs do well with once-daily supplementation at 0.02 mg/kg PO q24h (0.1 mg levothyroxine per 10 pounds is a general rule of thumb and I round down, especially in larger breeds or obese patients); many Angell clinicians still start twice-daily supplementation. Sometimes I decide based on the very unscientific “how real” I think the diagnosis is. You could also attempt to reduce the dosing to once daily after clinical signs are well controlled. First, rechecks should not be before six weeks. Although steady states are reached sooner than that and TT4 could be checked as early as 10 to 14 days, clinical conditions often do not start to improve for 4 to 6 weeks, so it makes more sense to recheck both clinical conditions and labwork together at the six-plus week mark. For dogs on BID dosing, TT4s can be checked usually four to six hours after pill administration (by three hours post-pill, peak concentrations should be reached). Aim for the high end of your reference range to even a little above. Ideally, for dogs on SID dosing, trough levels are measured (just before the next pill is due). This can be tricky depending on what time of day your client administers medication.

APPENDIX

1. **Libre section supplies:** <https://www.freestyle.abbott/us-en/products/freestyle-libre-app.html>
Data management site (clients can send data to you through this site): <https://www.libreview.com>
<https://skingrip.com/products/free-samples-freestyle> (Libre coverings and skin tac wipes can be purchased here)

Suitical: <https://www.chewy.com/suitical-recovery-suit-cats/dp/140901>

2. **Hyperaldosteronism treatment:** https://www.mspsca.org/angell_services/feline-hyperaldosteronism/

3. **Pasireotide** is a novel multi-receptor ligand somatostatin analog that has been shown to improve biochemical control of human patients with hypersomatotropism. Somatostatins act on the pituitary gland to inhibit growth hormone release. In addition, they can act peripherally by interfering with GH receptor binding on hepatocytes and may induce apoptosis in pituitary adenomas resulting in shrinkage. The drug is given SQ every 12-24 hours or can be administered monthly with a long-acting formulation. The main adverse effects reported are gastrointestinal upset, including soft, voluminous stools and gas-distended intestines. Cost remains a limiting factor in the use of this drug.

4. **The urine cortisol:creatinine ratio (UCCR)** is a useful screening test for HAC in cats as in dogs and should ideally be collected at home on two consecutive days. An alternative ‘at home’ oral dexamethasone suppression test has been suggested in dogs and may be considered in cats, especially with skin fragility syndrome. The owner is instructed to collect two urine samples from the patient on two consecutive mornings and store them in the refrigerator. After collecting the second urine sample, the owner should administer three doses of dexamethasone (0.1 mg/kg/dose) orally at eight-hour intervals. Urine is collected on the morning of the third day, and UCCR is determined on all three samples. The first two urine samples establish the diagnosis of hyperadrenocorticism; both results must be abnormal. If both values are abnormal, then the average of the two values is used as the ‘baseline’ value and compared with the third value obtained after dexamethasone administration. A pituitary-dependent hyperadrenocorticism (PDH) diagnosis is established if the UCCR result from the third urine sample is less than 50% of the ‘baseline’ value. Patients failing to meet these criteria could have either adrenal-dependent hyperadrenocorticism (ADH) or PDH. – Courtesy of Shawn Kearns, DVM, DACVIM

5. <https://www.isvma.org/wp-content/uploads/2019/10/TrilostaneTreatment-MonitoringIsTheACTHStimulationTestGoneForGood.pdf>
Analyzing Pre-pill Cortisol Levels In clinically well dogs in whose clinical signs are well controlled and prepill cortisol levels are as follows:

- <2 µg/dL: An ACTH stimulation test should be performed (or the dose decreased).

- >2 µg/dL: It is likely safe to continue the current dose.

In clinically well dogs with persistent clinical signs of HAC and prepill cortisol levels are as follows:

- <2 µg/dL: History and clinical signs should be re-evaluated, and an ACTH stimulation test should be performed.
- >2 and <5 µg/dL: An ACTH stimulation test can be considered before increasing the dose, or doses being given once daily can be split and given twice daily; increasing the dose can be considered if cortisol levels are >3 µg/dL.
- >5 µg/dL: It is likely safe to increase or split the dose.

6. **Summary article for feline diabetes:** <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6053045/>

7. **Macroadenoma syndrome** develops in dogs with pituitary-dependent HAC when the pituitary tumor begins to grow and applies pressure to surrounding structures in the brain. Neurologic signs associated with macroadenoma syndrome occur in approximately 10% to 30% of dogs with pituitary-dependent HAC, with most cases showing signs after initiation of treatment. The most common signs are behavior changes (e.g., dullness, restlessness, loss of interest in normal activities, disorientation, pacing) and decreased appetite. Initial or mild signs may be dismissed as changes associated with normal aging or as side effects of trilostane. You should keep the progression of pituitary macroadenoma in the back of your mind. Advanced imaging is necessary for antemortem diagnosis of pituitary macroadenoma, and treatment most commonly involves radiation therapy (they can do quite well if clients can afford it and the patient is a good candidate for it). **Electrolytes:** Almost quite predictably, potassium will be elevated +/- slightly low sodium. We see hyperkalemia with enough frequency that it would seem almost odd for it not to be at least slightly elevated. A mild increase is “ok” if the patient is feeling well. Still, with any concurrent signs of illness or concurrent potassium-sparing medications such as potassium-sparing diuretics, ACE inhibitors, and angiotensin-receptor blockers [e.g., telmisartan], you could cause more serious issues.

8. **Helpful/thorough review of the use of insulin pens in veterinary patients:** <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6067590/>



Approaches to Diagnosing Blindness in Cats

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Blindness in cats can stem from a single ocular change, such as a cataract, to a more complicated systemic disease affecting multiple parts of the visual axis. Working through a relatively long list of differentials can be daunting. The primary goal of this article is to provide more familiarity with the diseases and abnormalities affecting the clarity and function of the feline visual axis. With a thorough physical examination, a methodical eye evaluation, and a good history from the client, you can get an excellent idea of what pathological processes are going on and what treatment options, if any, are possible.

Asking the right questions

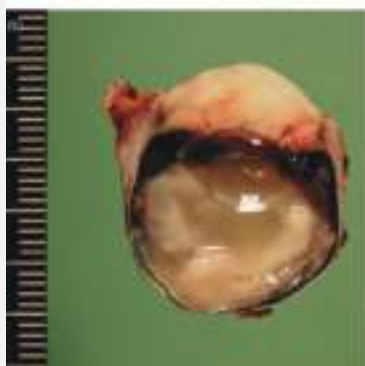
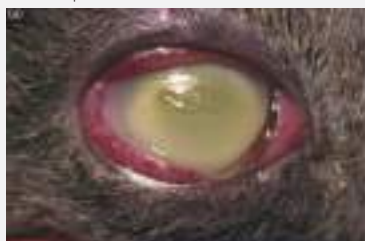
While the physical and ophthalmic examinations are the initial tangible steps in getting to a diagnosis, asking the right questions along the way is just as important to guide you toward localization and treatment. Does signalment alone lead to certain considerations? What specific changes in the eyes does the client notice? Is this

a new problem or an old one? Did it come on suddenly? Does the vision loss come and go? Is it a one-time change, or is it evolving? What other medical or surgical conditions has the pet encountered recently? Any episodes of pain? Is the pet taking medication? These questions may not be specific for blindness, but they will generate your plan forward. We will entertain these essential questions for each rule out we consider in this overview.

Having the right diagnostic tools

It is good to briefly review the tools and tests that will help diagnose the basic workup. For blindness, particularly, tonometry, direct or indirect ophthalmoscopy, and a diffuse, bright illumination source such as a Finoff transilluminator (below) will provide the essential tools for an eye examination. Testing the visual reflex pathways is usually where most evaluations will start. The menace reflex, dazzle response, and pupillary light reflexes are integral to any eye examination, especially with reported vision loss. Ancillary ophthalmic testing, such as fluorescein staining and Schirmer tear testing, is less critical in the workup for blindness unless the cornea is involved. If the visual axis cannot be fully visualized, then ocular ultrasound may help characterize the ocular structures. When tissue changes are destructive or proliferative and do not respond to symptomatic treatment, cytology, bacterial culture, and even histopathology can be

▷ Endophthalmitis



▷ Finoff transilluminator



▷ Neonatal ophthalmia



helpful if the tissue in question is readily accessible. When the lesions are deep or inaccessible and infectious disease is suspected, serology can assist, especially in posterior segment disease. Ocular toxoplasmosis and fungal diseases are often diagnosed with serology, among other systemic infections.

Ocular surface causes

Infections on the ocular surface can trigger significant eyelid and ocular surface changes at a young age, including eyelid fusion and conjunctival proliferation over the cornea, excessive corneal neovascularization, scarring, and at worst, deep corneal ulceration and perforation. Neonatal ophthalmia (above), ocular herpes keratitis, and conjunctivitis are the leading causes of changes like these. Ocular herpes can happen at any age, with more severe, cyclic, or relentless cases of inflammation taking a toll on the corneal clarity and comfort. In cats, chronic ulceration (from ocular herpes or other causes) can also lead to corneal necrosis or sequestrum formation, where brown plaques develop in the ulcer bed of nonhealing ulceration. Brachycephalic cats are overrepresented. If untreated, these affected corneas can become obscured entirely with or without a neovascularization response. In severe or known

OPHTHALMOLOGY

Approaches to Diagnosing Blindness in Cats

CONTINUED FROM PAGE 8

▷ Anterior Segment - Cataract



progressive cases, surgical excision via lamellar keratectomy can restore some vision. Eosinophilic keratitis is another manifestation of chronic corneal and conjunctival inflammation unique to cats and, if untreated, can spread over the entire cornea, causing vision loss. Immunomodulatory therapy can be implemented topically to control the inflammation, but treatment is often long-term, if not life-long, to prevent relapses. Extensive corneal trauma, nonulcerative chronic keratitis (idiopathic), and diffuse corneal edema-attributed conditions ranging from acute bullous keratopathy or congenital mucopolysaccharidosis can lead to permanent vision loss. However, cats can recover vision from acute bullous keratopathy with supportive and specific treatment, including ophthalmic hypertonic saline preparations, third eyelid flaps, or conjunctival grafting (Gunderson type).

Anterior segment causes

Cataract and glaucoma are the leading anterior segment causes of blindness in cats. Feline cataracts can be primary or hereditary, but a more common cause is cataract progression related to chronic uveitis. Because most cataract cases in cats are intrinsically linked to chronic uveitis and the real potential for secondary glaucoma, cataract surgery is far less often done in cats than in dogs. The causes of uveitis are linked to idiopathic causes despite the usual workup of the identifiable differentials, including toxoplasmosis, fungal disease, lymphoma, and trauma. Uveitis per se does not cause vision loss unless a substantial amount of hyphema, hypopyon, or fibrin fills the anterior chamber, replacing the clear aqueous humor. Symptomatic medical treatment for the inflammation or identifying and addressing the nature of the bleeding quickly and aggressively is the best way to tackle loss of anterior chamber clarity—ocular sepsis with bacteria due to trauma or a penetrating foreign body.

Other changes in the anterior segment that can cause blindness are expansive tumors within the eye, including neoplasia (adenomas, sarcomas, or nodular melanomas), lens luxation, and miosis in conjunction with scarring/adhesions. These conditions in advanced stages can obliterate the visual axis or trigger other secondary problems in vision, including retinal detachment, glaucoma, or corneal edema.

Posterior segment causes

The most common presentation in our practice for sudden blindness in cats is hypertensive retinopathy (below). The retinas will detach and often bleed due to undiagnosed high blood

pressure. Varying degrees of hyphema may also be seen if there is a tear to a retinal blood vessel as part of the presentation. These patients tend to be older and have coexisting heart or kidney disease. Managing systemic blood pressure is the best course of treatment for these patients and addressing any other associated systemic conditions.

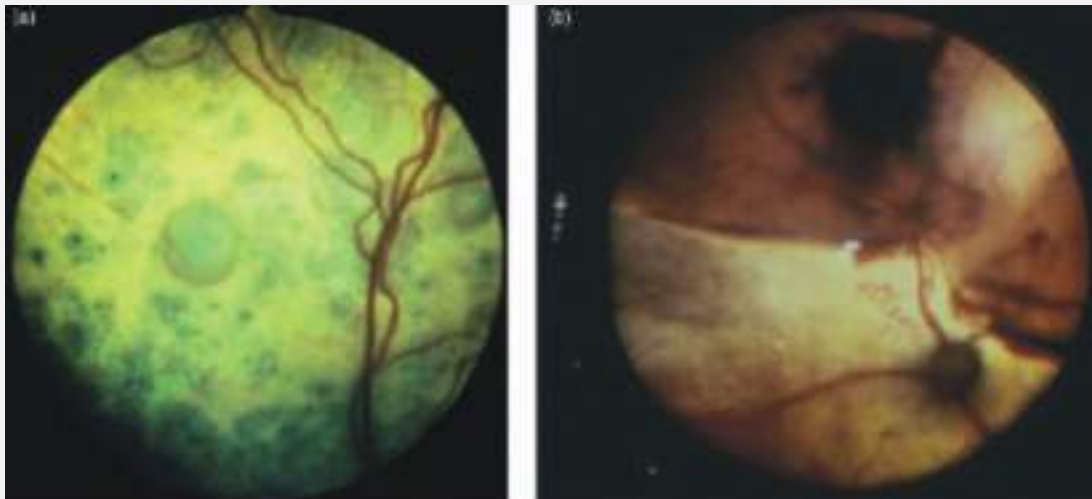
The second most common posterior segment cause of blindness we see is diffuse retinal degeneration, which can result from chronic glaucoma, hereditary rod-cone photoreceptor disease, or in some cats, associated with a toxic effect of systemic enrofloxacin. There is no treatment for retinal degeneration in these cases. Other less severe forms of retinal degeneration typically do not cause complete blindness (e.g., taurine deficiency retinopathy). Even with extensive retinal degeneration, pupillary light reflexes in cats often remain intact, a unique feature of feline retinal degeneration.

Finally, infiltrative retinopathies may include infectious diseases such as toxoplasmosis, cryptococcosis, and tick-borne disease. Ocular changes resulting in retinal detachments, cellular granulomatous intraretinal plaques, and sub- intra- or pre-retinal hemorrhage can obscure the visual axis and render permanent changes if not caught early or progresses to affect the entire retinal surface.

Extraocular and miscellaneous causes

Proper orientation and movement of the globe are essential for normal vision. Vision may be affected when there is severe globe deviation (strabismus) or erratic movement (nystagmus). Thankfully most types of strabismus and nystagmus found in cats are not severe enough to cause blindness, as the

▷ Hypertensive retinopathy



OPHTHALMOLOGY

Approaches to Diagnosing Blindness in Cats

CONTINUED FROM PAGE 9

brain can compensate for the most common ranges of these disorders. Certain acquired conditions affecting globe position in cats include feline restrictive orbital myofibroblastic sarcoma (right), or FROMS (also known as feline orbital pseudotumor), or traumatic orbital fibrosis from previous orbital infection, trauma, or inflammation, which can render a globe blind simply from causing severe malorientation of the visual axis. CNS and optic nerve diseases can cause blindness without disturbing the ocular visual axis. Atrophy or hypoplasia of the nerve may develop in cats due to congenital malformation, trauma, certain infections (panleukopenia in kittens), or other ocular changes, including glaucoma, low blood pressure within the eye, retinal degeneration, or inflammation. Most of these changes are irreversible, but there may be no clues to this condition in some cats with unilateral changes other than a single dilated pupil. Optic neuritis in cats is the more common optic nerve cause of blindness and can sometimes be detected with a combination of visual reflex testing, direct or indirect fundoscopy, orbital imaging, and analysis of the CSF serology cytology and culture. Blood serology may also be helpful in screening for systemic involvement. As with retinal disease, cats may get optic neuritis from infection (toxoplasmosis, cryptococcosis, neospora), cancer (e.g., lymphoma), or autoimmune disease.

Every once in a while, you may get a cat with a clear visual axis, normal globe orientation, and no CNS disease (normal visual reflexes) but still acts blind. Sciascopy or retinoscopy could be done to evaluate for abnormal visual refraction and is typically found in pediatrics, veterinary university settings, or some veterinary ophthalmology practices. You may consider visual focusing problems (ametropia) or behavior issues as differentials for these patients. Corrective lenses are not available for cats (or dogs), but at least you have something to discuss with your client as a possible explanation for the poor vision when nothing else pans out.

Summary

Cats share some causes of blindness in dogs, but certain conditions affect cats specifically and more frequently, including blindness from feline herpes keratitis, corneal sequestrum, hypertensive retinopathy, baytril toxicity, post-traumatic intraocular sarcoma, and FROMS. Diagnosing blindness in cats requires a good understanding of the components of the visual axis and the eye reflexes that govern it. Having the proper tools and access to the right tests are essential to localize the lesions present and formulate a plan and expectations for your clients.

› Feline restrictive orbital myofibroblastic sarcoma (FROMS)





The Ins and Outs of Chest Tubes

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Thoracostomy tubes or chest tubes are an important part of post-operative care following thoracic surgery. Chest tubes can be placed either pre-operatively or during surgery. Patients that have a pneumothorax or pleural effusion should have a chest tube placed prior to surgery to help with pre-operative imaging and stability for anesthesia. In all other patients, placement during surgery is safer and easier. A chest tube must be placed in any patient undergoing thoracic surgery or any abdominal surgery where the diaphragm is compromised, such as a diaphragmatic hernia. The chest tube is used for evacuation of residual fluid or air in the chest as a result of surgery and to reestablish negative pressure, allowing the lungs to expand. The chest tube is also used to drain any continued fluid or air associated with the thoracic pathology such as chyle in patients with chylothorax. Chest tubes can be used to monitor for any post-operative hemorrhage or air leakage from the surgical site as well and can be used in post-operative pain control.

There are several types of chest tubes available to veterinarians. The most common type is the Argyle™ thoracostomy tube (see Figure 2). Argyle tubes are made of polyvinyl chloride (PVC) and come with a large sharp trocar for introducing the tube into the thorax. A second type of trocar tube

› Figure 2: Argyle™ thoracostomy chest tube <https://www.cardinalhealth.com>



is the Axiom® which is made out of silicone. Silicone is softer than PVC and therefore is thought to be more comfortable. Because Axiom trocar tubes are softer, they may be more prone to collapse when aspirating the tube. Trocar tubes are typically placed with the tube tunneled under the skin for two to three intercostal spaces before entering the chest. Alternatively, forceps can be used to guide the tube into the chest cavity rather than using the trocar. This is not recommended routinely as a study by Yoon et al. showed that trocar-implemented thoracostomy tube placement resulted in less air leakage when compared to the forceps technique. All Argyle and Axiom tubes have a radiopaque line that makes them visible on radiographs. Additional fenestrations can be

added to the tubes with scissors as long as the openings that are created do not exceed 1/3 the diameter of the tube as this can result in part of the tube breaking off in the chest at removal of the chest tube.

Trocar tubes are available in a wide variety of sizes, from 8 French to 32 French. Traditionally the recommendation was to use the largest bore tube that would fit in a patient to reduce the risk of clogging. A tube the same diameter as the main stem bronchus on radiographs was recommended. This recommendation has not been supported in the human literature as occlusion and complication rates between large and small bore tubes was found to be similar. Because large bore tubes have been shown to be more painful than small bore tubes, the recommendation is to choose the tube size based on need for a particular surgical condition rather than the size of the patient.

› Figure 1: A chest tube must be placed in any patient undergoing thoracic surgery or any abdominal surgery where the diaphragm is compromised.



Another popular chest tube option is the MILA™ Guidewire Inserted Chest Tube. MILA tubes are made of polyurethane and have multiple fenestrations along the tube. They are small bore, only 12 or 14 gauge. A new 12 French version has been introduced but that is still considered small for a large dog. Because of the size, use in conditions that have very thick exudate or large amounts of fibrin should be avoided. MILA tubes are placed using the Seldinger technique where an 18 gauge over-the-needle catheter is introduced into the chest and guidewire is placed into the chest through the catheter and the catheter is then removed. A dilator may be used to increase the size of the opening. The thoracostomy tube is then advanced into the chest over the guidewire and the guidewire is removed. The MILA tubes are not

SURGERY

The Ins and Outs of Chest Tubes

CONTINUED FROM PAGE 11

tunneled under the skin because of their small size but we have occasionally run in to problems with air leakage with these tubes. One advantage of MILA tubes is that they can be placed in mildly sedated animals because of their small size.

Radiographs should be taken post chest tube placement to confirm position within the chest. The tube should run along the sternum but not extend into the cranial mediastinum where the fenestrations can be occluded by tissue. All fenestrations should be within the thorax and there should be no kinks in the tube.

Once a chest tube is in place, intermittent aspiration is recommended. I will usually start with aspiration every hour for the first two hours followed by every four hours after that. If large amounts of air or fluid are being removed, I would continue with hourly aspiration until the amount decreases. If the volume is excessive or if negative pressure is not obtained, continuous suction should be used as in the case of patients with damaged lungs. Additional surgery may be necessary if a leaking staple line or bleeding is suspected. All chest tubes should have a one-way valve or an adapter with a clamp and a three-way stopcock securely attached to avoid an iatrogenic pneumothorax and to make aspiration easier. Sterile technique should be used while aspirating the chest tube and no more than 3 to 5ml of negative pressure should be applied with a syringe to avoid damaging the pleura and pulling tissue into the fenestrations in the tube.

Chest tubes may also be used to help with pain control as they can be used to introduce bupivacaine into the thoracic cavity. Conzemius et al. showed that slow infusion of 1.5mg/kg of bupivacaine into the chest tube while the patient is positioned with the incision side down, resulted in significantly lower pain scores when compared to intravenous buprenorphine.

Chest tube removal should be considered when there is little production over a 12 hour period. What defines normal production from a chest tube is debatable. The general rule is often 1-2ml/kg/day. Marques et al. reported removal of chest tubes at a mean production of 3ml/kg/day in dogs and 5ml/kg/day in cats. A recent study by Hung et al. looked at fluid production from chest tubes in normal dogs. A minimal amount of fluid was produced with the mean production at 0.48 mL/kg. A majority of dogs in that study developed a pyothorax between day 4 and 6 and the authors concluded that chest tubes should be removed by day 4 in most dogs. Removal should be based on numerous factors including patient status, disease process, fluid cytology and culture and radiographs to assess residual fluid and air.

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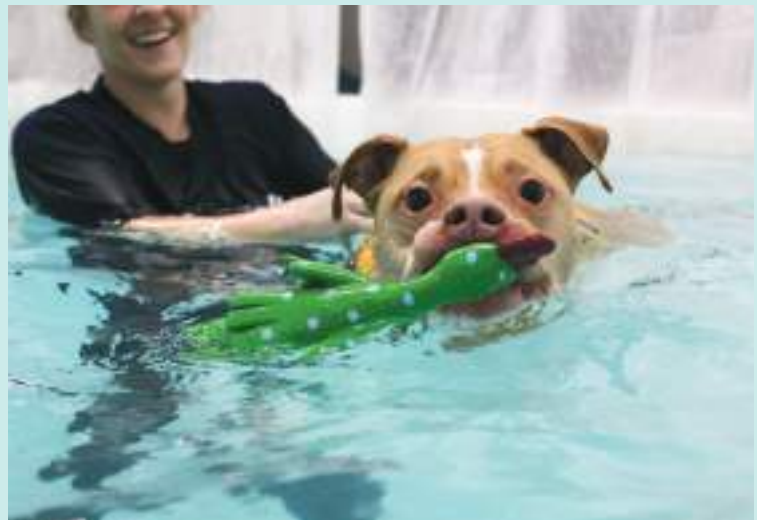
mspca  **angell west**



Land-based Exercise Area



Hydrotherapy – AquaPaws Water Treadmills



Hydrotherapy – Indoor Pool



Color Atlas of Canine & Feline Liver Cytology

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Introduction

Image-guided, fine-needle aspiration (FNA) cytology of the liver can be a rewarding, practical, and economical diagnostic tool for diagnosing certain liver disorders. Moderate to highly cellular aspirates are readily obtained in many cases. Judicious use of this diagnostic tool is warranted because results can be incomplete or inaccurate in some instances. This article will review indications, limitations, contraindications, and common cytologic findings of selected common liver disorders using FNA liver cytology.

Indications

Indications for performing liver cytology or incisional biopsy include persistently abnormal liver parameters, hepatomegaly, and abnormal echogenicity or masses noted on abdominal ultrasound (AUS). Liver cytology is often useful for the initial evaluation of hepatomegaly or mass lesions but frequently requires incisional biopsy/histopathology for a definitive diagnosis. Liver conditions that may be diagnosed via liver cytology include certain types of neoplasia (examples: hematopoietic neoplasia such as lymphoma, mast cell tumor, sarcoma, and metastatic neoplasia), inflammation and infectious disease, hepatic lipidosis, and non-lipid hepatocellular vacuolar changes.

Limitations

Liver cytology does not allow for architectural assessment required for the diagnosis of certain liver abnormalities such as ductal plate malformation and circulatory disorders (e.g., portal vein hypoperfusion/microvascular dysplasia and congenital portosystemic shunts). Liver cytology may miss disease that is patchy, focal, or multifocal in distribution, such as inflammation or hepatocellular degeneration/necrosis. The zone of liver affected by inflammation, copper accumulation, or degeneration/necrosis cannot be determined cytologically. Likewise, diagnosis of hepatic fibrosis, lobular atrophy, or parenchymal collapse requires histopathologic assessment. Subtle features of canine chronic hepatitis are routinely missed by cytologic evaluation.

Correlating cytology results with biochemical findings may help overcome some of the limitations of liver cytology and better characterize liver disease. For example, finding increased serum bilirubin and serum alkaline phosphatase (ALP) that is markedly higher than serum alanine aminotransferase (ALT) with increased numbers of inflammatory cells in the liver aspirate is supportive of cholangitis/cholangiohepatitis.

Cytologic evaluation cannot differentiate nodules or masses composed of hepatocytes, including nodular hyperplasia, regenerative nodules, hepatocellular adenoma, and well-differentiated hepatocellular carcinoma. Cystic lesions of the liver generally require histopathology for diagnosis, given low cell yield or non-specific findings on cytology.

Contraindications

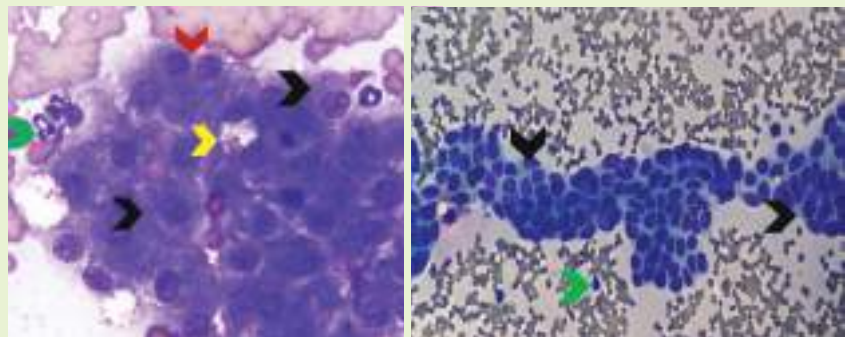
Primary contraindications of liver FNA include abnormal hemostasis and risk for clinically significant hemorrhage. A platelet count, assessment of platelet function (if warranted), and standard coagulation profile (aPTT and PT) are recommended precautionary tests. Inquiring about recent bleeding episodes, nonsteroidal anti-inflammatory drug (NSAID) use, and anti-coagulant drug use is prudent. A cavitary mass or lesion (such as suspicion of a vascular tumor,

septic abscess, or risk of rupture) is a relative contraindication for liver FNA.

Normal Liver

FNA of liver typically produces a moderately cellular smear. Hepatocytes, frequently in clusters, represent the majority of nucleated cells obtained. Hepatocytes are 4-5 times the diameter of an RBC, polygonal in shape, and have distinct cell margins. Nuclei are round, centrally located, and have a single prominent nucleolus. Hepatocytes have abundant lightly basophilic cytoplasm with fine pink to blue granularity (see Figure 1). Occasional canine hepatocyte nuclei have rectangular inclusions, which are incidental findings of no known diagnostic significance (see Figure 2). A low proportion of hepatocytes may be binucleated and have enlarged nuclei or cytoplasmic vacuolation. Small to moderate amounts of finely to coarsely granular green cytoplasmic pigment can be observed in normal hepatocytes (see Figure 2). Other cell types found in low numbers include endothelial or stromal cells, differentiating hematopoietic precursors and bile duct epithelium. Bile duct epithelium occurs in cohesive aggregates. The cells are of uniform size, noticeably smaller than hepatocytes, and have a small amount of pale basophilic cytoplasm and a round, regular nucleus (see Figure 1).

▶ **Figure 1. Aspirates from a normal canine (left) and feline (right) liver.** **Left panel:** The majority of nucleated cells are large polygonal epithelial cells (hepatocytes) in clusters that have finely granular basophilic cytoplasm (black arrows). The green arrow identifies a neutrophil for size comparison. An occasional binucleated hepatocyte (red arrow) is a normal finding. The yellow arrow identifies amorphous pink material consistent with ultrasound transmission gel, a common contaminant in liver aspirates (Diff-Quik, 750x magnification). **Right panel:** Note flat sheets of uniform small polygonal to cuboidal epithelial cells arranged in tubular structures that are consistent with bile duct epithelium (black arrows). They are smaller than hepatocytes and have scant pale blue cytoplasm, a small round to oval nucleus, and dense, granular to homogeneous chromatin. The green arrow identifies a neutrophil for size comparison. (Diff-Quik, 500x magnification)



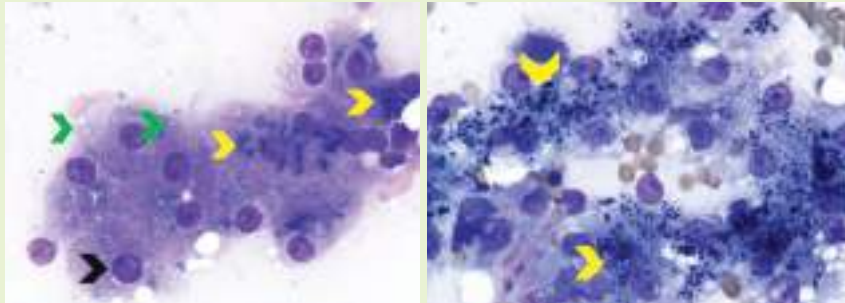
Pigments

Different types of pigment are commonly found in both normal and abnormal liver aspirates. Because most of the pigment is within the cytoplasm of hepatocytes and green in color in Wright-Giemsa- or Diff-Quik-stained cytologic specimens, special stains are usually required to definitively differentiate the various types. The most common pigment found in the cytoplasm of normal hepatocytes is lipofuscin, a “wear and tear” pigment associated with accumulated indigestible material within lysosomes. Large amounts of granular dark green pigment may be observed in hepatocytes of older dogs and cats (see Figure 2). Accumulation of lipofuscin is considered part of the normal aging process and is not representative of disease. A modified Ziehl-Neelsen stain is used to confirm the presence of lipofuscin pigment. Bile accumulation in hepatocytes appears as variably-sized yellow to olive green or dark green to black pigment. Abundant amounts, especially when present as bile-filled canalicular plugs, are suggestive of cholestasis and may precede clinical icterus or hyperbilirubinemia. The plugs appear as distinctive intact and fragmented tubular accumulations of dark green, yellow, or olive green pigment in cytologic specimens (see Figure 3). A Hall’s bile stain may be useful for confirming the presence of bile (bilirubin). The cause of cholestasis, such as hepatic lipidosis or a neoplastic cell infiltrate, may be observed in cytologic specimens, although in many cases, the cause is not identified. Copper may be visible in liver aspirates stained with Diff-Quik or Wright-Giemsa as coarse, granular, pale blue, and refractile pigment in hepatocytes when present in large amounts, although confirmation requires a special stain, such as rubeanic acid. Excess amounts of copper may cause hepatocyte injury or necrosis with inflammation. Copper accumulation can be a primary disorder, such as the familial condition in Bedlington Terriers, or a secondary finding in chronic hepatitis and other liver disorders. Hemosiderin appears as a granular golden-brown to blue-back pigment in the cytoplasm of hepatocytes stained with Diff-Quik- or Wright-Giemsa-stained cytologic specimens. Confirmation requires a special stain, Prussian blue. Hemosiderin is an iron-containing pigment that accumulates in hepatocytes during disease states such as hemolytic anemia and chronic inflammation, as well as in patients that have received repeated blood transfusions or iron injections.

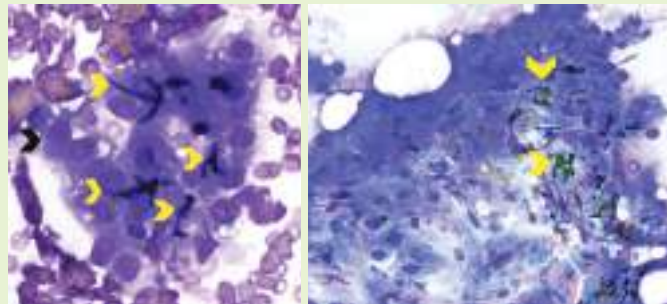
Hepatocellular Vacuolar Changes

The two most common types of hepatocellular vacuolar change, lipid and non-lipid, are shown in comparison to normal hepatocytes in Figure 4. Lipid vacuolar change in hepatocytes represents

› **Figure 2. Aspirates from a canine (left) and feline (right) liver. Left panel:** Note granular dark green pigment in hepatocytes (yellow arrows) consistent with lipofuscin (normal “wear and tear” pigment). The black arrow identifies an intranuclear rectangular inclusion, an incidental finding of no known clinical significance in the canine liver. Smaller amounts of pale blue, slightly refractile pigment (green arrows) found in hepatocytes were determined to be copper based on staining with rubeanic acid. (Diff-Quik, 1000x magnification) **Right panel:** Yellow arrows identify abundant granular dark green pigment consistent with lipofuscin in hepatocyte cytoplasm of a clinically normal aged cat. (Wright-Giemsa, 1000x magnification).



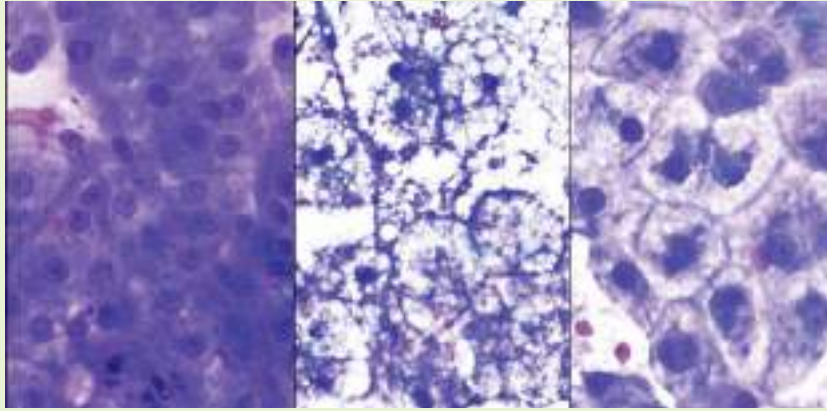
› **Figure 3. Aspirates from the canine liver with cholestasis. Left panel:** Note cluster of hepatocytes (black arrow) with interspersed dark green to black, bile-filled canalicular plugs (yellow arrows). (Wright-Giemsa, 1000x magnification) **Right panel:** Yellow arrows identify several bile-filled canalicular plugs, yellow to olive-green in color, associated with a thick cluster of hepatocytes. (Diff-Quik, 500x magnification).



› **Table 1. Hepatocellular Vacuolar Change and Associated Conditions**

Vacuolar Type	Associated Conditions
Lipid	Idiopathic feline hepatic lipidosis Secondary feline lipidosis (anorexia, pancreatitis, gastroenteritis, hepatitis, neoplasia) Certain drug toxicities (example: canine aflatoxicosis) Lysosomal Storage Disease Juvenile hypoglycemia Diabetes mellitus
Non-lipid (glycogen or water)	Corticosteroid administration Endogenous corticosteroid excess (hyperadrenocorticism) Breed-specific progressive vacuolar hepatopathy (Scottish Terrier) Hyperaldosteronism Progesterin excess Diabetes mellitus Insulinoma Hyperglucagonemia Metabolic disorders Copper chelation therapy Hepatotoxic insults Foci of nodular hyperplasia or regenerative hyperplasia Hepatocellular adenomas and carcinomas

Figure 4. The panel shows normal hepatocytes (left), lipid-laden hepatocytes from a cat with hepatic lipidosis (middle), and cell swelling with indistinct vacuolation or rarefied cytoplasm in a dog with steroid hepatopathy (right). (Diff-Quik stain, 1000x magnification.)



accumulation of triglycerides. The discrete clear (non-staining) vacuoles may be of variable size (very small to large). Lipid content can be confirmed with special stains including Sudan Black and Oil Red O. The most common clinical condition with marked hepatocellular lipid vacuolation is feline hepatic lipidosis, which may be primary (idiopathic) or secondary to underlying diseases such as pancreatitis, gastroenteritis, non-infectious or infectious cholangiohepatitis (see Figure 6) and neoplasia. Obese cats are predisposed to developing hepatic lipidosis. The patient history often includes a period of anorexia. Other possible causes of hepatocellular lipid vacuolation are shown in Table 1. Non-lipid vacuolar change typically results from the accumulation of glycogen or water in the cytoplasm and appears as rarefaction or pale, feathery, to indistinctly vacuolated cytoplasm. It is the most common type of hepatocellular vacuolation in the canine liver. Glycogen content can be confirmed with a special periodic acid-Schiff (PAS) stain. One of the most common types of glycogen accumulation is induced by exogenous or excessive endogenous corticosteroids (including hyperadrenocorticism), referred to as steroid hepatopathy. Marked elevation in serum ALP and the finding of non-lipid hepatocellular vacuolar change support steroid hepatopathy. Other possible causes of non-lipid vacuolar change are shown in Table 1. Hepatocytes can exhibit a combination of lipid and non-lipid vacuolar change (see Figure 7).

Hepatic Inflammation

Evaluation of hepatic inflammation via cytology is typically incomplete because of the inability to assess inflammation relative to lobular architecture and because foci of inflammation may be missed in fine needle aspirates. Additionally, inflammation may be incorrectly diagnosed due to blood contamination with peripheral neutrophilia or

lymphocytosis, creating the illusion of inflammation. Inflammation may be primary, reactive, clinically insignificant, multisystemic, or secondary to inflammation at other locations such as the pancreas, gallbladder, or gastrointestinal tract. Inflammation can be characterized as

neutrophilic, lymphocytic, eosinophilic, mixed cell, or granulomatous/pyogranulomatous. Finding inflammation in liver aspirates should always prompt a search for infectious agents (bacteria-see Figure 5, fungal or protozoa-see Figure 6). Finding pyogranulomatous or mixed cell inflammation in a feline liver aspirate may also prompt consideration of feline infectious peritonitis. Neutrophilic inflammation is suggested in aspirates with a high concentration of segmented neutrophils relative to the amount of peripheral blood contamination present or when clusters of neutrophils are associated with aggregates of hepatocytes (see Figure 5). A diligent search for bacteria is warranted, but they are infrequently found. A culture of bile may be worthwhile to evaluate for a bacterial cause when cholangiohepatitis is suspected. Lymphocytic-predominant hepatic inflammation is more commonly found in cats than in dogs. Older healthy cats can have mild lymphocytic or lymphoplasmacytic inflammation restricted to portal tracts without clinical significance. Moderate to marked numbers of lymphocytes found in feline liver aspirates may suggest lymphocytic cholangitis/cholangiohepatitis. Differentiation of lymphocytic

Figure 5. Aspirates of septic neutrophilic hepatitis in a dog. Left: Low magnification view showing a marked increase in neutrophils (green arrows) relative to the amount of peripheral blood contamination present and clusters of neutrophils associated with degenerate hepatocytes (yellow arrows). (Diff-Quik, 200x magnification) Right: Higher magnification view showing degenerate neutrophils containing phagocytized bacterial rods (yellow arrows) and extracellular bacterial rods. (Diff-Quik, 1000x magnification)

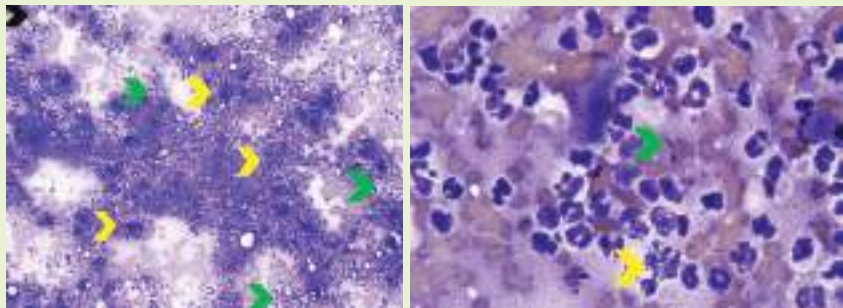
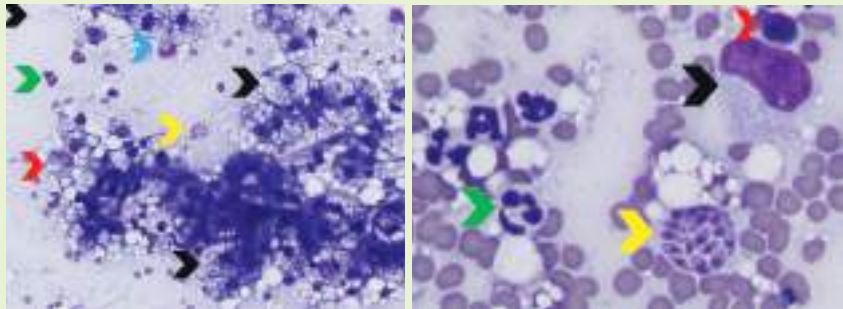
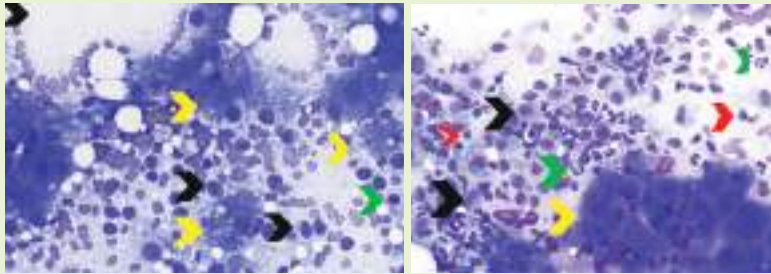


Figure 6. Aspirates of feline protozoal hepatitis and concurrent hepatic lipidosis. Left: Note mixed inflammation (neutrophils-green arrow, macrophages-red arrow), myeloid (neutrophilic) precursor shown by the blue arrow [extramedullary hematopoiesis], lipid-laden hepatocytes (black arrows), and a cluster of *Toxoplasma gondii* tachyzoites (yellow arrow). (Diff-Quik, 500x magnification) Right: Higher magnification view showing a cluster of *Toxoplasma gondii* tachyzoites (yellow arrow), neutrophils (green arrow), a lymphocyte (red arrow), and a macrophage (black arrow). (Diff-Quik, 1000x magnification)



► **Figure 7. Aspirates of feline hepatic lymphocytic infiltrate and canine chronic hepatitis. Left:** Note the increased number of lymphocytes relative to the amount of peripheral blood contamination present. Lymphocytes are small (green arrow) to intermediate (black arrows) in size. Cytologic differentiation of feline lymphocytic hepatitis/cholangiohepatitis and small- to intermediate-cell lymphoma is often not possible, as in this case. Hepatocytes exhibit both lipid and non-lipid vacuolar change (yellow arrows). (Diff-Quik, 500x magnification) **Right:** Note the cluster of hepatocytes (yellow arrow) adjacent to a large number of inflammatory cells that include neutrophils (green arrows), lymphocytes (red arrows), and macrophages (black arrows). A presumptive diagnosis of canine chronic hepatitis was made based on histopathology. (Diff-Quik, 500x magnification)



cholangitis/cholangiohepatitis and small- to intermediate-cell lymphoma can be nearly impossible based on cytology alone. Integration of all clinicopathologic findings, histopathology, and immunophenotyping +/- PARR (PCR for antigen receptor rearrangement) assay may help differentiate these two causes of hepatic lymphocytic infiltrates. Given the limitations of liver cytology, canine chronic hepatitis requires histopathology for diagnosis. A wide range of inflammatory cell types (neutrophils, lymphocytes, plasma cells, macrophages, and eosinophils) can be found in aspirates of canine chronic hepatitis. In some cases, inflammation is not detected due to patchy distribution, low numbers of inflammatory cells, or fibrosis that leads to low cell yield.

Extramedullary Hematopoiesis (EMH)

The adult feline and canine liver retains the ability to produce hematopoietic precursor cells. EMH is typically a non-specific finding in liver aspirates. The canine liver commonly develops EMH (especially granulopoiesis) in response to chronic hepatic disease due to a wide variety of causes. Late stages of erythroid precursors +/- granulocytic (see Figure 6) and megakaryocytic precursors are commonly found in liver aspirates from anemic patients, especially when hemolysis or hemorrhage is the cause of the anemia. Hematopoietic precursors are also found with mature adipocytes in aspirates of myelolipomas.

Neoplasia and Hepatic Masses

Hepatocellular Masses

Masses composed of hepatocytes are commonly observed in the liver of middle-aged and older dogs and less commonly in older cats. Cytologic appearance of nodular hyperplasia, regenerative nodules, hepatocellular adenoma, and well-differentiated overlap; thus, histopathology is typically required for differentiation. Aspirates

may be composed of normal-appearing hepatocytes or hepatocytes exhibiting variable cytologic atypia. Some hepatocellular carcinomas exhibit sufficient cytologic atypia to warrant a presumptive diagnosis of carcinoma (see Figure 8).

Bile Duct-Associated Masses

Masses or cysts of bile duct origin occur more commonly in cats than dogs. Cholangiocellular carcinoma (CCC) is the most common primary hepatic neoplasm in cats. Feline congenital polycystic disease frequently involves the liver. Both entities can appear as many nodules (CCC) or cysts of variable size involving multiple liver lobes. Ultrasonographic appearance may help differentiate them. Aspirates of biliary cysts may yield mostly clear or pale yellow fluid and very few cells for cytologic evaluation. Aspirates of CCCs tend to yield more cellular aspirates. The epithelial cells obtained from either entity can be relatively uniform cuboidal epithelial cells with scant cytoplasm arranged in tubular/acinar formations or cohesive aggregates (see Figures 1 and 8) or densely packed sheets. Despite the well-differentiated cytologic appearance, bile duct

carcinoma exhibits aggressive biological behavior and a high rate of metastasis. Canine cholangiocellular carcinomas may exhibit a greater degree of cytologic atypia but often cannot be differentiated cytologically from metastatic ductal carcinomas.

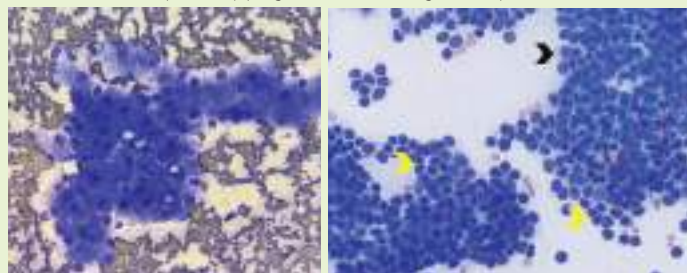
Hemolymphatic Neoplasia

Lymphoma and hematopoietic neoplasia typically result in diffuse hepatomegaly (lymphoma or leukemia) and, less often, in one or more mass lesions (lymphoma). Large cell lymphoma in dogs' liver is usually a component of multicentric lymphoma. Hepatosplenic lymphoma in dogs is a rare subtype of T-cell lymphoma. Lymphoma in the liver of cats can be either large-cell multicentric lymphoma or small- to intermediate-cell lymphoma (refer to the discussion under Inflammation). Cytology is often a useful diagnostic tool for confirming the presence of large cell or high-grade lymphoma in the liver if sufficient cellular aspirates are obtained (see Figure 9). Acute leukemia (myeloid, lymphoid, or other) can infiltrate the liver and produce aspirates with large numbers of immature hematopoietic cell types that may overlap in appearance with lymphoma cells. Flow cytometry and immunophenotyping may be useful in differentiating acute leukemia and lymphoma.

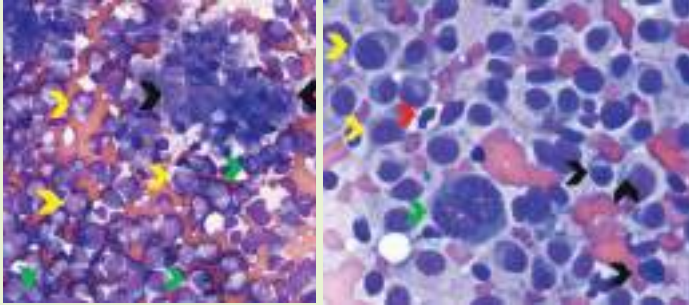
Mast cell neoplasia (mastocytosis) involving the liver generally represents visceral (hepatosplenic or GI) mast cell neoplasia in cats. In dogs, metastasis of cutaneous mast cell tumors can involve the liver. Low numbers of mast cells can be found in hepatitis and rarely normal livers; however, significantly increased numbers of mast cells, often in sheets or clusters, warrant a diagnosis of mastocytosis. Cell morphology can vary from unremarkable to atypical (decreased cytoplasmic granulation and pleomorphism).

Disseminated histiocytic sarcoma is a biologically aggressive round (discrete) cell tumor that may involve the liver of dogs and, less commonly, cats.

► **Figure 8. Aspirates from feline hepatocellular carcinoma (left) and cholangiocellular carcinoma (right). Left:** Note cohesive aggregate of hepatocytes exhibiting cytologic atypia, including increased nuclear to cytoplasmic ratio, moderate anisocytosis, anisokaryosis, one or multiple prominent nucleoli, and multinucleation. Histopathology is required for a definitive diagnosis. (Diff-Quik, 500x magnification) **Right:** Note epithelial cells that are smaller than hepatocytes and have a small amount of pale blue cytoplasm (black arrow) forming cohesive aggregates and vague acinar/tubular arrays (yellow arrows). The epithelial cells exhibit more variable cell and nuclear size than is observed in normal bile duct epithelium, and the chromatin is coarsely reticular rather than smooth (see Figure 1 for comparison to normal bile duct epithelium). (Wright-Giemsa, 500x magnification)



► **Figure 9. Canine hepatic lymphoma (left) and plasma cell neoplasia (right).** **Left:** The yellow arrows identify numerous neoplastic, medium to large lymphoid cells with round or cleaved nuclei, finely granular chromatin, and occasional bizarre mitotic figures (green arrows). A cluster of hepatocytes exhibiting vacuolar change is between the two black arrows. (Diff-Quik, 500x magnification) **Right:** Image shows a high density of neoplastic plasma cells in a liver aspirate. Black arrows identify more well-differentiated plasma cells. Yellow arrows identify larger plasma cells exhibiting cytologic atypia. The green arrow identifies a large binucleated plasma cell with coarse reticular nuclear chromatin. The red arrow identifies a neutrophil for size comparison. (Diff Quik, 750x magnification.)



Aspirates are often highly cellular and consist of pleomorphic mononuclear or multinucleated round cells exhibiting marked cytologic atypia and cytophagia. Immunocytochemistry (CD18 marker) may be useful in differentiating histiocytic sarcoma from other pleomorphic neoplasms. EMH is a common concurrent finding. A hemophagocytic variant of histiocytic sarcoma exists in dogs. Marked erythrophagocytosis is a common finding in this variant. Neoplastic histiocytes may appear well-differentiated and be difficult to differentiate from typical macrophages.

Plasma cell neoplasia is uncommonly found in liver aspirates, generally falls under the category of myeloma-related disorders, and occurs more commonly in feline than canine livers. Cytologic features include high numbers of plasma cells occurring in sheets or clusters. Plasma cells may be well-differentiated or exhibit a variable degree of cytologic atypia (see Figure 9).

Metastatic Epithelial and Mesenchymal Neoplasms

The liver is a common site of metastasis for many carcinomas and sarcomas. Liver metastasis is especially common for intestinal and pancreatic carcinomas because of the vascular and lymphatic relationships. In most cases, the tissue of origin cannot be determined cytologically for metastatic neoplasms to the liver (see Figure 10). Furthermore, differentiating metastatic carcinoma (especially ductal carcinomas) and primary cholangiocellular carcinomas based on cytology alone is challenging or impossible. Cytology may be used for the oncology staging process or to prompt further evaluation to identify a primary neoplasm.

Primary sarcomas of the liver are far less common than metastatic sarcomas. Hemangiosarcoma is the most commonly observed spindle cell tumor of the canine liver. Neoplastic spindle cells must be

differentiated from native/reactive stromal or endothelial cells and reparative fibroblasts, which can prove challenging in some cases. Moderate to marked cytologic atypia is useful in making a presumptive cytologic diagnosis of sarcoma (see Figure 10).

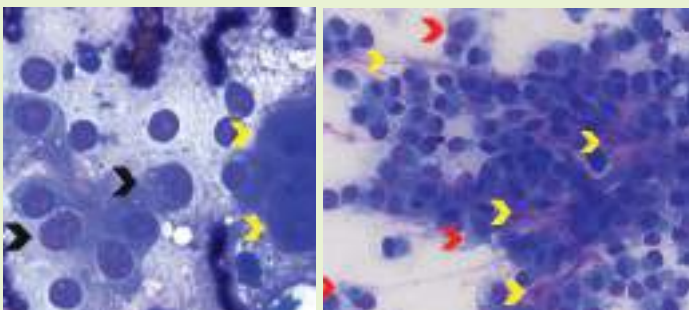
Summary

Image-guided, fine-needle aspiration (FNA) cytology of the liver can be a rewarding, practical, and economical diagnostic tool for diagnosing certain liver disorders. Liver cytology is most useful for the initial evaluation of diffuse hepatomegaly and hepatic mass lesions. It is not useful for diagnosing hepatic fibrosis, cystic lesions, ductal plate malformation, and circulatory disorders such as congenital portosystemic shunts and portal vein hypoperfusion. Incisional liver biopsy and histopathology are often required for a definitive diagnosis. Subtle features of canine chronic hepatitis are routinely missed by cytologic evaluation. Correlating cytology results with biochemical findings may help overcome some of the limitations of liver cytology and better characterize liver disease.

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► **Figure 10. Aspirates of canine metastatic carcinoma (left) and metastatic osteosarcoma (right).** **Left:** Note the cohesive aggregate of neoplastic polygonal epithelial cells (black arrows) that are smaller in size than hepatocytes (yellow arrows) and have larger nuclei. They exhibit mild anisocytosis and anisokaryosis and have multiple round to angular nucleoli of variable size. (Diff-Quik, 1000x magnification) **Right:** Note dense aggregates of neoplastic pyriform to spindle cells (red arrows) exhibiting moderate morphologic atypia (medium to large round nuclei, multiple round to irregular nucleoli, moderate anisocytosis, and anisokaryosis). The yellow arrows identify intercellular pink smudgy matrix that correlated with osteoid matrix on histopathology. (Diff-Quik, 600x magnification.)





Treating Hyperlipidemia in Dogs

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Hyperlipidemia is defined as an increase in plasma triglycerides and/or cholesterol. It results from a disturbance in plasma lipoprotein metabolism. The increase in plasma lipids or lipoproteins may be due to accelerated synthesis or delayed degradation. An increase in plasma lipids in the fasted state is considered abnormal; however, the decision to treat should be based on repeatability and the magnitude of the increase. The following will detail the basic physiology behind lipid metabolism, hyperlipidemia conditions, and current treatment recommendations.

To begin, the biologically essential lipids are outlined below:

Biologically important lipids

- Fatty Acids (FA)
- Triglycerides (TG)
- Phospholipids (cell membranes)
- Sterols (cholesterol)
- Fatty acids: bound to albumin in plasma
- TG/Cholesterol/phospholipid: transported as LIPOPROTEINS

Lipid Metabolism Overview

Due to the insoluble nature of free cholesterol and triglycerides, transport requires incorporation into various lipoproteins. The lipoproteins are arranged such that the polar regions (apolipoproteins, phospholipids, cholesterol) are on the outside, and the nonpolar regions (triglycerides and cholesterol-esters) are in the inner core. The apolipoproteins on the outer surface are responsible for the structure of the lipoprotein particle, the binding of the particles to the cell surface receptors, and the activation of various enzymes. Lipoproteins are classified based on size, density, electrophoretic mobility, and the concentrations of cholesterol and/or triglycerides.

There are four major classes of lipoproteins: 1. Chylomicrons 2. Very low-density lipoproteins (VLDL) 3. Low-density lipoproteins (LDL), and 4. High-density lipoproteins (HDL). Chylomicrons

and VLDLs are primarily involved in triglyceride metabolism and transport. In contrast, LDCs and HDLs are involved mostly in cholesterol metabolism and transport.

Apolipoproteins influence the function of various lipoproteins. For example, apolipoprotein A-1 (apoA1) is HDL's primary structural protein component. Apolipoprotein A-4 (apoA4) is present in chylomicrons and VLDL. It acts primarily in reverse cholesterol transport (see below) and intestinal lipid absorption via chylomicron assembly and secretion. Apolipoprotein C-3 (apoC3) plays a vital role in lipid metabolism, specifically regulating the metabolism of triglyceride-rich lipoproteins (chylomicrons and VLDL). Apolipoprotein B (apoB) plays an essential role in lipoprotein transport and is the primary organizing protein of many lipoproteins. Finally, apolipoprotein E (apoE) is involved in the transport and uptake of cholesterol by way of its affinity for lipoprotein receptors, including the LDL receptor.

Chylomicrons transport triglycerides and cholesterol through the lymphatics and plasma to the liver and adipose tissue. They are present in plasma 30 minutes to two hours after consuming a fat-containing meal. High levels of lipoprotein lipase (LPL) are found near the endothelial cells of both adipose and muscle tissue. Once LPL is activated, chylomicrons are hydrolyzed to free fatty acids and glycerol within 6 to 10 hours. The FFAs diffuse into cells and are either used for energy or stored as triglycerides in adipocytes. The chylomicron remnant remains in the plasma until removed by the liver. Of note, lipoprotein lipase is under positive feedback control by insulin.

Excess fatty acids not used for energy are re-synthesized into triglycerides and packaged as VLDL. The formation of VLDLs is important in removing excess fatty acids from plasma and aids in mobilizing it for storage elsewhere. Lipoprotein lipase hydrolyzes the triglyceride (note: a triglyceride is a glycerol molecule with three fatty acids attached) portion of VLDL into free fatty acids and glycerol, supplying cellular needs of fatty acids. The liver then takes up the VLDL remnant via a specific receptor-mediated mechanism. This is a very efficient process in dogs, decreasing the time in circulation for

VLDLs and their remnants. This is offered as one explanation for why dogs can eat higher-fat diets without developing coronary artery disease.

Removal of triglycerides, phospholipids, and apolipoproteins (C, E) from VLDL and the addition of apoB100 creates the cholesterol-ester-rich LDL. This molecule transports cholesterol to tissues for use in cell membrane synthesis and steroid hormone production. Although LDL and VLDL use the same receptor for removal from circulation, the efficiency of LDL removal appears to be less than that of VLDLs. Canine LDL is higher in triglycerides and contains less cholesterol than human LDL.

HDL is synthesized in the liver and secreted into circulation. Plasma *lecithin-cholesterol acyltransferase* (LCAT) esterifies cholesterol to hydrophobic cholesterol esters. This moves the esters from the outer surface to the inner core of the molecule, creating a concentration gradient such that excess tissue cholesterol is transferred to the HDL molecule. The excess cholesterol is then carried to the liver for excretion in bile. This process is known as reverse cholesterol transport and why HDL is called the 'good cholesterol.' Cats appear to lack LCAT and accomplish reverse cholesterol transport by direct tissue uptake of cholesterol esters.

Hormone-sensitive lipase (HSL) is another key enzyme that aids in the endogenous mobilization of lipids. Unlike lipoprotein lipase, HSL is under negative feedback control by insulin. Levels of this hormone are increased during states of poor nutrition and the presence of increased ACTH, corticosteroids, growth hormone, hyperthyroidism, and states of increased glucagon: insulin activity such as diabetes and pancreatitis.

Hyperlipidemia Disorders

Hyperlipidemia refers to an increased concentration of triglycerides, cholesterol, or both in the blood. Lipid metabolism has two main pathways: exogenous pathway and the endogenous pathway. The exogenous pathways are associated with the metabolism of dietary lipids. Post-prandial hyperlipidemia, mainly due to increased chylomicron concentration, is the most common

INTERNAL MEDICINE

Treating Hyperlipidemia in Dogs

CONTINUED FROM PAGE 19

cause of increased serum TG levels. This is considered normal and usually resolves in 2-10 hours. Cholesterol concentrations in patients with post-prandial hyperlipidemia are usually normal or only mildly increased. The endogenous pathway is associated with the metabolism of endogenously produced lipids, namely VLDL, LDL, and HDL.

Hyperlipidemia can be primary or secondary. Primary hyperlipidemia is usually breed-associated and observed in such breeds as Miniature Schnauzers, Shetland Sheepdogs, and Beagles. Secondary hyperlipidemia is more common in dogs and results from



endocrinopathies like hypothyroidism, diabetes, and hyperadrenocorticism. Other conditions associated with hyperlipidemia include pancreatitis, protein-losing nephropathy, cholestasis, obesity/diet, and some drugs.

Why Treat Hyperlipidemia?

Many animals will present with no clinical signs, and increased lipid levels may be found incidentally on routine blood screening. The lack of clinical signs does not justify ignoring the abnormal values however and may be an indication for rechecking prior to further investigation. Commonly animals will have waxing and waning courses of vomiting, diarrhea, and abdominal pain. Owners may report the resolution of clinical signs with fasting. Severe

hypertriglyceridemia (>1000 mg/dl) has been associated with pancreatitis, hepatic steatosis, glomerular disease, gall bladder mucoceles, lipemia retinalis, cutaneous xanthomas, peripheral nerve paralysis, behavior changes, and other neurologic signs. Seizures may be diagnosed as idiopathic epilepsy because of a lack of other clinical signs related to hyperlipidemia. However, the increased serum lipids should be suspected as a cause if present. Severe hypercholesterolemia (> 800 mg/ dl) may lead to atherosclerosis but is considered very rare in dogs. There has been no established correlation between the magnitude of the increase in serum lipids and the severity of the clinical signs.

Diagnosis of Hyperlipidemia

Lipemia is a turbidity of a sample caused by an accumulation of lipoprotein particles. The largest particles – chylomicrons – have the greatest potential to cause turbidity in the sample. Therefore lipemia usually indicates hypertriglyceridemia. Pure hypercholesterolemia should not result in lipemia, as the LDL/HDL molecules are too small to reflect light. During your investigation for hypertriglyceridemia, be aware that centrifugation removes chylomicrons which will artifactually lower the triglyceride level.

Step one ensures that elevated cholesterol and/or triglycerides are repeatable by testing the patient after a 12-hour fast. If an animal is diagnosed with a specific underlying disease, treat the disease first and then initiate follow-up therapy if needed. As of note, cats are rarely diagnosed with significant hyperlipidemia; rare cases can be due to a lipoprotein lipase deficiency.

Treatment of Hyperlipidemia

1. Diet: Low-fat. Dietary fat pet foods are listed as a percent metabolizable energy (ME), percent dry matter basis (DM), or present as-fed basis. Many follow fat labels on an ME basis. Success can be achieved with Royal Canin Low Fat (16.3% fat on

an ME basis in the canned and 15.7% fat on an ME basis in the dry) or the Waltham Low Fat diet. Other low-fat diets: Royal Canin GI low-fat, Hills I/D low-fat (not the regular Hills I/D), or Purina EN GI low-fat diets. Alternatively, you could have a home-cooked lower-fat diet (as low as ~12% on an ME basis) formulated by a veterinary nutritionist. Most diet-directed treatment of hyperlipidemia takes a month or more to see an effect.

2. Omega-3 fatty acids: Reduce serum cholesterol and triglyceride concentrations by decreasing the synthesis of VLDL and LDL. Recall that VLDL is important for TG transport; LDL for cholesterol transport. Dose: 10-220 mg/kg/ day.

3. Fibrates: Bezafibrate, fenofibrate, gemfibrozil. The primary mechanism of action: increases lipolysis of TG-rich lipoproteins by lipoprotein lipase; increases hepatic fatty-acid uptake; decreases hepatic TG production; increases clearance of LDLs.

a. Bezafibrate at a dose of 4-10 mg/ kg/ day normalizes both cholesterol and TG. As of 2018 not available in the US.

b. Fenofibrate (TriCor) acts similarly to bezafibrate. Fenofibrate is available in the US as 54 mg tablets and is administered as 0.5 to 1 tablet per dog per day, usually during the evening meal

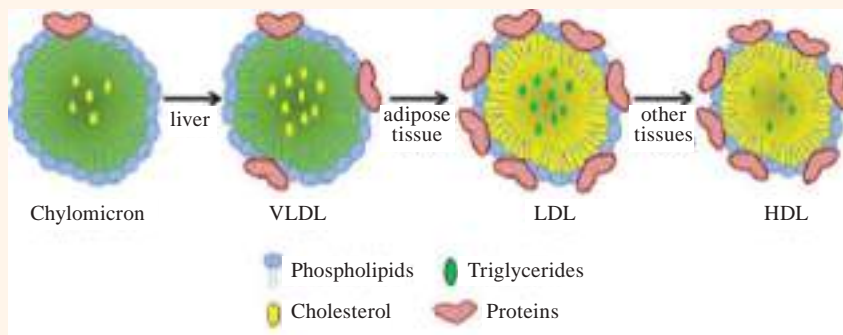
c. Gemfibrozil: not as efficacious as the two fibrates above

4. Chitin or Chitosan: For use in feline hyperlipidemia. Chitosan is a fiber supplement made from shellfish that reportedly binds lipids in diet and decreases absorption. No studies prove efficacy in dogs or cats.

5. Niacin: Acts primarily to reduce hepatic triglyceride synthesis and VLDL production. Newer agents, e.g., Acipimox, also act to reduce adipose lipolysis. Niacin has vasodilatory effects and could cause some skin reddening. It might be reduced by giving it with meals or using a “no flush” niacin product or a slow-release product. Occasionally dogs seem uncomfortable and may scratch at their face afterward. Dose: 50-200mg/day/dog; the dose can be divided into two daily doses. Some reports say Niacin is minimally effective.

6. Statins/HMG CoA-reductase inhibitors: (lovastatin, simvastatin, pravastatin, fluvastatin, cerivastatin, atorvastatin). Effective at reducing cholesterol levels by reducing hepatic cholesterol synthesis,

› Image from Lipoproteins/Study.com



INTERNAL MEDICINE

Treating Hyperlipidemia in Dogs

CONTINUED FROM PAGE 20

thereby up-regulating LDL-receptor activity. They are the most powerful cholesterol-lowering agents available. Adverse effects: increased appetite, possible hepatotoxicity. Myopathy if combined with a fibrate. Dose: 2 mg/kg/day

- 7. 5-Aminolevulinic Acid:** Used for hypertriglyceridemia by increasing mitochondrial activity, thereby improving lipid metabolism. This has been used to normalize triglycerides in overweight Miniature Schnauzers.

Summary

Understanding lipid metabolism aids in understanding lipid profile abnormalities in dogs and cats. Although primary conditions have been reported, secondary hyperlipidemia is more common in small animals. Therefore a thorough search for an underlying cause should be performed if persistently increased cholesterol and/or triglyceride levels are documented. Medical therapy should treat the underlying cause and restrict dietary fat. Other treatments can be considered if conservative therapy is adequate. However, the potential for adverse effects should be discussed with owners prior to instituting these therapies.

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Anticholinergics in Dogs and Cats

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Background and Pharmacology

Anticholinergics, also known as *antimuscarinics*, have long been used to treat and prevent bradycardia during the anesthetic period (Figure 1). Atropine and glycopyrrolate are the two most commonly used drugs of this class within veterinary medicine. More often than not, anesthetic bradycardia is due to drug effects or vagally-mediated processes. In determining whether or not to include and/or administer an anticholinergic as part of a premed or in response to bradycardia during the anesthetic period, one needs to consider certain patient factors and consider other concurrently administered drugs.

Anticholinergics' primary mechanism of action is to act as parasympatholytics in that they competitively block acetylcholine from acting as a neurotransmitter at muscarinic receptors. There are five muscarinic receptor subtypes, but the M_2 receptor plays the largest role in heart rate (HR) maintenance, given its location in the sinoatrial and atrioventricular nodes of the heart.^{1,2} Other known effects of anticholinergics include bronchodilation, decreased salivation and airway secretions, mydriasis (higher likelihood after topical administration), and gastrointestinal effects (e.g., reduced lower esophageal sphincter tone, which can increase the risk of gastroesophageal reflux and aspiration).^{1,2} These other effects are due to muscarinic receptor binding in different tissues throughout the body.

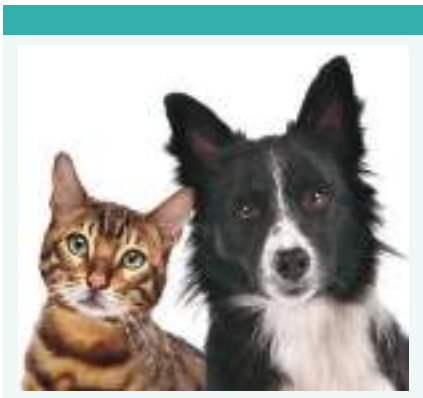


Figure 1. Second-degree AV block with 2:1 conduction and HR of 60 bpm. There is a repeating PR interval, but each QRS is followed by a non-conducted P wave. Sinus bradycardia and first/second-degree AV block are the most commonly treated anesthetic bradyarrhythmias.



Indications, Contraindications, and Dosing Information

There are a few absolute indications for anticholinergic administration in a premedication. These include neonatal and pediatric patients (those < 3-4 months in which cardiac output (CO) is dependent on HR), patients with low resting HR due to cardiac conduction disturbances, systemic disease, or high resting vagal tone, and lastly, patients with advanced degenerative valvular disease as bradycardia increases filling time and increases regurgitation.

The absolute contraindications for anticholinergics in premeds include patients with underlying tachydysrhythmias, patients with hypertrophic or other restrictive cardiomyopathies in which CO decreases with reduced filling time/reduced stroke volume, and hyperreflexic patients.

In following the indications and contraindications, there are a few hazy areas regarding anticholinergic use.

1. Many commonly used premedications cause bradycardia as a side effect (e.g., opioids and alpha-2 adrenergic agonists), which can be significant in the anesthetized patient. If a patient was given an alpha-2 agonist, one needs to determine if the bradycardia is reflexive due to peripheral vasoconstriction (early drug effect) or due to the delayed sympatholytic effect of the drug (bradycardia and hypotension present).^{1,2,3,4,5} An increase in HR while peripherally vasoconstricted dramatically increases the workload on the heart and myocardial oxygen demands. No study has shown a benefit to co-administration of an anticholinergic and alpha-2 agonist. In healthy dogs, this co-administration often results in arrhythmias and significant hypertension.^{3,4,5} If a patient was given an

Table 1: Atropine vs. glycopyrrolate – drug effects on the cardiovascular system similar in dogs and cats

*Depending on the dose of anticholinergic given, it is not uncommon to see a worsening of the bradycardia before HR increases. This is thought to be due to blockade of presynaptic M_1 receptors that normally inhibit acetylcholine release. HR should increase within 5-10 minutes, but if the effects of the bradycardia cannot be tolerated, a second smaller dose of the same anticholinergic can be given to initiate M_2 receptor blockade.^{1,2}

Drug	Dose*	Onset of Action	Duration of Action	Crosses Blood-Brain-Barrier
Atropine	0.015-0.02 mg/kg IM and IV	1 minute (IV)	30 minutes (IV)	Yes
	0.04 mg/kg IV (CPR) Increase dose 2-3X if giving via intra-tracheal route during CPR	10-20 minutes (IM)	60-90 minutes (IM)	
Glycopyrrolate	0.005-0.01 mg/kg IM and IV	Up to 5 minutes (IV)	Up to 1 hour (IV)	No
		30-45 minutes (IM)	60-90 minutes (IM)	

ANESTHESIA

Anticholinergics in Dogs and Cats

CONTINUED FROM PAGE 22

alpha-2 agonist and is later bradycardic and hypotensive, the author recommends treatment with an anticholinergic if >45-60 minutes out from the time of premedication. If the patient is bradycardic and hypertensive, the author recommends reversing the alpha-2 agonist via an intramuscular route before giving an anticholinergic.

2. In patients undergoing enucleation for underlying ocular disease, the oculovagal reflex is a common concern. Interestingly, in a single study of dogs undergoing enucleation, those given a preoperative retrobulbar nerve block were *less likely* to have an oculocardiac reflex than those given preoperative anticholinergic drugs.⁶ This indicates that the reflex is likely blunted with adequate analgesia, but should bradycardia occur, either removing the stimulus (surgery) or administering an anticholinergic are reasonable alternatives.
3. Historically, atropine or glycopyrrolate have been recommended as commonplace in anesthetic management of patients undergoing cesarean section, likely to inhibit vagal tone associated with manipulation of the uterus and increase maternal/fetal HRs.^{1,2} However, given the reduction in lower esophageal sphincter tone and decreased gastric motility in patients already at increased risk of regurgitation and aspiration, the author cautions against the inclusion of anticholinergics as standard of care in these patients.

As an overriding rule, the author recommends more common use of anticholinergics *as needed* in anesthetized patients to maintain HR in a normal range, helping to preserve blood pressure and cardiac output. It is advisable, as part of the anesthetic protocol or record, to have an emergency dose of atropine calculated and access to anticholinergics within a reasonable distance. In the face of non-life-threatening drops in HR, the author recommends starting with lower doses of anticholinergic, knowing you can always supplement more if HR does not sufficiently increase (Table 1). The effects of tachycardia, while short-lived, can be more detrimental to the anesthetized patient.

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