Aspergillosis in Cats – Sino-nasal and Sino-orbital Infection: A New Clinical Syndrome

Vanessa R Barrs BVSc(hons) MVetClinStud FACVSc (Feline Medicine)
Senior Lecturer in Small Animal Medicine
Valentine Charlton Cat Centre
Faculty of Veterinary Science
The University of Sydney
NSW 2006
Email: vbarrs@vetsci.usyd.edu.au

Canine sinonasal aspergillosis

In dogs the triad of profuse mucoid to haemorrhagic chronic nasal discharge, muzzle pain and depigmentation, crusting or ulceration of one or both nares is highly suggestive of nasal aspergillosis.

Sinonasal aspergillosis (SNA) is the second most common cause of nasal discharge in dogs after neoplasia. In most cases infection is caused by the ubiquitous saprophyte *Aspergillosis fumigatus*, a non-pigmented filamentous fungus. Typically medium to long-nosed (mesocephalic and dolicocephalic) breeds of dogs are affected. There is a large body of information about sinonasal aspergillosis in dogs (Peeters & Clercx 2007). Infection is typically confined to the sinonasal cavity. Response to topical infusions of antifungal drugs such as clotrimazole and enilconazole is good to excellent, although more than 1 treatment may be necessary to exact a cure.

By contrast, little is known about non-pigmented filamentous fungal infections of the upper respiratory tract of cats. Until recently reports have been confined to isolated cases and 2 small case series, with 13 cases being reported worldwide. Affected cats presented with signs referable to sinonasal cavity disease (8 cases) or sino-orbital involvement (6 cases).

The author has recently collated an additional 17 cases of sinonasal aspergillosis (SNA) and sino-orbital aspergillosis (SOA) from around Australia. The majority of these infections were diagnosed between 2005 and 2008. The identification of a relatively large number of cases over this 3 year period is likely to be in part due to greater recognition and diagnosis of the disease. Whether there is a genuine increase in the incidence is unknown. SOA forms of infection tend to present as an easily recognisable syndrome.

How Disease in Cats Differs to Canine SNA - Pathogenesis

Like SNA in dogs, infection in cats starts in the sinonasal cavity. Nasal discharge and sneezing are common presenting signs. Infections in cats tend to be more aggressive and locally invasive than in dogs. There is a propensity for invasion of tissues adjacent the sinonasal cavity including the nasopharynx, orbit, palate and cribriform plate. In many cats infection is not diagnosed until later in the course of disease, when more dramatic clinical signs are present. In these cats, signs of sinonasal disease may be subtle or may have resolved. Indeed the first presenting clinical sign may be exophthalmos due to orbital invasion. Once infection spreads to the retrobulbar space a large fungal granuloma often forms in the ventromedial orbit.

Epidemiology and Clinical Findings

Breed and signalment

When the 12 cases reported in the literature for which signalment was recorded and the 17 new cases seen within Australia are considered together, some interesting facts emerge. The median age of infection was 5 years, with a range from 2 to 13 years of

age. In contrast to dogs, there is a predisposition for infection in brachycephalic cats. Of 29 cases, 13 (45%) were of brachycephalic conformation, including cats of Persians, Himalayan, Exotic Shorthair and Rag Doll breed.

Of the 12 cases in the literature 3 were female, suggesting a male predisposition. However, of the 17 Australian cases there were 9 females and 8 males. Overall 12 of 29 (59%) of cases were male. There is probably no sex predisposition, but a larger number of cats need to be studied. All cats were desexed.

Clinical presentation
Cats were classified as having SNA or SOA on the basis of history and clinical findings at presentation. In total 12 cats had SNA and 17 cats had SOA.

SNA
The most common historical sign is sneezing and the most common clinical sign is unilateral or bilateral serous to mucopurulent nasal discharge (Table 1). A discharging sinus or mass may be present over the frontal sinus or nasal bone. Epistaxis is uncommon compared to dogs with SNA. Nasal depigmentation or ulceration has not been reported in cats with SNA to date.

Table 1: Clinical signs in cats with SNA

Clinical signs
Nasal discharge at presentation
Discharging sinus or mass
Stertor
Epistaxis

SOA
For cats with SOA the most common historical findings are sneezing or nasal discharge within the preceding 6 months. At the time of presentation nasal signs may be absent or subtle. The most common clinical signs at presentation are unilateral exophthalmos with third eyelid prolapse (Figure 2), a mass or ulcer in the pterygopalatine fossa (Figure 3), submandibular lymph node enlargement, stertor, pyrexia and exposure keratitis (Table 2). Interestingly, pain on opening the mouth was detected in 2 cats only where this was assessed (n=10). Lack of ability to retropulse the exophthalmic globe enables differentiation from buphthalmos (abnormal enlargement of the globe), which is most commonly seen in end-stage chronic glaucoma when there is thinning of the sclera. Differential diagnoses for retrobulbar disease in cats are listed in Table 3.

Table 2: Clinical signs in cats with SOA

Clinical Signs
Exophthalmos
Corneal ulceration
Mass/swelling pterygopalatine fossa
Ulcer pterygopalatine fossa
Ulceration of hard palate
Discharging sinus
Mandibular lymph node enlarged
Stertor
Pyrexia (temp > 39.3^{o}C)

Figure 2: Two cats with exophthalmos and prolapse of the nictitating membrane due to retrobulbar fungal granulomas.

Figure 3: Mass in the pterygopalatine fossa (left); deep corneal ulceration (right)
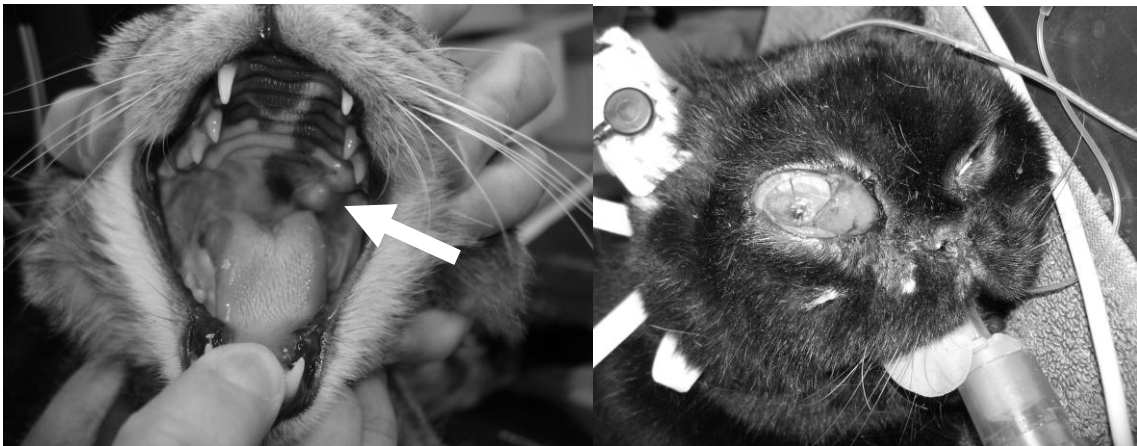
Table 3: Causes of orbital masses in cats

Differential Diagnoses of Feline Retrobulbar Mass Lesions

Foreign bodies, eg grass awns
Abscess (odontogenic, penetrating bite wound, haematogenous)
Orbital myofascitis (medial pterygoid muscle)
Zygomatic salivary gland and lacrimal gland disease
Fungal granuloma
       Phaeohyphomycosis
       Cryptococcosis
       Aspergillosis
Pythiosis
Orbital pseudotumour
Orbital fat prolapse
Neoplasia
       Squamous cell carcinoma
       Lymphoma
       Fibrosarcoma
       Osteoma/Osteosarcoma
       Teratoma

Aetiology and Pathogenesis – a New Fungal Pathogen is Identified in Cats
Aetiology
In the majority of those cases reported in the literature fungal culture was either negative or not performed. Positive fungal cultures were reported in 5 cases, including 4 *Aspergillus* spp and 1 *Penicillium* spp. Identification to a species level was reported on 2 occasions only; *A fumigatus* was identified on the basis of colony morphology in one case and *A niger* in the other.

Fungal culture was attempted in all of the Australian cases and was positive in all but one. In addition PCR was used to speciate the isolates using a panfungal PCR which targets the internal transcribe spacer 1 (ITS1) region of the ribosomal DNA gene cluster between the 18S and 5.8S rRNA genes. DNA sequencing of the PCR products and comparison of sequences with the GenBank database was performed to identify the fungal pathogen (Lau et al, 2007).

On fungal culture, *Aspergillus fumigatus* was the most isolate identified, on the basis of colony morphology, was. However, when PCR was performed on the same fungal cultures, the molecular identity of the organism was found in many instances to be a closely related *Neosartorya* spp. PCR was also performed on fresh or formalin fixed biopsy specimens from the same patients, and *Neosartorya* spp was again identified. In one case *Neosartorya pseudofischeri* was identified; in the other cases sequencing of the PCR product could not distinguish between *Neosartorya fischeri/udagawae/aureoloa.* Over the same period *Aspergillus fumigatus* was identified on morphology of fungal culture in 7 dogs with SNA. PCR of the fungal cultures and tissues of these dogs identified *Aspergillus fumigatus* as the causative agent in all 7 cases.

Neosartorya species belong to the Aspergillus section fumigati. This section consists of more than 33 taxa, including 10 strictly anamorphic *Aspergillus* species and 23 *Neosartorya* spp. The anamorphic or asexual state of *Neosartorya* spp closely overlaps that of *Aspergillus fumigatus.* Therefore it is often not possible to differentiate

between these two species on the basis of phenotypic fungal characteristics such as conidiophore morphology and thermotolerance (Balajee et al, 2005).

Aspergillus and *Neosartorya spp* are ubiquitous filamentous environmental fungi. Several *Neosartorya* species have been described as causing disease in humans including invasive aspergillosis, osteomyelitis, endocarditis and mycotic keratitis. All of the *Neosartorya* species produce heat-resistant ascospores that are frequently encountered in different food products.

In vitro fungal susceptibilities of the Australian isolates were performed in many cases. The typical pattern was resistance to ketoconazole and fluconazole and susceptibility to posaconazole and voriconazole. Most isolates were either susceptible or of intermediate susceptibility to itraconazole.

Risk factors for infection
Of the Australian cats tested, none were positive for FIV or FeLV and of those cases reported in the literature, only 1 was positive for FeLV. Since cryptococcosis is a common cause of feline respiratory disease, especially in Australia, latex cryptococcal antigen titres were performed in many cases before more invasive investigations, and were negative in all cats tested.

Apart from brachycephalic conformation, other possible risk factors identified were recurrent rhinosinusitis, previous craniofacial trauma and diabetes mellitus. In one cat with SOA a grass seed was found during surgical debridement of the pterygopalatine fossa. It appears that upper respiratory aspergillosis in cats occurs mostly in immunocompetent individuals, some of which have breaches in local defence mechanisms (eg trauma, viral upper respiratory tract infection). The reasons that brachycephalic cats are predisposed to infection are not clear. One possibility includes decreased drainage of upper respiratory secretions due to brachycephalic conformation, which could be compounded by concurrent upper respiratory infection. Decreased sinus aeration and drainage of respiratory secretions secondary to infection, polyps and allergic rhinosinusitis has been identified as a risk factor for invasive paranasal aspergillosis in humans (Siddiqui et al, 2004).

Diagnostic imaging
CT is the best imaging modality for documenting extent of infection in cats with both SNA and SOA. CT scans were performed in a number of cases previously reported and in 9 of the Australian cases.

The most common findings were destruction of turbinates together with increased soft-tissue densities in the nasal cavity, punctate lysis of the orbital lamina (ie the ventromedial part of the orbital face of the orbital bone), opacification of the sphenoid and frontal sinuses due to fluid or soft-tissue, and a soft-tissue mass in the choanae or nasopharynx. In cats with SOA there was irregular enhancement of the orbital mass in all cases after contrast administration. Orbital masses were present in the ventromedial aspect of the orbit, causing lateral displacement of the globe and exophthalmos. In some cats with SOA there was a mass-effect involving the soft-tissues adjacent the maxilla. Punctate lysis of the cribriform plate was seen in two cases, one cat with SNA and one with SOA. The tympanic bullae were normal in all cases.

Figure 4: Transaxial (transverse) CT images from a cat with severe SNA. Image on the left shows the left frontal sinus filled with fluid (long arrow) and the sphenoid sinus is also fluid filled (arrow head). Image on the right shows severe turbinate destruction and fluid/soft-tissue density, predominantly in the left nasal cavity.
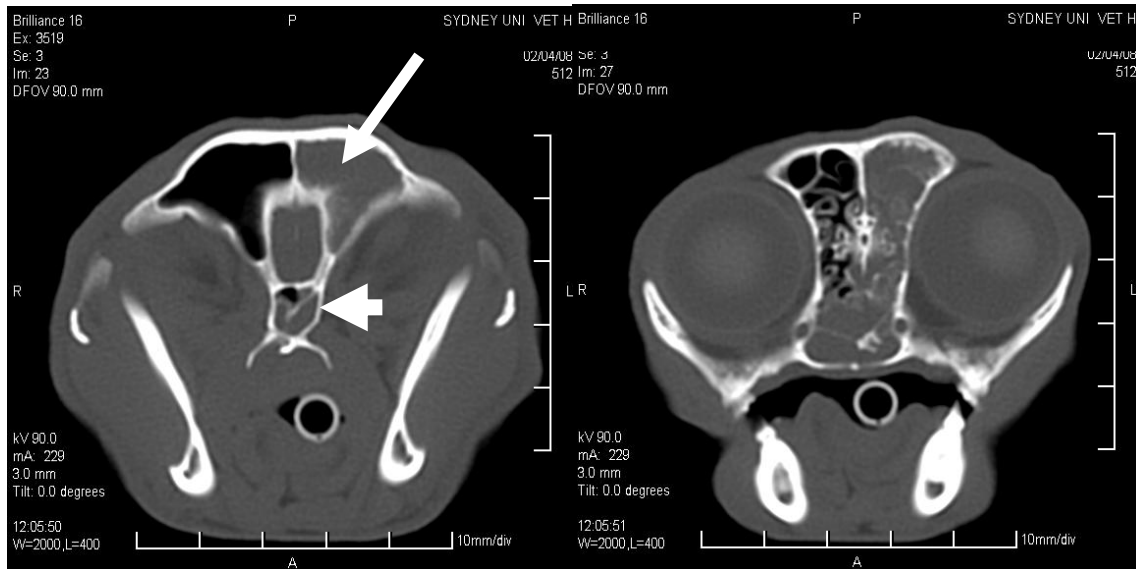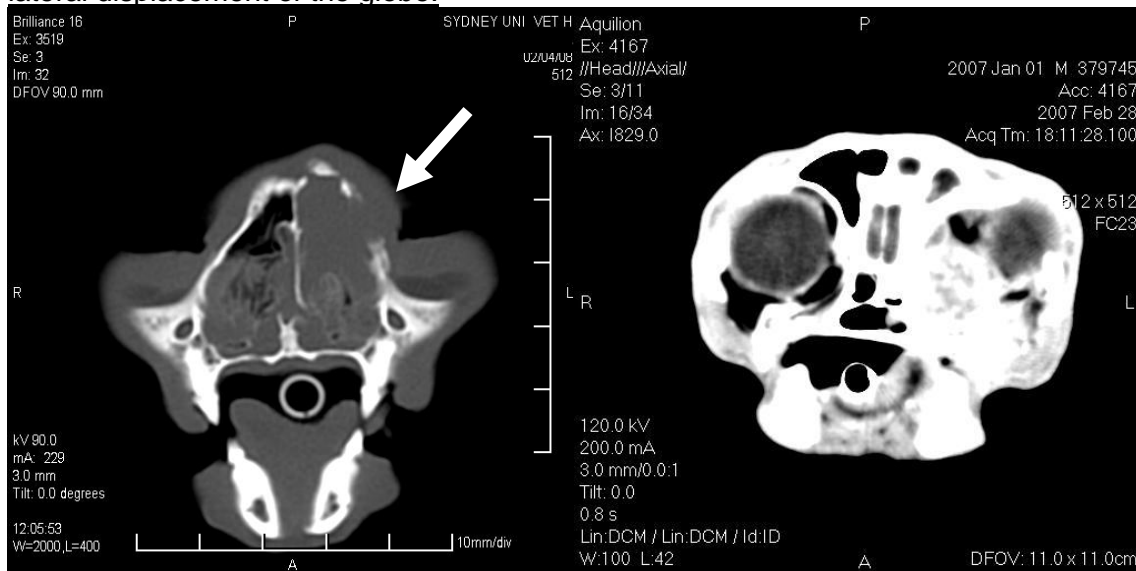

Figure 5: Image on left: transaxial CT image from a cat with severe SNA. There is lysis of the left nasal bone (arrow). Image on the right: transaxial CT from a cat with SOA. There is an irregularly enhancing ventromedial soft tissue mass in the left orbit, causing lateral displacement of the globe.

Endoscopy

Retroflexed nasopharyngoscopy is a useful technique for obtaining biopsies for cytology, fungal culture and histopathology where choanal or nasopharyngeal mass lesions are present. For cats with SOA, biopsies of retrobulbar masses can be obtained via the oral cavity.

Treatment and Outcome

To date SNA carries a better prognosis with treatment than SOA. Overall, the prognosis for resolution of SOA is poor.

Based on experience, the following practical approach is recommended currently for treatment of aspergillosis in cats:

(i) The fungal pathogen should be identified by culture and molecular analysis (PCR). PCR is not commercially available in Australia at this time. PCR can be arranged on a case-by-case basis by contacting the author. Nasal flushings or nasal swabs are generally not suitable diagnostic samples, since *Aspergillus* spp isolated from these samples could be contaminants. Tissue biopsies are the best diagnostic specimens.

(ii) Antifungal susceptibility testing should be performed. It should be noted that *in vitro* susceptibility does not necessarily correlate well with *in vivo* susceptibility.

(iii) Systemic antifungal therapy is warranted in all cases except where disease is proven to be confined to the sinonasal cavity by CT and where the cribriform plate is proven intact. In these cases treatment with topical antifungal infusions (Eg clotrimazole) under general anaesthesia, could be considered. There is no evidence, however, to document efficacy of these treatments in cats.

The mainstay of treatment of SNA and SOA in cats is combination systemic antifungal therapy using an azole antifungal drug and a polyene macrolide (amphotericin). Drugs, dosages and toxicities are listed in Table 4.

Ketoconazole and fluconazole are unsuitable azoles for treating feline aspergillosis. The antifungal triazoles with good in vitro activity against *Aspergillus* and *Neosartorya* spp are itraconazole, posaconazole and voriconazole. The pharmacokinetics of posaconazole and voriconazole has not been studied in cats. The author uses itraconazole or posaconazole in combination with amphotericin B and terbinafine (Table 4). If there is no clinical response to the first triazoles drug, after two weeks change to one of the other recommended triazoles. Cats being treated with voriconazole should be monitored carefully for the development of neurological side effects. Voriconazole should be discontinued if these signs occur.

Duration of treatment in successful cases of SNA in Australian cats was 3 to 6 months. Duration of treatment in successful cases of SOA in Australian cats was 7 to 18 months.

(iv) Surgical debulking. Radical debridement surgery of the orbit including extenteration, was performed in 6 Australian cases to surgically debulk large fungal granulomas. Infection did not resolve in any of the cases in which radical surgery was performed. However, these cases were also the most severely affected.

Table 4: Drugs used for treatment of aspergillosis in cats.

Drug	Dosage and Route of Administration	Toxicities
Itraconazole 100 mg capsules (Sporanox)	10 mg/kg q 24 h PO.	Hepatotoxicity Monitor ALP/ALT monthly. If hepatoxicity occurs, reduce dose to 5 mg/kg q 24 h or 10 mg/kg q 48 h PO
Posaconazole 40 mg/ml liquid (Noxafil)	5 to 7.5 mg/kg divided twice daily PO	Hepatotoxicity. Unlikely to occur at 5 mg/kg q 24 h
Voriconazole 50 mg tablets (Vfend)	5 mg/kg q 24 h PO	Neurological problems – blindness , ataxia, dazed.
Terbinafine 250 mg tablets (Lamisil)	30 mg/kg q 24 h PO	May cause GIT side effects - anorexia, vomiting, diarrhoea
Amphotericin B deoxycholate (Fungizone 50 mg vial)	0.5 mg/kg of 5 mg/ml stock solution in 350 ml of 0.45% NaCl + 2.5% dextrose SC 2 – 3 x weekly to a cumulative dose of 10 mg/kg	Nephrotoxicity. Monitor urea/creatinine every 2 weeks. Discontinue for 2 to 3 weeks if azotaemic.
Liposomal Amphotericin (Ambisome)	1 mg/kg IV q 2 days for 12 treatments	Azotaemia.

References:
Balajee SA, Gribskov J, Brandt M, Ito J, Fothergill A, Marr KA. Mistaken identity: *Neosartorya pseudofischeri* and its anamorph masquerading as *Aspergillus fumigatus*. J Clin Microbiol 2005;43:5996-5999

Barrs VR, Martin P, Beatty JA, Malik R, O'Brien C, Angles J, Halliday C. Feline Sino-orbital Aspergillosis: An Emerging Clinical Syndrome? *Journal of Veterinary Internal Medicine* 2007; 21(3):579

Barrs VR, Beatty JA, Lingard AE, Malik R, Krockenberger MB, Martin P, O'Brien C, Angles JM, Dowden M, Halliday C. Feline Sino-orbital Aspergillosis: An Emerging Clinical Syndrome. *Australian Veterinary Journal* 2007; 85(3):N23

Davies C, Troy GC. Deep mycotic infections in cats. *J Am An Hosp Assoc* 1996;32:380-391.

Goodall SA, Lane JG, Warnock DW. The diagnosis and treatment of a case of nasal aspergillosis in a cat. *J Sm Anim Pract* 1984;25:627-633.

Hamilton HL, Whitley RD, McLaughlin SA. Exophthalmos secondary to aspergillosis in a cat. *J Am An Hosp Assoc* 2000;36:343-347.

Halenda RM, Reed AL. Ultrasound/Computed tomography diagnosis – fungal sinusitis and retrobulbar myofascitis in a cat. *Vet Radiol & Ultrasound* 1997;38:208-210.

Lau A, Chen S, Sorrell T, Carter D, Malik R, Martin P & Halliday C. Development and clinical application of a panfungal PCR assay to detect and identify fungal DNA in tissue specimens. *Journal of Clinical Microbiology* 2007;45:380-385.

McLellan GJ, Aquino SM, Mason DR, Kinyon JM, Myers RK. Use of posaconazole in the management of invasive orbital aspergillosis in a cat. *J Am An Hosp Assoc* 2006; 42:302-307.

Peiffer RLJ, Belkin PV, Janke BH. Orbital cellulitis, sinusitis, and pneumonitis caused by Penicillium sp in a cat. *J Am Vet Med Assoc* 1980;176:449-451.

Siddiqui A, Ali Sha A, Bashir SH. Craniocerebral aspergillosis of sinonasal origin in immunocompetent patients: clinical spectrum and outcome in 25 cases. *Neurosurgery* 2004; 55:602-613.

Sissener TR, Bacon NJ, Friend E, Anderson DM, White RA. Combined clotrimazole irrigation and depot therapy for canine nasal aspergillosis. *J Small Anim Pract.* 2006;47):312-5.

Tomsa K, Glaus TM, Zimmer C, Greene CE. Fungal rhinitis and sinusitis in three cats. *J Am Vet Med Assoc* 2003;222:1380-1384.

Whitney BL, Broussard J, Stefanacci JD. Four cats with fungal rhinitis. *J Fel Med Surg* 2005;7:53-58.

Wilkinson GT, Sutton RH, Grono LR. Aspergillus spp infection associated with orbital cellulitis and sinusitis in a cat. *J Sm Anim Pract* 1982;23:127-131.

1. **With regard to Aspergillosis of the upper respiratory tract of cats:**

   a) Infection typically occurs in FIV positive or FeLV positive cats
   b) Brachycephalic cats are predisposed to infection
   c) Is commonly characterised by purulent nasal discharge, epistaxis and depigmentation of the nares.
   d) Infection is most frequently caused by *Aspergillus fumigatus*

2. **The clinical presentation of SOA in cats could include:**

   a) A recent history of sneezing or nasal discharge
   b) Exophthalmos with third-eyelid prolapse and corneal ulceration
   c) A swelling or ulcer in the pterygopalatine fossa in the oral cavity
   d) All of the above

3. **To diagnose SOA in cats:**

   a) A nasal swab for fungal culture is an adequate diagnostic sample
   b) A nasal flush for fungal culture is an excellent diagnostic sample
   c) A biopsy from a retrobulbar mass for cytology, culture and histopathology obtained via the pterygopalatine fossa is an excellent diagnostic sample
   d) An LCAT would be diagnostic

4. **With regard to SNA and SOA in cats.**

   a) *Neosartorya* species are the most common cause
   b) *Neosartorya* species and *Aspergillus fumigatus* can look alike on fungal culture
   c) PCR of fungal culture may be required to differentiate *Neosartorya* species from *Aspergillus fumigatus*
   d) All of the above

5. **For treatment of SNA and SOA in cats:**

   a) Combination therapy with antifungal triazoles such as itraconazole, posaconazole or voriconazole, amphotericin B and terbinafine is recommended.
   b) Ketoconazole or fluconazole are the best azoles to use.
   c) Treatment duration of 3 months is usually adequate
   d) Cats with SOA have a better prognosis than cats with SNA

Answers:
1. b
2. d
3. c
4. d
5. a