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**Aspergillus** infections in birds: a review

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Aspergillosis is an infectious, non-contagious fungal disease caused by species in the ubiquitous opportunistic saprophytic genus *Aspergillus*, in particular *Aspergillus fumigatus*. This mycosis was described many years ago, but continues to be a major cause of mortality in captive birds and, less frequently, in free-living birds. Although aspergillosis is predominantly a disease of the respiratory tract, all organs can be involved, leading to a variety of manifestations ranging from acute to chronic infections. It is believed that impaired immunity and the inhalation of a considerable amount of spores are important causative factors. The pathogenesis, early diagnostic methods and antifungal treatment schedules need to be further studied in order to control this disease. The aim of the present review is to present the current knowledge on aspergillosis with the main emphasis on *A. fumigatus* infections in captive and free-living birds rather than domestic poultry. The review covers aetiology, epidemiology, pathogenesis, clinical signs and lesions, diagnosis, treatment and prevention.

**Aetiology**

Aspergillosis is mostly caused by *Aspergillus fumigatus* but *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus glaucus*, *Aspergillus nidulans*, and other *Aspergillus* species or mixed infections can play a role in the disease (Barton et al., 1992; Perelman & Kuttin, 1992; Joseph, 2000). The reason why *A. fumigatus* is the predominant species of airborne fungal infections might be that the spores are much smaller than the spores of other *Aspergillus* species (Richard & Thurston, 1983).

**Epidemiology**

An increased concentration of spores in the environment may predispose a bird to aspergillosis. A warm environment, humidity, poor ventilation (Phalen, 2000; Tell, 2005), poor sanitation (Oglesbee, 1997) and the long-term storage of feed (Khosravi et al., 2008) may increase the amount of spores in the air. Factors impairing the bird’s immunity can also predispose to mycosis. Examples of this include the administration of tetracyclines (Oglesbee, 1997) or long-term steroids (Verstappen & Dorrestein, 2005), vaccination (Barton et al., 1992), metabolic bone disease (Vanderheyden, 1993), an inadequate diet (Bauck et al., 1992; Dorrestein, 1992) resulting in hypovitaminosis A (McMillan & Petrak, 1989; De Herdt, 1996), overcrowding (McMillan & Petrak, 1989), shipping (Tsai et al., 1992), quarantine or capture of wild birds (Abrams et al., 2001), starvation, thermal discomfort, migration (Young et al., 1998), inbreeding (Low et al., 2005), circovirus infection (Soike et al., 1999) and lymphoproliferative disorders (Kelly et al., 2004), toxicosis (Young et al., 1998; Carrasco et al., 2001; Jung et al., 2009), traumatic injuries (Xavier, 2008) and reproductive activity (Jones & Orosz, 2000).

**Pathogenesis**

Inhalation is considered the main infection route for *A. fumigatus* in birds (Oglesbee, 1997), and because *A. fumigatus* spores are too small to be trapped completely in the nasal cavity or trachea, some are able to reach the lungs and air sacs (Fedde, 1998). The air sacs are usually the primary infection sites, since inhaled air reaches the posterior thoracic and abdominal air sacs prior to contacting epithelial surfaces in the lungs (Nardoni et al., 2006). In the lung parenchyma, spores get embedded in the atra and parts of the infundibula in the parabronchus and are engulfed (surface) phagocytic epithelial cells (Maina, 2002). When there are too many spores or the bird has an impaired immune response, the innate defence mechanisms do not succeed in eliminating infection at the site of the air capillaries. This may lead to the development of loosely attached plaques, which may or may not become overgrown by connective tissue of the host. These plaques or necrotic debris in the respiratory tract can obstruct the trachea or bronchi and/or fill up the air sacs (Oglesbee, 1997). Occasionally, sporulation occurs in the lungs and air sacs (Nardoni et al., 2006; Cacciuttolo et al., 2009). Hyphae containing fruiting bodies can fill the lumen and may penetrate the air sacs, causing serositis and superficial necrosis in the adjacent organs (Tsai et al., 1992). Besides direct extension of the infection through the air sac wall, disseminated mycosis also occurs by haematogenous spread. Hyphae, which are known to be tissue and angio-invasive (Dahlhausen et al., 2004), as well as host cells play a role in this spreading mechanism. Macrophages in the respiratory tract ingest spores and find their way through the interstitium into the blood and lymphatic stream and thus to other organs (Richard & Thurston, 1983).
The relevance of virulence factors in avian aspergillosis is not well known, as research on this is minimal (Peden & Rhoades, 1992; Richard et al., 1994, 1996). Ongoing studies suggest that *A. fumigatus* conidia may be able to resist killing by the avian respiratory macrophage (Van Waeyenberghe et al., 2009).

Two types of tissue reaction are recognized: the granulomatous or deep nodular form, and the infiltrative or superficial diffuse form. In the first type, neither exudative inflammation nor vascular lesions in the neighbouring tissues are seen. This type of encapsulated reaction develops both in non-aerated and aerated organs (Nardoni et al., 2006; Femenia et al., 2007; Cacciuttolo et al., 2009). In the non-ridged, non-encapsulated infiltrative type, the fungus frequently invades blood vessels. In aerated organs such as the lungs and the air sacs, the fungus may form aggregates of radiating hyphae containing large numbers of conidio-phores and conidia in the absence of a structured granuloma formation (Nardoni et al., 2006; Cacciuttolo et al., 2009). A mixed type composed of both tissue reactions in the same tissue section is also possible (Tsai et al., 1992; Atasever & Gümüşsoy, 2004).

The popular assumption that the paucity of free avian respiratory macrophages results in an inadequate or incompetent avian respiratory immune system and is therefore responsible for the high susceptibility of birds to respiratory pathogens (Toth & Siegel, 1986) lacks scientific foundation. Instead, the susceptibility of birds to *Aspergillus* spp. may be attributed to differences in anatomical, physiological and respiratory immune system characteristics compared with mammals (Toth, 2000; Maina, 2002; Tell, 2005).

### Clinical signs and lesions

Clinical manifestations depend on the infective dose, the spore distribution, pre-existing diseases, and the immune response of the host (Dahlhausen et al., 2004). Avian aspergillosis is often classified as acute or chronic. Acute aspergillosis is thought to be the result of inhaling an overwhelming number of spores, while chronic aspergillosis is generally associated with immune suppression (Vanderheyden, 1993).

Although aspergillosis is predominantly a disease of the respiratory tract, any organ can be infected. Nasal aspergillosis causes exudative rhinitis (Tsai et al., 1992), possibly accompanied by malformation of the nostrils, beak and cere (Bauck et al., 1992). Mycotic keratitis can cause blepharospasm, photophobia, periorbital swelling, turbid discharge, swollen and adhered eyelids, cloudy cornea and cheesy yellow exudates within the conjunctival sac (Beckman et al., 1994; Hoppes et al., 2000). Neurological signs can be caused by *Aspergillus* spp. (Jensen et al., 1997). Epidermal cysts associated with *A. fumigatus* have been described in the comb of a silkie bantam chicken (Suedmeyer et al., 2002). *Aspergillus* blepharitis and dermatitis involving the eyelids and the head have been described in a peregrine falcon–gyrfalcon hybrid (*Falco peregrinus* × *Falco rusticolus*) (Abrams et al., 2001). Right ventricular dilatation (cor pulmonale) due to pulmonary hypertension, with or without ascites, and congestion of the lungs caused by ventricular failure occasionally occurs (Julian & Goryo, 1990; Höfler et al., 2001). Birds suffering from aspergillosis do not always show respiratory problems. The owner of a trained raptor, for example, may rather observe that the bird’s reactions are impaired. Unilateral drooping of the wing (due to infection of the thoracic air sac, the clavicular air sac or the proximal humerus) or repeated vomiting (due to lesions in the anterior air sacs) is also seen (Forbes, 1991, 1992).

### Diagnosis

The signs of aspergillosis are non-specific, making diagnosis difficult (Dahlhausen et al., 2004). Moreover, no single test provides certainty. Diagnosis usually relies upon an accumulation of evidence from the history, clinical presentation, haematology and biochemistry, serology, radiographic changes, endoscopy and culture of the fungus (Jones & Orosz, 2000).

The history of the bird can reveal a stressful event and/or some underlying environmental factors and/or an immunosuppressive condition or treatment (Jenkins, 1991). It may also reveal chronic debilitation, voice change or exercise intolerance (Oglesbee, 1997).

The clinical signs depend on which form of aspergillosis the bird develops and which organs are involved (Jones & Orosz, 2000). Hence, aspergillosis should be included in the differential diagnosis of respiratory tract and systemic diseases (Jenkins, 1991; Jones & Orosz, 2000).

Results of haematology and plasma biochemistry can be considered indicative rather than diagnostic (Jones & Orosz, 2000). Leukocytosis of 20,000 to more than 100,000 white blood cells per microlitre (Jenkins, 1991; Oglesbee, 1997), heterophilia with a left shift (degenerative shift), monocytosis and lymphopenia have been described in aspergillosis cases (Forbes, 1992). In addition, non-regenerative anaemia, increased total protein and globulin fraction can be observed (Vanderheyden, 1993; Reidarson & McBain, 1995; Jones & Orosz, 2000). Acute infections often present an increase in β-globulins, while chronic infections show an increase in β-globulin and/or γ-globulin fractions. However, immunosuppressed birds may have hypoproteinaemia (Ivey, 2000; Cray et al., 2009a) and white blood cells may be in the normal range (Flammer & Orosz, 2008). Overall, changes in protein electrophoresis are non-specific, but can be useful to estimate disease progression and the response to therapy (Ivey, 2000; Cray et al., 2009a).

Serological tests have been developed to confirm an early and more definite diagnosis of aspergillosis (Peden & Rhoades, 1992). However, in the acute stage, antibody production trails behind antigen exposure by 10 to 14 days (Brown & Redig, 1994); and if the bird is immunosuppressed, the low antibody production results in false negative results (Redig, 1994). In these cases, detection of circulating *Aspergillus* antigen in the serum may be more helpful (Cray et al., 2006). In chronic cases in which antigen levels may be low, detection of antibodies may be useful (Jones & Orosz, 2000). A number of serological test methods have been applied in birds, including counter-immunoelectrophoresis, agar gel immunodiffusion and enzyme-linked immunosorbent assays—but, in general, negative serological tests do not rule out aspergillosis, and positive tests are only
considered diagnostic when backed up by other evidence (Peden & Rhoades, 1992; Brown & Redig, 1994; Redig, 1994; Redig et al., 1997; Le Loch et al., 2005; Arca-Rubal et al., 2006; Cray et al., 2006, 2009a,b). Although radiographs may not be helpful, lateral and ventrodorsal views can be taken in a bird suspected of having aspergillosis. For those that are unlikely to survive anaesthesia, standing or perching lateral views as well as dorsoventral views are helpful (Jones & Orosz, 2000). The radiographic changes of pneumonia and consolidating airsacs are nonspecific (McMillan & Petrak, 1989). Consistent with radiography, computed tomography scans reveal the extent of lesions—but the diagnosis of aspergillosis still requires identification by biopsy, smear or culture (Phalen, 2000).

Endoscopy is invasive and requires anaesthesia, but it allows the extent of the lesions to be seen as well as the progress of infection during treatment (Redig, 1994; Jones & Orosz, 2000). This technique enables evaluation of the entire respiratory tract. Tracheal endoscopy is useful for showing a single lesion, such as a thick white discharge or plaque occluding the trachea or syrinx (Jenkins, 1991; Marks et al., 1994; Redig, 1994). The lower respiratory tract is best evaluated by laparoscopy (Jones & Orosz, 2000). Endoscopy of the abdominal air sac can show a diffuse cloudiness or white or yellow plaques. In the event of sporulation, plaques are covered with green–gray pigmented mould. Samples for culture and cytology should be taken directly with biopsy forceps or via air sac lavage (Jenkins, 1991; Taylor, 1993; Oglesbee, 1997).

On necropsy, the yellow, green or white granulomatous foci can be noted in chronic aspergillosis patients (Jenkins, 1991; Vanderheyden, 1993). Acute aspergillosis causes numerous miliary granulomatous foci (McMillan & Petrak, 1989; Jenkins, 1991).

Definitive diagnosis requires demonstration of the presence of the organism by cytology or histopathology and its identification by culture (Dahlhausen et al., 2004). It is important to mention that isolation of the fungus alone does not confirm the infection because Aspergillus organisms are ubiquitous and can be contaminants (Jensen et al., 1997; Flammer & Orosz, 2008). However, an abundant culture from any organ should be regarded as diagnostic. On the contrary, a negative culture does not rule out aspergillosis (Redig, 1994; Jensen et al., 1997).

Histopathological lesions can be suggestive, but because in vivo hyphae of hyaline filamentous fungi are very similar and their in situ manifestations are not pathognomonic, this technique does not allow fungal species identification (Kaufman et al., 1997; Cray et al., 2009a). Thus the aetiologic diagnosis should ideally be confirmed by immunohistochemistry, although few reports on immunohistochemical techniques using monoclonal or polyclonal antibodies in birds with aspergillosis are available (Carrasco et al., 1993; Jensen et al., 1997; Beytut et al., 2004, Beytut, 2007).

A few reports of different polymerase chain reaction assays (including real-time polymerase chain reactions) tested on heparinized whole blood, tracheal washings, air sac fluids, respiratory tract granulomas, or (biopsy) tissue samples from birds support the value of this assay in diagnosing avian aspergillosis (Dahlhausen et al., 2004; Cray et al., 2009a). However, further research is necessary before such assays can be included in the work-up of the avian practitioner.

**Treatment**

Treating avian aspergillosis is a challenge due to a number of factors. These include the limited knowledge on the pharmacokinetics of antifungal agents in different bird species, the granulomatous inflammation that makes it difficult for the drug to reach the target fungus, the presence of concurrent disease and/or immunosuppression, and the late stage at which birds are usually presented (McMillan & Petrak, 1989; Flammer, 1993; Orosz & Frazier, 1995). The best way to overcome the disease is topical therapy after removing the granulomatous tracheal lesions by suction (Westerhof, 1995), and this can be used in combination with an early, aggressive systemic antifungal therapy. In most birds, however, granulomatous lesions are difficult to remove because of their location within the respiratory system and because of the risk of surgical trauma and anaesthesia (Hernandez-Divers, 2002). Hence, in most cases, only antifungal therapy is applied. Topical therapy can be administered by nebulization, nasal or air sac flushing, or surgical irrigation of the abdominal cavities (Bauck et al., 1992; Oglesbee, 1997; Abrams et al., 2001), while systemic therapy can be administered intravenously and orally.

The role and prevalence of acquired resistance to antifungal drugs as a potential contributing factor is not well known. Since drug resistance has been increasingly reported in human medicine (Snelders et al., 2008), standardized susceptibility testing is also becoming necessary in avian medicine. Literature regarding in vitro susceptibilities of antifungal agents for avian *A. fumigatus* strains in birds is scarce. The minimal inhibitory concentration of thiabendazole, 5-fluorocytosine, fluconazole, ketoconazole, caspofungin, amphotericin B, itraconazole and voriconazole for a limited number of *A. fumigatus* strains isolated from raptors has been determined using non-standardized methods (Redig & Duke, 1985; Silva-Nose et al., 2006, 2009). Currently, a reference method is available to test the antifungal susceptibility of filamentous fungi (Clinical and Laboratory Standards Institute document M38-A2), thus solving the lack of standardization. Using this method, the *in vitro* susceptibility of 59 avian *A. fumigatus* strains against amphotericin B, itraconazole and voriconazole has been determined. Four isolates showed acquired resistance to both itraconazole and voriconazole, a fact that may harbour implications for the treatment (Beernaert et al., 2009c).

Specific drug properties, toxicity and dose regimens of a number of antifungal drug classes commonly applied in avian aspergillosis are summarized in Table 1.

**Prevention**

Protective immunity following vaccination is thought to be useful in treating and preventing avian aspergillosis. However, attempts to devise vaccination strategies appear questionable in immunosuppressed animals that would need passive immunization with immunoglobulins (Schmidt, 2002). Nevertheless, a number of different
vaccination strategies have been attempted in birds using different vaccine preparations, but with inconsistent results (Richard et al., 1991; Bauck et al., 1992; Meredith, 1997). Future knowledge regarding virulence factors and the role of cellular immunity in avian aspergillosis may contribute to newer and more effective vaccination strategies.

The use of immune stimulants has been suggested (Jenkins, 1991). Levamisole, a derivative of imidazothiazole, has been found to possess an immunostimulant effect as an adjunct in the treatment of chronic infections. However, levamisole did not decrease aspergillosis-associated lesions in turkeys (Perelman, 1993). In humans, clinical improvement of aspergillosis has been documented after the addition of interferon-γ and granulocyte-macrophage colony-stimulating factor to the antifungal treatment (Bandera et al., 2008). Whether the favourable effect of interferon-γ and granulocyte-macrophage colony-stimulating factor could also play a role in future treatment protocols for avian aspergillosis needs to be investigated.

**References**


### Table 1. Summary of the administration routes and doses of antifungal agents used for avian aspergillosis.

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>Administration route</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>Intravenous</td>
<td>1.5 mg/kg × 8 h 3 to 5 days (Flammer, 1993; Joseph et al., 1994), 10 to 14 days (Jenkins, 1991)</td>
</tr>
<tr>
<td></td>
<td>Intratracheal</td>
<td>1.5 mg/kg q 8 to 12 h (raptors) (Redig &amp; Duke, 1985)</td>
</tr>
<tr>
<td></td>
<td>Nebulization</td>
<td>1 mg/kg q24 h 10 to 14 days (Jenkins, 1991), q12 h (raptors) (Joseph et al., 1994)</td>
</tr>
<tr>
<td></td>
<td>Into air sac</td>
<td>1 mg/ml 15 min to 7 days every other week (Orosz &amp; Frazier, 1995), q12 h (Joseph et al., 1994)</td>
</tr>
<tr>
<td></td>
<td>Topical (wound)</td>
<td>Dose not specified (Flammer, 1993)</td>
</tr>
<tr>
<td></td>
<td>Topical</td>
<td>1.35 mg/kg q24 h (liposomally encapsulated amphotericin B) (Bonar &amp; Lewandowski, 2004)</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>Topical</td>
<td>Dose not specified (Flammer, 1993)</td>
</tr>
<tr>
<td></td>
<td>Nebulization</td>
<td>10 mg/ml polyethylene glycol for 30 to 45 min q24 h 3 days on/2 days off (1 to 4 months) (Joseph et al., 1994; Orosz &amp; Frazier, 1995)</td>
</tr>
<tr>
<td></td>
<td>Nebulization</td>
<td>0.1 ml/kg for 30 min q24 h 5 days on/2 days off (raptors) (Healy et al., 2007)</td>
</tr>
<tr>
<td></td>
<td>Nebulization</td>
<td>Dose not specified (Flammer, 1993)</td>
</tr>
<tr>
<td></td>
<td>Nebulization</td>
<td>Dose not specified (Flammer, 1993)</td>
</tr>
<tr>
<td></td>
<td>Disinfection</td>
<td>Environment: flush with solutions as recommended for use in poultry houses (Flammer, 1993)</td>
</tr>
<tr>
<td>Miconazole</td>
<td>Oral, intravenous</td>
<td>5 mg/kg q24 h 7 days (Bauck et al., 1992; Flammer, 1993)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>15 mg/kg q12h (psittacines) (Pericard, 2005)</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Oral</td>
<td>5 to 15 mg/kg q12h with food for 7 to 21 days (Bauck et al., 1992)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>10 mg/kg q24h 3 weeks (Verstappen &amp; Dorrestein, 2005) (falcons) (Jones et al., 2000)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>15 mg/kg per orally q12 h q24h (Abrams et al., 2001), 10 to 20 mg/kg q12 h q24h (Flammer, 1993)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>5 mg/kg q24h 30 days (African grey parrots) (Orosz &amp; Frazier, 1995)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>5 to 10 mg/kg q24h (Amazon parrots) (Orosz et al., 1996), 6 mg/kg q12h (pigeons) (Lumeij et al., 1995)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>Preventive: 10 mg/kg q24h 10 days (Forbes, 1992), 20 mg/kg q24h (Meredith, 1997), 15 to 25 mg/kg/day for 1 week (Xavier, 2008)</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Oral</td>
<td>10 to 30 mg/kg q12h 21 days (resuspending in orange juice q5 days) (Bauck et al., 1992)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>20 to 30 mg/kg q12h (Flammer, 1993), 30 mg/kg q12 h 14 to 30 days (Orosz &amp; Frazier, 1995)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>q12 h (Flammer, 1993; Orosz &amp; Frazier, 1995; Abrams et al., 2001; Suedmeyer et al., 2002)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>pH balanced solution, aqueous base, dilute in saline: 15 to 20 min q12h (Orosz &amp; Frazier, 1995)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>5 mg/kg, 10 mg/ml, q12h (diluted to maximum 0.5 ml with saline) (Westerhof, 1995)</td>
</tr>
<tr>
<td>Terbinaine</td>
<td>Oral</td>
<td>10 mg/kg q12h to q24h, 15 mg/kg q12h (psittacines) (Flammer &amp; Orosz, 2008)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>Can be combined with itraconazole (Flammer, 2006). Dose not mentioned</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Oral</td>
<td>10 mg/kg q12h (pigeon) (Beernaert et al., 2009a,b), q24h (chickens) (Burhenne et al., 2008)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>(African grey parrots) (Scope et al., 2007)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>12 to 18 mg/kg q12h (African grey parrots) (Flammer &amp; Orosz, 2008)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>12.5 mg/kg q12h, 3 days loading dose, then q24h (raptors) (Di Somma et al., 2007; Schmidt et al., 2007)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>40 mg/kg q24h (quails) (Tell et al., 2009)</td>
</tr>
<tr>
<td>5-fluorocytosine</td>
<td>Oral</td>
<td>50 to 100 mg/kg q12h (Flammer, 1993)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>60 to 250 mg/kg q12h (cage birds); 40 mg/kg q6 to 8 h (raptors) (Jenkins, 1991)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>150 to 250 mg/kg q12h 21 days (Bauck et al., 1992)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>120 mg/kg q12h 3 weeks (Westerhof, 1995)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>75 to 120 mg/kg q24h (dose/4 q6 h) (Redig &amp; Duke, 1985)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>120 mg/kg q6h (Joseph et al., 1994)</td>
</tr>
</tbody>
</table>

*Every.*
colony stimulating factor therapy in three patients with pulmonary aspergillosis. Influenza, 36, 368–373.


