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Infectious Diseases

Feline Infectious Peritonitis

Ophthalmology

Topical Antibiotics in Ophthalmology: How, What and When?

Endocrine Diseases

Canine Insulinoma

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Editor's Note

Dear Collegues

I'm back and looking forward to getting stuck in again.

Thanks to Marianne Lombard for looking after the VET 360 in my absence.

This edition has an article by Dr Rowena Watson, outlining on how she has been treating cats for FIP over the last several years. It seems as if she was really quite pioneering in her efforts to help her patients and her article combined with available literature should motivate others to follow suit.

The CPD article may seem esoteric, but these cases exist in our practices and just need to be picked up. I had a hypoglycaemic Miniature Pinscher cross with diarrhoea in my clinic a few months ago which ended up being an insulimona once investigated further.

And then, in these difficult retailing times - who doesn't need to manage their stock levels - and our business article gives us some tips on what to do.

I hope you enjoy and learn as you read .

Liesel

vet360

VET360 aims to be a leader in the field of continuing veterinary development in Southern Africa by providing veterinary professionals from diverse disciplines with tools to help them meet the challenges of private practice. The magazine aims to make information accessible, both paper and electronic, and provide clinical, business and other veterinary information in a concise form to enable the practitioner to rapidly acquire nuggets of essential knowledge

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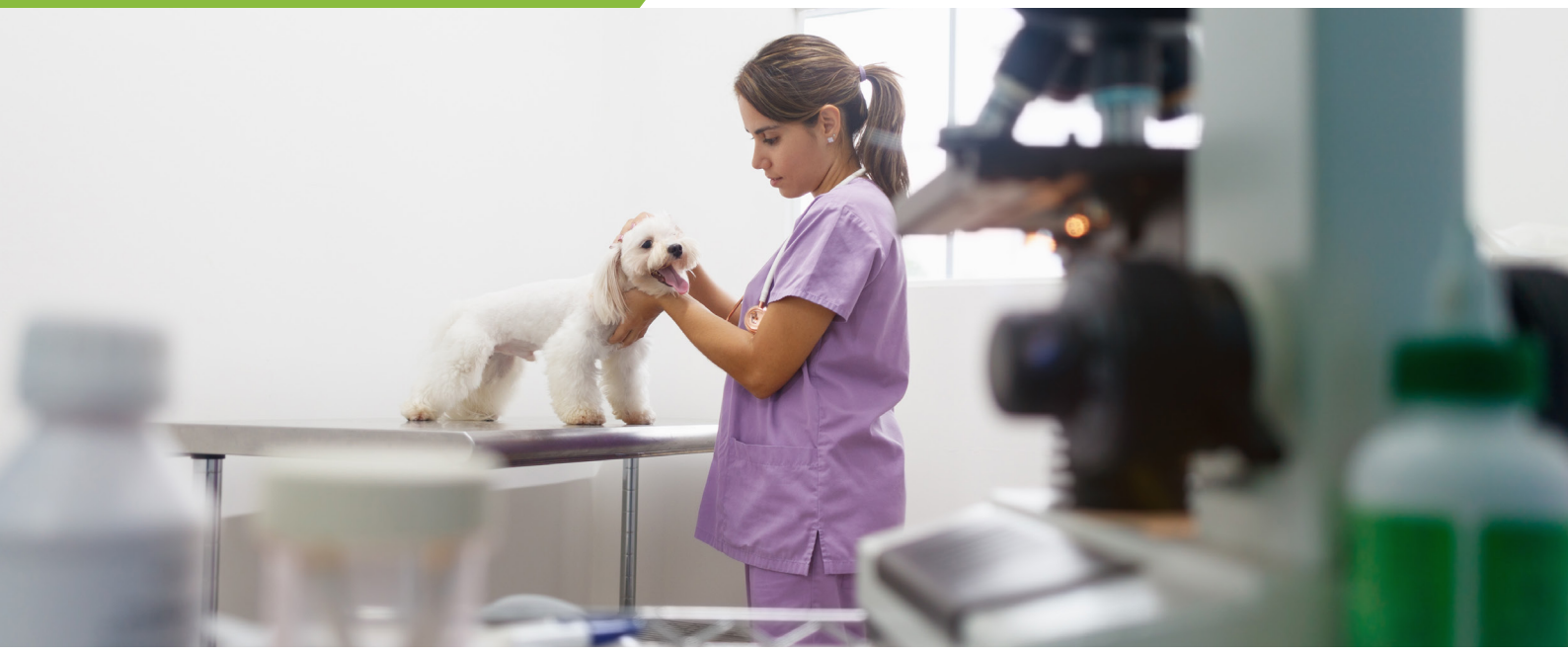

Marlene Du Toit
Head of Customer Success and International Support
at Digitail

Stock management is the unsung hero of a thriving veterinary practice. Mastery of your inventory is the secret sauce that keeps your clinic running like a well-oiled machine. With efficient stock management, you'll have the precise supplies, medications, and equipment at your fingertips to deliver top-notch care to your furry patients.

Neglecting this crucial aspect can spell financial woes, disrupt patient care, and erode customer satisfaction. In this article, we're diving headfirst into the world of stock management tailored for veterinarians. Get ready to unlock key strategies that will supercharge your practice's success!

Understanding Product Velocity: The Need for Speed

Picture this: You're at the helm of your clinic, and it's a bustling day. Understanding how fast your products move is like knowing which lane to take in a race. If you underestimate the demand for specific items, you might as well be racing with a blindfold on. Incorrect quantities can lead to cluttered shelves, ballooning storage costs, and missed opportunities to cater to the needs of your four-legged clients.

Additional Tip: Track Product Demand Trends for a Winning Edge

- Tap into historical sales data to spot seasonal product trends.
- Keep your ear to the ground by considering customer feedback and preferences when loading up on certain products.

Rotating Stock with Finesse: Don't Let Profits Go Stale

Veterinarians are no strangers to products with expiration dates. But mishandling rotation? That's a recipe for throwing money down the drain.

An unvigilant approach to rotation can lead to a graveyard of expired items, haunting your practice's profitability. So how do you overcome this problem? Implement a bulletproof alert system to keep you one step ahead of those pesky expiration dates.

Additional Tip: Categorize Inventory for Maximum Impact

- Organize your inventory into sleek categories like medications, medical supplies, and pet care essentials.
- Prioritize the rotation of items with shorter shelf lives, such as medications, to minimize waste and amplify savings.

Identifying and Slaying the Shrink Monster

Shrinkage – it's the stuff of nightmares for business owners, including those in the veterinary world. But don't fret; your inventory management skills can be your trusty torch to illuminate the darkness. Identifying and addressing shrink is pivotal in safeguarding your bottom line. With clear visibility into your stock levels, you'll be equipped to combat theft, damage, and other lurking threats.

Additional Tip: Fortify Your Defenses

- Deploy a battalion of security cameras in your stock storage areas to discourage potential thieves.
- Enlist your team in a rigorous inventory security training regimen to fortify your practice's defenses.

Implementing the Mighty Pareto Principle (80-20 Rule)

Enter the Pareto Principle, a mighty tool for streamlining your stock management. In this power-packed concept, a mere 20% of your efforts yield a colossal 80% of your results.

Translate this into stock management, and you'll see that a handful of inventory items are your practice's financial superheroes.

Additional Tip: Be the Profit Detective

- Scrutinise the profit margins of each product to spotlight the high-rollers.
- Combine popular products with slower-moving items for a dynamic duo that boosts sales and elevates your revenue game.

Setting Par Levels: The Stock Superhero's Shield

Imagine setting par levels as your force field against stock shortages. Par levels represent your practice's stock safety net – ensuring you always have the essentials in stock, even in the heat of the busiest days.

Additional Tip: Be a Seasonal Chameleon

- Adapt your par levels with the changing seasons to meet demand fluctuations. Load up on flea and tick products before the summer swarm.
- Forge alliances with suppliers to establish automatic reorder triggers based on historical consumption data.

Championing the First In, First Out (FIFO) Principle

For veterinarians handling perishables or items needing rotation, the FIFO principle is your secret weapon.

It's your guarantee that old stock gracefully bows out first, preventing costly waste and ensuring your freshest supplies iare always front and center.

Additional Tip: Rack 'Em for Efficiency

- Design your storage shelves with finesse, making it a breeze to access older items first.
- Proudly display expiration dates to encourage FIFO compliance and save the day – and dollars.

Contingency Planning and Teamwork: The Avengers of Stock Management

In your stock management saga, your trusty team is your league of superheroes. Appoint vigilant souls to handle stock ordering, regular counts, and purchasing precision. Enlist your team's powers to reduce losses and streamline stock operations.

Additional Tip: Cross-Train for a Super Squad

- Equip your team with a versatile skill set, making them capable in various stock management tasks to ensure seamless coverage.
- Instill a culture of accountability by routinely reviewing stock procedures, strengthening your practice's collective resolve.

Always remember, stock management is a collaborative endeavor, and armed with these strategies, your veterinary practice is primed for success. Efficient stock management isn't just important; it's the essence of your practice, ensuring you're always equipped to deliver top-tier care to your beloved animal patients.

Ready, set, thrive!

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Topical Antibiotics in Ophthalmology: How, What and When?

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Introduction

Globally, the alarming increase in the rate of bacterial resistance to antibiotics is currently considered one of the 7 major threats to the human race, along with terrorism, nuclear proliferation and air pollution.

Antibiotics are one of the most cost-effective, ocular saving medicines. In ophthalmology, and the rest of the body, the effect of antibiotics is compromised by the rapid escalation of antibiotic resistance (ABR), which, combined with the paucity of development of new antibiotics is considered a major threat.

Indiscriminate use of topical antibiotics may have the detrimental effect of breeding antibiotic resistance in the conjunctival bacterial flora.

Antibiotic resistance

The importance of selecting the appropriate antibiotic and deciding if an antibiotic is indeed required is of the utmost importance. A good example of this is the indiscriminate use of topical fluoroquinolones.

Fluoroquinolones offer broad-spectrum antimicrobial coverage and good ocular penetration when used topically. In human ophthalmology prophylactic topical fluoroquinolones are often used after intravitreal bevacizumab or ranibizumab injections for age-related macular degeneration. However, studies have shown that endophthalmitis still occurs despite use of these agents.

Milder E et al. reported that after an average of seven intravitreal injections, the fluoroquinolone resistance rate was 87.5% among the subset of eyes exposed to topical fluoroquinolones for four days after each injection. This suggests that repeated exposure to fluoroquinolones, even just a single drop on the eye after each injection, can lead to increased rates of resistance.

Available topical antibiotics

In ophthalmology we are very limited to choices of topical

antibiotics for various reasons including penetration of the drug and the epitheliotoxic effect of certain products.

The commonly used topical antibiotics include:

- Chloramphenicol
- Doxycycline
- Triple antibiotic formulations (Polymyxin B, Neomycin and Bacitracin / Gramicidin)
- Fluoroquinolones (second generation ofloxacin & ciprofloxacin, third generation levofloxacin and fourth generation moxifloxacin)
- Aminoglycosides (Tobramycin)

Indications for and choice of topical antibiotics

The normal cornea is very resistant to bacterial infection. With the exception of a very small group of niche adapted bacteria like *Moraxella bovis* (the cause of pinkeye in cattle), almost all bacteria isolated from diseased corneas represent purely opportunistic infection of a cornea stripped of its natural defences by previous mechanical or chemical injury.

Keratomalacia (melting corneal ulcers) is one of the common sight threatening conditions seen in veterinary practices. (Figure 1) This stromal destruction is the result of excessive amounts of proteolytic enzymes like matrix metalloproteinases (MMPs) and serine proteinases. These enzymes play an important role in the normal turnover of epithelial cells and remodelling of corneal stroma. Proteolytic enzyme activity is normally balanced by protease inhibitors, which prevents degradation of healthy tissue. Increased amounts of proteases can lead to rapid degradation of the corneal stroma. Proteolytic enzymes are secreted by epithelial cells, inflammatory cells and fibroblasts. Pseudomonas also secretes MMP's leading to excessive amounts and consequent keratomalacia.

Topical antibiotics are often, and rightly, so used prophylactically after both extra and intra-ocular surgery. Good examples of this include surgical repair of a prolapsed gland of the third eyelid, grid keratotomy and conjunctivectomy. Most corneal ulcers are also not infected but are **at risk** of becoming infected.

Topical antibiotics are therefore definitely indicated as part of the routine treatment of corneal ulcers, in most cases as a prophylactic drug.

The use of antibiotics with a spectrum of activity against Pseudomonas should not be used as prophylactic antibiotics. These antibiotics include third and fourth generation fluoroquinolones and aminoglycosides. Appropriate choice of antibiotics in these cases are chloramphenicol, doxycycline and triple antibiotic solutions. The abovementioned drugs are reserved for truly melting ulceris.

Inappropriate use of topical antibiotics

Topical antibiotics are often prescribed for non-infectious ocular disease, this should be avoided as far as possible. **Common examples of conditions where antibiotics are not required include most cases of conjunctivitis in dogs, cats and horses, keratoconjunctivitis sicca, uveitis and hyphema.**

Conjunctivitis in dogs is almost never primarily bacterial but is commonly secondary to mechanical irritation of the conjunctiva for example entropion ectropion and eyelid neoplasia. Another very common non-infectious cause of conjunctivitis in dogs is allergic. disease in cats conjunctivitis is mostly virally induced, especially feline herpes virus and also allergic.

Keratoconjunctivitis sicca (KCS) often presents as a thick tacky mucoid ocular discharge (Figure 2). If secondary bacterial infection is suspected this should be confirmed with conjunctival cytology before antibiotics are prescribed KCS patients.

Summary

Topical antibiotics play a very important role in the treatment of ocular disease in veterinary practices. A good selection of topical antibiotics to have available as well as indications for their use are listed in the following table.

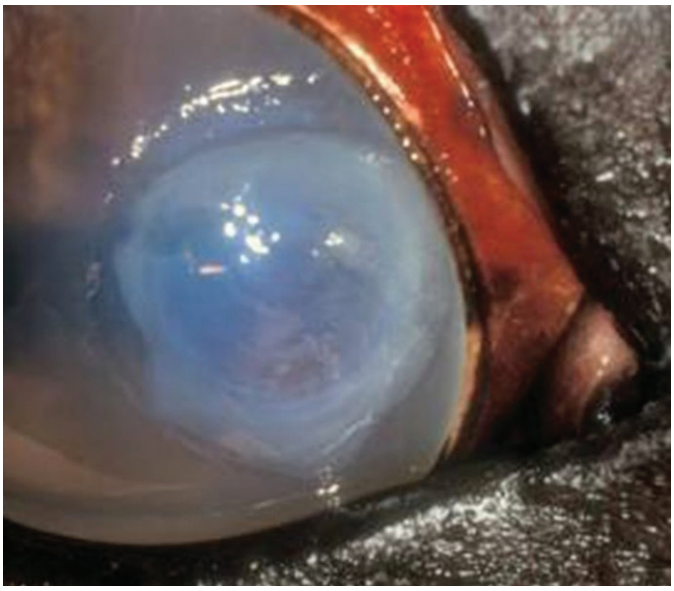

Figure 1: *Typical appearance of keratomalacia. Note the jelly like appearance of the corneal stroma.*

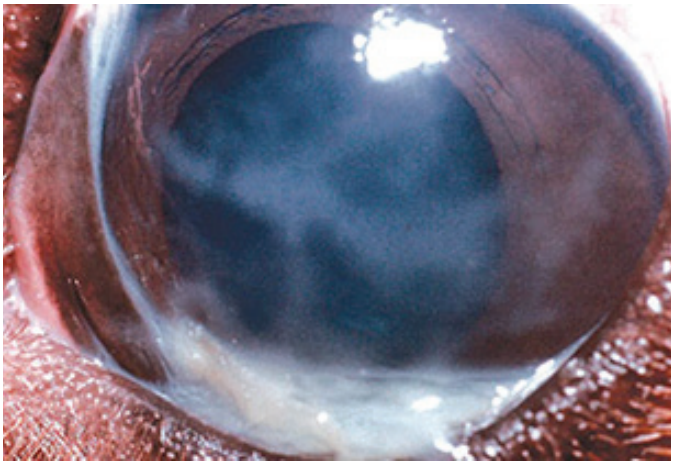

Figure 2: *Dog with keratoconjuncitivits sicca. Note the mucoid and not purulent discharge.*

Antibiotic	Indications	Examples
Chloramphenicol	Non infected uncomplicated corneal ulcers Prophylactic, after ocular surgery Infectious conjunctivitis	Chloramex® Chlornicol® Optiphen® Chloramphenicol 0.2 % w/v eye drops [VetScripts]
Doxycycline	Infectious conjunctivitis Chlamydial conjunctivitis in cats Keratomalacia [Anti collagenolytic] Chalazions	Doxycycline 0.1% w/v eye drops [VetScripts]
Enrofloxacin	Corneal ulcers Chlamydial conjunctivitis in cats	Exocin®
Levofloxacin	Corneal ulcers	Levofloxacin 0,5% w/v eye drops [VetScripts]
Moxifloxacin	Keratomalacia Equine stromal abscesses	Vigamox®
Tobramycin	Keratomalacia Equine stromal abscesses	Tobrex® Toryn®
Triple antibiotic [Polymyxin B, Neomycin, Gramicidin]	Non infected uncomplicated corneal ulcers Prophylactic after ocular surgery Infectious conjunctivitis	Tribiotic [VetScripts]

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Canine Insulinoma

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Introduction

Insulinoma is an insulin-secreting tumour of pancreatic beta cells that results in excessive insulin secretion and clinical signs of hypoglycaemia. It is an uncommon condition in dogs and rare in cats. Canine insulinoma was first described in the dog in 1935 (Slye & Wells, 1935). Subsequently, approximately 600 canine cases have been described

Pathophysiology

Insulin-secreting pancreatic beta cells comprise approximately 70% of cells in the islets of Langerhans, which in turn only comprise approximately 1 – 2% of pancreatic volume. About 80% of insulinomas are solitary, located in one pancreatic limb rather than in the body of the pancreas. Occasionally no discrete nodule is seen during gross pancreatic examination, in which case histology is required to identify the tumour.Most canine insulinomas are malignant.

The rate of detected metastatic lesions in dogs from different studies ranges from 45% to 64%, being higher in studies based on necropsy versus studies using samples obtained surgically. Most dogs with insulinoma have stage II or III disease (Table 1) and the most common sites of metastases are regional lymph nodes and the liver. Although the aetiology of insulinoma is not known, local growth hormone (GH) production which is not associated with increased plasma GH concentrations, has been documented in primary and metastatic canine insulinoma, possibly promoting islet cell proliferation via paracrine or autocrine mechanisms.

Stage of disease	Primary tumour	Regional lymph node	Distant metastases
Stage 1	T_1	N_0	M_0
Stage II	T_1	N_1	M_0
Stage III	T_1	N_0/N_1	M_1

Figure 1. *World Health Organisation Clinical staging of insulinoma*

Neoplastic proliferation of pancreatic beta cells causes autonomous and excessive secretion of insulin with resultant episodes of hypoglycaemia. The most important compensatory mechanisms for hypoglycaemia are inhibition of insulin secretion and stimulation of counter-regulatory hormones secretion. In healthy animals, insulin secretion is completely inhibited when blood glucose is <4.4 mmol/L. However, insulin secretion from neoplastic beta cells is independent of blood glucose concentration and persists despite low blood glucose concentrations.

As a consequence, one of the biochemical hallmarks of insulinoma is high or normal blood insulin concentrations despite low blood glucose concentrations. The four counter-regulatory hormones secreted in response to hypoglycaemia are glucagon, catecholamines, GH and glucocorticoids. Of these, glucagon and catecholamines are the predominant drivers of the short-term responses to low blood glucose concentrations.

Clinical features

Signalment

The mean age of dogs with insulinoma is 9 years, with a range of 3 to 15 years. Although any breed of dog may develop insulinoma, it has been reported most in medium- to large-breed dogs. Breeds reported to be at increased risk include Boxers, German shepherd dogs, Golden Retrievers, Labrador Retrievers, Irish Setters, Standard

Poodles, Collies, Springer Spaniels, Fox Terriers, West Highland White Terriers and Jack Russel Terriers. There is no apparent sex predilection for the disease.

Clinical Signs

Glucose is the single most important source of energy for the brain. Brain function is dependent on a continuous glucose supply because both carbohydrate storage and the brain's ability to utilise other fuels are limited. Clinical signs are thus usually due to the effect of episodes of hypoglycaemia on the central nervous system (neuroglycopenia), or to hypoglycaemia-induced release of catecholamines.

Clinical signs attributable to neuroglycopenia include mental dullness, disorientation, weakness, proprioceptive ataxia, visual disturbances, collapse and focal or generalised seizures. Sometimes the signs might resemble those of a paroxysmal dyskinesia (Ryan et al., 2021). Clinical signs related to excess catecholamine release and stimulation of the sympathetic nervous system includes hunger, nervousness and tremors.

The severity of clinical signs is partly correlated to the blood glucose nadir. Severe hypoglycaemia may ultimately result in coma and death. However, clinical signs may also be related to the duration and the rate at which hypoglycaemia develops, because gradual decreases in blood glucose concentration are less likely to stimulate catecholamine secretion.Although most dogs have more than one of these clinical signs, some dogs have none. Some cases may gain weight because of the anabolic effects of insulin. Post-ictal changes may be apparent if a seizure occurred quite recently. A peripheral polyneuropathy characterised by posterior paresis or tetraparesis and decreased or absent appendicular reflexes has been described in dogs with insulinoma (Ryan et al., 2021). The aetiology of this insulinoma-associated peripheral neuropathy has not been firmly established, yet it is most likely a paraneoplastic immune-mediated disorder.

Insulin secretion and clinical signs are typically episodic and the secretion of counter-regulatory hormones tends to increase blood glucose concentration, transiently resolving the neuroglycopenic signs. Feeding can also alleviate clinical signs if blood glucose concentration is restored to normal. Feeding however, may also exacerbate clinical signs by stimulating further insulin secretion. Fasting, exercise or excitement worsen clinical signs by decreasing blood glucose concentration or increasing sympathetic stimulation.

Diagnosis

The causes of hypoglycaemia may be broadly separated into those caused by decreased glucose production, those associated with excessive glucose utilisation or a combination thereof.

Clinicopathological abnormalities

Clinical suspicion of insulinoma begins with the documentation of appropriate clinical signs, hypoglycaemia (blood glucose concentration less than approximately 3.5 mmol/L) and concurrent normo- or hyperinsulinaemia (serum insulin concentrations within or above reference interval) (see Figure 2 for interpretation). Aside from the hypoglycaemia observed in most patients, complete blood count (CBC), serum biochemistry and urinalysis are usually unremarkable. Mild hypokalaemia and increased alkaline phosphatase and/or alanine aminotransferase activities have been documented (Harris et al., 2020).

Although hypoglycaemia is observed on randomly obtained blood samples from the vast majority of dogs with insulinoma, especially if repeated, some patients are euglycaemic at the time of presentation. When a dog suspected of insulinoma is euglycaemic, it should be fasted and closely monitored for hypoglycaemia while blood glucose concentrations are measured every 30 to 60 minutes. Point-of-care analysers are usually adequate for this purpose. In most dogs with insulinoma, hypoglycaemia (blood glucose <3.5 mmol/L) develops within 12 hours of the previous meal. When hypoglycaemia is documented, serum for the measurement of insulin concentration should be submitted from the same sample. Yet, a limited number of dogs with insulinoma do not exhibit hypoglycaemia, even with repeated measurements or after a prolonged fast of 48-72 hours. Low fructosamine has been used to strengthen the clinical suspicion of insulinoma in such dogs. Glycosylated hemoglobin A1c concentration has been low in some, but not all, dogs with insulinoma. Repetition of serum insulin measurements at a reputable laboratory may also aid in the diagnosis.

Other tests have been described for the diagnosis of insulinoma in euglycaemic dogs with equivocal serum insulin concentrations. Of these, insulin-to-glucose and glucose-to-insulin ratios are not recommended because of their low sensitivity and the amended insulin-to-glucose ratio is not recommended because of its low specificity. Additional tolerance and stimulation tests have been described, but are also not advocated because of questionable

Figure 2. *Interpretation of serum insulin concentrations in hypoglycaemia*

Glucose concentration	Insulin concentration	Interpretation and further action	Possible alternative diagnosis
< 3.5 mmol/l	Insulin above reference interval (> 140 pmol/L)	Insulinoma	Nesidioblastosis (Hyperplastic beta cells secreting insulin)
< 3.5 mmol/l	Insulin high end of reference interval (70 - 140 pmol/L)	Insulinoma	Nesidioblastosis
< 3.5 mmol/l	Insulin lower end of reference interval (35 - 70 pmol/L)	Equivocal; repeat insulin concentration on another day; consider measuring fructosamine	Nesidioblastosis
< 3.5 mmol/l	Insulin undetectable (< 35 pmol/L)	Unlikely to be insulinoma	pancreatic tumour secreting somatostatin or IGF-1

usefulness, unnecessary complexity and/or potentially fatal side effects due to hypoglycaemia

Diagnostic Imaging

Radiography and ultrasonography

A pancreatic mass may be identified with imaging studies and this strengthens the suspicion for insulinoma. The diagnosis of insulinoma is ultimately confirmed with histologic examination and immunohistochemical staining of a pancreatic mass.

Most dogs with insulinoma have unremarkable abdominal and thoracic radiographs, because most insulinomas are quite small (<4 cm) and isoechoic on ultrasonographic examination when compared with surrounding pancreatic parenchyma. Metastases most commonly occur in the liver and regional pancreatic lymph nodes. Abdominal ultrasonography may be helpful in supporting the clinical suspicion of a pancreatic mass and metastases with a reported sensitivity of around 50 - 75%. Nonetheless, a negative ultrasonographic examination does not rule either primary mass or metastases out.

Conversely, pancreatic nodules are not specific for insulinoma and may represent changes due to chronic pancreatitis, adenomas, adenocarcinomas, endocrine-active tumours of other cell types (gastrinoma, somatostatinoma), abscesses and cysts. Recently, contrast-enhanced ultrasound was successfully employed in discriminating insulinoma from pancreatic carcinoma.

Advanced diagnostic imaging

High-quality, dual-phase, thin-section multidetector computed tomography (CT) of the pancreas is effective in identifying a pancreatic mass in most affected humans. The use of CT has been reported in a sizeable number of dogs with insulinoma. Contrast-enhanced CT proved more sensitive than ultrasound at detecting insulinomas and the overriding majority of cases demonstrated hyper-attenuation of the pancreatic and metastatic masses during the arterial phase of the study. Overall arterial phase sensitivity was 94% for detecting insulinomas. Nevertheless, non-contrast CT examinations still have some merit, because a high proportion of lesions deformed the shape of the pancreas, rendering them visible on pre-contrast views.

Treatment

Acute hypoglycaemia

During an acute hypoglycaemic crisis 50% dextrose should be given as a slow IV bolus of 1 ml/kg, diluted to a 1:4 solution in 0.9% sodium chloride. The bolus should be followed with a continuous rate infusion (CRI) of a2.5 – 5% dextrose solution. The lowest concentration of glucose deemed necessary must be administered because glucose stimulates insulin secretion and this may cause rebound hypoglycaemia and a subsequent vicious cycle which may be difficult to break. Dextrose administration should be discontinued when clinical signs resolve, even if mild hypoglycaemia persists.

In most dogs, neuroglycopenia will resolve with administration of dextrose, even without complete resolution of the hypoglycaemia. However, some animals fail to respond clinically to dextrose administration alone. In such situations, dexamethasone (0.1 mg/kg IV BID) may be considered. Glucagon administration may also be helpful, because glucagon increases blood glucose concentration by promoting glycogenolysis and gluconeogenesis. While doses vary, a CRI of glucagon (approximately 10 (range, 5-25) ng/kg/min with or without concurrent 10% dextrose) may be successful in increasing glucose concentrations and in resolving clinical signs. However, like glucose, glucagon also increases insulin secretion and rebound insulin secretion is always possible but appears to be uncommon when these more conservative doses are used (Harris et al., 2020).

Some cases may be refractory to dextrose, glucococorticoids and glucagon and this may be due to persistently high insulin secretion and/or glycogen depletion because of chronic hyperinsulinism. Additionally, prolonged and profound hypoglycaemia may result in a series of changes which culminate in cerebral oedema and ultimately irreversible brain damage. Continued neurological signs despite normalisation of blood glucose concentration are suggestive of this complication. If this is considered possible, ancillary treatment for seizures and cerebral oedema may be implemented but the prognosis is ultimately poor.

Longer Term Treatment

Surgery

The long-term treatment of choice for insulinoma is surgical resection of both the tumour and any obvious metastases. Most tumours are readily discernible or palpable by the surgeon. Surgical exploration and biopsy of a pancreatic mass can confirm a diagnosis and may help in estimating survival time. When postoperative hyperglycaemia develops, it is usually transient and resolves once the normal beta cells, which have been suppressed by autonomous insulin secretion from neoplastic cells, regain function. About 10 - 20 % of dogs with insulinoma develop diabetes mellitus after tumour removal and require exogenous insulin for an unpredictable length of time (Del Busto et al., 2020). Other postoperative complications include pancreatitis, diabetic ketoacidosis, delayed wound healing, cardiac arrhythmias or arrest, haemorrhage, sepsis and leukopenia.

Medical Therapy.

This review of medical therapy is limited to agents that have been reported in dogs with naturally occurring insulinoma. Medical treatment is indicated prior to surgery, postoperatively if needed and in dogs in which surgery is not performed. Medical therapy can be divided into cytotoxic treatment directed at destroying insulin secreting beta cells and treatment aimed at relieving hypoglycaemia.

Cytotoxic therapy

Toceranib phosphate (Palladia®) a veterinary targeted multi-receptor tyrosine kinase inhibitor, which has shown benefit in a range of solid-type tumours in dogs, has recently been evaluated in the treatment of canine insulinoma (Sheppard-Olivares 2021). Thirty dogs were treated orally at a dose of 2.7 mg/kg (range 2 - 3.3 mg/kg). Most dogs were given this dose on a Monday, Wednesday, Friday regimen and 67% of dogs with measurable disease experienced either complete remission, partial response

or stable disease for a minimum of 10 weeks. Their overall median survival time was 656 days. Larger dogs were at increased risk for disease progression and the most common adverse events were mild gastro-intestinal toxicities. It was concluded that Toceranib afforded these patients clinical benefit whilst causing minimal adverse events.

Streptozocin, a nitrosourea antibiotic, selectively destroys beta cells in pancreatic or metastatic locations. The drug is nephrotoxic in dogs, but diuresis with saline will decrease drug contact time with renal tubular epithelial cells and may reduce the risk of nephrotoxicity. In one study, 17 dogs, most of whom had surgery with incomplete resection of gross lesions, were treated with 0.9% sodium chloride (18 mL/kg/hr IV) for three hours prior to, two hours during, and for two hours following streptozocin infusion. Streptozocin (500 mg/m^2) was given every three weeks for five treatments. Butorphanol (0.4 mg/kg IM) was administered immediately following streptozocin therapy as an antiemetic, but vomiting was still observed in approximately one-third of treatments.

Other side effects included: diabetes mellitus; transient hypoglycaemia and seizures; transient hyperglycaemia; transient increase in alanine amino transferase activity; azotaemia; mild thrombocytopenia; or mild neutropenia. Median duration of normoglycaemia in streptozocin-treated dogs was between 163 and 196 days.

This is not significantly different to the duration of normoglaecaemia in dogs that have been treated medically. The adverse event profile of Streptozotocin appears less tolerable than that of Toceranib and further studies are necessary before Streptozocin therapy can be recommended with confidence.

Relieving hypoglycaemia (Medical Management)

The main modes of relieving hypoglycaemia include dietary modification and treatment with prednisone, diazoxide or synthetic somatostatin. Small, frequent meals (every 4 to 6 hours) of a diet high in proteins, fats and complex carbohydrates are recommended. Simple sugars (present in soft moist dog foods) should be avoided.

Prednisone, the least expensive and most commonly used drug, increases blood glucose concentration by increasing gluconeogenesis and glucose 6-phosphatase activity, while decreasing blood glucose uptake into tissue and stimulating glucagon secretion. Prednisone is given at an initial oral dose of about 0.2 mg/kg/day, increasing to 0.5 mg/kg/day as needed. Doses can be gradually increased as needed, usually until the drug is no longer perceived to be decreasing seizure episodes or in cases where intolerable signs of iatrogenic hyperadrenocorticism (PU/PD) develop. Corticosteroids at higher doses of 1 - 2 mg/kg/day may also resolve the polyneuropathy in some cases.

Diazoxide is a benzothiadiazine derivative whose main action is to inhibit closure of pancreatic beta cell ATP-dependent K+ channels, preventing beta cell depolarisation and inhibiting opening of voltage-dependant Ca^{2+} channels. The resultant decreased Ca^{2+} influx causes decreased exocytosis of insulin-containing secretory vesicles. Diazoxide also increases blood glucose concentration by increasing glycogenolysis and gluconeogenesis and inhibiting tissue uptake of glucose.

About 70% of dogs respond to diazoxide doses of 10 - 40 mg/kg/day PO divided BID or TID. As is the case with prednisone, begin with the lowest dose of diazoxide and gradually increase the dose if required. Side effects in dogs are uncommon and include ptyalism, vomiting and anorexia.

Octreotide is a long-acting synthetic somatostatin analogue whose primary mode of action is the inhibition of insulin secretion through its binding affinity to any of five somatostatin receptor subtypes present in insulin-secreting tumours. Dogs show a variable response to octreotide, likely because octreotide variably inhibits glucagon and GH secretion. If the suppression of glucagon and GH secretion is of greater magnitude and duration compared to the suppression of insulin secretion, octreotide may worsen hypoglycaemia.

While some canine insulinomas may lack somatostatin receptors, 12 dogs with insulinoma treated with a single octreotide dose of 50 µg/dog SQ (median weight 23 kg), had decreases in plasma insulin concentration, yet concentrations of glucagon, GH and ACTH were not changed. These findings warrant studies using long-acting octreotide in dogs with insulinoma. No adverse side effects were reported with the use of octreotide. Side effects in people include mild pain at the injection site (which is lessened if the preparation is warmed before administration), nausea, vomiting, abdominal pain, constipation or steatorrhea.

Prognosis

Median survival time of dogs that underwent partial pancreatectomy, reported in various older studies, range from 12 to 14 months, whilst the two latest studies (which had a combined total of 165 dogs) demonstrated almost identical median survival times after surgery of approximately 20 months (Cleland et al., 2020; Ryan et al., 2021). It is postulated that earlier recognition and perhaps more radical surgery and better post-operative care account for this improved survival.

Moreover, dogs with clinical stage I disease have a significantly longer disease-free interval, whilst those with persistent post-operative hypoglycaemia have a poorer prognosis (Cleland et al., 2020, DelBusto 2020).

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CPD Questions

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CPD QUESTIONS: CANINE INSULINOMA

1. Which one of the following statements regarding insulinoma in dogs is CORRECT?

a. An insulinoma causes a decrease in endogenous insulin and affects the Langerhans cells of the pancreas.
b. An insulinoma causes and increase in endogenous insulin and affects the beta cells of thepancreas .
c. An insulinoma causes a decrease in endogenous insulin and affects the beta cells of the pancreas.
d. An insulinoma causes and increase in endogenous insulin and affects the Langerhans cells of the pancreas.
e. An insulinoma causes and increase in endogenous insulin and affects both the Lagerhans and bets cells of the pancreas.

2. Which one of the following statements regarding canine insulinoma is CORRECT?

a. Insulinomas are generally present diffusely through the pancreas.
b. Insulinomas are generally located in the body of the pancreas.
c. Most insulinomas are malignant.
d. Insulinomas are easy to detect on gross examination of the pancreas.
e. Insulinoma are common but underdiagnosed in dogs.

3. Which one of the following statements best describes the pathophysiological changes in a patient with an insulinoma?

a. Insulinoma causes the stimulation of counterregulatory growth hormone which results in hypoglygaemia.
b. Insulinoma results in hyperglycaemia and consequent inhibition of insulin production.
c. Insulinoma causes hypoglycaemia which stimulates systemic secretion of growth hormone, glucocorticoids and catecholamines.
d. The increased local production of growth hormone in insulinoma causes hypoglycaemia.
e. Insulinoma causes hypoglycaemia which results in a negative feedback mechanism to decrease insulin secretion .

4. Which one of the following statements regarding normal glucose metabolism is INCORRECT?

a. Insulin production is inhibited when glucose falls below 4.4 mmol/L.
b. Low blood glucose will cause the secretion of four counterregulatory hormones .
c. Glucagon and catecholamines are the main drivers of short-term response to hypoglycaemia.
d. Gradual decreases in glucose are less likely to stimulate catecholamine release.
e. Rapid decreases in glucose will stimulate glucocorticoid release.

5. Which one of the following statements regarding the clinical presentation of insulinoma is INCORRECT?

a. The mean age of dogs with insulinoma is 9 years (3 – 15yrs).
b. Insulinoma is most common in large breed dogs.
c. Female animals are predisposed to insulinoma.
d. Clinical signs are initially intermittent and unpredictable.
e. Some dogs with insulinoma may be obese.

6. Neuroglycopaenia is the cause of most of the clinical signs of an insulinoma. Which one of the statements below best describes this phenomenon?

a. Brain function is adapted to multiple sources of energy apart from glucose.
b. Clinical signs are due to the effect of episodes of hypoglycaemia on the brain function.
c. Mental dullness, disorientation, weakness and ataxia will occur due to the catecholamine response to hypoglycaemia.
d. Hypoglycaemia itself causes tremors and nervousness.
e. Catecholamine response to hypoglycaemia causes seizures.

7. Which one of the following serum chemistry diagnostic criteria for Insulinoma is CORRECT?

a. A blood glucose concentration of 3.5 mmol/L with low insulin levels.
b. A blood glucose concentration of 3.5 mmol/L with normal to elevated insulin levels.
c. Euglycaemia in the face of a 12 hours fast.
d. Euglycaemia with elevated insulin levels.
e. Hypoglycaemia with low insulin levels.

8. Which one of the following statements regarding imaging in patients with an insulinoma is CORRECT

a. Demonstration of a pancreatic mass is diagnostic for an insulinoma in a patient with intermittent hypoglycaemia.
b. Insulinomas are large masses which are distinct from the surrounding tissue.
c. Regional metastases are uncommon.
d. Routine imaging with CT and ultrasound is supportive of a diagnosis in a suspect case.
e. Routine CT is very effective in diagnosing insulinoma in dogs.

9. Which one of the conservative management methods suggested for insulinoma below is INCORRECT?

a. Glucocorticoid treatment to provide insulin resistance.
b. Diazoxide to decrease insulin production.
c. Octreotide a somatostatin analogue inhibit insulin secretion.
d. Multiple small meals of a diet hi in fat and protein with low levels of complex carbohydrates.
e. Phenobarbitone to control seizure activity.

10. Which one of the following statements regarding surgical management of a patient with an insulinoma is CORRECT?

a. Surgical excision is not the long term treatment of choice.
b. Tumour location is best determined with pre-operative imaging.
c. Obvious metastases will make surgery an unviable treatment option.
d. Most tumours are easily palpated by the surgeon.
e. Post operative hypoglycaemia is a major post operative complication and most dogs will develop diabetes mellitus.

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Interdigital Furunculosis: Medical and Surgical Options

The reasons for these interdigital cysts and the ins and outs of treatment

Disease description and mechanisms

Interdigital furunculosis (IF) and folliculitis, sometimes called interdigital cysts, can occur for multiple reasons. Lesions include interdigital erythema, oedema, nodules, haemorrhagic bullae, haemorrhagic draining tracts, ulcers, and scarring. The most common reason for IF is allergy (Figs 1,2). The skin of the paws, especially the interdigital skin, becomes inflamed with an allergy flare, leading to barrier dysfunction and pedal pruritus. Pruritus is manifested as licking, which can cause trauma to the hair follicles, causing folliculitis. Pieces of hair shaft (keratin) will become pushed into deeper tissues, causing a foreign body reaction.

Due to continued inflammation and licking, secondary infection becomes a problem, which causes more inflammation. A cycle of inflammation/infection ensues, which can lead to antibiotic resistance, scar tissue, and cellulitis. In allergic dogs, multiple paws and interdigital spaces will be affected and there often will be other signs of allergic skin disease (eg, more general pruritus, and recurrent skin infections). Affected animals are often short-coated, allergy-prone dogs such as pit bull terriers, Great Danes, English and French bulldogs, Labrador retrievers, Chinese shar-pei, and bull terriers.

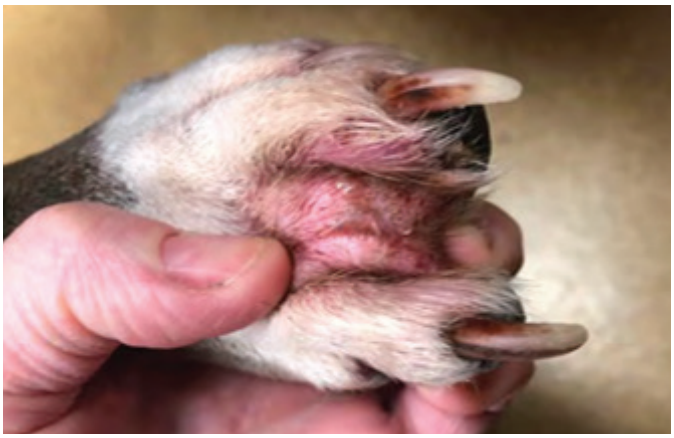

Figure 1: *Allergy related interdigital furunculosis, Note the interdigital erythema and brown staining/paronychia*

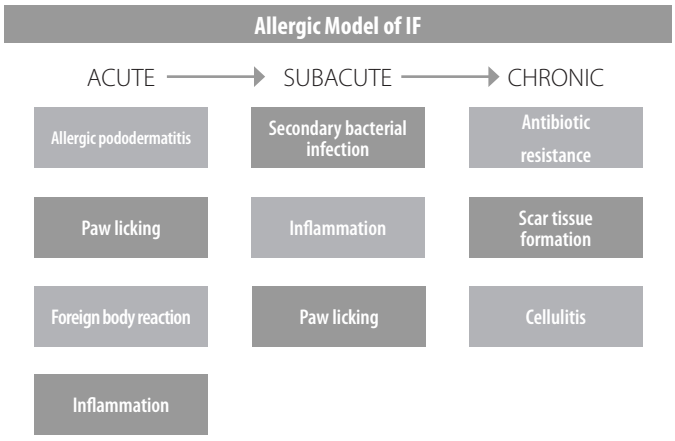

Figure 2: *Allergic model of Interdigital furunculosis*

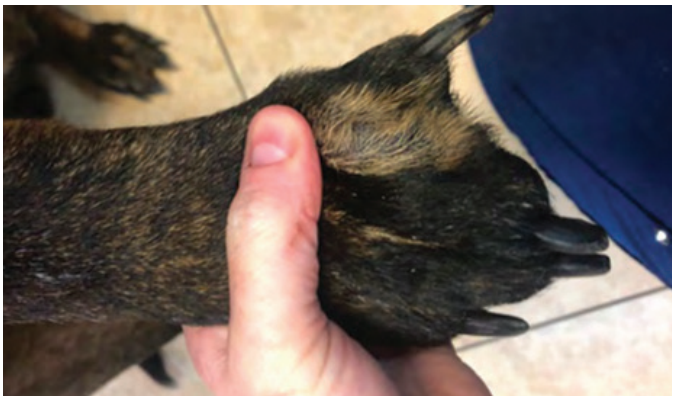

Figure 3: *Mechanically related Interdigital furunculosis. Note the position of the nodule between digits 4 and 5 without evidence of allergic inflammation.*

In non-allergic dogs, the mechanism of IF is mechanical. Furunculosis will often develop only between digits 4 and 5 on the front paws (Figs 3-5). Affected animals are often larger-breed, heavy dogs like mastiffs, English bulldogs, and Labrador retrievers. Dogs with webbed paws, deep palmar interdigital pockets, obesity, and conformation abnormalities are more prone to this type of IF. The increased weight of these heavier dogs will cause friction between this interdigital space, resulting in follicular plugging and comedo formation on the palmar surface of the paw. Dogs with conformation changes secondary to arthritis and resulting in valgus deviation of digit 5 are also prone to interdigital friction and comedo formation. Smaller dogs prone to arthritis-related IF are Shetland sheepdogs and Cavalier King Charles spaniels.

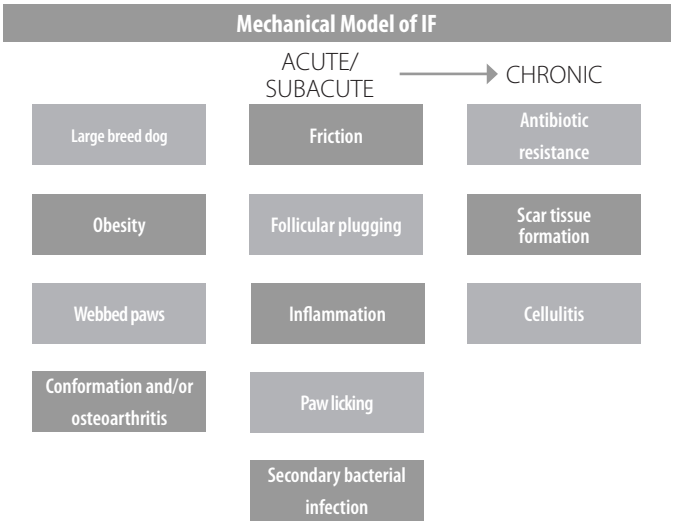

Figure 4: *Mechanical disease model of Interdigital Furunculosis*

Some dogs may have a contribution of both mechanisms; for example, an obese and allergic Labrador retriever with pedal pruritus and other signs of allergy with more IF on multiple paws but more pronounced disease between digits 4 and 5 on the front paws. Other mechanisms of IF include demodicosis and foreign bodies. (VDM - It has also been speculated that trauma to interdigital skin caused by short,bristly hairs rubbing against the skin of apposed interdigital webs can play a role and chronic friction due to abnormal conformation.)

Chronic IF can lead to scar tissue and soft tissue proliferation, resulting in false paw pad formation. False paw pad formation occurs when the palmar interdigital skin becomes thickened, callused, and confluent with the adjacent paw pads, resulting in conjoined pads (Fig 6). False paw pad formation results in even deeper palmar interdigital pockets, leading to trapped keratin, moisture, and infection. Hyperkeratosis and deep crevices that harbor debris and ingrown hairs are contributory factors.

Figure 5: *Mechanically related Interdigital furunculosis. Note palmar interdigital comedo formation between digits 4 and 5 without evidence of allergic inflammation.*

Figure 6: *Development of a false paw pad due to scarring and tissue proliferation.*

Diagnosis

History and a complete physical with a dermatology-focused examination is essential in determining whether the IF is allergy-related or mechanical. Skin cytology and scraping (or hair plucks) are important in determining if a secondary secondary bacterial infection or demodecosis is present. Demodex mites may not be easy to find due to the presence of so much purulent material; a parasite treatment trial with an isoxazoline product is recommended. Bacterial culture and sensitivity testing is often indicated because there is often a history of multiple courses of antibiotic treatment.

Treatment

The primary cause should be identified and controlled. If the cause is allergic in nature, follow your standard allergic work-up. Many dogs with IF have a combined food and environmental contributors and do best with a prescription hypoallergenic diet and aggressive medical management for environmental allergies.

Because there is so much inflammation involved in IF, lokivetmab (Cytopoint®) and oclacitinib (Apoquel®) often fail to control significant or chronic disease. Systemic glucocorticoids and cyclosporine are usually needed in my practice.

Secondary infections must be treated and might involve longer courses of antibiotics (6 to 8 weeks). Pentoxifylline (Trental®) can improve antibiotic efficacy and reduces inflammation. Topical therapy involving antimicrobial paw soaks (chlorhexidine and/or diluted bleach) is essential.

Topical antimicrobials mixed with a topical glucocorticoid and dimethyl sulfoxide (like fluocinolone acetonide 0.01% (Synalar®) and dimethyl sulfoxide 60% (Synotic®) mixed with enrofloxacin (Baytril®) can be helpful for treatment and flares. (VDM- Mupirocin topical therapy is also extremely effective and well absorbed through the skin)

If there is a mechanical cause of IF, management of arthritis and/or obesity is critical. In markedly obese dogs with IF, significant weight loss to "unload" the front paws results in substantial improvement. Managing secondary infection is important and topical antimicrobials and anti-inflammatories are helpful. Dogs with mechanical IF rarely need systemic anti-inflammatories unless they have a mixed pattern of allergic and mechanical IF.

Pain medications can be helpful for skin reasons and management of concurrent arthritis. Protection of the paw with shoes and controlling substrates on walks can help with the discomfort of IF. In cases of mechanically caused IF which fail to respond to weight loss and topical therapies, laser surgery following the Duclos method is often successful.

This laser surgery is not fusion podoplasty. The details can be found on the Aesculight website.

Fusion podoplasty is the last resort because the abnormal weight-bearing present with mechanically caused IF is then transferred to the adjacent toes, causing IF in the associated interdigital space.

Definitions: by: Dr L L van der Merwe

- *Folliculitis is the inflammation of the hair follicle, often secondary to a bacterial infection.*
- *Furunculosis is the inflammation, generally due to a bacterial infection, and rupture of a hair follicle , thus affecting the subepidermal tissue causing draining tracts.*
- *Follicular Cysts: It is suspected that the cause of follicular cysts may have a genetic or congenital basis and may also be due to injury or a predilection to follicular hyperkeratosis. This injury can be classified as microtrauma, which can be caused by licking, infections, inflammation and solar damage. This trauma results in narrowing or plugging of the follicular openings which in turn causes retention of follicular contents, dilation and eventually cysts. When cysts rupture a foreign body reaction occurs.*

Surgical removal of the follicular cysts

By: Dr L.L. van der Merwe

With interdigital furunculosis and cysts, surgical removal of the follicular cyst and keratinaceous foreign material inside these cysts is the only way to get complete resolution. Laser surgery is the preferred technique as it minimises risk to the adjacent tissues compared to traditional scalpel surgery or cautery and thus has more rapid healing and less post operative discomfort.

Use of the laser minimises the risk of damage to adjacent tissues when compared to traditional surgical methods. Therefore, healing time is quicker and there is less post operative discomfort than with traditional methods which require a scalpel and/or cauterizing procedure. The normal healing period is four to 6 weeks where the paw needs to be bandaged

In the case series by Duclos, the 28 dogs included in the study had recurrent lameness, pain, and nodules, or draining sinuses in the dorsal interdigital skin, had failed to respond to antibiotic therapy, and were negative for Demodex mites and dermatophytes. All 28 had laser surgery and nine dogs required two surgical procedures and two dogs required three surgical procedures.

The CO^2 laser energy quickly ablated normal soft tissue bordering the cysts which has a high water content, thus leaving tissue with low water content(e.g. keratin) unaltered. This differential in speed of ablation assisted with the identification of the comedones and cysts. Additionally there is markedly less haemorrhage with laser surgery.

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About us:

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Purpose:

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The survey will be conducted online, ensuring convenience and flexibility in your participation. It should take approximately 5 minutes to complete, and all responses will be treated confidentially. Your individual information will be anonymised, and the aggregated results will be used solely for research purposes.

To participate in the survey, please Click Here or scan the QR Code above.

Should you have any questions or require further information, please feel free to contact me at phuti@raphta.com or 076 635 6053. We greatly appreciate your time and expertise, and we are excited to receive your valuable input.

Thank you in advance for your support and contribution to this important research endeavor.

Yours sincerely,
Thulani S Gcabashe
Chairman

Feline Infectious Peritonitis

Dr Rowena Watson
Small Animal Medicine Resident
Johannesburg Specialist Veterinary Centre

Feline Infectious Peritonitis (FIP) has been a longstanding implacable enemy of every cat-lover. It arises via a perfect storm of events: a cat must be infected with the normal Feline Corona Virus, which must then undergo multiple mutations to allow a change in tropism from enteric cells to macrophages and an alteration in virulence, and then the host immune response must fail (Pedersen, 2014).

Introduction

It must be noted that not every cat with feline coronavirus will develop the mutations and that not every cat that develops the mutations will develop FIP. Stress and superinfections can increase the risk of FIP development.[2] It is thought that much of the pathology and manifestations of FIP are associated with how the macrophages and the immune system respond to infection. Cats that do not develop clinical FIP despite mutations in the virus are thought to mount a vigorous cell-based immune response.[3] Antibodies are considered to be counterproductive in a FIP infection by enhancing viral uptake and replication by macrophages, an effect called antibody dependent enhancement.[1,4] Antibodies are also thought to contribute to type III hypersensitivity vasculitis.[3]

Within these assumptions, it is believed that the effusive form of FIP is due to a failure to mount a T-cell response in the face of a vigorous B-cell response.[3] The dry form of the disease represents an intermediate state – the cellular response is effective at confining the virus in macrophages in focal sites.[3] The different forms, however, can be somewhat interchangeable: in experimental infection, the dry form usually follows a brief bout of effusive disease, and in the terminal stages of the disease, immunity may completely collapse, and a dry form of FIP can become somewhat effusive.[3]

Diagnosis

Diagnosis of the disease remains challenging and is based mainly on a compatible history, signalment, and clinical signs, supported by clinical assays. FIP is typically seen in young cats, often from multi-cat backgrounds (shelters, breeders).[5] CBC findings often include non-regenerative anaemia, total leukocytosis and possibly lymphopenia. Interestingly, although lymphopenia is a variable finding, flow cytometry shows a selective decrease in T-lymphocytes, even in cats with normal lymphocyte counts.[3] Pederson et al. (2015) found that the degree and timing of onset of lymphopenia can be associated with the severity and rapidity of disease progression.

Biochemical changes often, but not always, include an increased albumin-to-globulin ratio, with an increase in gamma-globulins.[5] It may be accompanied by a monoclonal gammopathy demonstrated on serum electrophoresis. Most cases also show bilirubinaemia and bilirubinuria due to haemolysis. No biochemical changes are specific for a diagnosis of FIP, but the finding of a high A:G ratio has a high negative predictive value when the prevalence in a population is low.[5] Azotaemia and increased liver enzymes are also possible. Acute phase proteins can be analysed but cannot distinguish between FIP and other inflammatory conditions.[5]

Diagnostic imaging can increase suspicion of FIP, although it is a relatively non-specific test. On abdominal ultrasound, enlarged lymph nodes and pyogranulomatous lesions on kidneys, intestines and liver.[5] Granulomas can also be seen on thoracic radiographs. Effusion analysis is instrumental for diagnosis. Effusions contain high levels of protein (>35 g/l) and have a relatively low cellularity, which consists mainly of non-degenerate neutrophils and macrophages.[5] Rivalta's test on effusion simply discriminates between a transudate and exudate – it is not specific for FIP, with other possible diagnoses being septic peritonitis and lymphoma.[5] The effusion can also be used for immunohistochemical staining of viral particles within macrophages or RT-PCR.[5]

PCR is another frequently used diagnostic method. It was previously believed that only cats with FIP would have detectable levels of FCoV in their blood or tissue – this has proven to be false. Up to 80-90% of FCoV-infected cats will have positive RT-PCR results.[5,6] An assay to detect FCoV mRNA was also not a guaranteed diagnosis, with up to 52% of non-FIP cats having positive results.[5] RT-PCR run on effusion samples tended to have a much higher specificity, although FCoV RNA has still been detected in effusions from cats without FIP.[5] Fewer studies are available on PCR analysis on CSF and aqueous humour, although results seem to be more promising.[5] An assay is also available for real-time RT-PCR to detect S-gene mutation, but this has not proven any significant advantage over other PCR assays.[7]

Coronavirus titres are often high in FIP cases, but surprisingly, low titres and even negative titres have been documented.[8] It is thought to be due to antibody binding to massive amounts of the virus or immune exhaustion.[3] Additionally, healthy cats may have exceptionally high titres. A positive titre, whether high or low, only indicates exposure to FCoV.

Treatment

Until very recently, no treatment for FIP has been available. In 2018, the first in-vitro assessment of the efficacy of GS441-524 was published, followed by the first clinical trial in 2019.[9,10] This trial showed remarkable results, with 25 of 31 cats surviving to longterm follow-up (the longest follow-up so far is seven years). GS-441524 is the metabolite of Remdesivir and is itself metabolised intracellularly to an active triphosphate metabolite.[9] This molecule acts as a nucleotide analogue and, when incorporated into RNA, triggers the termination of RNA replicase, halting viral replication.[9] Due to the patent being held by Gilead, all research on GS-441524 in cats (and its parent compound, Remdesivir) was halted. However, a roaring black-market trade sprung up, with many "brands" of GS-441524 products being produced and exported. Thousands of cats were treated successfully via this black market trade, with large amounts of anecdotal data collected. Over time, the doses used have been titrated upwards to reduce the chances of relapse.

As COVID swept the world, Gilead seized the opportunity and registered Remdesivir R for use in COVID patients. It has opened the door for legal use of Remdesivir® across most of the world and the production of GS-441524 by compounding pharmacies, including in South Africa.

GS-441524 is administered once or twice daily, depending on whether injectable or oral medication is used, and the dose. It is administered daily for 84 days. Different starting doses are reported, depending on what barriers the virus has crossed, i.e. breaching the blood-brain-barrier or blood-eye-barrier. Side-effects are mostly relatively benign, with the main side-effect being pain on injection and the possibility of fibrosis and skin lesions forming. Increases in hepatic enzymes have been reported, but with no apparent liver toxicity, as well as mild, non-progressive renal toxicity (also not associated with renal failure).[11] A larger concern emerging with the use of injectable GS441524 or Remdesivir is the occurrence of feline injection site sarcomas (FISS). Although this was considered a concern when GS441524 therapy first emerged, injectable medication was considered superior to oral medication, so it became a calculated risk.

However, although no formal data has been published, there are anecdotal reports of an increasing prevalence of feline injection site sarcoma amongst cats treated with injectable medication. Additionally, in August 2023, the Minnesota Urolith Centre discovered uroliths comprised entirely of GS441524.[12] As GS441524 is primarily excreted via the kidneys, and it's sparingly soluble in water, the formation of uroliths is understandable, although it appears to be a relatively low risk (only three reported cases out of thousands of cats treated).

Thus far, no studies have been large enough to accurately demonstrate the relapse rate of treatment with GS-441524, but relapses are estimated to be between 5 and 15%, with most relapses being associated with neurological disease.[11,13] Unfortunately, there is no way to predict which cats will relapse. A recent study has investigated the use of alpha-1-acid-glycoprotein in predicting which cats will relapse has shown promise, but this assay is unavailable in South Africa. Deciding if it is safe to stop treatment should be based on clinical progress, with weight gain being a crucial prognosticator and normalising haematological and biochemical parameters.[11,14]

COVID has also led to the release of novel antivirals. Of these, molnupiravir has shown promise as a second-line medication in the treatment of resistant FIP, with one of the black-market Chinese companies having performed "clinical trials" and claiming good efficacy.[15] Molnupiravir has a interesting history; it was originally studied in the late 1970's as part of biological weapons research. Focus shifted to its medical use as the cold war ended,and it was found to have efficacy against a wide range of viruses, including coronaviruses.[16]

Molnupiravir was granted emergency use authorisation in December 2021 due to COVID. Although molnupiravir had been speculated as a potential treatment for FIP, black-market "research" was the first to realise its benefit. This study treated 286 cats with FIP, including small numbers of cats with ocular and neurological involvement, with all cats in remission and healthy at three to five months after treatment ending.[15] Molnupiravir is metabolised to β-D- N4-hydroxycytidine 5'-triphosphate (NHC-TP), which can exist as two tautomers.[16,17] In one form, it mimics cytidine, and in the other, it mimics uridine. NHC-TP is easily incorporated into viral RNA and is able to escape proofreading.[17] When viral replication

occurs, it may be read as either a cytidine or a uridine, depending on it's tautomer at that point and this induces lethal mutagenesis in subsequent viral copies.[16,17]

Safety and efficacy has been established in in vitro studies have established safety and efficacy, although cytotoxicity is shown at high concentrations.[18] Very little however, is published on its use in cats. In 2022, Roy et. al. published retrospective survey data on cats treated with black-market molnupiravir.[19] Most of these cats had failed GS441524 therapy (once, twice or three times), although it was used as a first line treatment in a small number of the cats. This study showed good efficacy with 24 of the 26 cats responding to treatment and in remission.[19]

A recent case series was published detailing the treatment of 18 cats with molnupiravir, including cats with neurological or ocular involvement.[20] Clinical response in 14 cats was rapid, with those cats still healthy at 55 to 107 days after discontinuation of treatment.[20] The potential side effects of molnupiravir are what limited its use in human medicine until COVID.[16] Molnupiravir demonstrates significant cytotoxicity in vitro at higher concentrations, and when authorising its use for COVID, the concern was that it may induce mutations within the virus that enhance disease.[16] A recent study suggested this may not be the case in COVID, but this does not necessarily extend to FIP.[17] Additionally, as a mutagen, the concern is whether it may not cause cancer in the long-term in treated cats.[16] Short term side effects seem relatively innocuous, with Roy et al. (2022) documenting GIT effects, skin and coat changes, muscle wasting and reversible bone marrow suppression at high doses, and Sase (2023) describing elevations in ALT and icterus.

A big question is whether molnupiravir should be recommended as a first line treatment, ahead of GS441524 / Remdesivir. A big advantage for molnupiravir is the cost. Although GS therapy is becoming significantly cheaper, it is still a costly endeavour, with molnupiravir being a fraction of the price. The lack of data on long term side effects and efficiency for molnupiravir should also form part of the consideration, as well as the potential for the development of viral resistance. FIP is no longer the undefeatable enemy of every cat-owner. Although diagnosis and treatment are not easy nor inexpensive, the chances of cure of FIP are high. Research is ongoing into FIP with current research areas including novel antivirals, combination protocols and protocols to optimise existing antivirals and gene engineering to "re-programme" the immune response. Hopefully, the next five years will yield even better discoveries.

Figure 1: *Squirrel, at the start of treatment*

Case 1: Squirrel

A neutered, domestic longhair named Squirrel had been found as a stray at about five months old. Squirrel was rehomed at nine months old. Since rehoming, the new owners had been struggling with a capricious appetite – which the foster owners had never encountered. He presented at 15 months old after the owners noted an abnormality in his right eye and anorexia. On presentation, Squirrel was lethargic and had an overall unkempt

appearance, with a poor coat and the presentation of weight loss (BCS 2.5/9). He was slightly dehydrated, evidenced by sunken eyes and decreased skin turgor. He was pyrexic with a temperature of 40.1°C, struggled to walk, had anterior uveitis of the right eye with an obvious aqueous flare. On haematology, he showed a moderate, non-regenerative, normocytic anaemia (Ht of 28%, which dropped to 21% in the following days) and a neutrophil count of 11.8 x 10^9 /l. On biochemistry, his albumin was normal (28g/l), but globulins were elevated (67g/l), giving a ratio of 0.4. ALT was top normal at 108U/l (*Table 1*).

Abdominal ultrasound revealed a severe bilateral hypoechoic subcapsular renal halo with an extension of hypo to anechoic material or fluid into the retroperitoneal space. There were oval, hypoechoic renal cortical lesions with mild renal enlargement. A diffuse moderate abdominal lymphadenopathy was evident, and the liver was hypoechoic and heterogeneous. All else was within normal limits. Cytology from fine needle aspirates of the subcapsular kidney material and the retroperitoneal material was consistent with a pyogranulomatous reaction. Coronavirus titres

Table 1: *Haematology values: Squirrel*

RCC	4.8 x 10^{12}/l	(5.3-10.60)
Ht	28%	(29.7-44.5)
Retic	32K/ul	(3.0-50.0)
Neutrophils	11.8 x 10^9/l	(2.5-12.5)
Lymphocytes	1.2 x 10^9/l	(0.40-6.80)
Monocytes	0.9 x 10^9/l	(0.15-1.7)

Table 2: *Serum biochemistry values : Squirrel*

Glucose	5.18mmol/l	(4.11-8.84)
Creatinine	153umol/l	(71-212)
Urea	7.2mmol/l	(5.7-12.9)
TP	95g/l	(57-89)
Albumin	28g/l	(22-40)
Globulin	67g/l	(28-51)
Alb/Glob	0.4	
ALT	108U/L	(12-130)
ALKP	<10U/L	(14-111)

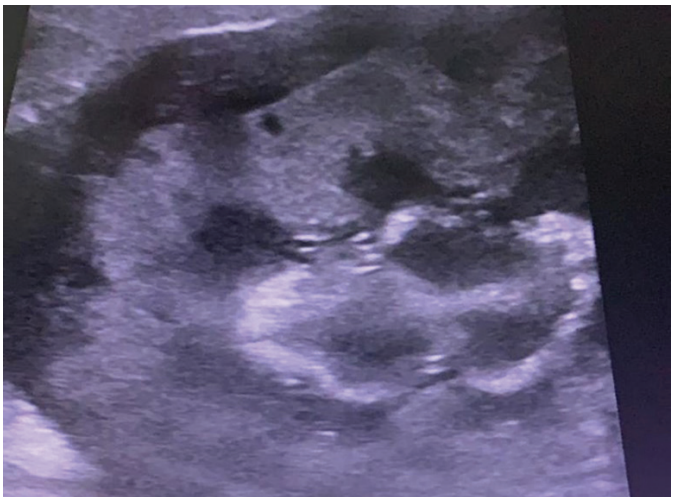


Figure 2: *Squirrel: right kidney*

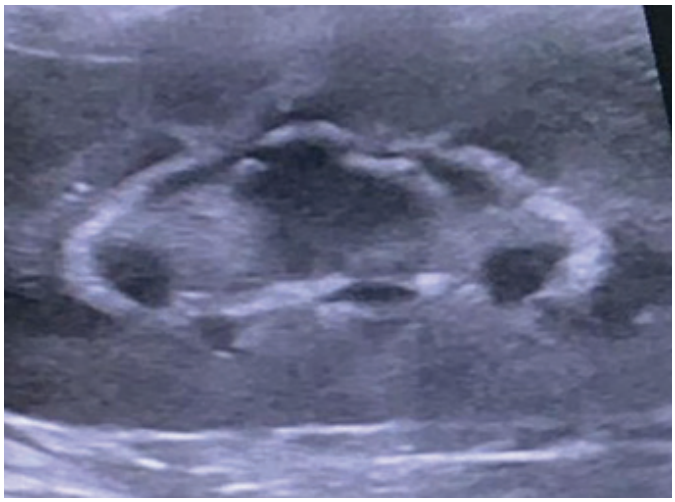


Figure 3: *Squirrel right kidney, after 12 weeks treatment*

were performed for interest and were 1:86. A likely diagnosis of FIP was made, with ocular and possible neurological involvement. Treatment with a compounded injectable form of GS-441-524 was started at 10mg/kg due to suspected neurological involvement. Additional supportive treatment included B12 due to the anaemia and anti-emetics. Within 48h, Squirrels pyrexia had resolved, and within five days, he was eating sufficiently to be discharged. He appeared to have a thrombo-embolic event whilst in hospital, resulting in the tip of his ear and the tip of his tail necrosing and eventually sloughing off. The owners continued medicating him at home with no other intervention necessary.

Routine follow-ups were performed at four weekly intervals, with clinical improvement and improvement in haematological and biochemical parameters. By week 12, when treatment was due to stop, Squirrel had gained 1.7kg with a BCS of 6/9. His uveitis had cleared entirely, as well as all neurological deficits. He was clinically normal. His haematocrit had increased to 33% with a normal leukocyte count and a lymphocyte fraction of 20%. His albumin was 26g/l and globulins were 47g/l, with a ratio of 0.6. All other biochemical parameters were normal. A breathtaking change was seen on abdominal ultrasound, with the improvement of the kidney lesions being the most prominent. Three years after the end of treatment, Squirrel is alive and healthy.

Figure 4: *Squirrel at 2 year follow-up*

Case 2: Raven

Raven, a nine-month-old male, castrated, domestic shorthair, presented after being diagnosed with FIP at his primary vet, based on signalment, clinical signs and appropriate blood work. He had been syringe-fed for the past three weeks and treated with prednisolone. On presentation, Raven was emaciated, with BCS 1/9, and overall, small for his age. He was severely dehydrated, and ad pale mucous membranes. He was tachypnoeic, tachycardic and hypothermic on presentation (35.8°C). He presented with iritis, and later developed a severe keratitis. He was paretic and only able to lift his head. He was urinary and faecally incontinent. Twelve hours after presentation, Raven started to show seizure activity.

Raven had severe non-regenerative anaemia (Ht 16%), mild mature neutrophilia (14.25 x 10^9/l (per litre)), and low normal lymphocytes (0.8 x 10^9/l (per litre)) (table 3). Biochemistry showed mild hyperglycaemia, likely due to stress, with low normal albumin (25g/l – however, this was probably higher due to severe dehydration) and a hyperglobulinaemia (70g/l), giving a ratio of 0.4. ALT and ALKP were both raised (212U/L and 117U/L, respectively). Creatinine was low, reflecting severe muscle wasting (Table 4). Thoracic radiographs showed lesions suggestive of pulmonary granulomas. An abdominal ultrasound showed enlarged abdominal lymph nodes and hypoechoic subcapsular halos, with hypoechoic lesions within the kidneys – a classical FIP appearance. Raven was started on a locally compounded GS-441524 injectable

Figure 5: *Raven shortly after presentation*

Figure 6: *Raven showing iritis of the left*

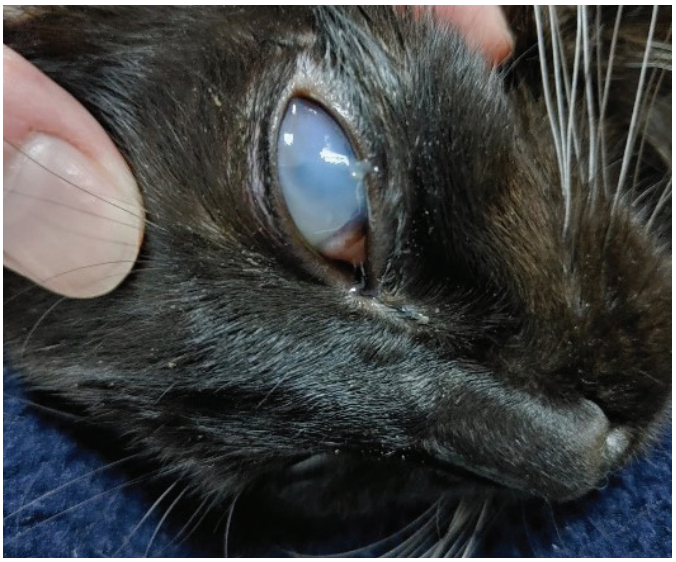


Figure 7: *Raven with keratitis of the left eye.*

Table 3: *Serum biochemistry values: Raven*

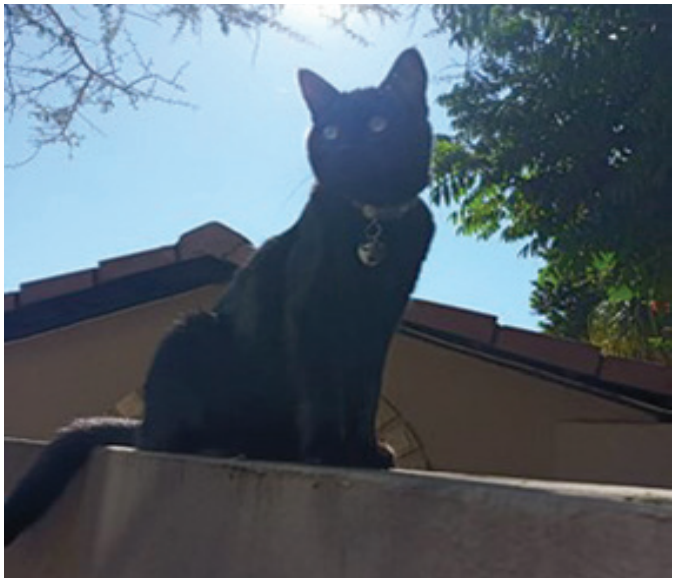
Glucose	9.6mmol/l	(4.11-8.84)
Creatinine	43umol/l	(71-212)
Urea	7.4mmol/l	(5.7-12.9)
TP	95g/l	(57-89)
Albumin	25g/l	(22-40)
Globulin	70g/l	(28-51)
Alb/Glob	0.4	
ALT	212U/L	(12-130)
ALKP	117U/L	(14-111)

Table 4: *Haematology values: Raven*

RCC	3.4 x 10^{12}/l	(5.3-10.60)
Ht	16%	(29.7-44.5)
Retic	23.2K/ul	(3.0-50.0)
Neutrophils	14.25 x 10^{9}/l	(2.5-12.5)
Lymphocytes	0.8 x 10^{9}/l	(0.40-6.80)
Monocytes	1.5 x 10^{9}/l	(0.15-1.7)

product at 10mg/kg. He was started on Levetiracetam to control seizures and given supportive treatment of vitamin B12, anti-emetics, and SAMe. He remained critical for several days, with his haematocrit dropping to 12% on day five. He had further seizures on days two and three of treatment. Nutritional support was maintained via a nasoesophageal tube.

Over the next two weeks, he gradually strengthened, partially regained bladder and bowel control, and started eating by himself. He was discharged on continued therapy with GS-441524 and SAMe. After 12 weeks of therapy, Raven's body weight had more than doubled (from 2.05kg to 4.3kg), and his BCS was 5/9. His ocular exam was normal, with the keratitis fully healed. He was fully mobile and showed no neurological signs; all haematological and biochemical parameters had normalised. He was fully continent.



Two years after treatment ended, Raven is still doing well.

Figure 8: *Floof, shortly after starting treatment (had already shown improvement)*

Case 3: Floof

Floof, a 10 week old, male intact, domestic longhair, was found as part of a feral colony at 6 weeks old. He was taken into a foster home and had been vaccinated at 8 weeks old. Shortly after vaccination, he became progressively lethargic, his appetite decreased and he showed intermittent pyrexia, with no response to antibiotics. His breathing had become abnormal a day prior to presentation.

On presentation, Floof was emaciated, weighing only 0.65kg. He was tachypnoeic, which progressed to overt dyspnoea with exertion. He was pyrexic on presentation (39.5°C), but showed no ocular or neurological abnormalities. On the day after presentation, his dyspnoea progressed to requiring oxygen supplementation. Haematology showed a severe anaemia (Ht 14%), that was inappropriately regenerative (reticulocyte count 62), with a mature neutrophilia. On biochemistry there was a low normal albumin (23g/l) with a normal globulin level, but a lowered A:G ratio of 0.6. Creatinine was low, reflecting a poor muscle mass (Tables 5,6). He was tested twice for FIV and FeLV, and was negative for both. Thoracic radiographs showed a mild pleural effusion, and a large space-occupying lesion in the cranial mediastinum. On ultrasound, the mass had a mixed echogenicity, with a small amount of fluid surrounding it. Fine needle aspirates of the mass showed predominantly macrophages with non-degenerate neutrophils. PCR on the small amount of fluid obtained was negative for toxoplasmosis. Although differential diagnoses for Floof included lymphoma, mycobacterium, fungal disease, toxoplasmosis and FIP, the latter was considered most likely based on cytology not supporting lymphoma, the rarity of fungal and mycobacterial disease, and the negative toxoplasma PCR. Finances and Floof's size and dyspnoea precluded further diagnostics.

Table 5 *Haematology values : Floof*

RCC	3.34 x 10^{12}/l	(5.3-10.60)
Ht	14%	(29.7-44.5)
Retic	62K/ul	(3.0-50.0)
Neutrophils	15.4 x 10^{9}/l	(2.5-12.5)
Lymphocytes	2.86 x 10^{9}/l	(0.40-6.80)
Monocytes	2.19 x 10^{9}/l	(0.15-1.7)

Table 6 *Serum biochemistry values: Floof*

Glucose	6.02mmol/l	(4.11-8.84)
Creatinine	<9umol/l	(71-212)
Urea	6.1mmol/l	(5.7-12.9)
TP	59g/l	(57-89)
Albumin	23g/l	(22-40)
Globulin	36g/l	(28-51)
Alb/Glob	0.6	
ALT	75U/L	(12-130)
ALKP	16U/L	(14-111)

As Floof was a welfare kitten, and finances were limited, after a full discussion of risks and consequences, it was decided to treat Floof with molnupiravir, at a dose of 10mg/kg, twice daily. Within two days, Floof no longer needed oxygen support, and was eating ravenously (Figure 8). Five days after starting molnupiravir, his radiographs showed distinct improvement. Floof completed a 10 week course of molnupiravir, weighing 2.7kg at the end of his treatment, and is currently healthy seven months after finishing treatment.

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