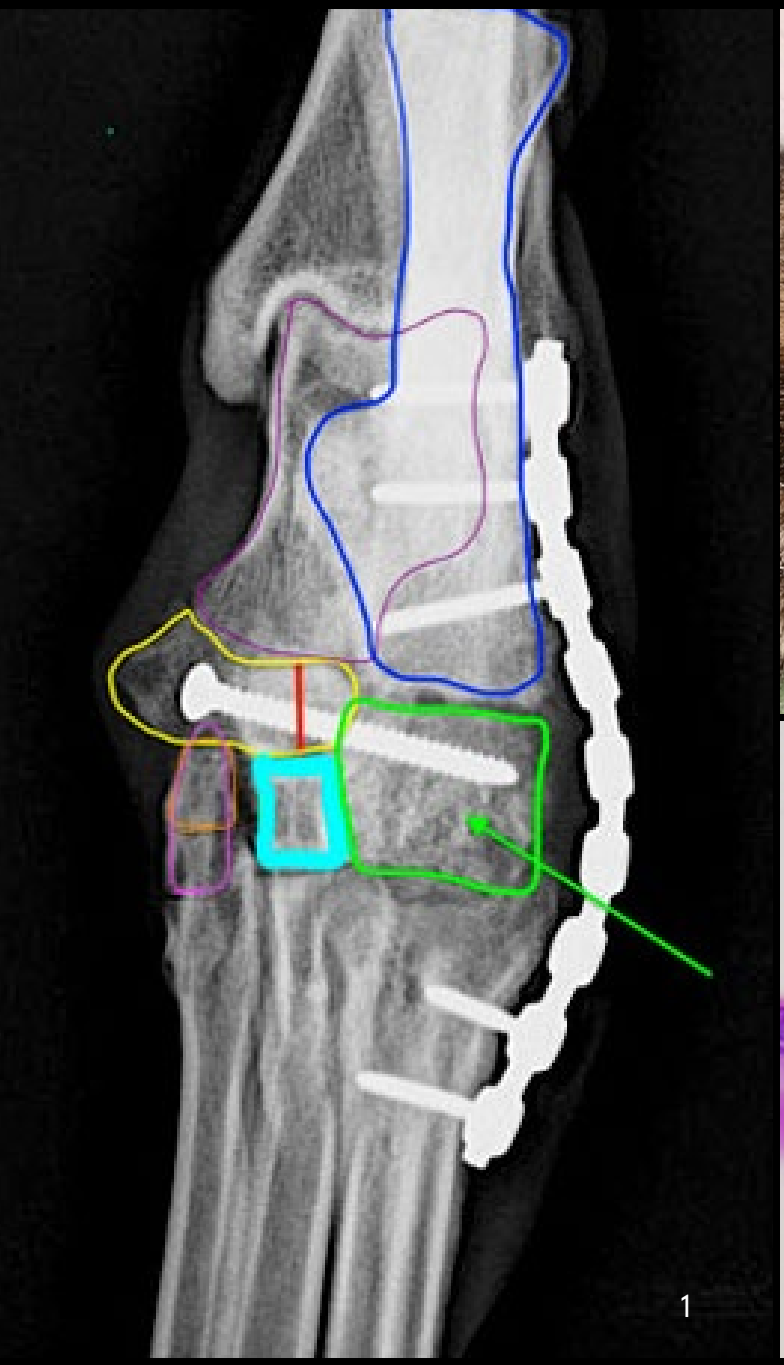
# C&T

THE UNIVERSITY OF SYDNEY
Centre for Veterinary Education

*Control & Therapy* Series
Issue 310 | March 2023



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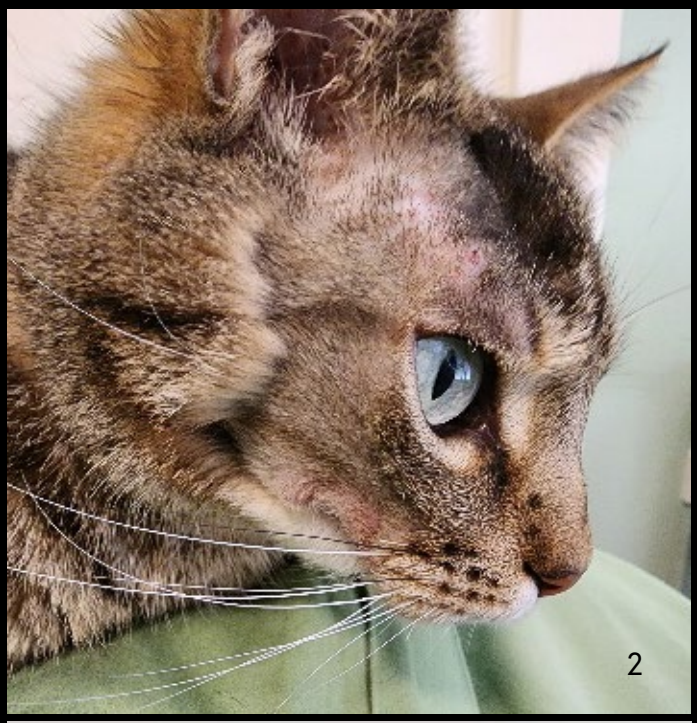

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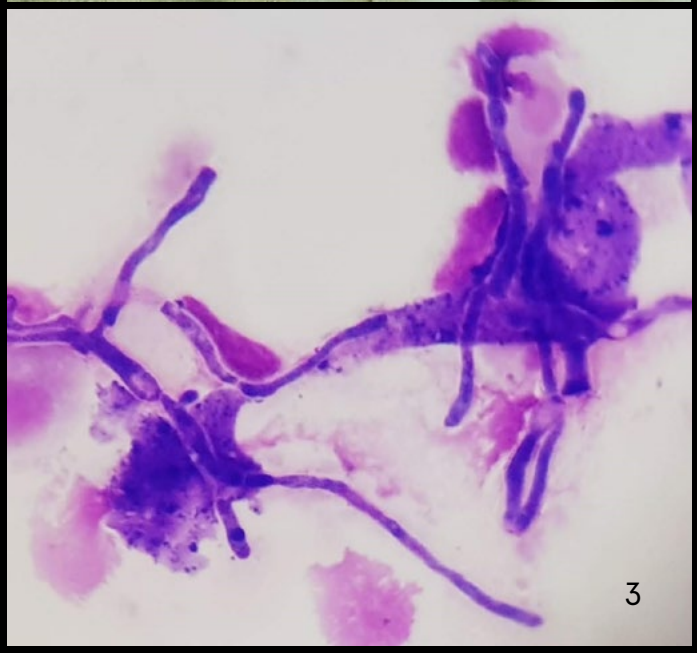

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The *C&T* Series thrives due to your generosity. If you're reading this and have been contemplating sending us an article, a reply or comment on a previous *C&T*, or would like to send us a' What's YOUR Diagnosis?' image and question or seek feedback from colleagues, please don't hesitate to contact us.

The *C&T* is not a peer reviewed journal. We are keen on publishing short pithy practical articles (a simple paragraph is fine) that our readers can immediately relate to and utilise. And the English and grammar do not have to be perfect—our editors will assist with that.

## Join in—write up that interesting case

*C&T* authors agree that it is extremely satisfying to read their articles in print (and the digital versions) and know they are contributing to veterinary knowledge and animal welfare.

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# FROM THE DIRECTOR

We all know that disruption – particularly of the unexpected and unwelcome kind – can be a great catalyst for change. Being forced into a different vantage point might challenge our assumptions or beliefs, or simply expose us to possibilities we didn't consider viable. Such is the case for Pete Coleshaw of Jaffa's Health Centre for Cats in the UK, where post-covid, a permanent model of excluding the client from the consultation room has been adopted. Now, I must say that this particular approach seems suited only to certain climates and clientele – but it's an interesting move and one that thus far, is working for them. I'd love to know what you think after reading the article on page 25.

Speaking of change, David Larrett spent more than 2 decades as an on-track veterinarian for greyhound race meets. He's now passionate about improving their welfare through disseminating his findings on the pathogenesis, radiographic identification and treatment of tarsal fracture, a common career-ending injury in racing greyhounds. Read the summary on page 6 and go to the link for the complete article.

Richard Malik's update on FIP treatment is essential reading for anyone seeing cats in practice. In his particularly practical way, Richard discusses financial barriers to treatment and emerging evidence for modified protocols, as well as pathways for procurement of these drugs.

There are, as ever, some terrific case studies with great photos and a Perspective on fungal disease. Like the 156 C&T Perspectives before it, this one crystallises emerging research and merges it with insights, recommendations and practical tips. Worth reading, sharing – and keeping on hand for future reference.

Happy reading!

Simone

Winner

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Exotic

# SPARGANOSIS – A SHORT REVIEW

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## Terminology

### Sparganum

This generic term was proposed by Diesing in 1845 to describe unidentified plerocercoid larvae of Pseudophyllidea found in cysts in the connective tissue under the skin, between the muscles and elsewhere, in frogs, snakes, birds and various mammals.[1]

The term sparganosis is derived from the Ancient Greek:[2] σπάργω (spárgō, `to swaddle') v., σπᾰ́ργᾰνον (spárganon) n.

1. band for swathing infants
2. (in the plural) swaddling clothes

### The parasite[3]

Members of the order Pseudophyllidea include the genera *Bothridium*, *Bothriocephalus* and *Spirometra*. *Spirometra* is a pseudophyllidean cestode that is widely distributed in different species of snakes, which serve in most cases as intermediate or paratenic hosts. There is no additional development of the parasite in the paratenic host. When released from the definitive host, each egg releases a larva (coracidium), which when ingested by a copepod (a small aquatic crustacean), develops into a procercoid. After ingestion by a second intermediate host (amphibian, reptile, or mammal), procercoids develop into plerocercoids also known as *spargana*, and can be found throughout the body *(Figure 1)*. When present subcutaneously, *spargana* may result in soft swellings of the body *(Figures 2,3)*. Oedema and haemorrhage of soft tissues may be associated with this stage. The definitive host is generally a mammalian carnivore (often felids).

Figure 1. Sparganosis detected in the coelom of a common tree snake


Figure 2. Sparganosis in a common tree snake, *Dendrelaphis punctulatus*

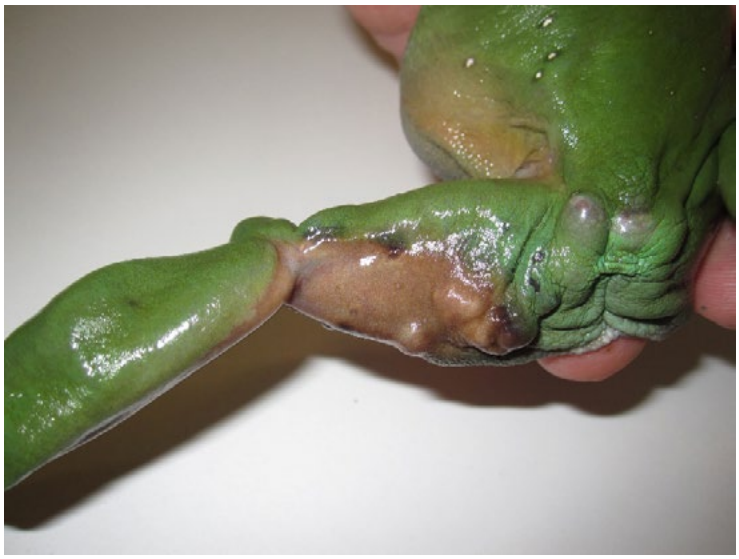

Figure 3. Sparganosis in a green tree frog, *Litoria caerulea*

## The reptile and amphibian connection

The intermediate or immature stage of the *Spirometra* tapeworm (plerocercoid) occurs in snakes that are frog or reptile eaters in the wild. *Spargana* may appear as small distinct swellings under the skin but rarely cause serious disease.[4] The author commonly sees the condition in red bellied black snakes *Pseudechis porphyriacus*, common tree snakes *Dendrelaphis punctulatus*, and green tree frogs *Litoria caerulea*.

Sparganosis does not occur in captive bred snakes which eat frozen/thawed mammalian prey items. Diagnosis of pseudophyllidean infections is based upon the identification of the *Spirometra* larvae.[3] Parasitism may be difficult to detect at gross examination of the animal.[5] Faecal testing is of no use in diagnosing this condition as the worms are in their larval stages—immature and not egg-layers. Anthelmintic treatment is ineffective. The only definitive treatment is surgical removal *(Figures 4,5)*; however, in most cases this is not carried out as the condition rarely causes clinical disease.

Presence of the parasite (sparganosis, detected at clinical examination or necropsy) may indicate that the reptile was sourced from the wild, often illegally. In these snakes haemogregarine parasites (intracellular protozoa) may also be detected in circulating erythrocytes *(Figure 6)*. The author (RJ) has also seen concurrent infestations of acanthocephalans in red bellied black snakes, *Pseudechis porphyriacus*.

## In the wild[4]

A survey carried out in free-ranging amphibians in eastern Australia between 1993 and 2000 revealed


Figure 4. Surgical removal of a sparganum in a common tree snake

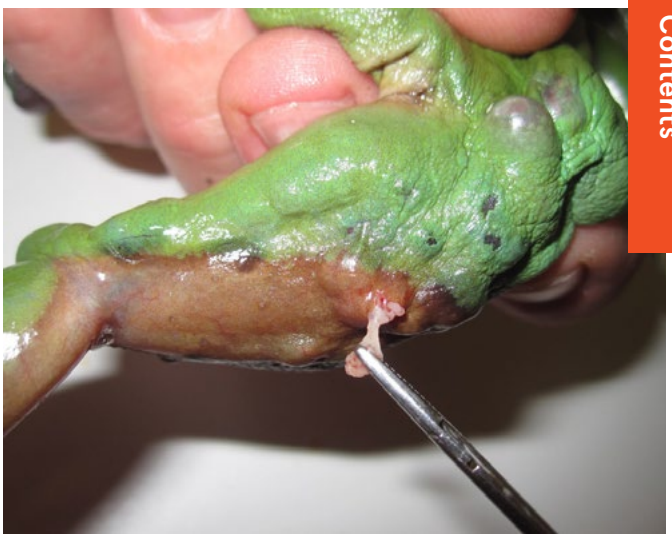

Figure 5. Surgical removal of a sparganum in a green tree frog, *Litoria caerulea*

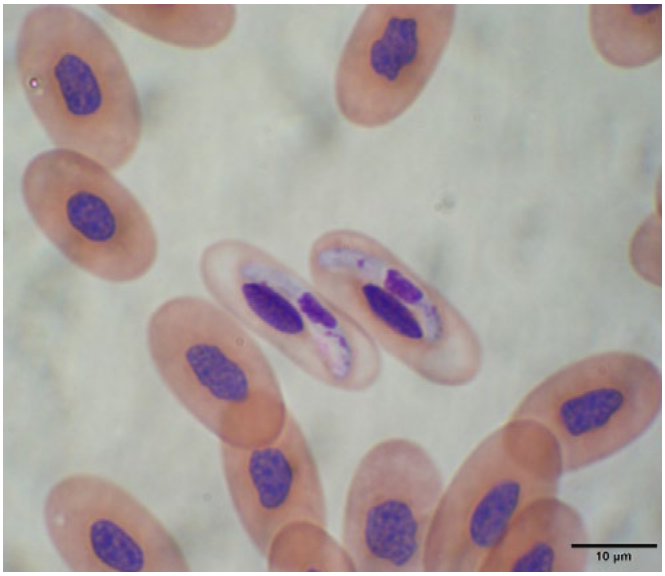


Figure 6. Haemogregarines detected in the erythrocytes of a diamond python. Photo courtesy of Prof. Bob Doneley

that infection with *spargana* (plerocercoids) of *Spirometra erinacei* occurred in 12/243 (4.9%) sick frogs.[4] Infections occurred in skeletal muscle and subcutis, especially the thighs, of large adults of multiple species (green tree frog, *Litoria caerulea*, green and golden bell frog *Litoria aurea*, dainty green tree frog *Litoria gracilenta*, and Peron's tree frog *Litoria peronii*) *(Figure 7)*. Three frogs were also infected in the coelomic cavity. Heavy burdens in seven frogs were associated with poor body condition and debilitating lesions, whereas lighter infections in five sick frogs were considered likely to be incidental to other diseases. In severe infections, a large proportion of thigh muscle was replaced with *spargana* and various amounts of fibrosis, and some frogs also had myonecrosis, granulomatous inflammation, haemorrhage, and skin ulceration. Concurrent infections were common.

Figure 7. Severe sparganosis of the hindlimb of a green tree frog, *Litoria caerulea*

## In humans and other species[1]

Larval *spargana* (plerocercoids) and adult *Pseudophyllidea* may be found in Canidae, Felidae and other animals. Heavy infestations with the plerocercoids of *Spirometra erinacei* in wild pigs fattened in captivity were recorded in NSW by Gordon in 1954. The *spargana* were infective for dogs and cats. Numerous *S. erinacei* were found in foxes in areas in which domestic pigs could become infected with the *spargana* from procercoids in copepods, frogs, and perhaps other hosts of these, and the spargana of the pig could probably infect humans if they were eaten uncooked.[1]

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Major Winner

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# THE BRUTAL REALITY OF HOCK FRACTURES IN RACING GREYHOUNDS

## Introducing Radiographic Guidelines for the Early Warning of Impending Fracture

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C&T No. 5965

*Dr David H Larratt BVSc. IVAS with rescued greyhound, Star*

My journey with greyhounds started soon after graduation from the veterinary faculty at *The University of Sydney* in 1989. My first veterinary employment was in a mixed practice in Newcastle, NSW with a high caseload of greyhound and equine cases. From my second week, I also commenced the duty of On Track Veterinarian (OTV) at a local greyhound racetrack.

For 22 years, I was an OTV at various greyhound racetracks in NSW and the United Kingdom with an average attendance of 2 meetings per week. The OTV is responsible for the euthanasia of dogs suffering serious on-track injuries. I performed euthanasia almost weekly and the most common injury was, by far, fracture of the right hock (Tarsus).

In 2012, I ceased work as an OTV and, in collaboration with the charity rehoming organisation *Friends of the Hound (FOTH)*, I undertook the surgical repair of the majority of bone fractures in greyhounds that presented for euthanasia at *Wallsend Veterinary Hospital*.

In 2018, I presented a lecture at the annual Australian Greyhound Veterinarians (now known as *Australian Greyhound, Working and Sporting Dogs Veterinarians*) conference on the surgical repair of hock fractures.

Having used 4-view radiographic angles with horses to investigate lameness, I then used this approach in greyhounds. This radiographic sequence has revealed distinct correlations between radiographic markers and the tarsal joint stability of racing greyhounds.

It is now my mission to share this radiographic diagnostic tool with veterinarians, to be used as prevention of this common career-ending injury.

### Introduction

In the racing industry, the greyhound is not yet receiving the same injury preventative measures that the racing horse receives. Unlike the equine industry, prepurchase radiography for greyhounds is not a standard protocol.

For a horse, it is standard to perform 4 radiographic views when investigating the joints of the legs. Currently, the standard greyhound radiographic procedure is restricted to the examination of 2 angles, perpendicular to each other with the focus on the detection of fracture lines.

### In this report, I would like to achieve the following:

A. Create an awareness of the extent of tarsal fracture statistics in the racing greyhound industry.

B. Highlight the role of demineralisation in the pathogenesis of tarsal fracture and that this weakening process may occur without an obvious pain response.

C. Present a series of radiographic images of the right tarsus in 6 greyhounds that reveal diagnostic markers to highlight a progression of mineralisation changes that may eventually lead to fracture. Corresponding CT images are also presented to assess correlation with radiography.

D. Present 4-view radiographic guidelines to detect the diagnostic markers that are distinct to the racing greyhound and indicate a predisposition to fracture. This is the foundation for routine radiographic screening to prevent fracture of the Tarsus.

## A $9.4 Billion Industry in Australia

The commercial greyhound racing industry in Australia is one of the biggest in the world, with 55 active racing tracks (Coalition for the Protection of Greyhounds, 2022); it generates millions of dollars in tax revenue on the $9.4 billion wagered on results in the 2020 to 2021 financial year (Dobbin, 2021). This economic impact comes at a significant risk to all greyhounds participating in racing.

## Tarsal Fracture

A persistent serious orthopaedic welfare issue continues to plague greyhound racing. Severe trauma to the right rear Tarsus often results in surgical repair or euthanasia. Injuries to the Tarsus account for 25% of all greyhound racing injuries (Sicard *et al.*, 1999) and tarsal fracture is by far the most common cause of premature retirement from racing (Thompson *et al.*, 2012).

***Greyhounds usually start racing at the age of 2 years. There is a 400% increased risk of serious tarsal injury after only 12 months of racing (Beer, 2014).***

Euthanasia rates have been reduced with the recent introduction of industry sponsored orthopaedic repair. However, the prevalence of major injuries appears to be increasing (GWIC, *Analysis of Greyhound Racing Injuries, December 2021*).

Tarsal fractures cause significant trauma to the animal and should be one of the highest preventative welfare priorities for the greyhound industry (Thompson *et al.*, 2012) and (Beer, 2014).

Within the right Tarsus, the Central Tarsal Bone (CTB), is the most common bone to fracture (Gannon, 1972), (Prole, 1976), (Boudrieau *et al.*, 1984) and (Anderson *et al.*, 1995).

## Setting the Record Straight

A commonly held view within the industry is that a tarsal fracture is spontaneous and random, occurring mainly due to racing interference. This belief has now been strongly challenged with the confirmation that the right CTB suffers a dramatic loss of bone mineral density (BMD) prior to collapse fracture (Hercock, 2010). This reduction in bone density *(demineralisation)* may occur without triggering an obvious pain response, remaining undetected by trainers and veterinarians.

Bone strengthens in response to athletic activity *(adaptive load)*, by depositing a dense calcium matrix into its structure *(mineralisation)*. The inner architecture of spongey bones is organised into a flexible mesh scaffold called the *Trabeculae* and it is this zone within the CTB that suffers both demineralisation and fracture. Changes in mineralisation of the tarsal bones are observable with conventional radiography.

The bones in the Tarsus overlap, making radiography challenging to interpret, deeming it to be of limited use by researchers (Hercock, 2010). However, the majority of greyhound research papers published have been based on only the examination of 2 radiographic angles, perpendicular to each other. This restriction appears to have been entrenched with the publication of the first classification system for grading CTB fractures (Dee *et al.*, 1976).

## Radiographic Tarsal Screening Guidelines

The guidelines provided in this report extend beyond the traditional search for fracture lines by using the following criteria:

1. The use of additional oblique radiographic views

2. Close examination of the inner Trabeculae of all the tarsal bones enables assessment of the state of adaptive load or overload in the entire tarsal structure.

3. The collaborative use of Computer Tomography (CT imaging) to confirm the radiographic interpretation.

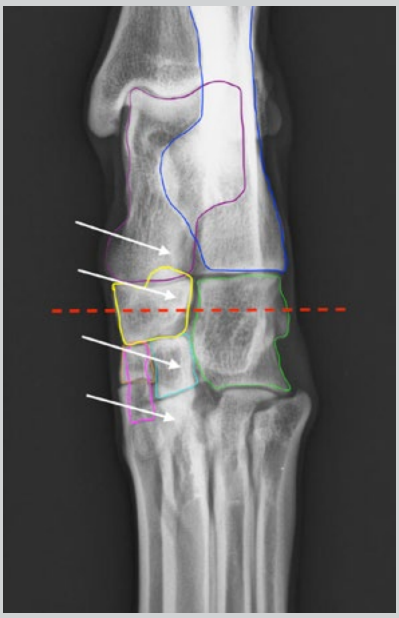
This Report:

- challenges the belief that tarsal fractures occur randomly
- challenges the belief that standard radiography is not useful as a preventative tool to detect impending fracture
- is a synthesis of scientific literature review, personal surgical experience, multiple view radiography and collaborative CT imaging.

## Figure 2. Plantar-Dorsal (AP) Radiographic Sequence of Right Tarsus: Intact, Collapse and Repair.

** (Download the complete article in the eBook for a description of the 6 dogs in the study)*

**A.** Intact



*Radiograph kindly provided by:*
*The Lake Veterinary Hospital*

**Outline of tarsal bones in *Dog #1.**

**Yellow** – CTB

**Green** – T 4

**Light blue** – T3

**Orange** – T2

**Pink**- T1

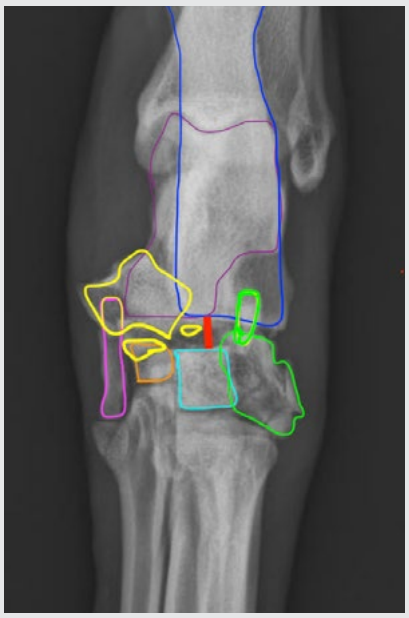
**Purple**- Talus

**Dark blue** - Calcaneus

**Red dotted line** shows position of transverse CT image.

**White arrows point to a vertical white line of increased mineralisation. (A response to increased vertical load).**

**B.** Collapse Fracture



*Radiograph kindly provided by:*
*Wallsend Veterinary Hospital*

**Outline of tarsal bones in *Dog #5**

This is a Type V comminuted fracture of CTB

**Yellow –** fragments of CTB

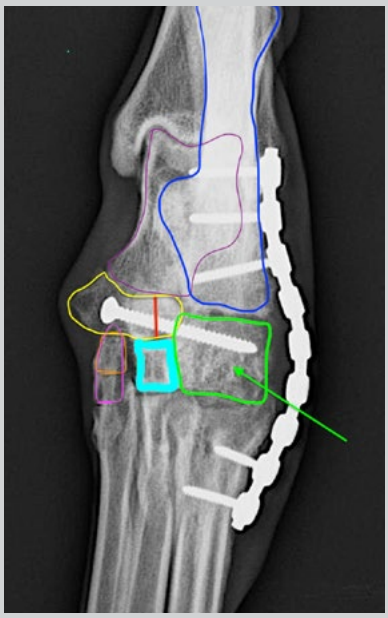
**Green –** collapsed sections of T4

**Light blue –** T3

**Red bar** indicates the space normally occupied by the CTB. The height is reduced as the T4 has collapsed.

T3 remains intact.

**C.** Repair



*Radiograph kindly provided by:*
*Wallsend Veterinary Hospital*

**Outline of tarsal bones in *Dog #5**

Surgical repair of the collapsed fracture of CTB and T4 with a single 2.7mm mediolateral screw in the CTB and 2mm lateral locking plate.

**Green arrow** points to the irregular trabeculae within the crushed T4.

**Red bar** is now taller, indicating partial restoration of the height of T4.

**This dog returned to racing after a 9 month recovery period.*

Figure 1. Right Hock collapse. Photo from https://www.cagednw.co.uk/greyhoundinjuries.html

## Please share this article far and wide

Due to space constraints, unfortunately we cannot provide the complete article in print. The full article contains many amazing images which the editors consider a valuable anatomy refresher for all vets, not just those treating greyhounds.

To assist the sharing of the information and accompanying images, the CVE has made the article available for open access to the general public◆

**Download the PDF**
**cve.edu.au/radiographic-tarsal-screening**

Winner - Best Visuals

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# FELINE LEPROSY

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C&T No. 5966

Henry is a 4-year-old, 4.5kg male neutered Domestic short haired cat who was adopted from a shelter. Adoption records were not provided but the owner reported Henry was approximately 1-year-old at adoption and had been confined indoors since, living with two elderly pugs.

Henry developed three dermal masses on his face within a short period. He was treated repeatedly at the primary vet with long-acting corticosteroid injections and prednisolone tablets. The lumps reportedly reduced in size but never resolved. Henry presented for a second opinion 8 months after initial treatment, when one lump became ulcerated—he was still on oral prednisolone at the time.

On presentation to our clinic, Henry had three discrete, hairless dermal swellings on his face: right preauricular *(Figure 1)* 9mm diameter which had recently developed a central ulcer; chin *(Figure 2)* at mucocutaneous junction, 10mm diameter; and right cheek *(Figure 3)* at mucocutaneous junction, 16mm diameter. Regional lymph nodes were not enlarged and there were no other abnormalities on physical exam. FNA samples were collected—each had moderate numbers of red blood cells, moderate numbers of neutrophils, and large numbers of highly variable round cells (some giant, some multi-nucleated). This appeared consistent with granulomatous inflammation. The macrophages appeared to contain numerous negative-staining rods. Suspicion of mycobacterial infection was discussed with the client, pending confirmation from the pathology lab.

I suspected the likely causative agent to be *Mycobacterium lepraemurium*, as this typically presents in systemically healthy young cats with cutaneous nodules on the head (which occasionally ulcerate) and 'lepromatous' cytology.

The patient was rapidly tapered off oral prednisolone and surgery was planned for a week after the medications were discontinued.

Just prior to surgery, oral clarithromycin 62.5mg (1/4 of the commercially available 250mg tablet) q12h and rifampicin (50mg, compounded as suspension via BOVA) q24h was commenced. Monitoring liver enzymes monthly is recommended with use of rifampicin. Haematology and biochemistry results prior to treatment were unremarkable (marginally elevated triglycerides; patient not fasted).

Surgery was performed to reduce the bulk of infection. Complete excision of the preauricular nodule was achieved. Due to the mucocutaneous location of the two other nodules, they were debulked only. The subcutaneous infected tissue was visibly atypical but extended to the mucosa. Gentamicin solution (50 mg/mL) was infused along wound margins at closure (total dose 5mg/kg).

Henry's wounds are healing routinely.

We expect to repeat blood tests monthly and to continue with both oral antibiotics for 2 months post clinical resolution of infection—literature suggests this may be from 2-14 months duration.

This case is interesting given Henry's indoor lifestyle and the opinion that *Mycobacterium lepraemurium* is considered to infect cats via bites from rodents.

With many thanks to both Dr Richard Malik and Dr Carolyn O'Brien for their comments on Henry's case and care!

*Note: Carolyn O'Brien is co-tutor of the CVE's Feline Medicine Distance Education course.*

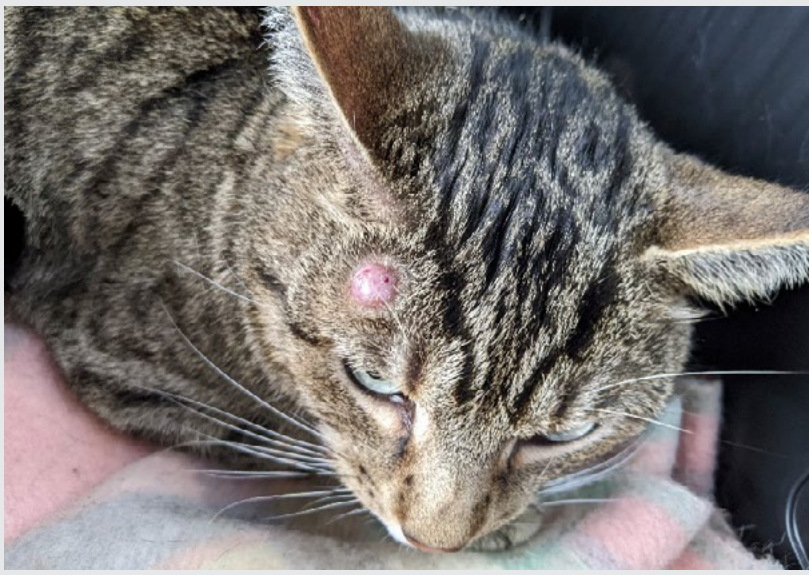
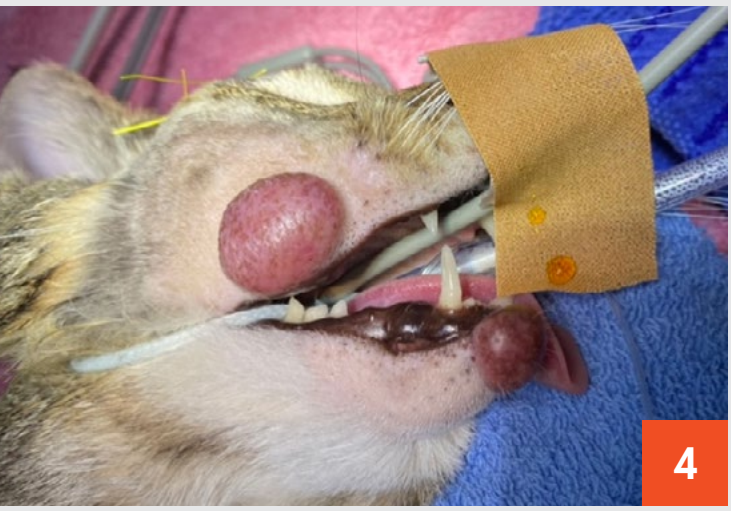
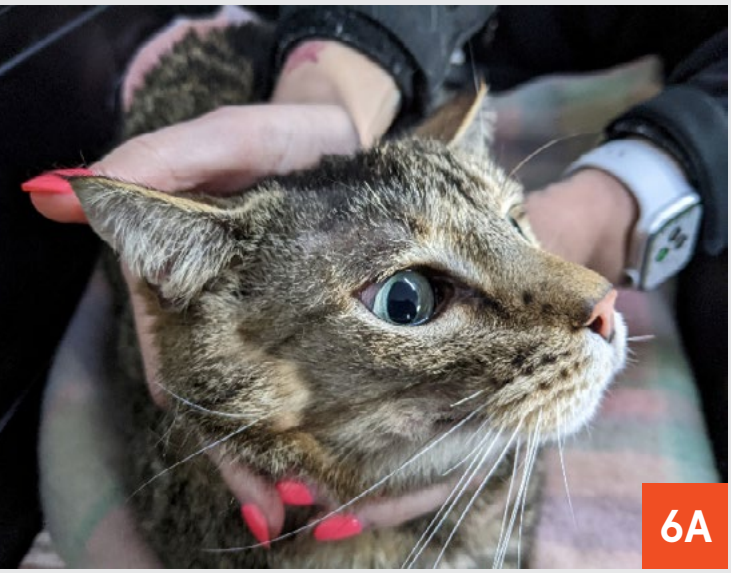
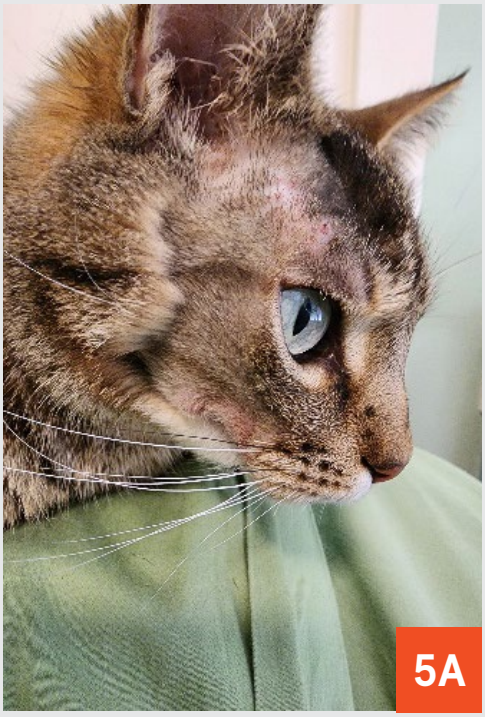


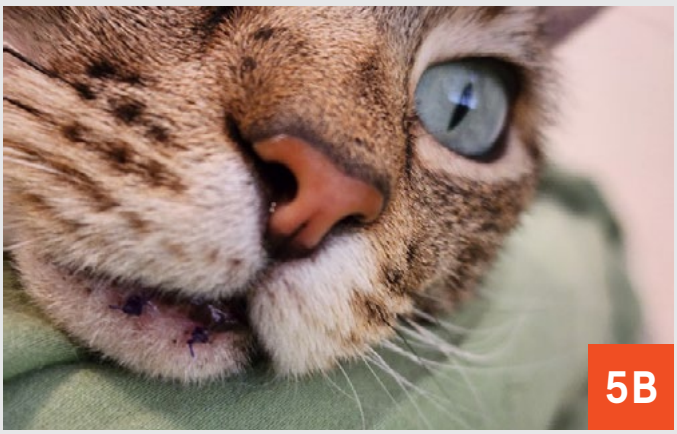
Figure 1. Right preauricular lesion

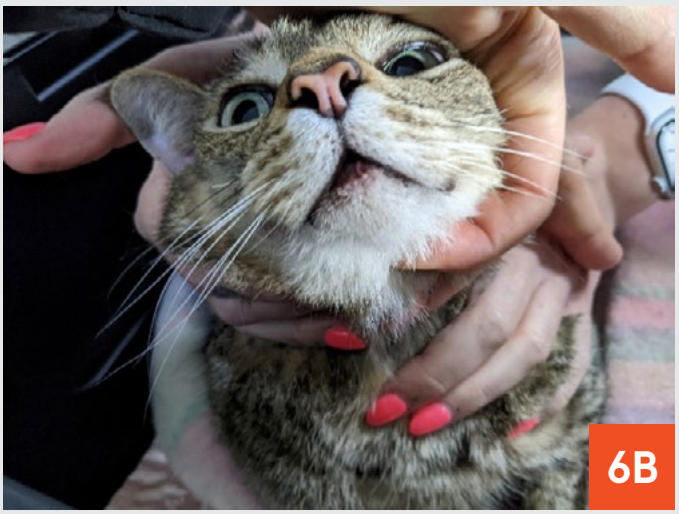

Figure 2. Chin lesion
Figure 3. Right cheek lesion and chin lesion
Figure 4. Lesions clipped for surgery
Figure 5A & B. 2 weeks post-surgery
Figure 6A & B. 3 weeks post-surgery

## Update January 2023

Henry presented for monitoring blood work 23/1/23. Henry's owner reported that since Christmas, she observed Henry had thinning hair, increased pigmentation of the nasal area (clearly evident in comparison to his early photos), and irregular pigmentation changes on the pinnae.

Whilst the hypotrichosis isn't obvious on the photo, it was readily apparent on exam.

A trichogram did not identify any anagen follicles. This is suggestive of telogen effluvium (thank you to Richard for this idea). However, I cannot find any literature reports of pigmentation associated with either telogen effluvium, leprosy, or the medications he is on (clarithromycin and rifampicin). Our very helpful experts Richard and Carolyn also are unaware of cases of pigmentation associated with the drugs or disease.

His haematology and biochemistry results were all normal and as he was due to finish medications in 2 weeks, we elected to monitor. There was no worsening of the changes in the subsequent 3 weeks and we are anticipating full recovery with time◆

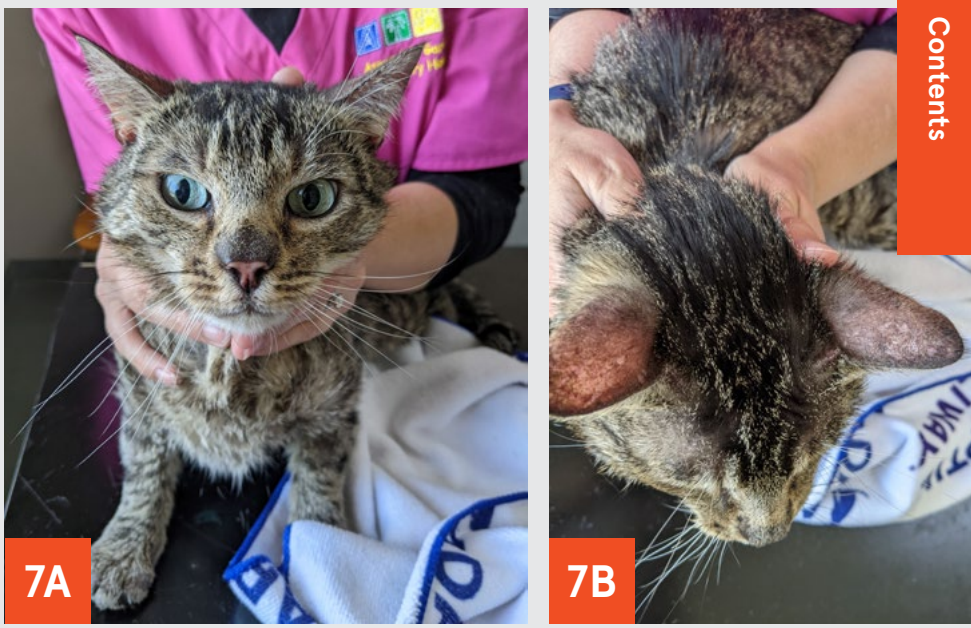



Figure 7A & B. Henry in January 2023

Winner

*Entitled to a CVE$100 voucher*

Small

# REDBACK SPIDER BITE TO A VET

**John Sandford BVSc**
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C&T No. 5967

## Mid-afternoon

In 2009, I was clearing up garden rubbish (including old tin and rotting wood etc) on our farm 120km from our inner Melbourne suburban vet practice and home. Mid- afternoon I got annoyed by what felt like a grass seed poking into the front of my left ankle. Eventually, 10 to 15 mins later I took off my boot and sock and found not any grass seed but a very recently squashed Red-Back Spider (nearly full size and I still have the 'sod'), and nearby, two 5mm diameter inflamed areas each with a central dark red spot.

I assumed I had been bitten by the spider and that I would not suffer any major effects, and so continued the day's odd jobs—it was only annoyingly very itchy at that stage, but gradually became more and more intense—deep pins and needles from metatarsals to very low tibia as I recollect. I was able to drive safely, and arrived at another property approx. 30 km from Melbourne aiming to stay the night for other chores the next morning.

## Evening

About 10pm that evening when it was getting more intense, I phoned 'nurse on call'. They indicated that if the pain was sensibly bearable, to see my own GP in the morning. I think at this stage I asked how long they thought symptoms might last and was told possibly 3 to 4 weeks without antivenene treatment.

Around 11pm, I started to get IDENTICAL intense pins and needles in EXACTLY the same position in the right ankle! I had no nausea, diarrhoea, ataxia, blurred vision, or mental aberration. The general level of pain increased, (scratching or massaging made no difference) but was still tolerable and I was extremely restless and did not sleep a wink overnight.

## 24 hours later

Approximately 2pm the next day, I visited the local GP in Melbourne but they had no antivenene, and so made arrangements to go to the Epworth (large Melbourne hospital) emergency department at 2.30pm. I received a single dose of C.S.L. Redback Spider antivenene I/V over approximately one hour, and began to feel better half way through and nearly fully normal an hour after I/V finished.

## Then how's this for a fluke?

Out of the blue, the head of the toxicology department walked in and we got chatting. He then started to explain to me (1966 graduate) that a reflex arc? via the spinal cord was responsible for the well-known occurrence of identical pain in the identical position in the other leg. Interestingly, a young admitting nurse had heard of identical symptoms in the other leg, but the 60-year-old medico had not—it is hard to know everything! I have had no long-term local or systemic effects.

## Could any of this information be included in any useful way in a presumptive /differential diagnosis of Redback Spider bite in especially dogs?

Would a dog get the same aggravating pins and needles type effect (and I guess bilaterally), and how would we humans pick that up? The astute owner may hold some clues here.

### References

**Emergency Department Guidelines for Spider Bite**

The Red Back Spider *(Latrodectus hasselti)* is usually found in dark, dry places. Envenomation (latrodectism) can be very painful but is usually non-life threatening. The main symptom is pain, which builds over minutes to hours and may last for days. The efficacy of RBS antivenom has been questioned. It should be considered for cases of persistent pain or distress after adequate analgesia and should only be administered after consultation with an ED consultant or a clinical toxicologist.

https://pch.health.wa.gov.au/For-health-professionals/Emergency-Department-Guidelines/Spider-bite

**Study Finds Nerve Damage Can Affect Opposite Side Of Body**
April 13, 2004
Massachusetts General Hospital

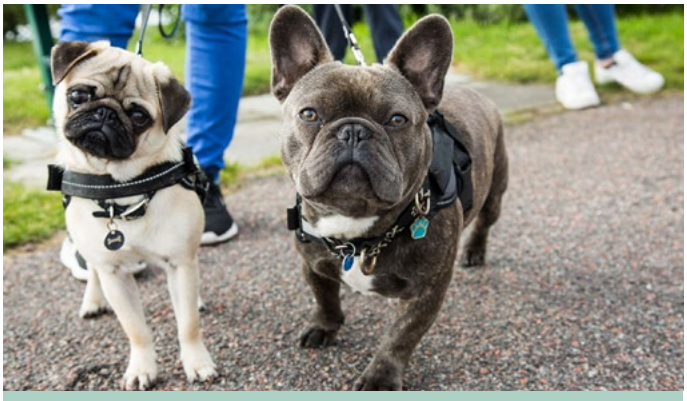
Researchers from Massachusetts General Hospital (MGH) have found physical evidence of a previously unknown communication between nerves on opposite sides of the body.

**Reports of opposite-side sensory effects of injury date back to the American Civil War.**

*'Patients with pain syndromes related to nerve damage sometimes report symptoms on the side opposite their injury as well, but those reports are usually discounted because there has been no biological framework for the phenomenon,' says Anne Louise Oaklander, MD, PhD, director of the MGH Nerve Injury Unit, the report's principal author. 'Our evidence means that these reports can no longer be ignored and gives us a new direction for research*◆

*Editor: We'd love to hear your comments on John's question. Please email: cve.marketing@sydney.edu.au*

**Read more**
Opposite-side-sensory-effects





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# CUTANEOUS XANTHOMATOSIS

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C&T No. 5968

Kenzie is a 2-year-old female neutered Domestic short hair cat. She was found on a farm with three other kittens (presumed litter mates), who were fostered out as a litter until Kenzie was adopted by our client when she was 17 weeks-of-age. She was fully vaccinated as a kitten and was desexed by the rescue.

Her owner brought her to our clinic because she had abrasions on her ears, bald spots on her hocks, a lip lesion and redness between her paws *(see Figure 1, 2 and 3)*.

Figure 1. Lesions on face

She had been to another veterinary clinic several weeks prior for the same skin lesions where she was treated with a long-acting antibiotic and long-acting steroid injection (her owner did not have details of what these were; presumed Convenia® and depomedrol). Her owner thought that she responded to these injections and the lesions healed within a couple of days.

She was an inside-only cat, who was harness trained but had not been outside in months. She had been previously treated with Bravecto® topical for the 6 months prior, which her owner thought made her a bit unwell. She was on a diet of wet food (Royal Canin and Black Hawk), freeze-dried

meat or jerky and human grade meat/fish. Kenzie was given no dry food. She had been on the same diet for over 6 months. Her owner did not consider her itchy or an excessive groomer. Her owner had no skin lesions; the last animal she had come in contact with was her mother's dog at Christmas time four months prior.

The initial list of differentials was

- eosinophilic granuloma complex (particularly the lip lesion)
- atopy
- flea allergic dermatitis
- adverse food reaction
- immune mediated disease.

She was started on a course of prednisolone (1mg/kg/day) and asked to return in 4 weeks for a follow up assessment, sooner if necessary.

Kenzie presented back to our clinic 2 weeks later with more lesions developing on her lips and worsening of the lesions on her hocks. Her owner thought that she was painful and lethargic. She also thought she was hiding away more. Her appetite was excellent, even more so on the steroids. Her owner was concerned that Kenzie had swollen pads (her owner was concerned about pododermatitis); although I did not agree, I did think her stopper pad on both front legs had lesions above them and were slightly swollen *(see Figure 3)*.

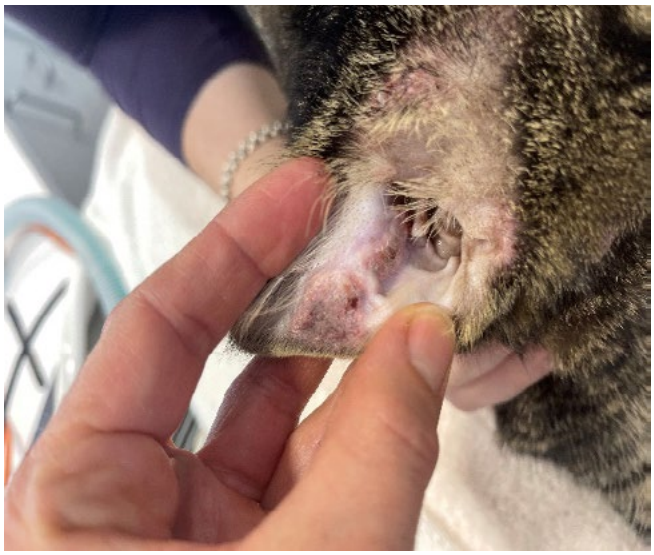

Figure 2. Lesion on pinna

Given the worsening of the lesions and little to no response to the prednisolone, I thought allergic skin disease was unlikely and discussed the option of biopsies. On the off chance that the lesions were an unusual presentation of feline herpesvirus dermatitis, I also placed her on doxycycline (25mg BID PO) and a Famciclovir® (125mg BID PO) course while we weaned her off the prednisolone.

Five days later, Kenzie's owners contacted me to say she was progressively getting worse; there were huge holes in her face around her whiskers and she had more lesions developing on her head. She was in obvious discomfort and not herself at home. Her owner did not think stopping the steroids had made things worse as she was no better on the steroids. I prescribed meloxicam oral (2.5mg SID PO) and gabapentin (50mg BID PO) and brought forward the biopsy date.

In-house pre-anaesthetic bloods and PoC FIV FeLV were performed prior to her general anaesthetic and no significant abnormalities were detected. She was routinely sedated with dexmedetomidine (13µg/kg) and Methone® (0.3mg/kg) IM, alfaxalone induction and maintained with isoflurane and oxygen. Her anaesthetic and recovery were unremarkable. Surgical preparation involved no clipping of the lesions and gentle wiping of the lesions with diluted betadine solution. Punch biopsies were taken using a 5 mm punch biopsy from the left and right ear, right and left cheek (at the base of the whiskers) and front left pads (see images). Closure was with 4-0 pdm in in a simple interrupted pattern. Samples were sent to University of Sydney for histopathology.

A direct smear of the biopsies was done prior to placement in formalin and on cytology; I thought I saw multiple rods. Based on this I also started her on marbofloxacin (12.5 mg SID PO).

Figure 3. Lesions on foot

Kenzie presented four days after her procedure for hyporexia and diarrhoea. Her owner noted however that her skin lesions were significantly better, and her paws were no longer swollen. Her current medications were marbofloxacin, meloxicam oral and gabapentin. I started Kenzie on maropitant (4mg SID PO) and mirtazapine (1.8mg transdermal SID).

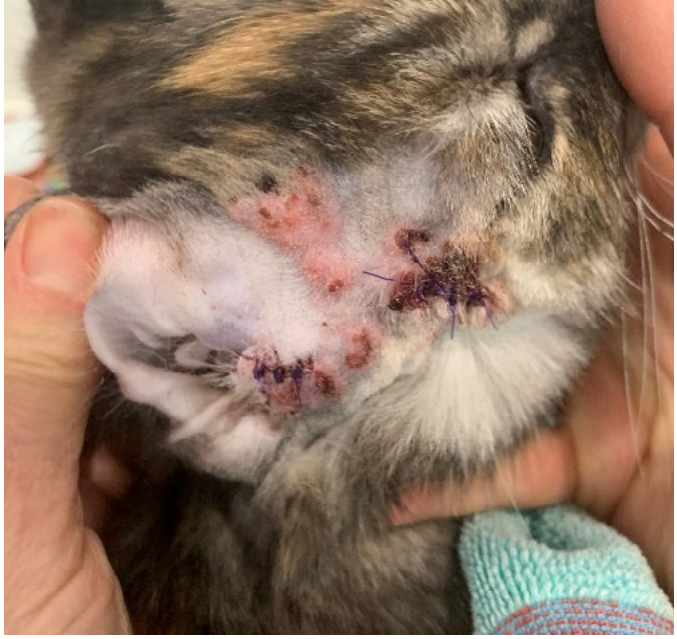

Figure 4. Close-up of lesions post biopsy

She represented 2 days later with watery diarrhoea and anorexia. She was sedated (same sedation as for biopsies) due to being fractious and placed on intravenous fluid therapy (13.7mL/hr.) Hartmann's with 20 mmol/L potassium chloride added, started on a fentanyl CRI (2ug/kg/hr.) and omeprazole (1mg/kg IV SID) and continued with maropitant. Overnight Kenzie removed her IV catheter; she had liquid diarrhoea that was bubbling in the tray. She had eaten overnight and was a little less fractious. She was started on all oral medication (given by her owner on visits); loperamide (0.66 mg PO BID), marbofloxacin (12.5 mg SID PO), pregabalin (25mg BID PO) prokolin supplement added to her food and buprenorphine (0.075 mg S/C BID). She remained in hospital mostly for us to deal with the diarrhoea. Kenzie was discharged the next day on her current medications.

## Diagnosis

The biopsy report arrived a few days later with a diagnosis of Cutaneous Xanthomatosis. This is not a condition that I had ever heard of before.

## Treatment

The plan was to try to get Kenzie to eat the lowest fat containing food that the owner could get her to reliably eat. Thankfully, her owner was very dedicated and did an extensive amount of research on the fat content of the diets she was feeding her. My basic plan for the owner was to feed her a diet that she liked (that had a low-fat content) and then add in different diets as slowly as possibly, gauging if she had a skin flare up after the introduction of a new food. Like you would approach an elimination diet.

## Interesting things about this case

- Kenzie genuinely did not respond to any medical treatment initially and I believe that this was one of those cases where getting a biopsy was essential.
- On cytology I thought that I saw many rods and yet on histopathology this was not reflected.
- The most interesting thing was that I think that Kenzie's skin lesions improved clinically probably not because of the addition of marbofloxacin (as both the owner and I initially thought) but because she was hyporexic; therefore, reducing the fat content in her diet which was likely the main reason why her skin lesions actually improved.
- The final point of note was that because we ran in-house pathology, we never got a triglyceride result for Kenzie. I think it would have been interesting to see if it was elevated along with her elevated cholesterol reading, although ultimately it didn't change things as a diet change alone to a low-fat diet resolved all of her skin lesions.

Figure 5. Kenzie with lesions resolved

## Pathology report

All sections of skin exhibit similar features with the least severe changes in the sections of ears. Within the superficial dermis of all sections, there are moderate to abundant numbers of large foamy macrophages which commonly aggregate perivascularly and interstitially. Beyond those areas, the macrophages commonly surround large

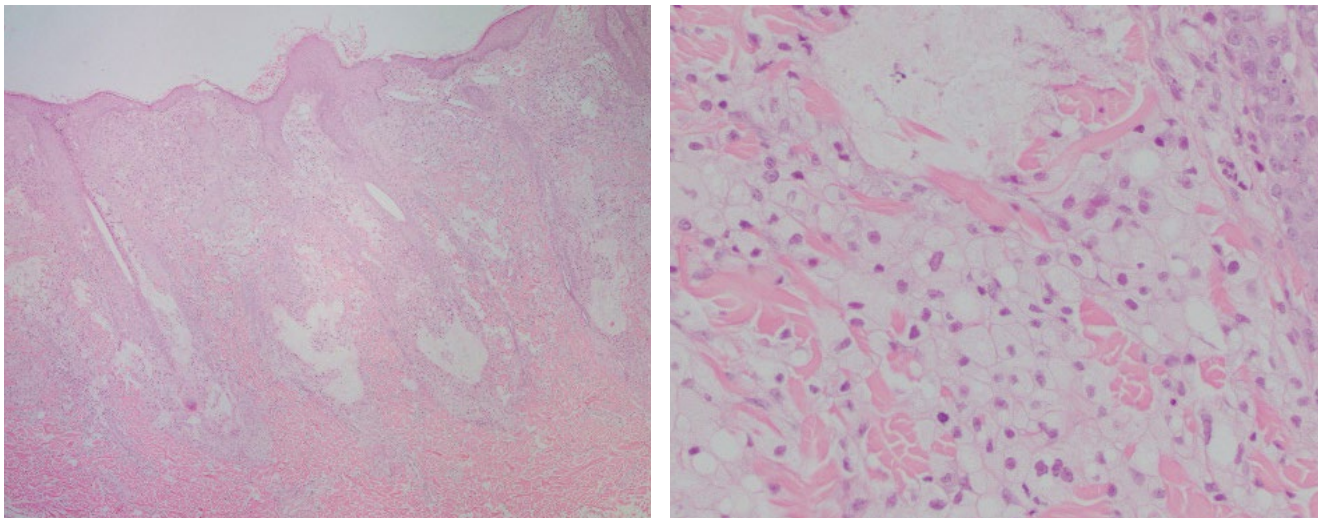

Figure 6A & B. See histopathology report

peri-adnexal spaces which contain faint wispy pale eosinophilic material. Within the superficial dermis and peri-adnexally there are many moderately to severely distended lymphatic vessels. Admixed amongst the macrophages are many eosinophils, some neutrophils and infrequent lymphocytes and plasma cells. The epidermis is moderately to severely acanthotic with prominent rete pegs, intercellular and intracellular oedema and there is exocytosis of inflammatory cells. The epidermis is sometimes ulcerated most notably over the paws with underlying granulation tissue. There are moderate numbers of apoptotic cells within the epidermis throughout the sections of skin. Frequently overlying the epidermis is a moderately thick serocellular crust. There is a dense colony of coccoid bacteria on one section embedded within the crust. Regionally within the superficial dermis is mild to moderate fibrosis. The adnexa sometimes have indistinct sebaceous units and the follicles are disrupted by the inflammatory cells. There is a focal organised fibrin thrombus within the superficial dermis of one section Some of the deeper blood vessels are slightly thickened with some slightly rounded endothelium.

## Diagnosis

Ulcerative dermatitis, perivascular and interstitial, histiocytic and eosinophilic, moderate to severe, subacute to chronic with large areas of pale wispy material and serocellular crusts.

## Comments

The most pronounced change in all sections was the infiltrate of large foamy macrophages accompanying large spaces of pale wispy material. These histologic features were suggestive of a diagnosis of cutaneous xanthomatosis.

Cutaneous xanthomatosis is usually associated with fasting hyperlipidaemia, elevated triglycerides and cholesterol and hence assessment of and correlation to clinical pathology is recommended to confirm this diagnosis. Hyperlipidaemia occurs from abnormal lipid synthesis, metabolism or transportation. There was no evidence of any bacterial, fungal or protozoal organisms to ascribe to the inflammation. Some of the additional features were interesting with possible underlying vasculopathy likely a secondary change◆

## Let's keep the *C&T* Series broad and interesting!

Birds, fish, guinea pigs, rabbits, reptiles, snakes, exotics, wildlife, cats, dogs, horses, goats, sheep, pigs... Please write up that interesting case and send it to us for publication. We promise, it's not an arduous process. Rest assured our veterinary editors will contact you before publication if they have any concerns or queries.

**Join in!**
Send your article complete with high resolution images, videos if you have them, figures and tables etc to: **cve.marketing@sydney.edu.au** and read your contribution in PRINT!

Call for Cases

# MELIOIDOSIS IN SMALL ANIMALS

**Krysten Lee**
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Melioidosis is the disease caused by infection with the bacteria *Burkholderia pseudomallei*, which is a soil dwelling pathogen known to cause disease in humans and animals living in tropical regions including Queensland, the Northern Territory and south-east Asia. The prevalence of this disease is expected to increase following recent heavy rain and flood conditions, when the soil is disturbed and bacteria are brought to the surface where they are more likely to infect animals and humans alike.

Little has been published to date on infections in small animals. Two case series have detailed primary ocular and disseminated infections in four cats. We are interested in publishing a larger case series to provide veterinarians with more information on the diagnosis, management, and outcomes of this disease.

## Please email us!

If you have diagnosed cases of melioidosis in cats or dogs, we would appreciate if you could send patient records (including pathology results and images, if available) via email for us to include in the study.

Image taken from: Parkes, H. M., Shilton, C. M., Jerrett, I. V., Benedict, S., Spratt, B. G., Godoy, D., O'Brien, C. R., Krockenberger, M. B., Mayo, M., Currie, B. J., & Malik, R. (2009). Primary ocular melioidosis due to a single genotype of *Burkholderia pseudomallei* in two cats from Arnhem Land in the Northern Territory of Australia. *Journal of Feline Medicine and Surgery*, 11(10), 856-863◆

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# UPDATE ON FIP TREATMENT

**Richard Malik**
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C&T No. 5969

The standard protocol for the treatment of Feline Infectious Peritonitis (FIP) in Australia entails the use of the RNA polymerase inhibitors remdesivir (intravenous or subcutaneous injection) and GS-441524 (tablets), in conjunction with the repurposed anti-malarial medication, mefloquine (compounded capsules or Lariam® tablets). These three drugs represent the current therapeutic options available for the treatment of FIP in Australia. The specific details and treatment regimens will vary from cat to cat. This will depend upon case-specific clinical signs (higher doses for ocular and CNS disease), the bias of the treating clinician and the financial resources of the owner.

**Remdesivir** has the advantage of being suitable for both intravenous and subcutaneous therapy. As the COVID-19 pandemic transitions to a continuously transmitted endemic infection, the cost of remdesivir will decrease, enabling it to also be used as an oral preparation. Compounded oral remdesivir is already in routine use in New Zealand, and is inexpensive. Intravenous or subcutaneous remdesivir is especially helpful in cases of FIP with advanced disease, or where abdominal disease is so extensive there are concerns regarding the bioavailability of GS-441524. My understanding is that Polyprenyl Immunostimulant is no longer in use, despite the recent paper from the Edinburgh group showing some efficacy.[1]

Some clinicians and clients will prefer to bypass remdesivir completely and instead initiate treatment with GS-441524 tablets. GS-441524 tablets are cheaper than remdesivir, and this approach may eliminate the need for hospitalisation.

There is some debate as to the optimum duration of treatment for injectable remdesivir prior to the initiation of oral GS-441524 treatment. Initially we recommended 2 weeks of parenteral therapy. However, colleagues at the Royal Veterinary College administer remdesivir IV for 4-5 days before changing to oral GS-441524 therapy, with satisfactory results.

Figure 1. A British shorthaired cat from Hong Kong with wet (effusive) FIP. Photos courtesy of Dr Chris Simpson.

**Mefloquine** is a useful drug which can be used in combination with GS-441524. It can also be given when a cat is stabilised, but not yet cured, if owners can no longer afford the high cost of GS-441524 therapy. There is some debate about the best dosing regimen for this repurposed antimalarial drug. The initial work suggested ¼ of a 250 mg Lariam® tablet (62.5 mg) given twice a week. Despite the additional costs associated with compounding 250mg tablets to a smaller dosage, I prefer to use 20 to 25 mg per cat orally once daily with food. I often start cats on this small daily dose as they approach the end of a course of GS-441524 therapy, and then continue mefloquine for several months in order to facilitate the eradication of any residual FIP virus which may be sequestered within cells of the mononuclear phagocytic system.

Regimens based on these drugs will usually result in the successful treatment of kittens and cats with FIP, although the occasional case can be incredibly challenging. Such clinical scenarios may involve the presence of CNS disease with seizures, or the development of viral resistance during the course of therapy.

Figure 2. High protein, straw-coloured fluid from the abdomen of the cat in Figure 1

The existing drugs are very expensive. This is especially an issue when treating adult cats (which weigh more), or when CNS disease is present. CNS involvement necessitates the use of higher doses on a mg/kg basis to ensure therapeutic concentrations are obtained within the brain, spinal cord, and CSF. In addition to the costs associated with initiating treatment, further expense is involved due to the need for ongoing veterinary consultations. Repeat pathology tests in addition to imaging in certain clinical scenarios are also required to monitor the progress of therapy.

**In my opinion, the greatest obstacle to successful therapy is the exceedingly high cost of treatment.**

**The associated problem is the requirement that the treatment course extends for a period of 84 days in order to completely eliminate the FIP virus.**

From the outset, the costs associated with treatment are beyond the financial resources of many owners. If the FIP virus develops mutational resistance during the course of therapy, the requirement for increased drug doses, often for prolonged periods, makes treatment more financially and emotionally challenging. This is problematic, even for the most devoted owner.

One way pet owners have circumvented the high cost of therapy is by using 'black market' GS-441524. This is widely available from many foreign suppliers. Although this is not legal, it is widely sourced by owners and especially by cat breeders. Many cats have been saved by these drugs.[2] The problem is that we are uncertain of the actual dosage of the active ingredient available in different preparations of foreign-sourced medications. Testing in Australia has shown that the actual dose may be higher or lower than the value quoted by the manufacturer. This difference may be substantial, so you just cannot be confident of the dosage cited on the product packaging. Furthermore, we have no feel for batch-to-batch variation of the black-market drugs.

Most Australian veterinarians encourage clients to use legal products provided by BOVA Australia, as the supply chain is robust and reliable. Regular quality control testing ensures that each tablet contains 50 mg of GS-441524, as labelled.

The COVID 19 pandemic has resulted in extensive research into prevention and treatment of Coronavirus disease. In Australia, two **oral** treatments are now widely available for human

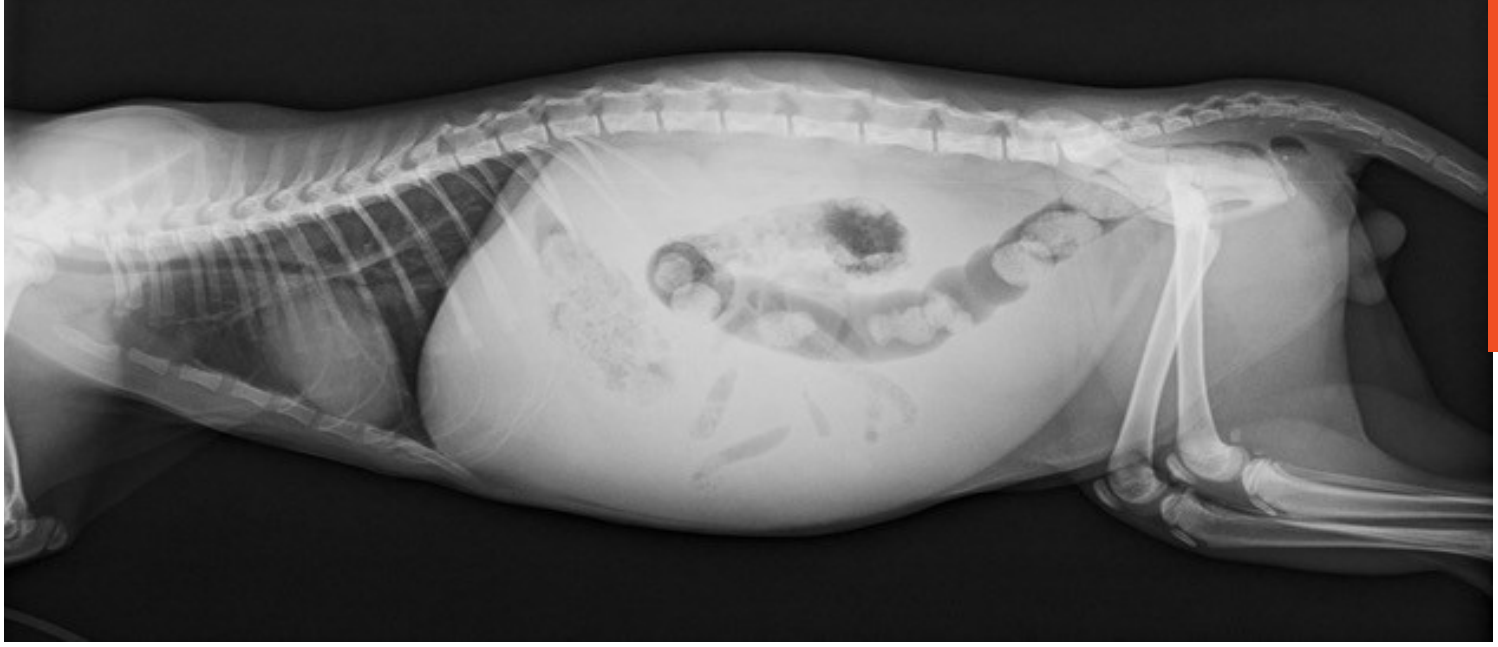

Figure 3. Whole cat radiograph of the patient in Figure 1 with wet FIP

patients infected by SARS-CoV-2, viz. molnupiravir and Paxlovid.[3]

**Molnupiravir** is an oral prodrug of the nucleoside analogue β-D-N4-hydroxycytidine (EIDD-1931). In coronaviruses, it causes guanine to adenine and cytosine to uracil nucleotide translation mutations. This leads to further mutations in downstream copies of the virus. As a result, the virus cannot survive, due to an effect called 'viral error catastrophe' or 'lethal mutagenesis.' Molnupiravir has been found to be safe and well tolerated at a dose of up to 800mg twice daily in COVID-19 patients.

Professor Niels Pedersen provided a summary of the history of the evolution of molnupiravir on his SOC FIP website. I have attached some of that to this monograph below, with some modifications:

Molnupiravir has recently been tested in cats with FIP by at least one Chinese distributor of GS-441524, and preliminary results reported on the FIP Warriors CZ/SK website (https://www.fipwarriors.eu/en/). Molnupiravir is sold under the brand name HERO Plus 2801. The field trial consisted of 286 cats with various forms of naturally occurring FIP seen in pet clinics in US, UK, Italy, Germany, France, Japan, Romania, Turkey, and China. No deaths occurred among the 286 cats that participated in the trial. This included 7 cats with ocular (n=2) and neurological (n=5) FIP. Twenty-eight of these cats were cured after 4-6 weeks of treatment and 258 after 8 weeks. All treated cats remained healthy 3-5 months later, a period during which relapses would be expected in cats not successfully treated.

**This data provides compelling evidence for the safety and efficacy of molnupiravir for cats with various forms of FIP. It is hoped that this field trial will be written in manuscript form, submitted for peer review, and published. Nevertheless, molnupiravir is now being sold to owners of cats with FIP. At least one other major seller of GS-441524 is also interested in using molnupiravir for FIP, with the product Aura 2801 attracting the most interest. This clearly demonstrates an unmet demand for additional antiviral drugs for use in cats with FIP.**

A safe and effective dosage for molnupiravir in cats with FIP has not yet been published. However, one distributor from China has provided some pharmacokinetic and field-testing data on molnupiravir in cats with naturally occurring FIP. This is contained in an advertising flier for

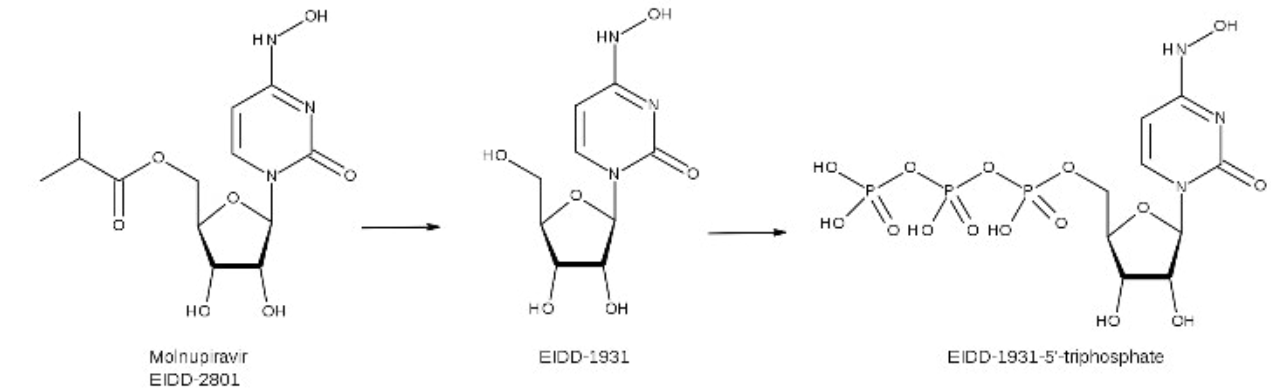


Figure 4. Chemical structure of molnupiravir, EIDD-1931 and the active triphosphate intracellular moiety

3rd Oral Nutritional Supplement
LICENSE # REIRUT (2020) 06029

Guideline for 3rd Gen Nutritional Supplement For FIP
HERO Plus 2801

[Introduction]
This is 3rd gen oral nutritional supplement for FIP treatment whose scientific name is 2801 with the totally different active ingredients from the ex two gens.

[Active Content]
Licorice Extract, Lecithin, AD cellulose, Lactose, Amino Acid, Sodium Chloride, etc.

[Traits] Tablets with white color

[Indications]
This product is suitable for cats with complications such as high fever, dizziness, hot spots, loss of appetite, ascites, pleural effusion, lymphadenopathy, inflammatory granulation, diarrhea, fever, thirst, coma, jaundice, red tongue, neurological symptom which are caused by infectious peritonitis.

[Specification] 13 pieces * 50 mg

[Usage]
It is recommended to purchase and use under the guidance of a veterinarian.

Recommendation
Take 1 piece for every 2 kilogram of body weight. It is recommended to take on an empty stomach. Do NOT need to take it again and continue to take the medicine as planned if vomiting occurs 30 minutes after taking the medicine.

Adjustment
The symptoms, course and prognosis of feline infectious peritonitis will vary with age and body condition.
The veterinarian should evaluate the cat according to the specific clinical conditions.
It is recommended to use 1.5 times as the standard dose when the cat has eye disease (uveitis).
It is recommended to use 2 times as the standard dose when the cat has neurological symptoms. Please follow the advice of veterinarian.

[Cycle of Treatment]
Usually it will last 5-10 weeks but still depends on the comprehensive health status and complications as well as the reactions on the individual case

[Reactions]
According to the prescribed dosage, there are no adverse reactions. And 2 out of 128 cats accounted for treatment (<2%) experienced vomiting during clinic experiment.

[Prohibitions]
Individual case who is allergic to any ingredient of this product should not be used. Use with caution in cats duringpregnancy and lactation.

[Attentions]
Avoid discontinuation or changing of the drug during the treatment on this product.
Failure to use the drug according to the course of treatment may lead to the occurrence of virus resistance.
Pay close attention to the weight of the affected cat during the treatment on this product and adjust the dosage according to the actual weight.
Cats with low renal function:
Adverse events of elevated SDMA and/or Creatinine have been observed in individual cases which may be affected by factors such as underlying diseases, food, and age in clinical trials.
The relevance for this product is not yet clear because it cannot be ruled out that SDMA and/or Creatinine increase during the treatment of cat with infectious peritonitis with this product. Therefore the renal index should be monitored before and at the beginning as well as during the treatment with this product.
If the ratio of increase of Creatinine exceeds 1.8 mg/dl during treatment the necessary measures such as reducing the dose or suspending treatment should be taken.

Figure 5. First page of the data provided in the package insert about 'Hero 2801' from FIP Warriors CZ/SK–EIDD-2801 (Molnupiravir).
https://www.fipwarriors.eu/en/eidd-2801-molnupiravir/

Hero-2801. This data describes that 28/286 cases received this medicine at a dose of 30-40 mg/kg every 24 hours i.e. equivalent to 15-20 mg/kg every 12 hours. For the purpose of comparison, the current recommended human dose is 800 mg every 12 hours, or approx. 10 mg/kg bid. This is consistent with the doses of molnupiravir used in ferrets, where 5-15 mg/kg was used safely and successfully in the prevention and treatment of experimentally induced COVID.

Dose recommendations seem to vary: Initially, the following doses were suggested:

- Dry/Wet FIP: 25mg/kg orally q24h
- Ocular FIP: 37.5mg/kg orally q24h
- Neurological FIP: 50mg/kg orally q24h

This was later modified after input from Niels Pedersen and the Davis group, based on presumptions from published information:

- Wet/Dry FIP: approx. 5-7 mg/kg q12h for 84 days.
- Ocular FIP: 8-10 mg / kg q12h for 84 days.
- Neurological FIP: 10-15 mg/kg q12h for 84 days

The duration of the course of treatment was for 5-10 weeks and was informed by the severity of the disease in addition to particular case-specific factors.

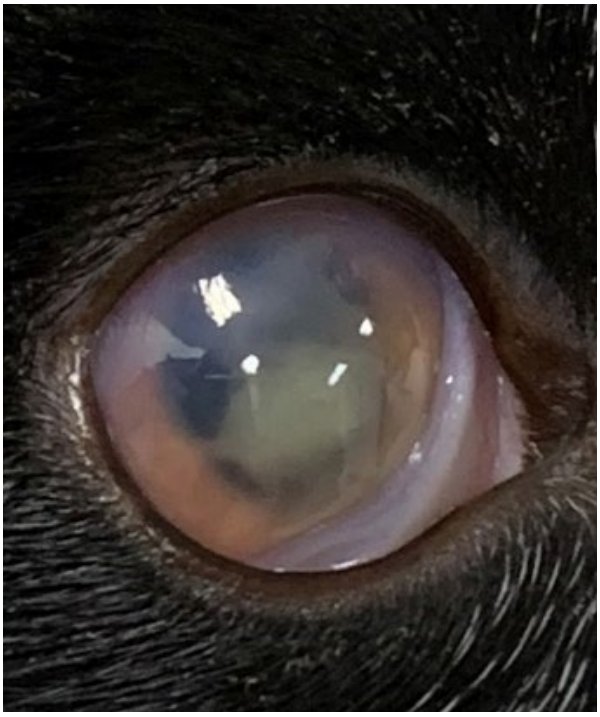

Figure 6. Anterior uveitis in a cat with FIP. Note the fibrin clot in the anterior chamber.

Dr Samantha Evans' group from Ohio conducted an internet-based survey on the use of unlicensed molnupiravir as first line therapy for suspected FIP and as a rescue therapy for cats with persistent or relapsed clinical signs of FIP following GS-441524 and/or GC376 therapy. This data was presented at the recent ISCAID meeting in Glasgow. Using owner-reported data, treatment protocols for 30 cats were documented. The 26 cats treated with molnupiravir as a rescue therapy were given an average starting dosage of 12.8 mg/kg and average final dosage of 14.7mg/kg twice daily for an average of 13 weeks. A total of 24/26 cats were still living disease-free at the time of writing. One cat was euthanased after completing treatment due to a prolonged seizure and the other cat underwent

**In Australia, my colleagues and I have been using molnupiravir in selected patients .**

**We have increased the dose since July 2022 at a dose rate of 10 mg/kg orally twice a day in routine FIP cases.**

**We have increased the dose to 15 mg/kg orally twice daily when there is ocular or CNS disease.**

**We have done this as a rescue treatment in cats that have relapsed after remdesivir or GS-441524, in combination with GS-441524 tablets in some new patients, and when clients cannot afford the standard of care treatments available.**

re-treatment for relapsed clinical signs. Few adverse effects were reported. Those reported included folded ears (1), broken whiskers (1), and severe leukopenia (1)—seen at doses above 23 mg/kg twice daily.

There is an on-going clinical investigation at UC Davis which involves Brian Murphy and Krystal Regan. This study commenced in July 2022 and aims to establish the optimal dose rate and dosing interval for the use of molnupiravir in feline populations with FIP, including relevant population pharmacokinetic data.

Niels Pedersen believes it is doubtful that molnupiravir will prove safer or more effective than GS-441524 for the treatment of FIP. However, a third antiviral drug may prove extremely helpful in preventing GS-441524 resistance. In particular, this would be the case if molnupiravir could be utilised as one component within a cocktail of antivirals with different resistance profiles. As identified in Sam Evans' survey, molnupiravir could also be used in the treatment of cats that no longer respond well to GS-441524.

It remains unknown whether molnupiravir will be free from long-term side effects.

As previously outlined, the recommended doses of molnupiravir used in early trials seemed to be excessive. And to make matters more problematic, no study has examined whether the two different unlicensed molnupiravir products, Hero and Aura, actually have the stated amount of active drug in each tablet!

Thus far in feline clinical practice, I have been using licensed human grade molnupiravir manufactured in India (purchased online and imported) at a dose rate of 10-15 mg/kg twice daily (see below).

A different product, **Paxlovid**, is a combination of two drugs (nirmatrelvir and ritonavir) within a single preparation. One drug inhibits the metabolism of the other drug. I can find no precedence for its use in cats, even though it is widely available and inexpensive when purchased online. Paxlovid has proven to be the more efficacious of the two available oral treatments for COVID 19 when used in human populations. However, the use of paxlovid has been associated with more side effects and many potential drug interactions. In Australia, Paxlovid is approximately the same cost as molnupiravir. When purchased from websites in India, Paxlovid is consistently more expensive than molnupiravir. Should Paxlovid demonstrate adequate safety when used in feline populations, it may prove to be an extremely useful drug for treating FIP in cats. In people, one reported side effect is an unpalatable aftertaste, so called `paxlovid mouth.' This would be problematic should it occur in cats, because of their propensity to froth saliva.

## What then is the place of molnupiravir in therapy of kittens and cats with FIP? How do you get it? How much does it cost?

Anyone can buy molnupiravir in Australia for their own use, or for use in their cat(s), by obtaining a prescription from a doctor or veterinarian (respectively) and presenting it to a pharmacy. The trade name is Lagevrio™ (Merck Sharp & Dohme), and a box contains 40 x 200 mg capsules. The drug was provisionally approved by Therapeutic Goods Australia (TGA) in February 2022 for the treatment of COVID-19 in adults who do not require oxygen supplementation and who are at risk of progressing to severe COVID-19. For those who qualify for subsidisation under the PBS, the cost is $45.

The cost of molnupiravir for people who do not qualify for special access, and for cats, is about $1,101.39, depending on the pharmacy mark-up.

See: https://www.pbs.gov.au/medicine/item/12910L

The treatment of a 4 kg cat at 10-15 mg/kg bid requires 80 mg to 120 mg of molnupiravir per day for 84 days. This equates to a cumulative dose of 6,720 to 10,080 mg. A box of 40 x 200 mg capsules represents 8,000 mg. The cost of initially procuring the molnupiravir, in addition to charges associated with compounding the medication to the correct strength for a cat translate to an overall cost of approximately $1,200 dollars. **This is appreciably cheaper than GS-441524 or remdesivir.** Thus, we now have an alternative therapy for the management of FIP in feline populations. This is achieved by obtaining a prescription, visiting a compounding chemist, and having capsules made up to 40-50 mg strength, (more if CNS involvement is present).

## What is the evidence supporting the use of molnupiravir in FIP? Are the pharmacokinetics well understood in cats?

At this point in time, we are not certain as the evidence has not been subjected to peer review. Our understanding from discussions at the International Society for Companion Animal Infectious Diseases meeting, is that Brian Murphy's group will soon publish pharmacokinetic data. However, compelling anecdotal unpublished

information suggests molnupiravir is an effective and safe therapy. Furthermore, robust population pharmacokinetic data is likely to be available within a year from the UC Davis group.

In summary, molnupiravir appears to be a highly effective treatment for FIP, comparable to remdesivir/GS-441524, and perhaps with less propensity for viral resistance to develop during a course of therapy. It can be purchased from any pharmacy and compounded to an appropriate strength for kittens and cats, and an 84-day course of therapy should cost approximately $1200 AU.

## Personal Importation Scheme

Australia has a scheme that allows the importation of drugs from overseas for personal use and for

'FIP buyers' club'?

(Referencing Matthew McConaughey's best actor Oscar for Dallas Buyers Club)

the use of one's family members. Human patients who are prescribed expensive 'off-label' medicines that are not eligible for subsidisation under the Pharmaceutical Benefits Scheme (PBS) need to find ways to access these drugs themselves. It is not known how many Australians import medicines, but it is legal under the Personal Importation Scheme. Perhaps the best example is the 'FixHepC Buyers Club' (https://fixhepc.com/) established by the Australian physicians Drs John and James Freeman.[5] Before the new hepatitis C antivirals were subsidised by the PBS, thousands of Australians used this 'buyers' club' to import affordable hepatitis C medicines at **1–2%** of the retail price. This initiative was supported by the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine. Many Australian physicians directed patients to purchase their medicines in this manner. They paid between $1,000 to $2,000 each to access treatment, rather than the $84,000 charged in America by Gilead Sciences. Although still expensive, for many this was affordable.

**This strategy does, however, come with some risk.** The internet marketplace for medicines is poorly regulated as it operates between jurisdictional boundaries. Substandard products are not uncommon. By some accounts, up to 25% of medicines formulated in lower income countries are substandard. The greatest risk is that they contain an insufficient amount of an active ingredient, leading to unintentional under treatment. This is a complex space for doctors (and veterinarians!) to navigate, both clinically and medico-legally. How far a clinician's duty of care extends is unclear. The current code of medical conduct states that proper medical practice includes 'upholding the patient's right to gain access to the necessary level of healthcare and, whenever possible, helping them to do so.'

There is no reason for believing this principle would not apply in veterinary practice and extend to helping owners import medicines they otherwise could not afford if it is clearly in the interest of their patients.

My view is that the historical precedent related to the procurement of hepatitis C medication from foreign sources for use in human populations can indeed be translated to the treatment of cats with FIP in Australia. The Veterinarian's Oath that recent graduates have taken would support this contention.

## So, how can a client order molnupiravir from India to treat their cat with FIP?

Go online and find the URL for a website called IndiaMART viz. https://www.indiamart.com/ and search for Molcovir 200mg—currently the URL is:

https://m.indiamart.com/isearch.php?s=Molcovir+200mg&prdsrc=1&countryiso=AU&qu-cx=1&stype=attr=1

After submitting your contact details and identifying which medication you are interested in purchasing, your enquiry is forwarded to several pharmacies requesting quotes. We suggest you correspond by e-mail and avoid the numerous text messages that will be sent to your mobile phone. The manufacturers with whom we have had the most experience are Dolphin Pharmaceuticals and Mediseller. One of these accepts PayPal payment rather than requiring credit card payment. The responsibility of negotiating customs rests with the Australian purchaser. The suppliers do their best to ensure that the medication is labelled so that it is clear that it is not an illicit drug. You cannot purchase any medication until a quote comes back.

Once you accept the quote, payment is arranged,


Figure 7. Generic molnupiravir (Molcovir 200mg capsules) purchased from IndiaMART and imported in Australia, after clearing customs

then postage. It is our experience that most importations are completely successful, although occasionally the parcel is opened, and a capsule sampled (presumably for testing by customs). Currently, if you buy five boxes, the cost is approximately $30 US ($42 Australian dollars) per box, plus $65 US dollars postage. The cost of treating a 4 kg cat with CNS FIP at 10-15 mg/kg bid for 84 days is likely to be in the order of $100 to $150 Australian dollars. The cost of treating the same cat with remdesivir/GS-441524 is typically $6,550, representing just the cost of the drugs.

A practical consideration remains: how to procure the molnupiravir in a timely manner. When purchasing from the IndiaMART website, it takes approximately 3 weeks for the drug to arrive in Australia and be processed through customs. One way forward would be to start treatment using remdesivir and/or GS- 441524, and then swap to molnupiravir as soon as the drug arrives.

The alternative is to develop a 'FIP owners buyers' club.' This could potentially serve as a source of molnupiravir until the client can arrange importation of their own supply. In the meantime, just send me an e-mail and I should be able to get some molnupiravir to you within a week or so.

To underpin this initiative, we would need to undertake assays on the purity of molnupiravir sourced from these manufacturers in India.

## What is the best way to treat a cat with FIP in 2022 in Australia?

The answer to this question is not as clear-cut as one might think. Remdesivir and GS-441524 have demonstrated efficacy as treatments for FIP in kittens and cats. These two treatments currently represent the standard of care for companion animal clinicians in Australia. We are also comfortable with low dose daily mefloquine as an adjunctive drug to consolidate therapy. However, most of us who have assisted in the treatment of cats will know of cases where the FIP virus acquired mutational resistance during the course of therapy. This can often be circumvented by escalating the doses of GS-441524 administered. However, for many owners, the cost of this dose escalation becomes prohibitive.

The routine use of combination therapy of FIP cases using GS-441524 and molnupiravir has much to recommend it as a concept. To date, no series of such cases has been published. It is indeed possible that combination therapy might be more rapidly effective by simultaneously targeting two distinct viral sites. Evidence for this approach has been demonstrated in trials where the protease inhibitor GC-376 has been given in concert with GS-441524. This approach may result in shorter courses of therapy. The protocol of 84 days of therapy comes from Neil's Pedersen's original seminal paper in JFMS and may be informed by knowledge regarding the lifespan of macrophages within the tissues. This is estimated to be some 84 days. Therefore, in order to eliminate all of the intracellular virus within the mononuclear phagocyte system, we need to extend treatment beyond the 84-day lifespan of a macrophage.

For many clients, the high cost of therapy can be prohibitive. I suggest that this problem may be circumvented for many clients, by utilising foreign-sourced molnupiravir which may be obtained at a cost of less than $100 AU.

Our colleagues in New Zealand have been equally imaginative in sourcing remdesivir inexpensively from India. This has been organised by a local compounder. The remdesivir is apparently now much cheaper, as demand for treating human cases has lessened. Remdesivir is typically used orally at high doses (25 mg/kg), with an 84-day course of therapy reported to cost $130 NZ dollars.

Figure 8. A British short hair with FIP getting IV remdesivir at initial therapy

## Is there a downside to molnupiravir?

Currently, it is unknown whether molnupiravir will be free from long-term toxicities. Some toxicity, such as bone marrow suppression, may be seen at dosages of 20 mg/kg and above, so these high dosages are not recommended in the treatment of FIP. The active ingredient in molnupiravir, N4-hydroxycytidine, is an extremely potent mutagen. The course of treatment for FIP extends far beyond the 5-day course recommended to treat COVID-19 in human patients. Therefore, the theoretical chance of side-effects is greater. This risk is however completely theoretical, as long as we utilise doses less than 15 mg/kg twice daily. However, it is something we need to monitor in the patients we treat, remaining mindful of the possibility of cancer developing in some cases in the future.

## Key resources about the personal importation scheme which underpin this article

- https://insightplus.mja.com.au/2022/28/importing-medicines-from-overseas-guidance-needed/
- https://www.tga.gov.au/products/unapproved-therapeutic-goods/personal-importation-scheme

Figure 9. One of these cats had FIP. Can you guess which one?

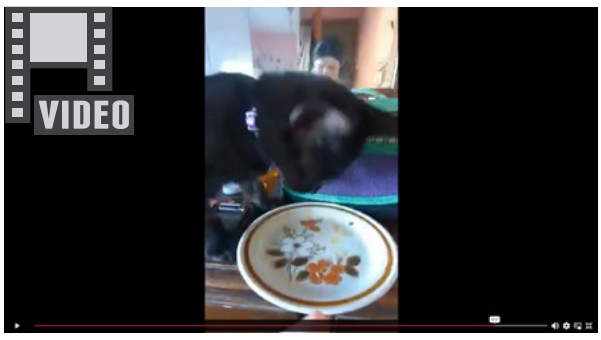


Figure 10. 'Squid' eating molnupiravir in a creamy treat. Video courtesy Jordan, Cat Clinic Hobart

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4. https://ccah.vetmed.ucdavis.edu > files > inline-files (this is a fantastic review of this subject, highly recommended for people who are interested in drug development and action.)
5. https://www.smh.com.au/healthcare/fixhepc-the-buyers-club-for-hepatitis-c-drug-inundated-with-inquiries-20151002-gjzud9.html
6. https://insightplus.mja.com.au/2022/28/importing-medicines-from-overseas-guidance-needed/
7. https://www.tga.gov.au/products/unapproved-therapeutic-goods/personal-importation-scheme◆


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# COMMENT COURTESY OF

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As things currently stand, if I have a debilitated patient that requires hospitalisation my preference is to administer remdesivir slowly IV as the initial treatment of choice, then transition onto oral GS-441524 tablets.

If patients are well enough to be managed as outpatients at the time of diagnosis, I am very comfortable now starting them off on oral GS-441524 and bypassing injections all together.

If 84 days of oral GS-441524 is cost prohibitive, I am comfortable transitioning these cats onto Molnupiravir once it has been legally obtained. I would say the biggest threat to a positive outcome is delaying starting treatment and using suboptimal dose rates. I would prefer to chop and change between antivirals to ensure rapid and continuous treatment than to delay commencing treatment whilst ordering and importing.

**C&Ts 5896 FIP treatment protocol, 5940 Update on FIP treatment protocol and 5883 FIP now a treatable disease**

Small

# COVID TIMES & CHALLENGING THE STATUS QUO

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I hardly need to point out that the whole world changed its way of working over the last 3 years. Working from home became the norm, as did telemedicine in some quarters (but not in our quarter!). Some of these changes were undoubtedly for the better but most were reversed as the pandemic subsided, regardless the consequence. Often this was for good reason, such as homeworkers finding the social isolation challenging. However, many reconsidered their positions and did not revert to the status quo.

There was plenty of banter in the veterinary press regarding the benefits of excluding the client from the consulting room, with little consideration that this might be beneficial in the long term. Whilst most of the vet world would appear to have gone back to in-house consultations, we have taken the bold move of keeping the client out of the consulting room long-term! Interestingly, the vast majority of our clients are very understanding of this with the few that make a fuss being the same ones that make a fuss about anything they can.

Now we are a cat-only practice and I am not suggesting that this is applicable to mainstream vet practice.

**However, my aim in writing this article is to challenge the status quo where practices persist simply because that is the way it has always been done.**

With the corporatisation of the industry and the standardisation of the whole small-animal consultation protocol, I would encourage those of you who are still independent to simply question whether a change of tack may have benefits.

**So let me relate our Covid-consulting journey.**

When Coronavirus hit we were the first practice locally to jump to a client-lockout situation, a scenario that we continued through all the UK Covid relaxations (and subsequent tightening) of regulations. Unlike the rest of the industry, we remained open throughout on the basis that telemedicine is a complete non-starter for cats. When I have the patient in front of me I can reach a definitive diagnosis without ancillary tests in perhaps 50% of cases. Anyone who can reliably and accurately diagnose a sick cat via a telemedicine-consultation is either very much cleverer than me or seriously deluded. I think to the times when cats have presented with a history of mild vomiting and anorexia over 36 hours, which proved to be in acute renal failure once investigated. The standard telemedicine advice of gastric rest followed by small digestible meals would probably see such cats in terminal renal failure by the time they were diagnosed face-to-face!

So, in order to work the system we had to make radical changes to the way we worked, and once these practices were established we were reluctant to change them at every whim of our government 'experts'. Like many of our peers, we found we actually really liked the system and found it a much more-efficient way of working. Moreover, at the same time it protected our staff and clients from transmissible respiratory disease of all descriptions. Like most of the industry, we have an excessive workload and are struggling to recruit staff. If we have even one staff member being off sick unexpectedly this has a huge impact on the team. Our policy on sniffles and sneezes has always been to send the staff member home immediately, avoiding transmission to the rest of the team. Since adopting our new way of working our upper respiratory illness record has improved dramatically and no team members have gone down with Covid!

**So how do we manage our system and how do we accommodate our clients?**

During the first summer, we bought a pop-up gazebo and planted it onto our front lawn. This was wonderful in summer but as autumn progressed, we included side-walls. As winter came along, we replaced the complete unit with a much-more sturdy commercial 3-metre by 3-metre commercial tent. Despite being on an exposed

hillside, this tent has survived numerous gales, though in one severe gale (our worst in living memory) I parked my van alongside for additional shelter.

- As clients arrive we ask them to place their cat baskets on a table outside the front door and then to take refuge in our tent or on our outdoor seating. During the summertime, we have a table and chairs on the lawn and also a picnic table under a large shady tree when it's getting hot.

- The receptionist then transfers the cat into what was the waiting room to await the clinician. We now use a shopping trolley for this as lifting cat baskets all day proved to be a risk factor for repetitive strain injury, especially when clients insist on putting 2 x 8kg bengals in the same container. Each cat basket is clearly labelled with the cat's name to avoid any confusion—being given the wrong cat might not go down well.

- The clinician will have already prepared themselves by reading the history and making any pertinent notes on the clipboard that they will take out the client. Whilst a full history is obtained outdoors, the consulting nurse extracts the cat from its basket, lets it wander around and acclimatise, obtains the current weight and prepares for likely follow-on procedures.


- Armed with the history our vet and nurse are then free to examine the cat unencumbered by the client.

- Once an action plan has been developed, the vet returns to the client to discuss the case, collectively formulating the way things will be managed.

- Next step is for the vet to return to the consulting room and implement any immediate treatment or organise hospitalisation and the appropriate paperwork. A consultation report will be completed whilst the nurse prepares the drugs for dispensing.

- The vet then finalises the consultation explaining the course of action and dispenses medications.

- And of course no consultation at Jaffa's is complete without appropriate dietary advice.

- Finally, the client is handed back to reception to receive payments and arrange follow-on appointments, sign insurance forms and the like.

So for nearly 3 years we have worked this system, initially out of necessity at a time when anything was acceptable—a case of making the best of a bad job.

**Having decided to continue this way there is no excuse now for not looking more seriously at the creature comforts of both clients and staff.**

During the winter our marquee gets very blustery with excellent air circulation—fine for Covid distancing, less so when circulating air is damp and 5°C. Moreover, taking payment from clients and getting forms signed is tricky especially when there are multiple clients waiting and limited covered space. To this end, we have made a number of modifications to our facilities.

- I have taken the covering of the gazebo, sidewalls and all, and used this to line the marquee, which is lit with globe LEDs and infrared heaters. Comfy chairs and a vase of roses returns us to the Jaffa's standards of care.

- In addition, I have erected a shelter, designed for bicycles, outside the front door. This has been fixed with flush-fitting baseplates such that the superstructure can be removed in summer.

**So why are we so keen to continue with this way of working?**

**Restraint**

Firstly the cat is restrained by skilled hands from the moment one commences examination. No phoning for assistance with the unavoidable delays.

**Clinical history**

Without the cat distracting the owner, it is much easier to extract a complete history without interruption. Moreover, we ourselves are not being distracted by a concurrent examination and letting ourselves jump to instant conclusions based upon first impressions. Cats are complex creatures and for anything other than obvious complaints; the main clues lie in the history. As an example, if a cat has chronic diarrhoea my physical examination may take a minute, but I may take 10 minutes discussing the history (and another 15 minutes explaining

our course of action). A thorough cat consultation takes time. Whilst our way is probably more time-consuming overall, the examination is probably 10 minutes quicker. We are therefore converting unfruitful time with the owner into hardcore clinical practice. I don't therefore see any cons here.

**Cats without their owner**

We find most cats are much more amenable without the owner present. For sure there is a subset of cats that are calmer with the owner present, and exceptions can always be made for these individuals. I had one owner who was in tears because we told that she could not come in with her cat; it transpired that she had a cat that had been physically abused at a previous practice. Once she saw that her supposedly-unmanageable cat was totally calm in our presence she acknowledged this fact and left us in peace!

The con here is when a demanding client sees the previous person enter the building and demands the same. A gentle explanation normally resolves this rare issue. To be fair quite a few clients would prefer to be with their cats—but most are happy to not be.

**Euthanasia**

We always make an exception for euthanasia reverting to the use of our 'snug'.

**Client flow**

Our step-by-step protocol clearly and cleanly terminates the consultation at an appropriate time and this is understood by the clients. It may be simply that we have learned (been forced) to take control of the situation. Certainly, we have taken a more disciplined approach to clients who don't wish to pay at the time or who mess us around with our scarce appointments. It's now a case of 'take it or leave it', and since we are no longer taking on any new clients I believe our existing ones value our service more, especially as they may find no other practice locally that will take them on. For too long we have bent over backwards to satisfy our clients' needs at our own and our staffs' expense. Having been pushed to the limits for such a long time I think we now appreciate the impact this has upon us all. My explanation to our clients is that our staff take priority, as without them we could provide no service at all. This does not imply any lowering of standards, or being less helpful, but most business people seem to be finding clients to be less tolerant and more demanding post Covid, and we now don't routinely capitulate.

**Quality of working life**

Quality of one's working environment is something that gets precious little consideration in the design of veterinary premises though I was delighted to read recently of a mega-referral facility that had the provision of outdoor lighting throughout its huge premises as a priority. We hear so much these days about workplace and job dissatisfaction—how depressing is it to be in premises with tungsten lighting all day, when you don't know if the sun is shining or if the clouds are emptying their bowels?

Images show genesis from gazebo in summer to big tent in winter, to tent lined by gazebo with front panel and door

Whilst we already have beautiful light-and-airy premises, the to-ing and fro-ing in and out of the premises keeps both vet and receptionist active and able to 'come up for air', experiencing the freshness of the outdoors on a regular basis. This is an unexpected benefit which actually improves one's working day rather than the other way round. It does require the donning and shedding of warm or waterproof clothing through the day but this is not something that has particularly bothered us.

So, in conclusion, this has been a lesson for us in re-evaluating our working practices to fit our own individual circumstances, with some unexpected outcomes◆

# MEMBER BENEFIT

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Go to: cve.edu.au and look for the drop down menu under the Resources tab.

# Challenges & Advances in Wildlife Rescue & Rehabilitation Training

**'Do the best you can until you know better. Then when you know better, do better'**

**- Maya Angelou**

With mass wildlife casualties of unprecedented bushfires and flooding events recently, it's clear we must do better, and faster, by better facilitating rescue and rehabilitation in the field and providing greater access to training in wildlife medicine as critical first steps.

**Guidelines for the Initial Treatment and Care of Koalas** have been released by the NSW Department of Planning and Environment (DPE). In collaboration with DPE and **Koala Conservation Australia**, **Versatile Vet** has produced 11 videos that demonstrate key skills required for their rescue and rehabilitation and feature renowned koala expert Cheyne Flanagan. These are to be used in parallel with the Guidelines, the Koala Code of Practice, and to support the **Taronga Wildlife Treatment and Care course**.

**Watch the DPE video:**


www.environment.nsw.gov.au/topics/animals-and-plants/native-animals/rehabilitating-native-animals/wildlife-rehabilitation-standards

Access the videos free via the Versatile Vet video library: www.versatilevet.com

Stay tuned to Versatile Vet for updates about more wildlife rehabilitation videos coming soon....

https://www.facebook.com/versatilevetvideos

https://www.instagram.com/versatile_vet/

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**Lean how to age a koala by tooth wear and why it is a critical skill in assessing koalas brought in for care.**


Video link:

nsw_-estimating_age_based_on_tooth_wear (1080p)...

B BRAUN
SHARING EXPERTISE

# DIRTY WOUNDS? WE HAVE THE SOLUTION!

**Wounds can vary widely in how they present, from straight forward through to complex, challenging us at every turn. Wounds may be superficial, gaping full thickness or punctures that go deeper than we can see, but no matter the depth of the wound, if it is not clean it cannot heal.**

## What is Biofilm?

Biofilm forms when bacteria adhere to surfaces by excreting a thick, glue-like substance known as the Extracellular Polymeric Substance (EPS). This substance forms a protective layer, where the bacteria are no longer free to move (planktonic) but adhere to the wound bed. New bacteria are produced, and the colony grows under the protection of the EPS. Biofilms are often difficult to detect visually, but they delay wound healing due to the protection they provide to the bacteria in the wound bed.[3]

## The Solution

Traditional wound cleansing with saline and water is ineffective at removing coatings and debris in many wounds, especially complex biofilms.[4] Prontosan® Irrigation Solution and Prontosan® Wound Gel/Gel X are specifically indicated for the prevention and removal of biofilms. Prontosan® contains two key ingredients: Betaine and Polyhexanide.

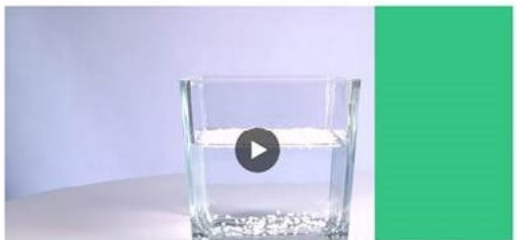
Betaine is a gentle surfactant which is able to disturb, penetrate, clean and remove biofilm and wound debris.

Polyhexanide (PHMB) is a broad-spectrum antimicrobial with demonstrated good clinical safety, no evidence of resistance and minimal toxicity. It functions as a preservative which inhibits the growth of micro-organisms.[5,6,7]

The unique combination of Polyhexanide and Betaine have a double effect on the wound bed to create a wound environment optimal for healing.

**For more information and to see how it works visit:**

## How it works?



There is a plastic granulate on the surface.

ADVERTORIAL


**References**

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# WHAT IS YOUR DIAGNOSIS?

## Answer to C&T No. 5959

## Patchy alopecia in a mature horse

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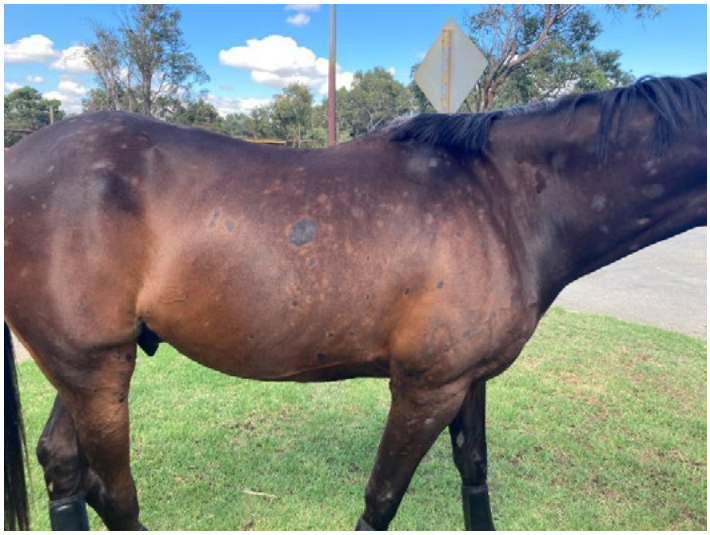
C&T No. 5971



An 18-year-old Arabian gelding presented for non-pruritic, patchy areas of alopecia. Lesions initially occurred on the ventral neck, then progressed to involve the trunk, limbs, rump and face. There were no other dermatological abnormalities noted; the horse was systemically well.

### Answer: Alopecia areata

**How would you investigate the patient?**

Skin scrapes, hair pluck, skin biopsy would all be possible, although the lesions are so characteristic that we made a presumptive diagnosis on the basis of the gross lesions.

### Treatment

The patient was treated with 0.584% hydrocortisone aceponate topical spray (Cortavance®.) This was applied daily to the affected areas for 14 days, then reduced to every other day for a further two weeks. After four weeks of treatment, new hair re-growth was noted in affected areas, in particular the white hairs of the star on the face. The owner was instructed to continue Cortavance® on an as-needed basis.

Treatment of alopecia areata may not be required due to the cosmetic nature of the disease. Immunosuppressive medications may cause adverse side effects that outweigh their clinical benefits. Other treatment options include oral prednisolone, 0.1% topical tacrolimus ointment, topical triamcinolone spray and 2% minoxidil solution. Spontaneous hair re-growth may occur in some cases; when hair re-grows it is often lighter and finer than normal.

I would like to acknowledge Dr. Janet Littlewood, my mentor for this case.

# ALOPECIA AREATA

**Linda Vogelnest BVSc(Hons), MACVSc (Feline Medicine), FACVSc (Dermatology) Specialist Veterinary Dermatologist**

Alopecia Areata is an uncommon auto-immune dermatosis that occurs rarely in horses (and also dogs and humans). It is characterised by non-inflammatory alopecia, most typically with one to small numbers of 2-4cm well-demarcated circular areas. Less commonly larger regions or numerous lesions can occur. The face, neck and trunk are commonly affected sites. Leukotrichia (loss of hair pigment) may occur initially or rarely dominate.

A key feature that helps differentiate from other causes of alopecia is that the skin surface in affected areas looks normal; there is an absence of scaling, crusting, swelling, erythema or other skin changes. This makes sense looking at the pathogenesis, as auto-antibodies are produced against components of the hair follicle, including actively growing anagen bulbs, resulting in the resorption of follicles, without furunculosis (follicle rupture) and the associated intense inflammation that follicular pathogens more typically produce.

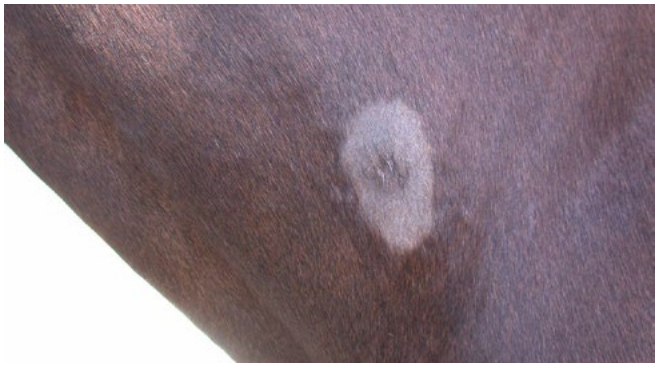
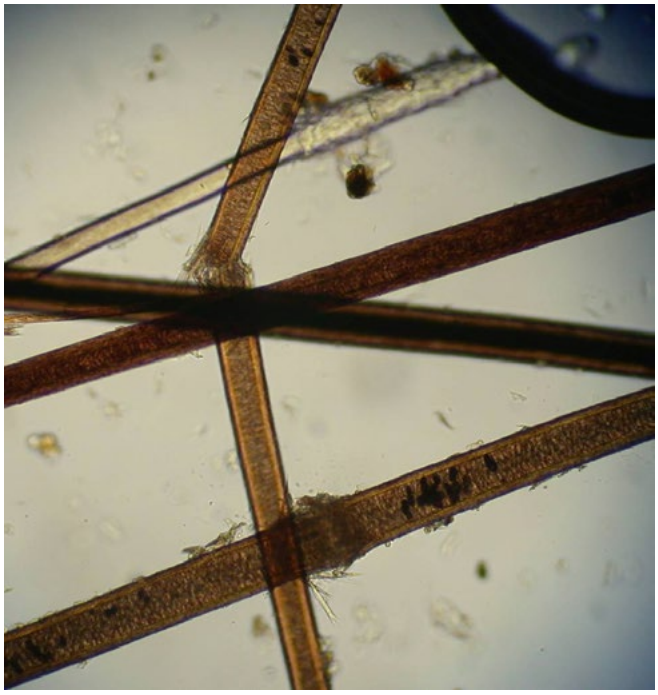


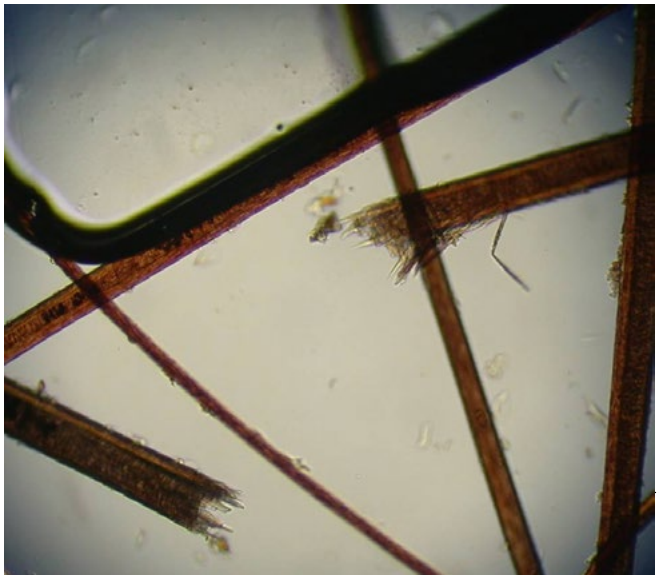
Figure 1. Localised circular to oval well-demarcated alopecia in a horse due to alopecia areata, with normal skin appearance, and some central hair regrowth.

There are several more common differentials to consider for this presentation, including follicular pathogens (staph bacteria, dermatophilus, dermatophytes), occult sarcoid, and local trauma (injection site reactions, trichorrhexis nodosa). Although other skin changes including scaling and crusting are mostly present with these causes of alopecia, occasionally the skin can appear normal.

Other less common considerations include interruptions to follicular cycling (anagen or telogen defluxion), and demodex mites (very rare in horses).

Some simple surface skin tests can help support a diagnosis of alopecia areata and exclude other more common causes of alopecia. Tape impressions should reveal an absence of inflammatory cells, fungal spores/hyphae and bacteria (normal skin surface bacteria are very sparse and rarely apparent on oil-immersion fields). A trichogram can be useful, with abnormally tapered, frayed or fractured hair shafts typical; and again the absence of fungal elements or demodex mites is important.





Deep skin scrapings (or potentially the new squeeze tape described for canine demodicosis) would exclude very rare cases of demodicosis. Biopsies provide firm diagnosis, revealing tightly follicular (peribulbar) lymphocytic infiltrates (often referred to as "a swarm of bees"... that pathologist might have been a bee keeper!) However, these changes are transient, and multiple samples from early lesions may be required, although biopsies also provide evidence for exclusion of infectious differentials (again, multiple samples of a range of lesions provide more reliable information) and occult sarcoid.

No reliable treatments are described for alopecia areata in horses, humans or dogs. Spontaneous resolution is well-reported (within months to years). Topical treatments are the mainstay, with glucocorticoids, skin irritants (inducing contact reactions), or less often tacrolimus or minoxidil potentially helpful, but some cases remain refractory to a range of treatments. Intralesional or occasionally systemic glucocorticoids have also been utilised, without consistent results. With cosmetic appearance important to many performance horses, the pressure may be on to help find a solution; the key may be quick treatment with a potent topical steroid such as Cortavance (off-label in horses) or Mometasone (e.g. Elocon lotion) - assuming you are pretty confident at excluding infectious differentials which could get worse–warning owners that response is variable, so you can claim success even if there is spontaneous resolution!

Figures 2 & 3. Trichogram from edges of lesion on horse from pic 1. Localised weak areas distally on otherwise normal hair shafts, resulting in fraying, bending (Figure 2) and fracture (Figure 3) of hairs.

Biopsy is required for definitive diagnosis of alopecia areata, but distally narrowed ('exclamation point') or weak, breaking of hairshafts on trichogram, with the absence of infectious causes, is supportive of this diagnosis.

## SEEN AN INTRIGUING CASE LATELY? OR HAVE AN INTERESTING PHOTO?

We welcome any images and content from our readers that would be suitable for our 'What's YOUR diagnosis?' column.

Please send them to: cve.marketing@sydney.edu.au and earn a voucher◆

Perspective No.157

# FUNGAL DISEASE: AN UPDATE

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## Introduction & Our Conceptual Framework

Veterinarians in Australia see cryptococcosis cases and dermatophyte infections (ringworm) like most of the world, but we do not have the endemic river valley mycoses like blastomycosis and coccidiomycosis that are such an important problem in the USA. We do have pockets where histoplasmosis occurs, but they are quite localised. So, in this *C&T* perspective, when we talk about fungal diseases, we generally refer to random fungal diseases which might be seen anywhere in the world.

The infections we wish to concentrate on in this essay are sporadic fungal diseases, usually in immune competent hosts, but sometimes in hosts that are immune deficient because of drugs administered to treat auto-immune diseases. We will also briefly cover dogs and cats with some inherited immune defects which predispose them to disseminated fungal infections with pathogens that rarely produce disease in normal hosts. We will also touch upon diseases caused by oomycetes and algae, which clinically can resemble fungal infections.

Many fungal infections of soft tissues occur after penetrating trauma. This might be a stick, grass awn or a metallic object. It might also occur after a scratch or after a bite injury where two combatants roll around in the dirt. **In all these scenarios, we are dealing with an immune competent host in which a heavy inoculum of fungal elements is introduced into the subcutis, with variable destruction of local tissues caused by the inciting trauma.** In some situations, foreign material coated with a fungal biofilm is left in the wound, whereas in others the penetration is transient, but results a heavy inoculum of fungal spores or vegetative fungal elements being deposited in the subcutis.

Normally, an immunocompetent mammalian host is protected from potential fungal pathogens in the environment by an intact epidermis, usually covered by protective fur, and the action of the innate immune system. **When these protective mechanisms are circumvented by traumatic inoculation, a localised fungal infection can develop.** Cleansing wounds will of course decrease the chance of this occurring.

This local infection may be: (i) constrained by innate and adaptive immunity, or (ii) it might spread via the lymphatics (so called sporotrichoid spread) or (iii) by local extension to contiguous tissues, or (less likely) (iv) it might undergo widespread haematogenous dissemination, although this usually only happens in immune deficient animals.

It is not just fungi that can cause disease in this manner. The somewhat related oomycetes *Pythium* and *Lagenidium* can do the same. Indeed, both can actually set up infection even without penetrating injury, as they have motile zoospores which can penetrate skin softened by maceration. A chlorophyll-deficient algal organism called *Prototheca* is also capable of giving rise to subcutaneous disease after penetrating trauma.

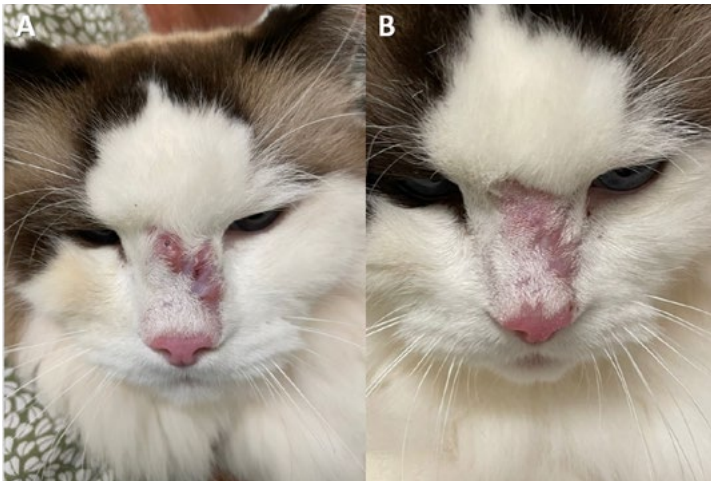


Figure 1. (A) This cat has a ***Fusarium solani*** infection in the naso-ocular region. This is a common site for deep fungal infections in cats, presumably as cat scratch injuries result in inoculation of fungal elements that are located on the nail of the perpetrator. A variety of fungi can be isolated from these types of infections, with a range of pathogens that are often refractory to commonly used antifungal drugs. Of course, you can also get unusual soil bacteria like ***Corynebacterium***, ***Nocardia*** and ***Mycobacteria*** in this location, and herpetic dermatitis is included in the differential diagnosis. This cat responded to long term oral treatment with posaconazole (B) during therapy. Some of these cases require intralesional amphotericin B, or debulking surgery followed by reconstruction of the resulting surgical wound to effect a cure.

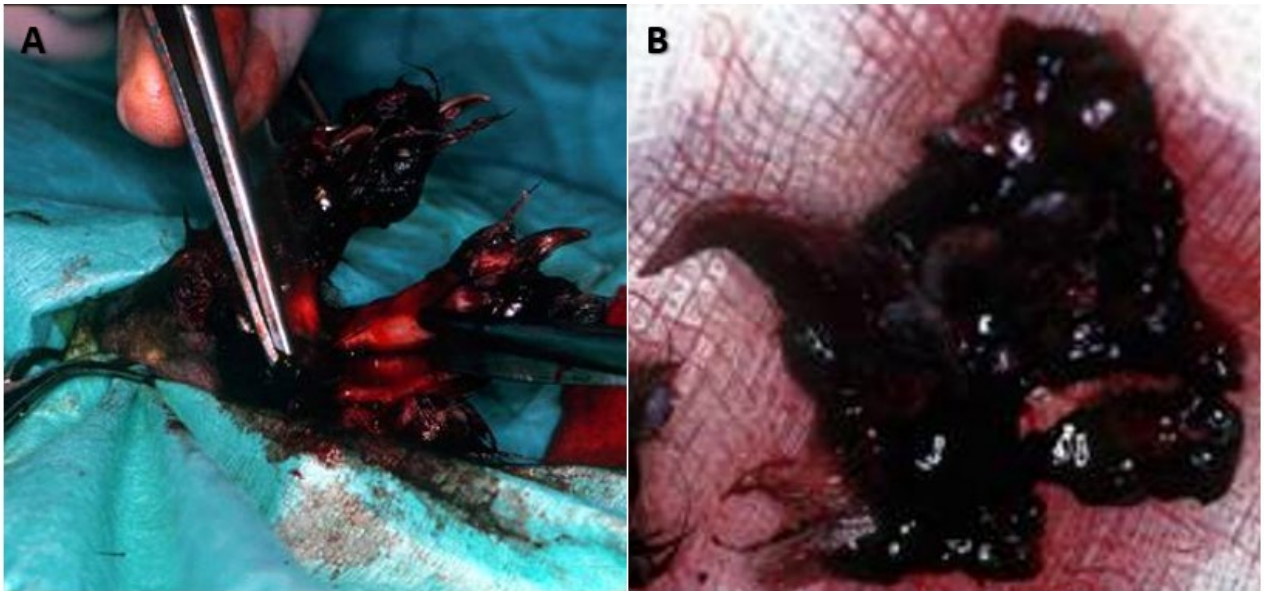


Figure 2. This cat has a deep soft tissue infection with a dematiaceous (pigmented) fungus – ***Wangiella dermatitidis***. This group of fungi normally live in the soil. A specialist surgeon is exploring the area and resecting all tissues which have a dark appearance from melanin imparted by the fungal pathogen. The surgeon has unfortunately placed the biopsy material on a gauze swab, which can be OK, but will sometimes prevent the growth of Mucormycetes such as ***Mucor*** as the large hyphae are easily fragmented by the cotton fibres. Better to just put the biopsy in a sterile urine container with a little sterile saline.

Lesions caused by saprophytic fungi introduced by penetrating trauma tend to have certain stereotypical anatomical distributions. For example, in cats, scratch injuries to a cat's naso-ocular region (face) can be contaminated by fungi, and also by mycobacteria and *Nocardia* spp—all having in common a domicile in the soil and dirt. Another common site for saprophytic fungal infection in cats is the distal limb, in the vicinity of P3 or the digital pads.

Although not the major focus of this article, mycotic rhinosinusitis (nasal aspergillosis) is another example of a localised infection (at least in the dog) in an immune competent host; although the exact pathophysiology has not been determined with certainty, it likely involves inhalation of a heavy load of fungal spores, or fungal elements on a grass seed foreign body.

A quite different scenario occurs when the immunity of the host has been compromised. This might be an acquired problem. Dogs with immune-mediated haemolytic anaemia, immune-mediated thrombocytopenia and polyarthritis are all generally treated with a combination of corticosteroids and immunomodulatory agents such as azathioprine, cyclosporine, or mycophenolate, which compromises innate and adaptive immunity, both cell mediated, and antibody mediated.

Dogs on combination immunosuppressive regimens are not infrequently afflicted by multifocal fungal infections of the skin and subcutis, possibly as a result of abrasions from grass awns and similar penetrative vegetable matter, where the foreign sharp object is often coated with fungal spores or vegetative fungal elements. A different type of immunosuppression occurs in the breed-associated immune deficiency states, where some as yet to be discovered chink in the normal immune response permits normally commensal fungi or environmental saprophytes to 'take off'. In some lines of Cavalier King Charles Spaniels and certain miniature Dachshunds, some defect in antibody or cell mediated immunity allows *Pneumocystis canis*, present as trophozoites in the lung of normal dogs in exceedingly small numbers, to multiply and give rise to what is eventually life-threatening pulmonary disease, often in association with cutaneous demodicosis and *Bordetella bronchiseptica* pneumonia. Recently, a Shih Tzu with *Pneumocystis* pneumonia was shown to have an X-linked CD40 ligand deficiency.

In German Shepherd dogs, Vizslas and a variety of other pedigree and pedigree hybrid dogs, filamentous fungi such as *Aspergillus terreus* or *A. deflectus*, the capsulated yeast *Cryptococcus* and a wide variety of other fungi, some of which are better known as plant pathogens, give rise to disseminated disease. The likely pathogenesis of these infections is that infectious propagules, most likely fungal spores, give rise to focal mycotic pneumonia, which is clinically silent, followed by lymphatic spread to the hilar lymph nodes, and subsequently haematogenous dissemination to tissues with a good blood supply but with some vascular tortuosity, such as the bony vertebral endplates, certain other bones, the anterior uveal tract in the eye, and the central nervous system. Treatment of such infections can be especially

challenging as certain immunological mechanisms that prevent fungal disease developing and help eradicate fungal pathogens are lacking in these breeds, which makes a successful outcome much harder to achieve. Furthermore, there is always the possibility for disease recurrence or the development of similar but unrelated infective insults.

## Diagnostic Tips

1. **Get a really good sample. Handle it carefully!**
   It is optimal to collect a sample which contains the fungal elements (yeast cells or hyphae) without contamination from normal bacterial skin flora present in the overlying skin. This is because bacteria generally grow faster than fungi, although you can to some extent circumvent this by adding antibiotics to the fungal media to inhibit their growth.

   So, to procure a good biopsy, first cleanse the biopsy site by washing thoroughly but gently with an iodinated soap, and then 70% ethanol. Allow sufficient time for the ethanol to evaporate. Then make an incision, debride the tissues, and obtain representative deep material for biopsy. This might be an open surgical biopsy (e.g., *Figure 2*) or a core biopsy (using a skin biopsy punch (usually 6 mm or 8 mm diameter) or a spring-loaded core biopsy gun), or even just a fine needle aspirate biopsy.

   Often, of course, we do not know at first if a specimen will be fungal, oomycete, algal, bacterial or neoplastic.

   Under such circumstances, cut the biopsy specimen and cut it in half. Put half in formalin. Put the other half in a sterile urine container containing a few drops of sterile saline (to keep the biopsy from drying out). Critically, keep the unfixed portion of the sample in the practice refrigerator at 5ºC (while you wait for the results of the examination of the formalin-fixed tissues).

   **Do NOT wrap the biopsy in a gauze swab, as this will fracture the hyphae of certain fungi and stop them growing later when they are plated out on Sabouraud's dextrose agar in the laboratory.**

   You can start off the microbiological investigation of the lesions by using a normal histological examination of the formalin-fixed tissues (initially stained with haematoxylin and eosin (H&E) and adding, when appropriate, special stains such as periodic acid Schiff (PAS) or Grocott-Gomori's methenamine silver stain (GMS )).

   ½ in formalin for histology; ½ in a sterile pot in the practice fridge

   This 2-step investigative process can save the owner some money!

   Keeping half the sample in the fridge (NOT freezer!) is an effective way to preserve fungi or other infectious agents in a viable state until it is clear that you need to submit a fresh tissue specimen for mycological culture. Freezing often kills eukaryotic organisms such as fungi, although their DNA remains intact for PCR and sequence analysis.

   If you are sure the infection is fungal (perhaps after seeing fungal elements in a preliminary fine needle aspirate), or if money is no object, then submit both specimens at the same time. However, when doing so, it is vital to adequately seal the formalin-containing specimen, or send it in a separate plastic container, as it is very easy for leaky formalin to contaminate the sterile sample and make it useless for fungal culture.

2. **Try to submit the sample to a reference mycology laboratory, either directly, or indirectly.**
   Although veterinary laboratories can often do a respectable job at handling fungal specimens, if you see a reasonable number of fungal cases, there is benefit in developing a relationship with a specialist human or veterinary mycology reference laboratory. They have expertise in both classical mycology, with excellent microscopy skills and a broad range of fungal media and special stains at their disposal as well as in the most modern molecular mycology methods, including panfungal PCRs with sequence analysis and many rapid tests (IMMY lateral flow for cryptococcal antigen, galactomannan index, β-glucan, etc.).

   If you use a veterinary laboratory for primary fungal isolation, it's often much better to ask them to forward the positive culture plates to a reference laboratory for specialist procedures such as definitive species identification (ID) and fungal susceptibility testing. Reference laboratories, in addition to employing scientists specialised in mycology to work at the bench, often have an association with infectious disease clinicians who may be willing to give you very good advice about case management.

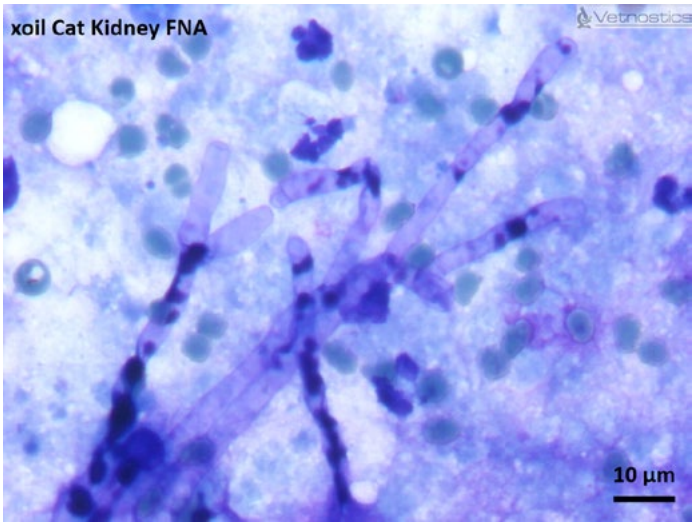


Figure 3. Fine needle aspirate from the renal pelvis of a cat with mycotic pyelonephritis. Diff-Quik stain of a cytospin preparation. Note the very broad ribbon-like hyphae, suggestive of a Mucoromycete. Culture PCR and sequence analysis was diagnostic of *Lichtheimia corymbifera*. The cat was treated with posaconazole based on susceptibility testing, although the cat succumbed. Most antifungal drugs do not reach sufficient concentration in the glomerular filtrate to effectively treat mycotic pyelonephritis.


Figure 4. Fine branching septate hyphae from a pellet after centrifugation of a urine specimen from a German Shepherd with mycotic pyelonephritis. The morphology of this organism is highly suggested of an Aspergillus species. 400X magnification; Diff-Quik stain.

An alternative is a veterinary lab in a veterinary teaching hospital that has a special interest in fungal infections. Veterinary teaching hospitals will often have academic staff who make fungal disease their research area.

In Australia, there are several human hospital laboratories that will process veterinary specimens for a fee. The key contact people are senior hospital scientists at Westmead Hospital (Dr Catriona Halliday catriona.halliday@health.nsw.gov.au), Adelaide Women's and Children's Hospital (Dr Sarah Kidd sarah.kidd@sa.gov.au) and Concord Hospital (Evanthia Tambosis). Veterinary Pathology Diagnostic Services at the SSVS at the University of Sydney is also worth an enquiry.

3. **Try to get the lab to fully describe the fungal morphology in cytology or histology specimens.**
Some labs just say, `fungal elements detected'. This is not helpful!

We need to know: Are there yeasts or hyphae? Do the yeasts have a capsule? Is there budding? Are the hyphae branched? What angle do they branch? Are the hyphae septate? Are the hyphae thin with parallel walls, or thick and irregular or ribbon like?
(See *Figure 3)*

If you have a good morphological description you can often guess the general class of fungus, which will help you select the best empiric agents for therapy.

If the lab will not do this for you, find another lab!

4. **Choosing empiric therapy and obtaining susceptibility data.**
Once you get a definitive identification of the fungal pathogen, ideally from a reference laboratory, do a key word search in Google Scholar or a PubMed search engine to find some recent veterinary or human papers on management of the pathogen. If they are behind a paywall—just fire me an e-mail and I will get them for you.

Each fungal pathogen behaves similarly in animals and man so both human and veterinary papers are equally germane to your cause. Even a horse paper might be informative for a companion animal clinician, and vice versa. For some unusual fungi, only human papers may be available. The reason why the host species is less important is that most fungi are environmental in origin so their biology, resistance pattern and behaviour are very much a feature of their normal environmental niche rather than the host in which they cause disease.

Based on the published information for the particular fungal species, you will be in a position to choose empiric therapy. It is ideal, however, to ask the reference laboratory to perform susceptibility testing, if possible (susceptibility testing may be difficult / impossible for poorly sporulating isolates). This takes time (often 5-10 working days, or more) and, in general, you cannot afford to delay therapy. So, start empiric therapy with one or more agents. You can change your drug choices in 1-2 weeks when susceptibility data becomes available. **In severe or acute cases, it is vital to be aggressive and use at least two agents, as then at least one is likely to be effective.**

Delay in appropriate therapy is a common reason for treatment failure. Unfortunately, the best drugs are often the most expensive and sometimes high efficacy is associated with injectable-only agents or comes at a cost of some toxicity.

When you are sure about ID and susceptibility, it is then appropriate to de-escalate and use the most cost-effective drug(s) that are likely to work.

It is bad medicine and generally poor value to choose a drug because it's less expensive and hope it might help. It is much better value in the long term to choose a drug which is expensive but likely to be effective against almost all fungal pathogens. In 2022, usually that is drug posaconazole.

5. **Learn about rapid tests for endemic fungi likely to be encountered where you practice.**
In Australia, cryptococcosis is the most common systemic mycoses in cats and probably dogs. The same is probably true in California and British Columbia in Canada. It is even more common in native Australian animals such as koalas. Obtaining representative material from nasal exudate, nasal washings, bronchoalveolar lavage fluid specimens or fine needle can often provide a rapid diagnosis because of the very characteristic organism morphology in smears stained with rapid Romanowsky stains such as Diff-Quik (see *Figure 5*).

There are exceptionally good rapid tests for this pathogen, of which the IMMY lateral flow was the first to appear on the market and to date its performance appears to be superior to the many imitators that have appeared subsequently. This test uses immunomigration technology (immunochromatography) to detect nanomolar concentrations of polysaccharide fungal antigen. The authors strongly recommend that this test be used before doing expensive testing such as cross-sectional imaging (CT, MRI) or endoscopy, as cryptococcosis is sufficiently common in endemic areas that an inexpensive screening test is worthwhile. The IMMY lateral flow test is highly sensitive but only moderately specific, making it a useful screening test. By this, we mean that false positives do occur. Positives need therefore to be confirmed by latex cryptococcal antigen agglutination testing, or by obtaining material for cytological examination and/or culture.

IMMY style tests can be done cage side in the practice. A similar test is available to diagnose histoplasmosis using urine as the diagnostic specimen. Histoplasmosis is rare and sporadic in Australia, so this test is rarely used, although it is widely used in the USA in places where histoplasmosis is endemic.

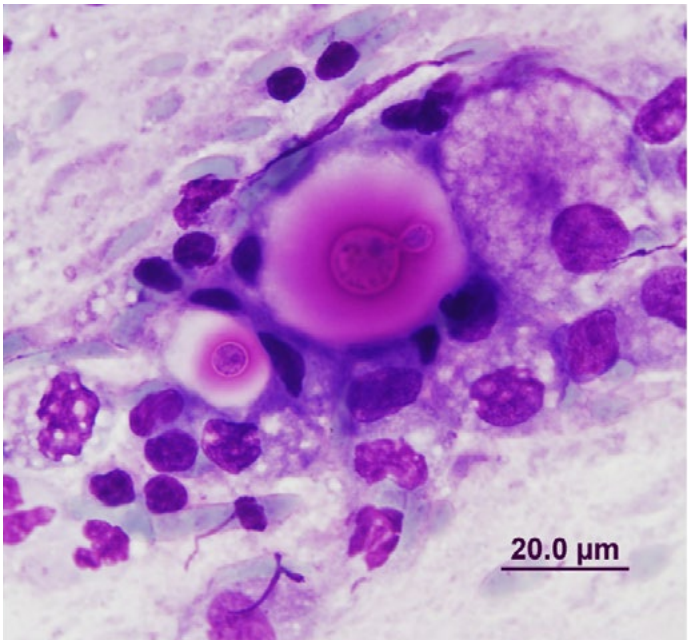


Figure 5. Diff-Quik stained smear of an aspirate from a nasopharyngeal mass that turned out to be a granuloma caused by *Cryptococcus gattii* in a cat. The presence of an abundant capsule that may or may not take up the stain, and narrow-necked budding are characteristic and thus many smears are pathognomonic for cryptococcosis.

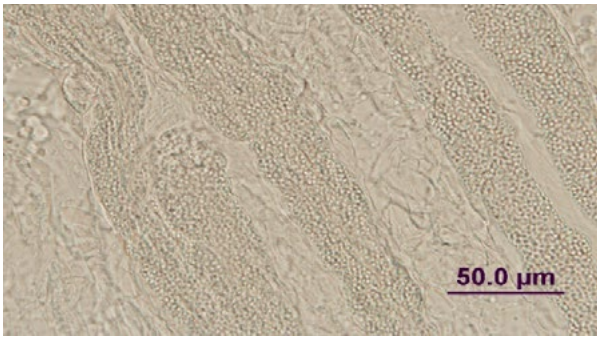


Figure 6. Ectothrix arthrospores of *Microsporum canis* in a KOH preparation of a hair plucked from a cat.

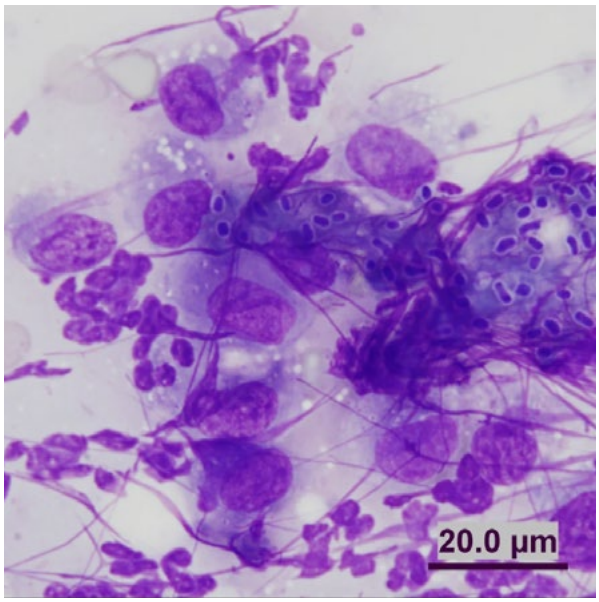


Figure 7. Diff-Quik-stained fine needle aspirate from a skin mass caused by the geophilic dermatophyte *Nannizzia gypsea*.

## Treatment Tips

1. **Treating dermatophyte infections**
   Perhaps the most common fungal infections of cats and dogs, especially young patients, is dermatophytosis. The most common dermatophyte involved is the animal-adapted organism *Microsporum canis*. Much less common are soil-associated organisms such as *Nannizzia gypsea*, (formerly known as *Microsporum gypseum*). The diagnosis and management of dermatophyte infections deserves a full article. It is worth mentioning in passing, that diagnosis can now be performed by PCR testing as well as the more traditional fungal culture in the practice (Fungassay®) or in the diagnostic laboratory (using selective medium).

   There is an incredibly good general article on management of dermatophyte infections by Karen Moriello, Kim Coyner, and colleagues available as an open access free download at onlinelibrary.wiley.com/doi/full/10.1111/vde.12440.

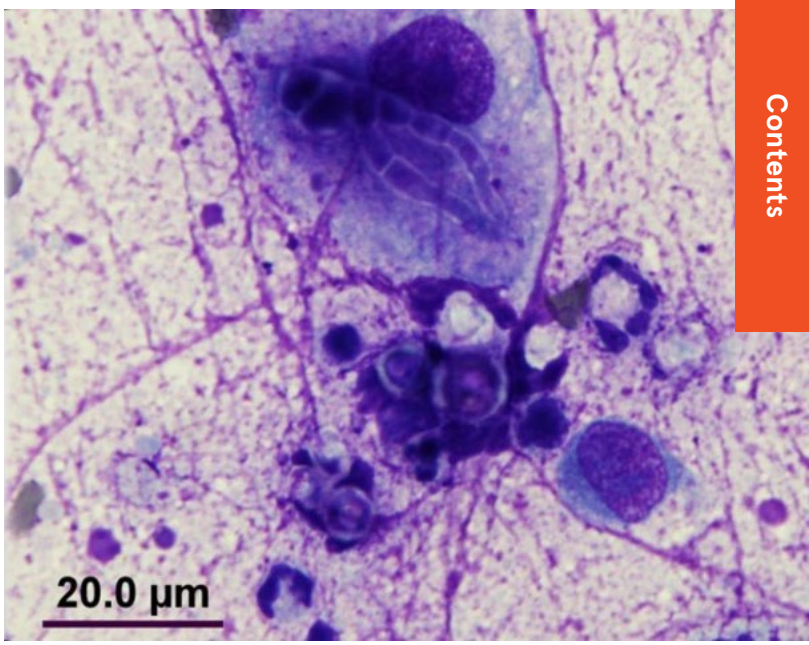


Figure 8. Diff-Quik stained fine needle aspirate biopsy from a subcutaneous mass in a cat caused by the plant pathogen *Microsphaeropsis arundinis* often thought to be associated with the garden escape weed elephant grass.

*Note that the doses of itraconazole used for treating dermatophytes (typically 5 mg/kg of Sporanox) are substantially lower than those used for systemic mycoses, as dermatophyte infections are usually limited to the skin, and itraconazole is concentrated in the skin because of its high lipid solubility.*

Therefore, do NOT use low dermatophyte dose regimens for itraconazole when treating more invasive infections. Use at least 5 mg/kg twice a day, or 10 mg/kg once a day.

Itraconazole should be given with food to enhance its absorption.

2. **Treating soft tissue infections following penetrating trauma with posaconazole ± terbinafine.**
   Subcutaneous and cutaneous infections can occur in dogs and cats after penetrating injuries with sharp objects, such as sticks, plant awns and barbs, sharp metallic objects, and after cat scratches and animal bites contaminated by dirt. A wide range of fungi can be implicated.

   The most common fungal pathogens encountered are likely influenced by geographical considerations such as soil types. For example, in Sydney, NSW, Australia a very unusual dematiaceous (pigmented) fungal pathogen *Microsphaeropsis arundinis* is the most common cause of soft tissue infections in cats. It also occurs in human patients, and to date, 1 dog. It is thought to be common here

because of its relationship as a pathogen of the garden escape weed known colloquially as Elephant grass.

Many different fungi can be involved, however, including the especially nasty pathogen *Fusarium*. The range of potential pathogens is so large that it is impossible to choose a single antifungal agent that will cover all possibilities. **Our considered advice is that posaconazole is a particularly good agent to use for empiric therapy while awaiting culture and susceptibility results.**

Posaconazole is a second-generation triazole agent. It is an exceptionally safe drug and tends to be very well tolerated. It is generally given orally once daily. Cats and very small dogs are best treated using the suspension, whereas in dogs the sustained release tablets represent the most cost-effective way to administer this agent. It has a very broad spectrum of activity. It used to be very expensive, almost prohibitively expensive, but it came out of patent in 2022 and several generic formulations of the sustained release tablets that are affordable and cost-effective are now available. THIS IS REALLY A GAME CHANGER—as it means posaconazole is affordable therapy for long term treatment in large dogs. Note that the tablets cannot be scored in any way—to dose smaller animals, use the 100 mg dose but give it every second day or even every third day.

The suspension is generally used in cats and small dogs at a dose rate of 8 mg/kg once a day, whereas the dose of the sustained release tablet is 5 mg/kg every day, or every other day, depending on whether you need to achieve really high blood concentrations. The drug levels obtained in individual patients can be unexpectedly high or low, such that measuring blood levels is a very cost-effective exercise. This is known as therapeutic drug monitoring (TDM). TDM is available in the pharmacology department of St Vincents Hospital in Sydney and is highly recommended for all antifungal drugs, especially expensive drugs, and drugs with potential toxicity.

Drugs commonly assayed for TDM include fluconazole, itraconazole, voriconazole and posaconazole. TDM is not widely used for amphotericin B, flucytosine or terbinafine.

To further broaden the spectrum of antifungal activity, terbinafine is often added to posaconazole in a combination therapeutic regimen. Terbinafine is available as a generic drug and is therefore much cheaper.

**Table 1 – Current costs of posacoanzole**

| |
|---|
| **Original products** |
| Noxafil Oral Suspension MSD $888.90 plus 10% GST |
| Noxafil tablets MSD 100 mg 24 $838.95 plus 10% GST |
| **Generics** |
| Pharmacor tablets 100 mg 24 $169.99 plus 10% GST |
| ARX MR tablets 100mg 24 $332.65 plus 10% GST |

In many instances, surgical debulking has a place after preliminary antifungal therapy. It is generally best delayed until after you have obtained susceptibility data for the pathogen, so you can make sure you have established effective blood levels of an appropriate antifungal during surgery, and CRITICALLY, during the healing stage following reconstruction of the surgical wound.

Debulking fungus impregnated tissues, followed by wound reconstruction, is a highly effective way to progress therapy in cases with extensive disease.

Sometimes the surgery can also remove foreign plant material which actually introduced the fungal inoculum into the host tissues.

By cytoreducing the extent of infection, the infective agent is better exposed to high levels of antifungals in the patient's blood.

A top tip for treating most fungal diseases is the drug levels in actual patients can be unexpectantly high or low, such that measuring blood levels is a very cost-effective exercise, and this is known as therapeutic drug monitoring (TDM).

Level too high – sometimes risks toxicity for some drugs.

Level too low – drug will not work!

3. **Intralesional amphotericin B as an adjunct to oral antifungal therapy.**
What do you do when the infection is present on an extremity, such as the nose or a distal

Figure 9. Deep subcutaneous infection in a cat presumably after penetrating injury. *Fusarium oxysporum* was cultured from the lesion.

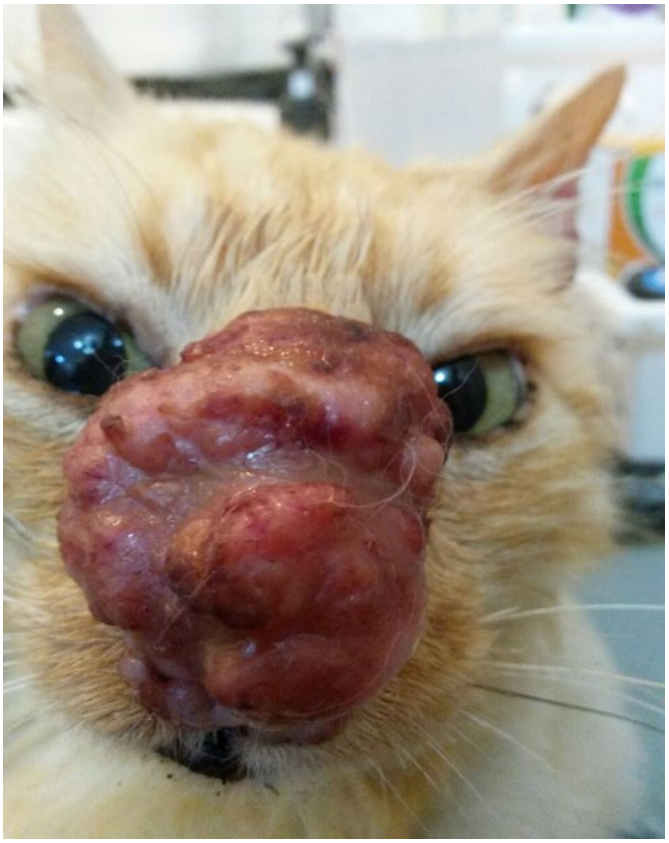

Figure 10. Sporotrichosis in a cat from Brazil caused by *Sporothrix brasiliensis*. This cat would be an excellent candidate for debulking surgery followed by intralesional amphotericin B therapy as an adjunct to systemic therapy with oral itraconazole.

limb, where debulking surgery is difficult to impossible, without recourse to amputation? This is not an unusual scenario!

A specialist surgeon has the ability to use an Esmarch's bandage as a torniquet and resect infected tissues and reconstruct the wound via fusion podoplasty, but this technique is possibly beyond the ability of an average practitioner.

A 'trick' which can be useful in such a setting is the use of intralesional amphotericin B. This agent is traditionally used systemically for life-threating fungal infections such as cryptococcosis, but Brazilian veterinarians have adapted a human procedure for treating refractory cases of feline sporotrichosis on the face near vital structures such as the nose and the eyes. Intralesional amphotericin, using a concentration of 2.5 to 5 mg/mL of amphotericin diluted to a volume of 2-3 mL can be used to infiltrate any fungal infected tissues, administered on a once weekly basis (or more often if necessary) under heavy sedation or light general anaesthesia. This has a potent local antifungal effect and is a nice intensive treatment for extra efficacy on top of oral therapy with posaconazole and terbinafine for a variety of fungal pathogens capable of causing lesions of the distal limbs or naso-ocular region.

4. **What about fluconazole, itraconazole, voriconazole and isavuconazole for systemic therapy of fungal disease?**
Fluconazole and itraconazole were the first two triazole antifungal agents. The original azole antifungal ketoconazole is no longer available, except from compounding pharmacists.

Fluconazole is active largely against yeasts, such as *Cryptococcus* spp and *Candida* spp. Its leading role is therefore in treating *Candida albicans* and other susceptible *Candida* species, and in the management of cryptococcosis. It is a narrow spectrum antifungal. It is very safe, and widely available as generic formulations which are

Itraconazole is an exceptionally difficult drug to compound, and treatment failures are often a direct result of using compounded itraconazole formulations that have poor bioavailability.

DO NOT USE COMPOUNDED ITRACONAZOLE – IT IS A FALSE ECONOMY

cost effective, but it generally has almost no efficacy against filamentous fungi like *Aspergillus* spp and other soil-dwelling fungi likely to be seen after penetrating trauma. It is a very important drug in the treatment of cases of cryptococcosis that are mild to moderate and in which there is no CNS involvement. In such cases, its low cost, safety, efficacy and good penetration of the CNS and eye make it the backbone of therapy. It has very little use for most other fungal infections. It is occasionally used for dermatophytes where its major advantage is low cost, but it does not concentrate in the skin like itraconazole.

Itraconazole has a much wider spectrum of activity compared to fluconazole and is effective for treatment of many fungal infections including sporotrichosis, blastomycosis, histoplasmosis and coccidiomycosis. Indeed, treatment regimens have been developed for treating these so-called river valley mycoses using itraconazole based on compelling evidence in the form of extensive case series. The original drug was developed by Jansen Cilag, with a capsule formulation and a liquid formulation, the latter having superior pharmacokinetics in companion animals. The capsules when opened contain many specially formulated little white spheres which can be mixed in with a cat or dog wet food, and this is a convenient way to administer therapy. There are some good human generic formulations of itraconazole but beware compounded itraconazole.

In Australia, we have a unique formulation of itraconazole called Lozanoc® with superior pharmacokinetics as a result of improved bioavailability; there is much greater consistency in achieving therapeutic blood levels, and a dose of 5 mg/kg of Lozanoc is used equivalent to 10 mg/kg of Sporanox. There are, however, some potential problems with itraconazole. When treating invasive fungal disease, doses of the order of 10 mg/kg once a day or 5 mg/kg twice a day are commonly used. It is not uncommon for such doses to cause clinically significant hepatotoxicity during a long course of therapy. This can be detected early by monitoring the ALT activity in plasma, which rises gradually before icterus and anorexia develop. Many internists administer liver tonics such as S-adenosyl methionine at the same time as itraconazole in an attempt to prevent liver injury, and anecdotally, this strategy appears to be successful. It is the view of this author, however, that in most clinical situations it is better to use voriconazole or posaconazole at recommended doses based on *in vitro* susceptibility testing combined with TDM, rather than using this older agent. Itraconazole can occasionally cause severe cutaneous vasculitis.

Voriconazole despite a slightly narrower spectrum and potential toxicity issues, is an important antifungal especially in the dog with systemic disease. Like posaconazole, it is often combined with oral terbinafine, and in some cases with parenteral amphotericin B.

Voriconazole is a second generation triazole agent with much enhanced activity against many fungi (including most members of the genus *Aspergillus*) compared to itraconazole. It is water soluble, and out of patent, so there are cheaper generic formulations available which are more affordable than the original drug developed by Pfizer. Voriconazole is a highly effective drug against *Aspergillus* species, with comparable efficacy to amphotericin B. But voriconazole is not as forgiving an agent to use as posaconazole. High doses can cause delirium and visual hallucinations in human patients, and in cats, high doses can cause serious neurological signs including seizures. Most likely, this could be avoided by careful TDM and gradual dose escalation, but many feline practitioners prefer to just not use voriconazole. It is a useful dose in the dog, but drug levels are hard to predict, even when using studies of pharmacokinetics in normal dogs as a guide, and in the opinion of the authors, TDM is mandatory. The drug is also known as a potent photosensitiser, and in human patients its use combined with UV exposure can result in actinic damage and even cutaneous neoplasia, so dogs on voriconazole should probably be kept indoors during the heat of the day, especially breeds not afforded the protection of a generous hair coat. Another advantage of voriconazole is that it is good at reaching effective CNS levels because it readily crosses the blood brain barrier, a conspicuous advantage over posaconazole.

5. **Amphotericin B – an old drug but a particularly important agent for severe disease.**
When fungal infections are severe, advanced, disseminated or involve the CNS, amphotericin B remains an important drug, and indeed, often the most important agent.

It was one of the first drugs to be used for systemic fungal infections and comes with

a reputation for nephrotoxicity. This can be largely circumvented by using the liposomal formulation AmBisome®, although this is a very expensive drug and beyond the resources of most owners and requires intravenous access for administration. Liposomal amphotericin B continues to be expensive due to high manufacturing costs even though its patent has expired. There are also lipid complex formulations that are available for IV use in the USA; however, they are not used in Australia, and we have little experience with them.

The original deoxycholate preparation of amphotericin B is much more affordable and can be given by other routes as well as intravenously. This is the formulation with which we have had the most experience and, although this experience is anchored in cats and dogs, it extends to native animals and zoo patients, including koalas with cryptococcosis.

In patients with severe disease, such as disseminated cryptococcosis (often with ocular and/or CNS involvement), amphotericin B is usually given intravenously for the first week of therapy. The protocol for its use is widely accessible in infectious disease textbooks. Usually, daily doses of 0.5 to 1.0 mg/kg are given as a continuous rate infusion intravenously (IV). If owners are exceptionally wealthy or the animal is generously insured, liposomal amphotericin can be used with less risk of acute kidney injury, at a daily dose of 2-3 mg/kg. Note that all formulations of amphotericin B are equally effective. The advantage of liposomal and lipid complex formulations is just reduced kidney damage as the lipid liposomal wall prevents the kidney 'seeing' the active drug which is delivered to the fungus inside macrophages.

Once the dog or cat is well enough to go home, we generally swap from IV therapy to subcutaneous infusions twice weekly. The rationale of the subcutaneous bolus infusion is based on slow absorption of amphotericin from a dilute subcutaneous reservoir. This largely circumvents the propensity towards nephrotoxicity, especially in the dog, which is usually young and therefore tends to have more resilient kidneys compared to an older cat.

The subcutaneous amphotericin B regimen works very well in the dog and in young cats, but in older cats that usually have lost some renal reserve, you need to be careful to 'back off' therapy when the serum urea and creatinine concentration creep up. For some reason, it is the serum urea concentrations that usually increases first rather than creatinine.

Over the last few years, we have been giving amphotericin B infusions INTRA-PERITONEALLY (IP), usually under sedation. The advantage of this IP route is that the fluids can be given faster (but make sure you microwave the fluids first so they are at about 37°C) and that sterile subcutaneous abscesses which can occur with subcutaneous infusions are circumvented. We have also used higher concentrations of IP amphotericin B for treating invasive sparganosis.

As an aside, vets who train in Brazil often use IP fluid therapy rather than SC fluid therapy for the same reasons, speed of administration and faster absorption of the fluids.

Over the last few years, we have started using intraperitoneal (IP) dosing rather than subcutaneous administration in some patients, usually larger dogs. This can be facilitated by sedation in unruly patients. IP administration is faster than IV, and you avoid the propensity for subcutaneous lumps or sterile abscesses developing, although there can be mild chemical peritonitis. It is a worthwhile option in some patients, especially dog breeds with thin skin such as Boxers and greyhounds, that seem more likely to get subcutaneous reactions.

6. **What about 5-flucytosine (5FC) & potassium iodide (KI)?**

5FC is an extremely useful drug in human and feline patients with cryptococcosis, as the drug acts synergistically with amphotericin B. Its downside is that it is expensive, can be hard to source, and it must be given at least three times a day and possibly four times a day.

5FC is a useful drug in cats with severe cryptococcosis but cannot safely be used in dogs together with amphotericin B for more than 7 days because of the development of a skin eruption resembling toxic epidermal necrolysis.

We find it extremely helpful for cats with cryptococcosis that is disseminated or if they have CNS involvement. Unfortunately, it is not a helpful drug in the dog, as almost all

dogs given this drug develop a drug reaction resembling toxic epidermal necrolysis after about 7-10 days of combination therapy. This is a severe cutaneous disease which represents a substantial set back during early therapy, and basically it precludes the use of 5FC in canine patients.
Saturated potassium iodide is an old-fashioned antifungal and antibacterial agent used to treat diseases such as actinobacillosis (wooden tongue) and actinomycosis (lumpy jaw) in large animals (cattle), and fungal diseases such as sporotrichosis and *Conidiobolus* and *Basidiobolus*. It has proved a cost-effective treatment for sporotrichosis in Brazil where *S. brasiliensis* is a hot feline and human pathogen. KI is usually combined with other antifungals such as itraconazole. Later, we will talk about the place of KI in treating pythiosis, as it has been successfully used for treating ovine pythiosis in some settings.

7. **Beware spurious isolation of fungi from clinical specimens.**
Fungal spores are everywhere!

If you do not clean your air-conditioners regularly, fungal spores will be present all throughout the veterinary hospital. They can also be widely present in veterinary microbiology laboratories. As a result, it is not difficult for fungal spores to make their way into clinical specimens that are then plated out on fungal media such as Sabouraud dextrose agar, or even on routine media such as blood agar. (After all, this is how Alexander Fleming discovered penicillin!).

**Sometimes the growth of these spores in culture can result in an erroneous diagnosis of fungal infections when no infection exists.**

In our experience, contamination is most common in samples obtained from the respiratory tract by bronchoalveolar lavage or deep unguided bronchial washings. A recent case the author consulted on was a small dog where *Purpureocillium lilacinum* (formerly known as *Paecilomyces lilacinus*) was cultured from a deep bronchial washing in which eosinophils were the predominant inflammatory cell present. The dog had nodular lung disease. We wasted time and money treating this alleged infection with voriconazole, only to eventually conclude it was likely a contaminant. To be certain, we repeated the bronchial washing—and on the second occasion eosinophils persisted, but no fungi were cultured. The dog responded rapidly to prednisolone, the presumptive diagnosis being eosinophilic pneumopathy. *Mea culpa!*

The authors are also aware of a scenario in a tertiary referral centre where the samples from several endoscopes were contaminated with various fungal species. This problem was resolved when hospital infection control officers and nursing staff were made aware of the problem by the diagnostic laboratory and improved routine cleaning practices.

**To diagnose a fungal infection, it is critical to establish that fungal elements are present in the original smears from the site of infection, in this case smears made from cytospin preparations of BAL fluid. If a true fungal infection exists, there should be yeasts or hyphae in evidence** (occasionally this is not the case when samples are collected from sterile sites such as CSF).

Contaminating spores in small numbers are usually not evident in smears, but they will grow on culture. Do not be too fast to blame the laboratory for growing a contaminant, as in our experience most contamination actually occurs in the veterinary practice. A common site of contamination is endoscopes used for bronchoscopy or rhinoscopy that are not cleaned appropriately. To avoid this problem, check that your scope is not contaminated by always submitting for culture a sample of sterile saline aspirated through the endoscope prior to the procedure as well as the actual BAL sample.

8. **Are there any new treatments for pythiosis and lagenidiosis (oomycete infections) in dogs, cats and horses?**
*Pythium and Lagenidium* species are oomycetes that are distinct from fungi in terms of their basic biology, being parasites of plants. They both are capable of producing refractory disease of the skin and/or alimentary tract. They establish infections using motile zoospores as their infectious propagule, and infections are most common in warm moist environments such as Texas and Louisiana in the USA and far north Queensland and the Northern Territory in Australia. Infections can involve the gastrointestinal tract, the skin and subcutis, or both these tissues.
Oomycetes have broad irregular hyphae which are somewhat characteristic, and they grow well on routine media. These infections traditionally had a very guarded prognosis, with treatment involving a combination of debulking

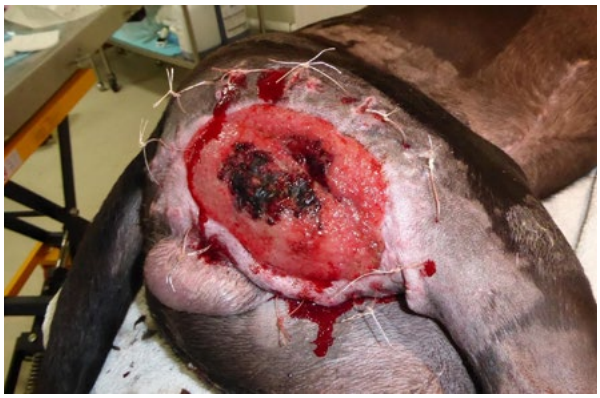

Figure 11. *Lagenidium* infection of the subcutis of a dog from the Northern Territory of Australia. The organism is pigmented, and the presence of melanin imparts a black colouration to the infected tissues.

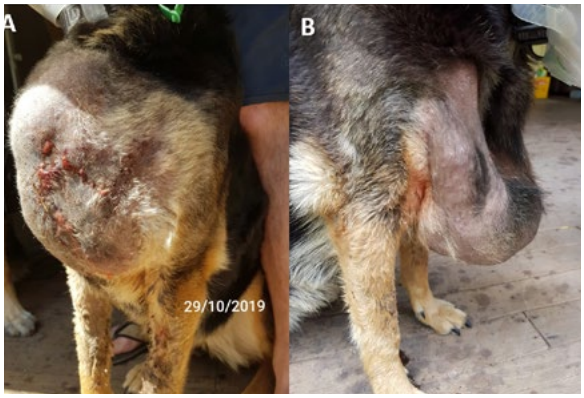


Figure 12. A oomycete in a German Shepherd dog from far north Queensland, before (A) and during (B) treatment with monotherapy using Metalaxyl. The lesion has improved to the extent that surgical resection which was initially impossible is now feasible.

surgery and azoles such as posaconazole combined with terbinafine.

Recently, the use of Metalaxyl or its optically active stereoisomer mefenoxam has greatly improved he prognosis for pythiosis in animals, although publications are scant.

Metalaxyl and its active optical isomer mefenoxam are used to treat oomycete infection in plants, so they are very inexpensive compared to antifungal drugs designed for human patients. This in itself is a huge advantage for therapy, especially in larger patients as posaconazole and terbinafine can be cost prohibitive.

Metalaxyl or mefenoxam can be used alone or combined with triazoles or terbinafine. There is also an experimental literature that suggests azithromycin, minocycline and linezolid (conventional antibiotics) are effective at killing *Pythium*. Corneal infections in people have been managed with combinations of topical linezolid and azithromycin combined with systemic azithromycin, and sometimes voriconazole topically. In sheep with nasal pythiosis, oral potassium iodide has been used successfully as therapy. Although a definitive treatment regimen has not been developed for disease in dogs and cats, the combination of mefenoxam plus KI and azithromycin is attractive as all the medications are inexpensive.

Our experience has been mainly in cats and dogs with cutaneous and subcutaneous disease, and we have used Metalaxyl or mefenoxam both topically and systemically (5 mg/kg orally twice daily). Topical treatment

Figure 13. Suspect early pythiosis lesions in a horse exposed to the floods on the north cast of NSW. A definitive diagnosis for this case was not obtained, but topical Metalaxyl was effective at treating the lesions. The protocol developed by Rosemary Cumings and Oliver Liyou, is set out below:

involves using concentrated Metalaxyl soaked swabs bandaged over the affected regions, with bandages changed daily or every other day.

A highly effective immunostimulant vaccine is also available from Dr Mendoza in the USA and from Dr Mark White in Australia. In jurisdictions in which this is obtainable, it can be very useful. The vaccine is most effectively prepared from the actual isolate causing the infection and can be sourced by contacting Dr Mark White at mark@treidlia.com.au. Ideally, Mark needs a pure culture of the oomycete from the patient to be sent to him. He formulates the vaccine using that isolate, a bespoke vaccine.

## Topical Metalaxyl Handling Protocol

*Developed by Rosemary Cumings & Oliver Liyou for use in Horses with swamp cancer but applicable to all species.*

**Wear safety goggles and gloves when preparing and applying and advise owners to do the same!**

*The ocular toxicity is the highest rating (like for many household cleaners/agricultural chemicals we use frequently) and it is not worth risking a splash injury. If any gets in a person's eye, they should immediately wash the eye out then go to the hospital for high volume lavage. Similarly, do not spray it on the horse's face if they have a lip lesion, just dab it on and I would not apply this near a horse's eye in case it dripped in.*

1. Dilute 1:1 with water. It is stable in water for a prolonged period of time and is not degraded by light so you could mix up 150mL, 500mL or 1L depending on the lesion size you are dealing with and either store it in a spray bottle or in a sealed container full of gauze swabs for ease of use. I would use distilled water, water for injection or even just bottled drinking water ideally in case of contaminants in the tap water after the floods that could grow in the container.
2. Clean any debris/discharge off the surface of the swamp cancer lesion with saline or water.
3. Put a rim of Vaseline around the lesion if the skin is already flood damaged and doesn't have hair left to protect it.
4. Place 1-2 gauze swabs soaked in the solution on the lesion and bandage in place OR spray the lesion surface it is too large/not in a spot that can be bandaged.
5. Repeat application daily.
6. Continue to monitor the swamp cancer and treat as you normally would with your usual medical therapy/immunotherapy and, if the lesions are failing to respond, consult a surgeon re excision/an ongoing treatment plan. It will likely take a long time for lesions to completely resolve but you would hope to see some initial shrinking after 3-5 days' treatment.

So, it is highly likely that over the next few years the guarded to grave prognosis for oomycete infections will improve substantially.

For some reason, we very rarely see the gastrointestinal cases of pythiosis that occur in the USA and Hong Kong, although one dog from The Northern Territory that initially had cutaneous disease later developed colitis.

Many animals were impacted by the floods that we have had on the north coast of NSW, with several horses developing lesions suspicious of 'swamp cancer' (pythiosis or lagenidiosis) on their distal limbs. In collaboration with Oliver Liyou (well-known equine dentist) and Rosemary Cumings (an equine internist at Scone Equine Group), we have used Metalaxyl or mefenoxam as topical spray to prevent pythiosis developing or to treat early cases with good effect.

9. **New drugs on the horizon.**
Isavuconazole is the most recently released azole antifungal. It is a safe agent with an extremely broad spectrum of activity, with efficacy against some fungi where other azoles are ineffective. It's expensive and its kinetics are unknown, but it might prove to be a useful agent in cats and dogs with unusual fungal infections. In people, it is useful for aspergillosis and mucormycosis.

There is a pile of exciting new antifungal agents that should soon be on the market, and these will improve our ability to deal with many resistant and hard to treat pathogens. Amongst these, fosmanogepix and olorofim are two of the stand-outs. They will of course be expensive, but they should prove particularly useful for cryptic *Aspergillus* species such as *A. felis* and for *Scedosporium* and *Lomentospora* infections which can be extremely challenging to treat using current agents.

## Some Unusual Fungal & Algal Infections

1. **Diagnosis and treatment of pneumocystis pneumonia (PCP)**
*Pneumocystis canis* is a host adapted fungus that is part of the normal lower respiratory mycobiome in many dogs and cats. Indeed, just about every mammalian species has a host adapted *Pneumocystis* species. With a normal immune system, small numbers of trophozoites or cysts (ascii) persist in the alveolar spaces but do no harm. However, in certain breeds with inherited immune deficiency states,

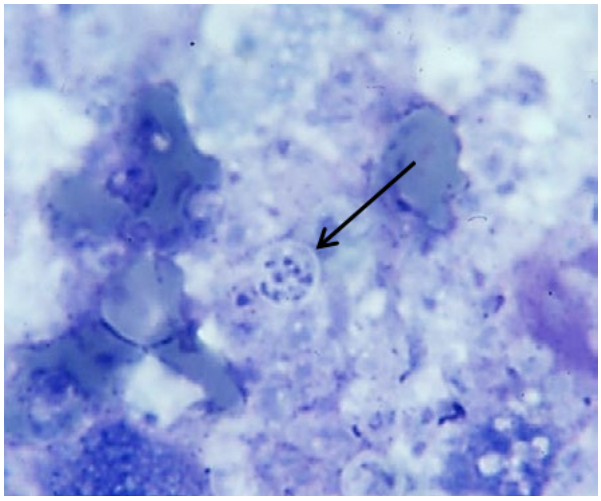

Figure 14. Cyst or ascii (arrow) of *Pneumocystis canis* in a cytocentrifuged BALF specimen from a young Cavalier King Charles spaniel.

especially Cavalier King Charles Spaniels, miniature Dachshunds, and their hybrids, the trophozoites can multiply unchecked and cause disease. This can also occur in dogs of a normal genetic makeup when subjected to immunosuppressive therapy, including drugs like Apoquel.

In dogs, PCP is mainly seen in Cavalier King Charles Spaniels, miniature Dachshunds, and their hybrids. An increased suspicion for this diagnosis in young members of these breeds with lower respiratory issues is a key to early diagnosis. Concurrent infection with *Bordetella bronchiseptica*, or a history of demodectic mange either currently or historically may be present.

Diagnosis is usually suggested by the breed, sometimes by the antecedent administration of immunosuppressive medications (corticosteroids, toceranib, cyclosporine), and by the presence of characteristic radiological changes in chest radiographs and CT scans. Chest X-rays tend to show a characteristic dense interstitial pattern, sometimes accompanied by right sided heart enlargement (cor pulmonale) due to pulmonary hypertension. CT shows a characteristic ground glass appearance of the pulmonary parenchyma.

Having large animal formulations of trimethoprim sulpmethoxazole suitable for slow intravenous injection is extremely helpful for treatment of PCP in dogs. Parenteral therapy offers important advantage in terms of rapidly achieving high blood and tissue levels in critically ill oxygen-dependent patients with PCP pneumonia.

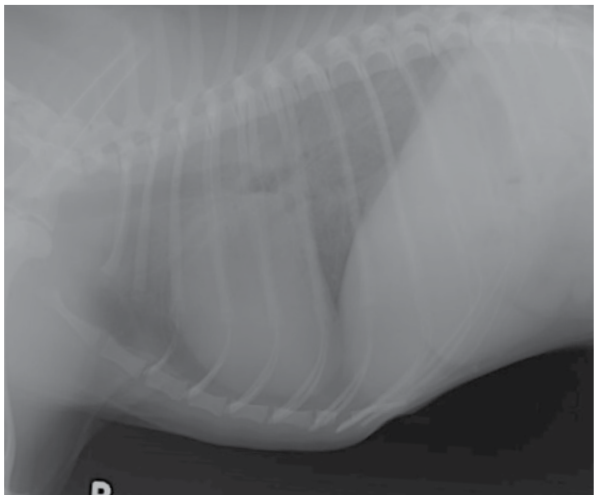

Figure 15. A hazy but dense interstitial pattern is highly suggestive of PCP pneumonia in one of the susceptible breeds. Cor pulmonale is usually also present.

Confirmation of a diagnosis of PCP pneumonia typically relies on seeing the organisms, yet only the cysts (ascii) (rather than the trophozoites) are readily seen.

Panfungal PCR and PJP PCR (for the human organism *Pneumocystis jirovecii*) do not detect *P. canis*. Canine specific PCR primers have, however, been published by Patrizia Danesi and colleagues and, recently, a pan-Pneumocystis PCR for all Pneumocystis species has been developed at the National Institute of Health in the USA.

Real time qPCR for PCP is available at Istituto Zooprofilattico Sperimentale delle Venezie, Legnaro (PD), Italy. Hopefully, specialist veterinary PCR labs will offer this as a test in the near future, ideally multiplexed into their respiratory PCR panels.

Figure 16. If you see dyspnoea without coughing in a young Cavalier King Charles Spaniel—immediately consider PCP pneumonia in the differential diagnosis. Photograph courtesy of Linda Abrahams.

Treatment is well worth attempting. High dose trimethoprim sulphamethoxazole remains the drug of choice, and ideally, it should be given intravenously to achieve high blood levels. It is important that this large animal formulation be available for companion animals as parenteral therapy offers important advantages over tablets for preliminary intensive therapy. In time, the use of intravenous echinocandin therapy (e.g., caspofungin, micafungin, anidulafungin) might also find a place in treatment of these cases. Monitor Schirmer tear test readings as keratoconjunctivitis sicca due to TMS can develop during the course of therapy.

If there is a strong index of suspicion for PCP pneumonia in a dog due to *P. canis*, do not feel an obligation to confirm a diagnosis by BAL fluid examination and PCR. These procedures typically require general anaesthesia which can be sufficient to decompensate this type of patient. A fine needle aspirate biopsy from a severely affected portion of lung can be a safer way to obtain material for cytological examination or PCR, and, perhaps, throat swabs might be sufficiently sensitive if subjected to a qPCR assay.

There is nothing wrong with making a strong presumptive diagnosis and embarking on therapy, when characteristic imaging findings are present in breeds that are predisposed to this condition. Remember that co-infection with *Bordetella bronchiseptica* is common, so it is often worthwhile to add doxycycline to the therapeutic regimen.

2. **Disseminated fungal disease in German Shepherd dogs, Hungarian Vizslas and other breeds.**

One of the most vexing entities for companion animal veterinarians to treat is widely disseminated disease due to a variety of fungi, most commonly *Aspergillus terreus*. German Shepherd dogs (GSD) and possibly Hungarian Vizslas possess some inherited immune defect which makes them especially susceptible to fungal pathogens. Sporadically, the same problem is seen in individuals of other breeds.

It is thought that infection starts by inhalation of a large dose of fungal ascospores which lodge in the alveoli. After germination and early hyphal formation, the infection spreads to the hilar lymph nodes.

From there infection spreads to a variety of well perfused tissues characterised by vessel tortuosity. Often the lesions in the lungs have healed by the time clinical signs emerge. **Clinical signs reflect the site of dissemination—vertebral and appendicular osteomyelitis, discospondylitis, anterior uveitis, meningoencephalitis and mycotic pyelonephritis are the most common clinical manifestations.**

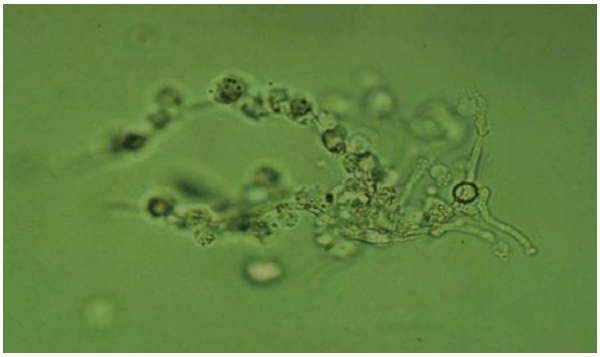

Figure 17. Hyphae of *A. terreus* in a wet preparation of the urine of a 2-year-old German Shepherd bitch.

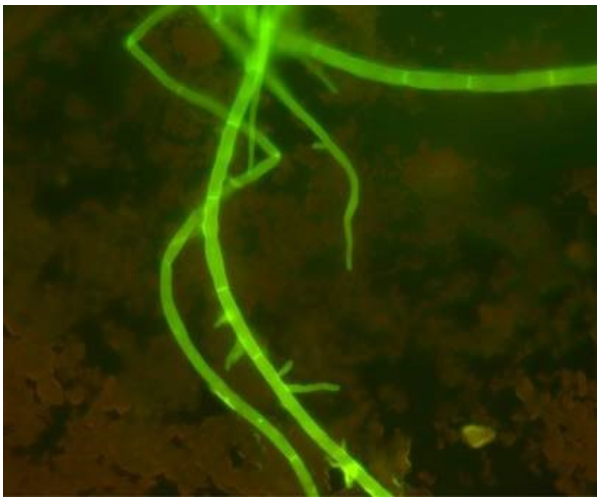

Figure 18. Calcofluor white stain of a positive blood culture from a dog with disseminated aspergillosis due to *A. terreus*. Photograph courtesy of Charlotte Webster, Concord Hospital.

*Aspergillus, Scedosporium* and related fungal species have a predilection for blood vessel walls and infection can track along large arteries giving rise to aneurysmal dilatations. The diagnosis of these infections is not difficult if one has a good appreciation of the 'illness script' and a high index of suspicion for a fungal aetiology.

Cytological examination of urine for fungal hyphae, either in wet preparations of urine sediment or in Diff-Quik stained cytocentrifuged smears of urine sediment can be a very cost-effective way to obtain a diagnosis. Determining the serum galactomannan index can also be very efficient


Figure 19. Poster requesting DNA samples from GSD with disseminated aspergillosis for WGAS and whole genome sequencing studies.

diagnostically. The diagnosis can be more difficult if an unusual breed is affected or if the fungal pathogen is unusually exotic.

Management of these cases is challenging. The underlying immune defect cannot be fixed, so there is complete reliance on antifungal therapy for disease control. The presence of unilateral or bilateral mycotic pyelonephritis mitigates against the use of amphotericin B, although perhaps liposomal formulation can be used at reduced doses.

Voriconazole or posaconazole in concert with terbinafine usually represent the most effective therapy, although treatment is expensive because (i) the drugs are expensive, (ii) long to life-long treatment courses are required and (iii) because dogs are large, high absolute doses are required. The only good news is that voriconazole and posaconazole are now out of patent, and generic options are far more affordable than the originator brands.

Infections in well perfused tissues such as the eye and bone can often be eliminated;however, the failure of almost all fungal drugs to reach high levels in the urine makes eradication of pyelonephritis futile unless treatment utilises nephrostomy tubes with topical instillation of antifungal agents into the affected renal pelvis.

Echinocandin therapy can be a useful adjunct in these cases, but, currently, these drugs are almost prohibitively expensive to use for more than several days at the start of treatment.

Truthfully, the best hope for managing these cases is by concentrating on developing a PCR test for whatever genetic defect underlies the condition. This is being undertaken by Danika Bannasch and colleagues at UC Davis (see *Figure 19*). My impression is that this condition is more common in Australia than any other jurisdiction, and we really should be biobanking DNA from all these affected dogs with a view to conducting a whole exome scan or a whole genome association scan (GWAS).

3. **Diagnosis and treatment of protothecosis**

Protothecosis is an algal organism that has lost the ability to make chlorophyll, but we touch on it here as it behaves somewhat like a fungal pathogen. It is a notable cause of refractory colitis in dogs, with the propensity for more virulent species to disseminate to the eye, CNS, and other vital organs. There would appear to be a strong breed predilection towards Boxer dogs and their crosses.

There appears to be some sort of link or association between the granulomatous colitis of Boxer dogs (a.k.a. 'Boxer colitis' or canine histiocytic ulcerative colitis) caused by adherent invasive *E.coli* and protothecal colitis *(Figure 20).*

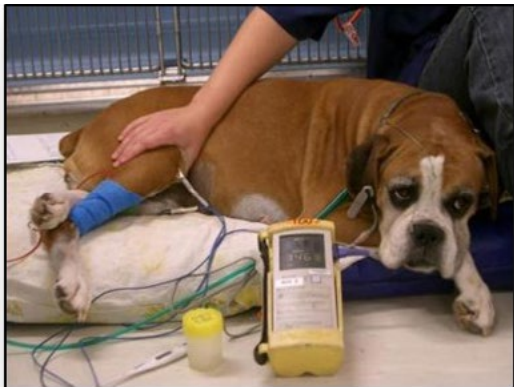

Figure 20. Boxer dog with disseminated protothecosis. Photo courtesy of Bruce Mackay and Vicki Stenner.

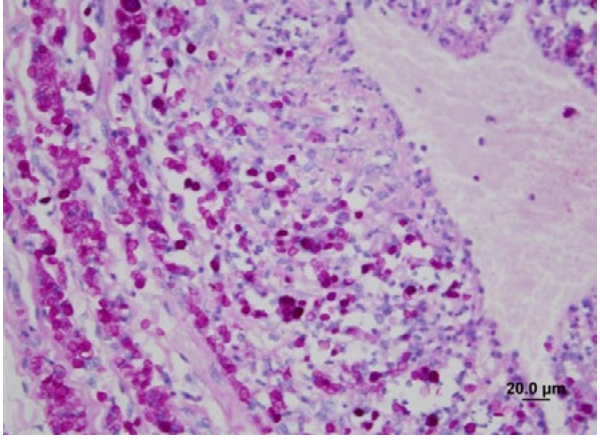


Figure 21. Protothecal algal cells stained with Periodic acid-Schiff (PAS) in the wall of a colonic vein. All the round pink cells are ***Prototheca*** cells.

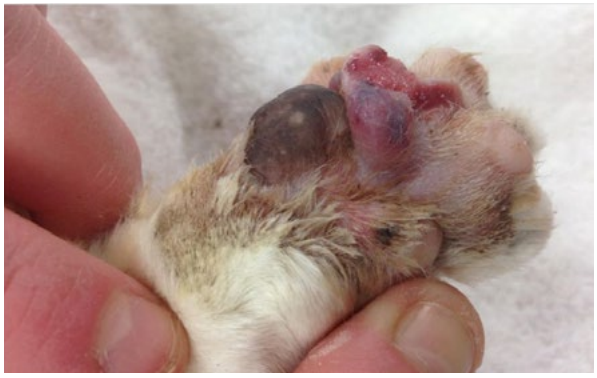

Figure 22. Ulcerated lesion on the pad of a cat referable to protothecosis.

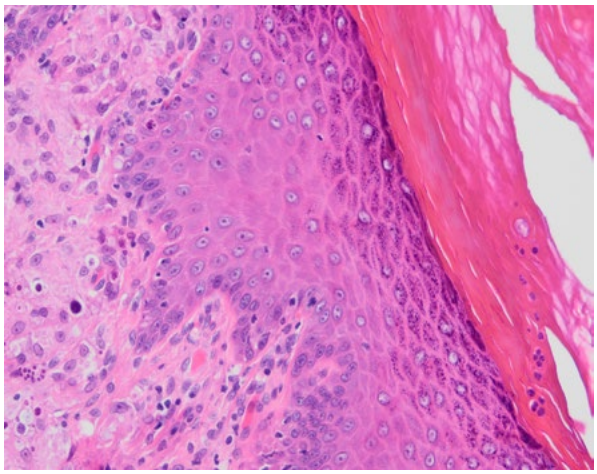

Figure 23. *Prototheca wickerhammi* organisms are evident in the stratum corneum of the the cat in Figure 22. Photo couresy of Allan Kessels.

Disease in cats is much rarer and takes the form of granulomatous cutaneous disease *(Figure 22)*.

Think of *Prototheca* when treating dogs with colitis signs that do not respond to standard therapy, and in Boxers with a combination of colitis and ocular and/or CNS disease. Diagnosis is not difficult once the 'illness script' is contemplated, as rectal scrapes are usually positive for characteristic organism morphology, and the organism can also be present in urine, ocular aspirates, or CSF. The taxonomy has undergone considerable revision by Polish researchers, and the two species we see in Australia are *P. bovis* (formerly *P. zopfii*) which is the 'nasty' one, and *P. wickerhamii*, which is milder and less likely to disseminate. Patrizia Danesi has developed an excellent PCR test for this organism which can be applied equally to fresh tissue and formalin fixed paraffin embedded (FFPE) tissues.

Currently, optimal treatment of protothecosis in dogs consists of amphotericin (whatever formulation is affordable and accessible; usually amphotericin B deoxycholate given by subcutaneous or IP infusions) plus posaconazole. Posaconazole seems the most effective of the oral azoles that have so far been used, with much better clinical efficacy than itraconazole. The availability of generic sustained release tablets means that daily therapy at 5 mg/kg is affordable and generally very well tolerated. Life-long therapy is often required to keep the disease under control or in remission. Professor Rui Kano in Japan is trialling a new azole only available in Japan.

In cats, the optimal treatment consists of wide surgical resection of lesions, with follow up therapy with posaconazole suspension at a dose rate of 8 mg/kg once a day for several months.

If a dog has signs of colitis that do not respond to standard therapy, think immediately of protothecosis and do a rectal scrape to look for the characteristic organism morphology in Diff-Quik stained smears.

That way you might diagnose it early when it's restricted to the colon, before it disseminates to the eye and CNS!

4. **What about cases of mycotic keratitis?**
Fungal disease of the cornea is much more of an equine problem than a dog or cat problem, but occasionally a cat scratch or grass seed foreign body can abrade the corneal epithelium and let a fungal pathogen establish itself in the corneal stroma. In this scenario, topical application trumps systemic therapy because of the high concentrations that can be attained by drops and ointment, and the two most effective agents are natamycin which is available commercially as an ophthalmic formulation, and voriconazole which can be compounded as drops and ointment by compounding pharmacists◆

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