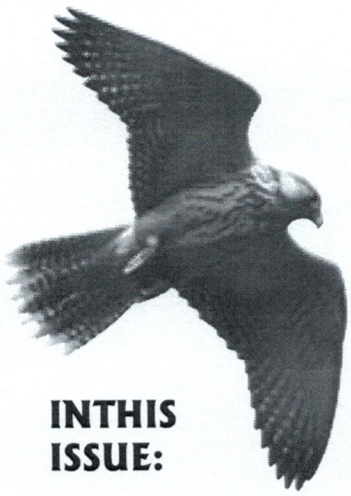

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Aspergillosis: Therapy and Prevention in Zoo Animals with Emphasis on Raptors

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Table 1. Factors associated with the susceptibility of animals to aspergillosis (Cooper, 2002; Wobeser, 1981; Prescott, 2000)

Destruction of normal host microflora by broad-spectrum antibacterial drugs	Environmental factors (e.g. low humidity, dust, decaying organic matter
Immunosuppression	Species susceptibility (e.g. gyrfalcons, sea ducks see Table 2)
Pre-existing disease conditions (e.g. haemochromatosis)	Malnutrition
Treatment with immunosuppressive drugs (e.g. corticosteroids)	Vitamin A deficiency
Exposure to respiratory irritants (e.g. cigarette smoke, ammonia)	Other causes of physiological stress (e.g. recent capture or oiling)

1. Background

Aspergillosis is a disease of increasing importance in human medicine because of rising numbers of immunosuppressed patients vulnerable to infection (Hill *et al*, 1995). Aspergillosis was the first mycotic disease to be described in animals, although accounts of an incurable disease of the lungs called 'pantas' by the falconer Latham (1615) pre-date this. Aspergillosis has implications in avian conservation programmes, the first generation of captive breeding projects are often derived from the wild, which are stressed and susceptible to infection. In a review of factors involved in the failure of the translocation and breeding programmes undertaken by the New Zealand Conservation Department of the rare stitchbird (*Notiomystis cincta*), aspergillosis was the single most important cause of mortality (Cork *et al* 1999). Aspergillosis is the most common systemic avian mycosis. Of 66 case reports published on aspergillosis from 1970-2000 in exotic species (Veterinary Librarian) 54 (81%) were avian species, 11 (17%) were mammals and 1 was a reptile. Established infections are challenging to resolve and this paper aims to review current approaches to therapy and prevention of aspergillosis with emphasis on raptors.

2. Treatment Considerations

2.1. Classification of Aspergillosis

Avian aspergillosis has been classified by Redig (1993a) as 1) an acute form caused by a single exposure to an overwhelming number of spores; 2) a tracheal form; 3) localised granulomas in the air sacs and lungs; and 4) an invasive form which initially affects the respiratory system and then spreads haematogenously and through the air sacs to the rest of the body. The success of treatment depends on location and extent of the lesions and effective treatment can usually only be instituted in the tracheal and semi-invasive or localised forms. Severe cases, where the patient exhibits cachexia, dyspnea and vomiting, are beyond the point of treatment (Redig 1993a). Treatment goals for aspergillosis are 1) removal of lesions that restrict airflow, 2) killing and elimination of the fungus and 3) provision of supportive care (Redig 1981). Unless the lesions are detected early, drug therapy alone is unlikely to be effective because of the thick caseous encapsulation which develops in the airsacs (Forbes 1996). Factors associated with the susceptibility of animals to aspergillosis are presented in Tables 1 & 2.

2.2. Antifungal Susceptibility Testing

Table 2. Avian species with a high probability of developing aspergillosis (Redig, 1993)

Raptors	Psittacines
Goshawks	Blue-fronted Amazon
Gryfalcons	African grey parrot
Immature red-tailed hawks	Mynah bird
Golden eagles	
Rough-legged hawks	Other
Bald eagles	Eider ducks, Trumpeter swans, penguins

There are over 185 species in the *Aspergillus* genus (Richardson 1998). In avian infections *A. fumigatus* is the most common etiological agent, followed by *A. flavus* and *A. niger* (Bauck 1994). Selection of antimicrobial drugs depends on knowledge of the susceptibility of the suspected pathogen (Prescott 2000), but clinical mycology has lagged behind clinical bacteriology with respect to uniform standardisation of susceptibility testing. *In vitro* antifungal activity does not correlate well with *in vivo* efficacy and without readily available susceptibility tests in veterinary medicine most therapeutic choices are empirically based (Papich *et al*, 2001). Resistance following antifungal drug use is recognised (Graybill *et al* 1998). Table 3 presents the activity (MIC) of antifungal agents against fungi & Table 4 summarises the susceptibility of *Aspergillus sp.* to available antifungal drugs.

Table 3. Activity (MIC$_{50}$ ug/ml) of selected systemic antifungal agents against selected fungi (Prescott, 2000)

Organism	Amp B	Flucytosine	Ketoconazole	Fluconazole	Itraconazole
Aspergillosis fumigatus	1	>64	16	>64	0.25
A. flavus	1	>64	8	>64	0.25
Candida albicans	0.5	0.13	0.13	0.25	0.03
Histoplasma capsulatum	0.25	-	0.25	2	0.06

Table 4. Summary of *Aspergillus* sp. susceptibility and routes of administration of commercially available antifungal agents

Antifungal Drug	Aspergillosis susceptibility	Route of administration
Griseofulvin	No	p.o.
Flucytosine	Majority of strains resistant**	p.o.
Amphotericin B	Yes, little resistance	i.v., intrathecal*, nebulisation
Clotrimazole	Yes	Topical
Ketoconazole	Many strains resistant	p.o.
Enilconazole	Yes, little resistance	Topical, nebulisation
Itraconazole	Yes	p.o. (capsules, suspension)
Fluconazole	Variably effective	i.v., p.o. (tablets, suspension)
Terbinafine	Yes	p.o. (tablets), topical

*through the theca of the spinal cord into the subarachnoid space
** synergises with amphotericin B

3. Antifungal Agents Effective Against *Aspergillus sp.*

Amphoteracin B

Mechanism of action: Amphoteracin B is a fungicidal polyene antibiotic. It binds ergosterol in the fungal cell membrane making it more permeable, leading to electrolyte leakage and cell death.

Spectrum of activity: Organisms with MIC < 1 mg/ml are considered susceptible (Prescott 2000). There is good correlation between MIC values & clinical response (Papich *et al*, 2001). *Aspergillus sp.* are the most frequently reported resistant fungi (Prescott 2000).

Chemical properties and pharmacokinetics: Its pharmacokinetics have been poorly studied in veterinary species. It is poorly absorbed from the GIT so must be given i.v., i.o. or i.t. Absorption from the lungs following aerosol administration is poor and this route is used to treat pulmonary aspergillosis (Prescott 2000).

Adverse effects: The most important clinical toxicosis is nephrotoxicity (Prescott 2000). It is dose-related and is seen clinically as increases in BUN and creatinine in mammals. Dosing every other day, electrolyte loading and slow infusion of amphoteracin B decrease the severity and rate of development of renal toxicity. Other adverse effects include phlebitis, fever, nausia, vomiting and hypokalemia with resulting cardiac arrhythmias (Prescott 2000). Measures to prevent vomiting include giving antiemetic drugs before infusion.

Clinical protocols: Dosage regimens are presented in Table 5. Treatment protocols should include pre-treatment with sodium chloride and it should be infused at a slow rate. It can be mixed with 5% dextrose solution during infusion. Administration of amphoteracin B in 0.45% saline with 0.5% dextrose s.c. in dogs/cats is a way of administering large quantities of amphoteracin B without producing the marked azotemia associated with i.v. injection (Malik 1996).

New formulations: New less toxic lipid-based formulations have been used in humans (Walsh *et al* 2001). These drugs can be given at higher doses with less toxicity. In humans daily doses of the lipid-based formulations are 3-5 mg/kg daily, whereas the dose of the conventional form are 0.5-1 mg/kg every 48 hours (Prescott 2000).

Flucytosine

Mechanisms of action: Flucytosine is a fluorinated pyrimidine which is deaminated to 5-fluorouracil and incorporated into mRNA in the fungal cell, producing faulty proteins. Spectrum of activity: It has a narrow spectrum of activity and few *Aspergillus sp.* strains are susceptible. Strains with MIC < 16mg/ml are susceptible (Prescott 2000). Two thirds of fungal isolates change from susceptible to resistant during treatment so flucytosine should only be used in combination with other antifungal agents (Papich *et al* 2001). Combination with amphoteracin B is synergistic because amphoteracin B increases fungal permeability to flucytosine (Orosz & Frazier 1995).

Clinical protocols: Dosage regimens are presented in Table 5 and only occasional side-effects are reported (Papich *et al* 2001).

The Azole Antifungal Drugs

These are broad-spectrum antifungal drugs that exert their antifungal mechanism on the cell membrane of the fungus by inhibiting synthesis of the sterol of the fungal cell membrane. They are generally fungistatic at concentrations achieved clinically and are slower acting than the polyenes.

Enilconazole

This drug has excellent antifungal activity. It has a residual effect after topical application and is used to treat topical dermatophyte infections. Enilconazole is the treatment of choice for nasal aspergillosis in dogs & local infusion is used in the treatment of guttural pouch mycosis in the horse (Prescott 2000). It can be given topically or nebulised and the Clinafarm-EC formulation is used in the environmental decontamination of poultry facilities (Table 5) and equipment to prevent aspergillosis.

Clotrimazole

This azole is inhibitory to *Aspergillus sp.* and concentrations above 10mg/ml are fungicidal (Prescott 2000). It is available as a topical product, can be nebulised and few strains of fungi are resistant (Prescott 2000).

Itraconazole

Spectrum of activity: Itraconazole is the drug of choice to treat aspergillosis infections (Papich *et al* 2001). Organisms with MIC < 0.12 mg/ml are susceptible, those with MIC 0.25-0.5 mg/ml are susceptible depending on dose and those with MIC > 1 mg/ml are resistant (Prescott 2000).

Pharamcokinetics: Absorbtion is increased in an acidic environment and when taken with meals. Bioavailability increases from 40% after fasting to 99.8% when given with food (Papich *et al* 2001). It is extensively distributed throughout the body. It is hepatometabolised and mainly eliminated in the bile. Therapeutically active concentrations are maintained longer in tissues than in plasma and the drug can be detected in vaginal epithelium and skin for 4 days and 4 weeks respectively (Papich *et al* 2001).

Clinical use: It is used to treat superficial and systemic infections and to treat and prevent aspergillosis in birds (Table 5). As oral absorbtion is pH dependent dosage adjustments are necessary if gastric pH is increased (Papich *et al* 2001). Oral capsules should be given with

Table 5. Dosage protocols for antifungal agents in birds.

Drug	Species	Route	Dose	Source
Birds				
Amphotericin B (Fungizone)	Raptors Psittacines,	i.v.	1.5mg/kg bid for 3-5 days g ven with 10-15 ml/kg of saline	Redig, 1993a; Blasia & Giovardi, 2001
Amphotericin B (Fungizone)	Raptors Psittacines	i t	1 mg/kg tid/bid diluted in saline and given via the glottis	Redig, 1993a; Blasia & Giovardi, 2001
Amphotericin B (Fungizone)	Psittacines	topical	0.05 mg/kg diluted in saline used as surgical irrigation	Blasia & Giovardi, 2001
Amphotericin B (Fungizone)	Psittacines	nebulis e	1 mg/ml saline and nebulised tid for 15 minutes	Ritchie & Harrison, 1994
Flucytosine (Ancobon)	Raptors	p.o	40-50 mg/kg tid Always combine with Amphotericin B	Redig, 1993a
Flucytosine (Ancobon)	Psittacines	p.o	20-60 mg/kg bid. Always combine with Amphotericin B	Ritchie & Harrison, 1994
Clotrimazole	Raptors	Topical , nebulis e	Suspend in polyethylene glycol and nebulise for 45 minutes a day	Orosz & Frazier, 1995
Enilconazole (Imaverol)	Raptors	i.t.	Dilute 10% solution 10:1 and give 0.5 ml/kg/day for 7-14 days.	Heidenreich, 1995
Itraconazole (Sporonox)	Birds	p.o	Treatment or prevention - 20 mg/kg sid for 30 days	Papich et al, 2001
Itraconazole (Sporonox)	Raptors	p.o.	10 mg/kg bid in combination with amphotericin B nebulisation tid for 6 weeks	Forbes et al, 1992
Itraconazole (Sporonox)	Raptors	p.o.	10 mg/kg sid	Jones et al, 2000
Itraconazole (Sporonox	Psittacines	p.o.	10 mg/kg sid from pharmacokinetic studies	Orosz et al, 1996
Fluconazole (Diflucan)	Birds	p.o.	2-5 mg/kg sid	Ritchie & Harrison, 1994
Terbinafine (Lamisil)	Birds	p.o.	10-15 mg/kg bid	Dalhausen, 2000
Terbinafine (Lamisil)	Birds	nebulis e	1 mg/ml solution bid/tid	Dalhausen, 2000
Enilconazole (Imaverol)	Mammal, Raptors	topical	Dilute 10% solution 50:1 to form an emulsion and sponge animal every 3 or 4 days for 4 treatments.	Forbes, 1996; Papich et al, 2001
F10	Raptors Psittacines	Fog or nebulis e	1:250 dilution of F10 superconcentrate fogged or nebulised for 15-30 min/day bid/tid.	Verwoerd, 2001; Bailey & Sullivan, 2001
Environmental Decontaminatio n				
Enilconazole (Clinafarm-EC)	Poultry facilities	Fog or spray	Dilute 13.8% solution 1:100 and spray or fog facility.	Papich et al, 2001
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Itraconazole (Sporonox	Psittacines	p.o.	10 mg/kg sid from pharmacokinetic studies	Orosz et al, 1996

food, but the oral suspension is better absorbed on an empty stomach. Orosz *et al* (1995) reported higher tissue concentrations when itraconazole is dissolved in acid and gavaged with orange juice in pigeons (*Columba livia*). Treatment of serious infections should be prolonged (>3 months) and relapses occur (Prescott 2000). An i.v. formulation is being developed and is effective against experimental disseminated aspergillosis in guineapigs (Odds 2000).

Adverse effects: Itraconazole is better tolerated than ketoconazole. Hepatic toxicosis occurs in 10% of dogs, while in cats there are dose-related GIT effects of anorexia and vomiting (Papich *et al* 2001). Long-term administration (3 months) to dogs and cats resulted in no side-effects, but maternal toxicity, embryo toxicity and teratogenicity were observed in rats; therefore, its use in pregnant mammals is not recommended (Prescott 2000). Itraconazole is considered to cause anorexia, depression and death in African grey parrots (*Psittacus erithacus*) at doses above 5 mg/kg bid (Birdmed discussion 2002).

Other Antifungal Agents

Terbinafine

This synthetic allylamine drug is highly fungicidal. Allylamines decreases the fungal synthesis of ergestrol and cause fungal death by disrupting the cell membrane (Prescott 2000). It is active against *Aspergillus sp.* but to date clinical use has been limited in veterinary medicine, although preliminary nebulisation results are promising (Dalhausen 2000).

F10-Disinfectant

F10 is a complete spectrum virucidal, bactericidal, fungicidal & sporicidal, but aldehyde free compound of six synergistic active ingredients (Verwoerd 2001). It has been tested against every significant animal/human pathogen and has outperformed other disinfectants during efficacy testing, over a range of temperatures, in the presence of organic material, at low concentrations, short contact times, without any corrosive effects on infrastructure, metal nozzles or any tissue irritation on workers and animals (Anon 2001). With these characteristics, F10 can be used to disinfect animal environments in their presence, lowering the environmental pathogen challenge significantly, with no side-effects. Using either a nebuliser or a 'smogger' unit, F-10 has been used to treat either individuals or groups of falcons with aspergillosis (Table 4; Bailey and Sullivan, 2001).

New Antifungal Agents

Voriconazole & echinocandin are new triazole & lipopeptide drugs respectively which show promise against aspergillosis (Prescott, 2000; Graybill, 2001).

4. Therapy

Combination Therapy

In vitro synergism of 2 antifungal compounds, seen as a 4x reduction in the MIC when given alone is seen when amphoteracin B is given with flucytosine (Papich *et al* 2001). Combinations of amphoteracin B and azoles have been less successful and both antagonism and synergism have been reported (Bajjoka *et al* 1999). Because of the slow onset of action of azole antifungals it is recommended to use initial amphoteracin B therapy of serious systemic fungal infections followed by an azole agent (Papich *et al* 2001). The treatment combinations used at Abu Dhabi Falcon Hospital are presented in Table 6.

Surgery

In advanced cases surgical removal of granulomas from the airsacs, or lesions that are blocking the trachea or syrinx and direct application of antifungal agents to the lesions are important therapeutic adjuncts in birds (Tully *et al* 2000). Studies in dogs with nasal aspergillosis have shown that while systemic therapy is successful in 50% of cases, systemic therapy and local irrigation of nasal lesions is successful in 90% cases (Clark 1999).

Table 6. Treatment regimens used at Abu Dhabi Falcon Hospital in aspergillosis cases (1999-2001)

Clinical case	Treatment (doses in Table 5)
Mild cases (good prognosis)	Nebulise amphoteracin B or F10 or enilconazole bid/tid (1 week) Atomise F10 (when nebulising finished for 2-3 weeks) Per os itraconazole bid (4-8 weeks)
Moderate-cases (guarded prognosis)	Nebulise amphoteracin B or F10 or enilconazole bid/tid (1 week) Atomise F10 (when nebulising finished for 2-3 weeks) I.V. amphotericin B 5-7 days Per os itraconazole bid (4-8 weeks)

Supportive Therapy

Supportive therapy including fluids (i.v., s.c., i.o.), tube feeding, antibiotics, antiemetic drugs, immune stimulants

and vitamin A supplementation should be given according to the needs of the case. The use of immunosuppressive drugs (steroids) in birds is controversial and should be avoided (Chitty 2001). Indeed cortisone-treated animals (rabbits) are more susceptible to invasive aspergillosis (Khosravi *et al* 1998).

Immune Stimulation

Interferon g augments the ability of human leucocytes to damage fungal hyphae *in-vitro* and clinical trials of colony stimulating factor have shown that it can be a useful adjunct to antifungal therapy (Richardson 1998). Immune stimulation may have a role in veterinary species in the future.

5. Duration and Response to Treatment

Duration of Therapy

Antifungal regimens in humans are often extended for 6-12 months (Jones *et al* 2000). For veterinary species treatment duration recommendations vary from 2 to 6 months and one month past the resolution of the disease (Jones *et al* 2000; Tully *et al* 2000).

Response Rate and Susceptibility to Re-infection

Interestingly, despite numerous treatment protocols (Table 5), little data has been published on the response to treatment so that the efficacy of different regimens can be objectively assessed. Mortality from invasive aspergillosis in immunocompromised humans is high (Patterson *et al* 2000). The average case fatality rate (CFR) of 50 published studies (1995-2000) on the treatment of invasive aspergillosis in humans was 58% (SwuJane 2001). In a survey of aspergillosis cases in a large falcon hospital the CFR for falcons was 37.5% (Table 7). Little has been published on the susceptibility of recovered animals to rechallenge with aspergillosis. Kunkle and Sacco (1999) demonstrated that convalescence from pulmonary aspergillosis in turkeys did not confer protection against rechallenge but instead decreased resistance to subsequent infection. Recrudescence of aspergillosis infections in falcons that have recovered from aspergillosis is common in the Middle East and it is likely that the CFR of 37.5% is higher as this does not account for recrudescence because of difficulties in case follow-up.

Table 8. Recommendations to prevent aspergillosis in captive avian collections (Harry & Cooper 1970; Wobeser 1981; Richard, 1991; Redig, 1993a; Dykstra et al, 1997)

High standards of hygiene to maintain a healthy environment (reduce exposure to mouldy vegetation in litter and food)
Environmental screening of aviculturalfacilities.
Increase ventilation within facility
Spraying litter, facilties with disinfectant
Fogging facilities in the presence of live animals/birds with F10 disinfectant
Reduce stress (especially newly captured birds)
Sero-logical screening programme (in raptors at the University of Minnesota)
Egg-transmitted aspergillosis in poultry has been controlled by treating the eggs with phenylmercuric dinaphthylmethane-disulfonate.

Table 7. Review of 49 Aspergillosis cases seen at Abu Dhabi Falcon Hospital 2000-2001 in Falcons (see Table 6 for treatment regimens)

Aspergillosis Grade (Redig, 1993a)	Group A Treated and recovered	Group B Treated and died	Group C Euthanased after diagnosis
1	0	2	0
2	0	0	0
3	16	3	0
4	4	7	17
Total	20	17*	17

*five cases the owner was advised that the birds carried a poor prognosis and euthanas a was recommended, but the owners insisted on attempting treatment

Case Fatality Rate - 46% (17/37) for all birds receiving treatment

Case Fatality Rate - 37.5% (12/32) for birds receiving treatment where the vet considered treatment carried a reasonable chance of success (Groups A and B excluding 5 cases where euthanasia was recommended after diagnosis, but owners insisted on treatment)

6. Prophylaxis, Prevention & Vaccination

Prophylaxis

Prophylactic antifungal therapy is recommended for high risk humans and itraconazole is considered the most effective antifungal agent at preventing aspergillosis (Kibbler 1999). Likewise, prophylactic itraconazole (Table 5) is recommended for captive-held birds undergoing a change in management, especially high risk species (Table 1) and during times of stress such as trauma (Redig 1993a) or as part of the management of oiled susceptible seabirds. *Aspergillus spp.* can colonise damaged airways (Richardson 1998), so probably prophylactic antifungal medication should be considered as part of the therapy of many respiratory tract infections (e.g. *Serratospiculiasis*) of susceptible species. Daily fogging with F10 of susceptible birds is used to lower the environmental load of respiratory pathogens such as *Aspergillus sp.* in the Middle East.

Vaccination

Vaccination has been proposed as a means of preventing aspergillosis. A heat-killed vaccine reduced mortality of aspergillosis in waterfowl (Yearout 1988) and a germinated conidia vaccine reduced turkey poult mortality (Richard *et al* 1984). Recently, Graczyk *et al* (1997) demonstrated that i.m. immunisation of Cape shelducks (*Tadorna cana*) with *Aspergillus spp.* mycelial phase cultures provided protection against experimental challenge. However, despite these reports no aspergillosis vaccinations are commercially available for any veterinary species.

Prevention

Recommendations to prevent aspergillosis in captive avian collections are presented in Table 8.

7. Conclusions

Aspergillosis is a manageable and treatable disease if detected early, but advanced cases are medically challenging. Well-designed studies to determine the correlation between the susceptibility of avian isolates and the clinical responses to antifungal drugs are needed so that therapeutic regimens can be optimised.

8. Glossary

bid = twice a day; i.o. = intraosseus; p.o. = per os; CFR = case fatality rate, i.t. = intratracheal injection; s.c. = subcutaneous; GIT = gastro-intestinal tract; i.v. =, intravenous injection; sid = once a day; i.m. = intramuscular injection; MIC = minimum inhibitory concentration; tid = three times a day

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