Antifungal Therapy in Birds
Old Drugs in a New Jacket

Gunther Antonissen, DVM, MSc, PhD[a,b,*],
An Martel, DVM, MSc, PhD, DECZM (Wildlife Population Health)[b]

KEYWORDS

• Amphotericin B • Antifungal • Drug formulation • Itraconazole • Nanoparticles • Nebulization • Terbinafine • Voriconazole

KEY POINTS

- Large interspecies and interindividual variability can be found in the pharmacokinetics of antifungal drugs in birds, which can significantly affect drug safety and efficacy.
- The absorption of antifungals is affected by numerous factors, including drug formulation and gastrointestinal anatomy and physiology.
- New antifungal drug delivery systems enhance drug stability, reduce off-target side effects, prolong residence time in the blood, and improve drug efficacy, and should therefore be considered in the treatment of mycoses.
- Nebulization seems to be a promising method to deliver antifungals in the respiratory tract of birds; however, therapeutic output is influenced by drug formulation and nebulizer type.

INTRODUCTION

The early diagnosis of systemic fungal diseases in birds, especially aspergillosis, remains challenging because the clinical signs are usually nonspecific and there still is no single reliable noninvasive diagnostic test available in birds.[1–3] Consequently, antifungal therapy is frequently administered empirically for presumptive invasive fungal infections in these patients without a definitive diagnosis being made. However, different factors need to be considered in the rational drug selection of antifungal therapy. First, the selected antifungal drug must be able to penetrate the center of infection in a concentration to which the fungus is susceptible. However, fungi, in

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[a] Department of Pharmacology, Toxicology and Biochemistry, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, Merelbeke 9820, Belgium; [b] Department of Pathology, Bacteriology and Avian Diseases, Faculty of Veterinary Medicine, Ghent University, Salisburylaan 133, Merelbeke 9820, Belgium
* Corresponding author. Department of Pharmacology, Toxicology and Biochemistry, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium.
E-mail address: Gunther.Antonissen@UGent.be

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contrast with bacteria, are eukaryotes, and consequently most antifungal agents are also toxic to the eukaryotic host cells. Therefore, taking into account their (often narrow) therapeutic index, no perfect antifungal agent exists. Nevertheless, in the last decades, newer and less toxic antifungals, including the azoles and echinocandins, have been developed for use in human medicine. Aside from the chemical structure, the impact of antifungal drug formulation and route of administration on treatment safety and efficacy have been investigated as well.[4]

Because knowledge of avian antifungal treatment is limited, treatment protocols are often developed empirically, based on case reports, or extrapolated from humans or other animal species. Because of the narrow therapeutic index, the dosing of antifungal drugs should be done carefully, with dose extrapolation preferably based on more advanced allometric and physiologically based pharmacokinetic (PK) modeling.[5] In avian medicine, different antifungal agents are being used, but most of these substances have not been approved for administration in birds.[6] However, recently (2014) the first antifungal product (itraconazole 10 mg/mL oral solution; Fungitraxx, Avimedical, Hengelo, The Netherlands) was registered for ornamental birds in Europe (EMA/698698/2013). The purpose of this review is to describe the interrelation of antifungal drug formulation, administration route, therapeutic–toxic range, and treatment outcome in fungal diseases, with a particular emphasis on aspergillosis in companion birds.

MECHANISM OF ACTION

In general, the main targets for antifungal drug development are cell wall polymer (glucans, chitin, mannoproteins), cell membrane (especially ergosterol) biosynthesis, DNA and protein synthesis (topoisomerases, nucleases, elongation factors and myristoylation), and signal transduction pathways (protein kinases and protein phosphatases).[7,8] The 3 major groups of antifungal agents in clinical use, that is, polyenes, azole derivatives, and allylamines, all owe their antifungal activities to the inhibition of synthesis or direct interaction with ergosterol (the predominant component of the fungal cell membrane).[8,9]

Amphotericin B and nystatin are polyene macrolides that act by binding to ergosterol. This binding alters the membrane permeability, causing leakage of sodium, potassium, and hydrogen ions, which eventually leads to cell death. Polyenes have a broad antifungal spectrum, including a variety of yeasts (eg, *Candida* spp) and molds (eg, *Aspergillus* spp).[9]

Azoles inhibit the enzyme cytochrome P450-dependent 14-α-sterol demethylase, which is required for the conversion of lanosterol to ergosterol. Exposed fungi become depleted of ergosterol and accumulate 14-α-methylated sterols. This action causes disruption of membrane structure and function, thereby inhibiting fungal growth.[9,10] Azoles are classified as imidazoles (including clotrimazole, miconazole, enilconazole, and ketoconazole) or triazoles (including itraconazole, fluconazole, and voriconazole) based on possessing 2 or 3 nitrogen atoms in the 5-membered azole ring, respectively. Depending on the particular compound, azole antifungal agents have fungistatic and broad-spectrum activity against most yeasts and filamentous fungi.[9] With the exception of voriconazole, azoles are known to be fungistatic at the doses used in birds and need several days to reach steady-state concentrations.[11]

Finally, allylamines (eg, terbinafine) act by a reversible, noncompetitive inhibition of the squalene epoxidase, a key enzyme in the cyclization of squalene to lanosterol, resulting in an ergosterol depletion and squalene accumulation. The antifungal spectrum of terbinafine includes yeast (fungistatic) as well as dermatophytes and molds (fungicidal).[6,9,12]

TOXICITY

The clinical use of amphotericin B has been associated with a dose-dependent nephrotoxicity in mammals. Because amphotericin B binds to mammalian sterols, including cholesterol, renal toxicity is related to binding of the drug to the sterol rich cell membranes in kidney tubules. As a result, amphotericin B affects the ionic permeability of the renal brush border cells, releasing mediators that cause an abrupt decrease in renal blood flow. However, no evidence of nephrotoxicity has been observed in birds, which might be associated with the shorter elimination half-life ($T_{1/2el}$) in birds compared with mammals after intravenous (IV) administration.[11,13] Nevertheless, clinicians are advised to monitor the renal function of their avian patients.

The relative toxicity of azoles depends on the specificity for binding to the fungal cytochrome P450 enzyme, instead of the avian/mammalian cytochrome P450 enzymes. The most common adverse side effects associated with azole administration in birds are gastrointestinal (GI) signs, such as anorexia and vomiting, and alterations in liver function.[14,15] In general itraconazole, is well-tolerated; however, caution should be used when considering the use of this drug in African or timneh gray parrots, because they are more sensitive to itraconazole present in the form of distinct anorexia and depression.[6,11] Remarkably, PK studies explaining this higher sensitivity in African or timneh gray parrots are still lacking (**Table 1**). The apparent sensitivity to azoles experienced by different bird species may be explained in part by the drug's PK and metabolism. In humans, cytochrome P450 isoenzyme CYP2C19 genotypic polymorphism has been linked to differential sensitivity to voriconazole toxicity.[16,17] Although undocumented in avian species, similar polymorphisms could be responsible for the wide variability in avian voriconazole PK properties. After a single oral administration of voriconazole, a 4 to 5 times longer $T_{1/2el}$ was observed in pigeons (*Columba livia domestica*) and African penguins (*Spheniscus demersus*), compared with Hispaniolan Amazon parrots (*Amazona ventralis*), timneh gray parrots (*Psittacus erithacus timneh*), mallard ducks (*Anas platyrhynchos*), and red-tailed hawks (*Buteo jamaicensis*; **Table 2**).[18–23] This prolonged $T_{1/2el}$ in pigeons and penguins presents a potential for drug accumulation with extended dosing and toxicity. After oral administration of voriconazole (10 and 20 mg/kg body weight [BW] twice a day) to pigeons, Beernaert and colleagues[19] observed hepatic changes, such as hepatomegaly and miliary hepatic necrosis and, on histology, vacuolization up to apoptosis of hepatocytes and heterophilic and lymphocytic infiltration. Similarly, Hyatt and colleagues[24] demonstrated signs indicative of toxicity in multiple penguin species after administering voriconazole (6.1–22.2 mg/kg BW once or twice a day), which ranged in severity and included anorexia, lethargy, weakness, change in mentation, ataxia, paresis, apparent vision changes, seizurelike activity, and generalized seizures. The toxicity and efficacy of all azole derivatives can furthermore be influenced by drug–drug interactions that are based on the mechanism of action of these drugs being potent cytochrome P450 inhibitors. Consequently, caution should be taken when azoles are coadministered with other drugs, such as midazolam, enrofloxacin, and clindamycin.[6,24]

Finally, terbinafine is generally associated with a low index of toxicity and few adverse effects. In humans, only mild GI toxicity and hepatobiliary dysfunction are reported. In red-tailed hawks, oral administration of a high dose of terbinafine (120 mg/kg BW) was furthermore demonstrated to induce regurgitation.[25] Anecdotally, some mild GI toxicity and hepatobiliary dysfunction were observed in some psittacine species including an African gray parrot, a blue-fronted Amazon parrot

Table 1
Plasma and lung itraconazole and hydroxyitraconazole concentrations after single bolus and steady-state pharmacokinetic studies of itraconazole in different bird species

	Animal Species	BW (g)	Dosage Itraconazole (mg/kg BW)	Drug Formulation	Frequency of Administration	Feed	Itraconazole (ng/mL)			Hydroxyitraconazole (ng/mL)			Reference
							C_{min}	C_{max}	C_{lung}	C_{min}	C_{max}	C_{lung}	
PK single bolus	Pigeon	488	10.3	ITRA-LAC	Single bolus	—	—	1130	250	—	—	—	Lumeij et al,[55] 1995
			5	ITRA-LAC + orange juice	Single bolus	No	—	100–200[a]	339	—	—	—	Orosz et al,[53] 1995
			5	ITRA-LAC + orange juice + 0.1 N HCl	Single bolus	Yes	—	100–200[a]	476	—	—	—	
	Blue-fronted Amazon parrot	306–424	5	ITRA-LAC + orange juice + 0.1 N HCl	Single bolus	Yes	—	1743	—	—	247	—	Orosz et al,[57] 1996
			10	ITRA-LAC + orange juice + 0.1 N HCl	Single bolus	Yes	—	2312	—	—	1976	—	
	Red-tailed hawks		5	ITRA-LAC + orange juice + 0.1 N HCl	Single bolus	Yes	—	50–300[a]	—	—	50–150[a]	—	Jones et al,[56] 2000
			10	ITRA-LAC + orange juice + 0.1 N HCl	Single bolus	Yes	—	250–300[a]	—	—	200–250[a]	—	
	Mallard Duck	979–1442	20	ITRA-LAC + orange juice + 0.1 N HCl	Single bolus	Yes	—	1070	730	—	340	275	Tell et al,[49] 2005
			20	ITRA-CD	Single bolus	Yes	—	1350	796	—	270	313	
	Black-footed penguin	2600–4400	7	ITRA-GEN	Single bolus	Yes	—	350	—	—	—	—	Smith et al,[80] 2010
			7	ITRA-CD	Single bolus	Yes	—	750	—	—	—	—	

PK at steady state	Pigeon	488	10.3	ITRA-LAC	QID, 3 d	—	—	3875	—	—	—	—	Lumeij et al,[55] 1995
			5	ITRA-LAC + orange juice	SID, 14 d	No	—	100–200[a]	250	—	—	3206	Orosz et al,[53] 1995
			5	ITRA-LAC + orange juice + 0.1 N HCl	SID, 14 d	Yes	—	500–600[a]	359	—	—	79,876	
	Blue-fronted Amazon parrot	306–424	5	ITRA-LAC + orange juice + 0.1 N HCl	SID, 14 d	Yes	—	1437	—	197	309	—	Orosz et al,[57] 1996
			10	ITRA-LAC + orange juice + 0.1 N HCl	SID, 14 d	Yes	—	3434	—	92	1976	—	
	Red-tailed hawks		5	ITRA-LAC + orange juice + 0.1 N HCl	SID, 14 d	Yes	—	300–360[a]	2598	—	150–360[a]	1750	Jones et al,[56] 2000
			10	ITRA-LAC + orange juice + 0.1 N HCl	SID, 14 d	Yes	—	150–500[a]	2941	—	120–480[a]	2113	
	Humboldt penguin	3420–5760	6	ITRA-GEN	SID, 14 d	Yes	—	ND	—	30	248	—	Bunting et al,[51] 2009
			12	ITRA-GEN	SID, 14 d	Yes	—	52	—	55	331	—	
			6	ITRA-CD	SID, 14 d	Yes	—	10–100[a]	—	166	829	—	
			12	ITRA-CD	SID, 14 d	Yes	—	175	—	525	2335	—	
			7	ITRA-CD	BID, 14 d	Yes	104	262	—	673	994	—	

Abbreviations: BID, twice a day; BW, bodyweight; C_{lung}, concentration in lung; C_{max}, maximum plasma concentration; C_{min}, minimal plasma concentration in multiple doses PK; ITRA-CD, itraconazole + hydroxypropyl-β-cyclodextrin; ITRA-GEN, generic bulk compounded itraconazole powder; ITRA-LAC, itraconazole-coated lactose granules; ND, not detected; PK, pharmacokinetic; QID, 4 times a day; SID, once a day.

[a] Estimated concentration based on graph or table in original study.

Table 2
PK characteristics of voriconazole after single bolus and multiples doses administration in different bird species

	Animal Species	BW (g)	Dosage Voriconazole (mg/kg BW)	Frequency of Administration	Feed	F (%)	C_{min} (ng/mL)	T_{max} (h)	C_{max} (ng/mL)	V_d (IV) V_d/F (Oral) (mL/kg)	$T_{1/2el}$ (h)	Cl (IV) Cl/F (Oral) (mL/h·kg)	C_{lung} (ng/g)	C_{liver} (ng/g)	Reference
PK IV bolus	Chicken: layers	740–1110	10[b]	Single	No	100	—	—	7400	1681	1.99	586	—	—	Burhenne et al,[59] 2008
	Pigeon	400–500	2.5[a]	Single	Yes	100	—	—	—	1110	6.62	120	—	—	Beernaert et al,[19] 2009
			5[a]	Single	Yes	100	—	—	—	1410	11.33	86	—	—	
			10[a]	Single	Yes	100	—	—	5576	1790	16.25	76	—	—	
	Mallard duck	1060 ± 110	10[a]	Single	No	100	—	—	—	1440	1.34	530	ND	ND	Kline et al,[22] 2011
PK oral bolus	Chicken: layers	740–1106	5	Single	No	—	—	0.83	350	—	1.35	—	—	—	Burhenne et al,[59] 2008
			7.5	Single	No	—	—	2.00	410	—	2.40	—	—	—	
			10	Single	No	—	—	0.83	440	—	1.23	—	—	—	
			10	Single	No	16	—	1.50	700	—	—	—	—	—	
			10	Single	No	20	—	0.75	880	—	1.45	—	—	—	
			15	Single	No	—	—	1.50	510	—	1.77	—	—	—	
	Pigeon	400–500	10[b]	Single	No	44	—	2.15	3317	2600	10.32	176	—	—	Beernaert et al,[19] 2009
	Japanese quail	104–179	20	Single	Yes	—	—	2.00	5800	1770	—	—	—	—	Tell et al,[60] 2010
			40[b]	Single	Yes	—	—	2.00	6900	6100	—	—	—	—	

	Hispaniolan Amazon parrot	260–320	12[c]	Single	No	—	—	1.00	2490	2054	0.90	1576	—	—	Guzman et al,[20] 2010
			24[c]	Single	No	—	—	2.00	5080	2349	1.25	1306	—	—	
	Timneh gray parrot	290–339	6[b]	Single	—	—	—	2.00	540	3498	1.11	2185	—	—	Flammer et al,[21] 2008
			12[b]	Single	—	—	—	4.00	1890	2634	1.59	1151	—	—	
			12[c]	Single	—	—	—	2.00	3020	1051	1.07	679	—	—	
			18[c]	Single	—	—	—	2.00	5670	1200	1.59	521	—	—	
	Mallard duck	1060 ± 110	10[b]	Single	No	61	—	0.77	3940	1504	—	—	ND	ND	Kline et al,[22] 2011
			10[b]	Single	Yes	—	—	1.50	7350	—	1.00	—	ND	0.04–0.06	
			20[b]	Single	Yes	—	—	1.50	10,600	—	1.75	—	ND-0.16	0.04–0.47	
			40[b]	Single	Yes	—	—	2.00	24,443	—	1.37	—	ND	0.06–0.17	
	Red-tailed hawks	926–1410	15[b]	Single	No	—	—	2.29	7230	1180	2.04	431	—	—	Parsley et al,[23] 2017
			15[b]	Single	Yes	—	—	4.86	6180	1349	2.29	485	—	—	
	African penguin	2200–3400	5[c]	Single	No	—	—	0.40	1890	—	10.92	—	—	—	Hyatt et al,[18] 2017
Multiple doses PK	Chicken: layers	1030–1770	10[b]	SID, 10 d	Yes	—	—	1.00	280	—	—	—	ND	140	Burhenne et al,[59] 2008
			10[b]	SID, 20 d	Yes	—	—	3.00	1590	—	—	—	765	5360	
			10[b]	SID, 30 d	Yes	—	—	3.00	400	—	—	—	255	817	
	Pigeon	400–500	10[b]	SID, 3 d	Yes	—	134–418	2.00	2417–3683	—	—	—	ND - 598	—	Beernaert et al,[19] 2009
			20[b]	SID, 10 d	Yes	—	154–1516	2.00	5352–9183	—	—	—	—	—	
			10[b]	BID, 4 d	Yes	—	ND-3500[d]	2.00	3350–8000[d]	—	1.60	—	100	—	
			20[b]	BID, 4 d	Yes	—	5847	2.00	15,876	—	—	—	ND-1241	—	

(*continued on next page*)

Table 2
(*continued*)

Animal Species	BW (g)	Dosage Voriconazole (mg/kg BW)	Frequency of Administration	Feed	F (%)	C_{min} (ng/mL)	T_{max} (h)	C_{max} (ng/mL)	V_d (IV) V_d/F (Oral) (mL/kg)	$T_{1/2el}$ (h)	Cl (IV) Cl/F (Oral) (mL/h·kg)	C_{lung} (ng/g)	C_{liver} (ng/g)	Reference
Hispaniolan Amazon parrot	260–320	18[c]	TID, 11 d	Yes	—	—	2.00	790	—	1.29	—	—	—	Guzman et al,[20] 2010
Timneh gray parrot	290–339	18[c]	BID, 9 d	—	—	58–63	—	2600–2800	—	—	—	—	—	Flammer et al,[21] 2008
Mallard duck	1060 ± 110	20[b]	SID, 21 d	No	—	—	1.00	9960	904	0.72	—	ND-0.19	ND-0.06	Kline et al,[22] 2011
		20[b]	SID, 21 d	Yes	—	—	1.08	8090	1624	1.11	—	ND	ND-0.12	
African penguin	220–3400	5[b]	SID, 8 d	Yes	—	500–3250	1.53	3640–5640	1193[e]	—	64[e]	—	—	Hyatt et al,[18] 2017

Abbreviations: BID, twice a day; BW, bodyweight; Cl or Cl/F, clearance; C_{liver}, voriconazole concentration in liver; C_{lung}, voriconazole concentration in lung; C_{max}, maximum plasma concentration; C_{min}, minimal plasma voriconazole concentration in multiple doses PK; F, absolute bioavailability; IV, intravenous; ND, not detected; PK, pharmacokinetic; SID, once a day; $T_{1/2el}$, elimination half-life; TID, 3 times a day; T_{max}, time point of maximum plasma concentration; V_d or V_d/F, volume of distribution.

[a] Voriconazole sulfobutylether-β-cyclodextrin was suspended in 0.9% NaCl.

[b] Water.

[c] Commercial suspending agent.

[d] Estimated concentration based on graph in original study.

[e] Calculated based on average bodyweight.

(*Amazona aestiva*), and a Senegal parrot (*Poicephalus senegalus*) after long-term administration of terbinafine (10–15 mg/kg BW, twice a day) alone or in combination with itraconazole or voriconazole (van Zeeland, personal communication, 2017).

DRUG RESISTANCE

Antifungal susceptibility testing is a useful tool to provide information to clinicians to help guide therapy. The European Committee on Antimicrobial Susceptibility Testing and the Clinical and Laboratory Standards Institute have developed a standardized in vitro antifungal susceptibility testing method for yeasts and molds, whereby the minimum inhibitory concentration (MIC) is measured and referenced to a clinical breakpoint. However, in birds, the interpretation of the MICs of different antifungal agents remains uncertain, because of lack of correlation of in vitro resistance with clinical outcome.[26,27] Although information on antifungal resistance in avian medicine is very limited, human medicine shows that antifungal resistance is increasing and is an emerging threat to patient management and clinical success. Beernaert and colleagues[28] reported an acquired resistance of *Aspergillus fumigatus* strains, isolated from companion and wild birds, to both itraconazole and voriconazole. However, current in vitro antifungal susceptibility tests do not (yet) take the impact of drug formulation into account. Consequently, interpretation of MICs of amphotericin B against *Aspergillus* spp remains uncertain because of lack of correlation of in vitro resistance with clinical outcome. For example, differences in PK characteristics (eg, tissue concentration of free drug in the site of infection) or immunomodulating properties between, for example, amphotericin B deoxycholate and liposomal amphotericin B, might be more important determinants of outcome of amphotericin B-based therapy than the MIC. In a murine model of disseminated invasive aspergillosis, treatment with liposomal amphotericin B resulted in a better outcome than treatment with amphotericin B deoxycholate, despite no differences in the MIC being observed between the drug formulations.[27]

DRUG FORMULATION

Several antifungal drugs are characterized by their insolubility in water at physiologic pH, poor oral bioavailability, and limited formulation approaches. In addition, a narrow therapeutic–toxic range and drug–drug interactions of systemic antifungal agents are other major problems that compromise optimal treatment.[29,30] Therefore, there is a strong need to develop innovative drug formulations to address these issues.

In an attempt to decrease the intrinsic toxicity and enhance the efficacy of amphotericin B, 3 lipid-associated formulations were developed and approved for use in human medicine in the 1990s, that is, amphotericin B lipid complex, liposomal amphotericin B, and amphotericin B colloidal dispersion. Amphotericin B lipid complex (Abelcet, Cephalon, Inc., Fraser, PA) forms ribbonlike particles of dimyristoyl phosphatidyl choline and dimyristoyl phosphatidyl glycerol with amphotericin B; liposomal amphotericin B (AmBisome, Gilead Sciences International Ltd., Cambridge, UK; and Fungisome, Lifecare Innovations Pvt Ltd, Gurgaon, India) is a true unilamellar liposome composed of a mixture of phosphatidyl choline:distearoyl:phosphatidylglycerol:cholesterol; and amphotericin B colloidal dispersion (Amphotec of Amphocil, Sequus Pharmaceuticals, Menlo Park, CA) is a formulation in which amphotericin B is complexed to cholesterol sulfate resulting in the formation of disclike structures. Knowledge based on in vitro and in vivo studies in rodents, dogs, and humans suggest that these lipid formulations of amphotericin B generally have a slower onset of action, because of the required dissociation of free amphotericin B from the lipid vehicle.

Moreover, incorporation of amphotericin B into the lipid vesicle will enhance drug uptake by the liver and spleen, and cause accumulation of the drug by the mononuclear phagocyte system and at sites of capillary damage and inflammation. Consequently, the PK characteristics of lipid-based amphotericin is strongly determined by its physicochemical properties. Amphotericin B lipid complex is the largest compound of the lipid preparations (diameter of 1600–11,000 nm), resulting in a fast recognition in the blood by activated monocytes/macrophages, which subsequently transport the drug to the site of infection, where phospholipases release the free drug. In addition, this compound is sequestered to a high extent in the tissues of the mononuclear phagocyte system (liver and spleen), including the lungs. This rapid and extensive distribution, predominantly to the liver, spleen, and lungs, is reflected in the PK characteristics by a very large volume of distribution and a low area under the plasma concentration time curve. Lung levels are considerably higher than those achieved with other lipid-associated preparations and amphotericin B deoxycholate. The small size of liposomal amphotericin B (diameter of 60–80 nm) and negative charge tend to result in a prolonged circulation in plasma, because these compounds are not readily recognized and taken up by the mononuclear phagocyte system. However, the clinical relevance of these PK differences between liposomal amphotericin B and amphotericin B lipid complex remains unknown. After IV infusion, amphotericin B colloidal dispersion (disks of 122 nm diameter and 4 nm thickness) is rapidly removed from the circulation by the mononuclear phagocyte system, predominantly by Kupffer cells of the liver, and to a lesser extent in the spleen and bone marrow. These differences in PK and pharmacodynamic characteristics are reflected in the dose recommendations in human medicine: amphotericin B deoxycholate 0.25 to 1.5 mg/kg once a day, amphotericin B lipid complex 5 mg/kg BW once a day, liposomal amphotericin B 1 to 5 mg/kg BW once a day, and amphotericin B colloidal dispersion 3 to 5 mg/kg once a day.[31] However, the impact of these differences in PK/pharmacodynamics on clinical efficacy in birds is still unclear. Comparatively, amphotericin B deoxycholate is administered at a dose of 1 to 1.5 mg/kg BW 3 times a day to birds.[3]

In humans, the superior safety profile of lipid-associated formulations is characterized by decreased acute infusion-related reactions and dose-related nephrotoxicity, allowing the administration of larger doses and therefore similar efficacy with fewer administrations. In vitro studies and human clinical data suggest that amphotericin B lipid complex and liposomal amphotericin B induce a Toll-like receptor 4 reaction instead of a Toll-like receptor 2 reaction, as observed with amphotericin deoxycholate, causing attenuation of the characteristic proinflammatory response. Unlike the other lipid-associated amphotericin B preparations, the amphotericin B colloidal dispersion is associated with a higher frequency of infusion-related reactions associated with an inflammatory gene upregulation similar as amphotericin B deoxycholate. The pathophysiology of amphotericin B–induced nephrotoxicity is associated with a vasoconstrictive effect on the afferent renal arterioles, decreasing the glomerular filtration rate and inducing tubular dysfunction. Complexation with lipids seems to stabilize amphotericin B in a self-associated state so that it is not available to interact with cholesterol in mammalian or avian cellular membranes, which is the presumed major site of toxicity. Moreover, amphotericin B alone binds preferentially to low-density lipoproteins and can be internalized into renal cells that express low-density lipoprotein receptors, resulting in toxicity. Amphotericin B from lipid-associated formulations binds preferentially to high-density lipoproteins, which reduces nephrotoxicity by decreasing the uptake of amphotericin B by renal cells because of their low level of high-density lipoprotein receptors.[32] Recently, Phillips and colleagues[33] demonstrated that a single dose (3 mg/kg BW) of liposomal amphotericin B delivered by

aerosol to healthy mallard ducks resulted in minimal systemic distribution of the drug after administration, characterized by low plasma and kidney amphotericin B concentrations and no signs of drug-associated damage on histopathologic examination of renal, hepatic, or cardiac tissue samples. Similarly, based on clinical examination and plasma uric acid levels, no signs of nephrotoxicity were observed in a goliath heron (*Ardea goliath*) with a deep infection with *Aspergillus* species of its pectoral muscle topically treated with liposomal amphotericin B (1.35 mg/kg, once a day) mixed with sterile, water-soluble, gelatin lubricant for more than 1 month.[34]

Studies in mouse and rabbit models of fungal infection and human metaanalyses have shown the liposomal formulation of amphotericin B to be at least as effective as amphotericin B deoxycholate in improving survival and resolving the infection.[35–37] After intratracheal aerosol administration of liposomal amphotericin B to healthy mallard ducks, drug concentrations in pulmonary parenchyma reached above the targeted MIC for avian isolates of *Aspergillus* species of 1 μg/mL.[33] Although these lipid formulations are reported to have excellent safety and efficacy, the high price of these drugs may currently preclude their use in veterinary medicine compared with the conventional form.

Among many new antifungal drug delivery systems currently under investigation, nanoparticles (NPs) have emerged as an innovative and promising platform able to enhance drug stability, reduce off-target side effects, prolong residence time in the blood, and improve drug efficacy. NPs are characterized by their small particle size ranging from 1 to 1000 nm.[30] Liposomal amphotericin is the first and most successful commercial NP of antifungal drugs in humans.[38] NPs used in drug delivery can be classified into phospholipid vesicles (eg, liposomes), nonphospholipid vesicles, polymeric NPs, polymeric micelles, solid lipid NPs, nanostructured lipid carriers, nanoemulsions, and dendrimers.[30] For example, liposomal nystatin allowed the IV administration of nystatin, increased the maximum tolerated dose in mice from 4 to 16 mg/kg BW, and increased the survival rate of mice infected with *Candida albicans*.[39] Itraconazole incorporated into poly(lactide-co-glycolide) (PLGA) resulted in a sustained-release formulation for IV administration with plasma itraconazole levels for more than 3 times longer than the commercial formulation.[40] PLGA containing voriconazole was detectable in lungs until 5 to 7 days after pulmonary disposition in mice via an inhalation chamber.[41] Recently, Pardeike and colleagues[42] demonstrated that nebulized itraconazole-loaded nanostructured lipid carriers penetrate deeply into the lungs and air sacs of a falcon, being a prerequisite for pulmonary treatment of aspergillosis.

Administration Route

The route of administration of antifungals will depend on the drug, available drug formulation, condition of the bird, ability of the owner and/or veterinary staff to deliver the drug, and the financial and emotional commitment of the bird's owner. Taking into account the narrow therapeutic–toxic range of all commercially available antifungal drugs, selecting the most optimal route of administration of a certain compound, in a certain patient, helps to decrease toxicity and to quickly establish effective local drug concentration.

Systemic Treatment

Most systemic fungal infections require long-term therapy that often extends for weeks to months.[3,6] Treatment protocols should not merely include drugs for IV administration because of problems related to maintaining a permeable venous pathway for long periods of time in birds. Nevertheless, vascular access devices have been suggested to be useful for cases that require long-term, frequent

venipuncture.[43] Despite these possibilities, the IV administration of antifungals (predominantly amphotericin B) in birds is only performed in rare cases, for example, in the initial treatment of acute aspergillosis, or in severely debilitated birds. IV administration should always be combined with an oral antifungal drug, which is often administered for at least several weeks to months.[6] PK studies of IV-administered amphotericin B deoxycholate in turkeys (*Meleagris gallapavo*), red-tailed hawks, broad-winged hawks (*Buteo platypterus*), and great horned owls (*Bubo virginianus*) have reported that the $T_{1/2el}$ for avian species is much shorter than that for mammals, suggesting that twice daily dosing is appropriate.[11,13] Amphotericin B can be administered IV under the form of amphotericin B deoxycholate or in a lipid-associated formulation. Standardized electrolyte supplementation and fluid management improve clinical amphotericin B efficacy by minimizing toxicity.[44] Voriconazole and fluconazole have the advantage compared with amphotericin B that, in addition to an IV formulation, an oral formulation is commercially available as well, rendering these drugs suitable for long-term use in birds.[45–47]

Recently, Souza and colleagues[48] assessed the efficacy of itraconazole, voriconazole and terbinafine containing implants in Japanese quails (*Coturnix japonica*). These implants were administered subcutaneously over the dorsum and between the scapulae. Targeted plasma terbinafine concentrations were achieved in some birds at various time points; however, concentrations were inconsistent. Itraconazole and voriconazole concentrations were also inconsistent and below the minimal MIC. Similarly, after subcutaneous administration of 2 itraconazole controlled release gel formulations, only very low or undetectable plasma and tissue concentrations of itraconazole and hydroxyitraconazole were found.[49] Consequently, the administration of an impregnated subcutaneous implant is not (yet) an effective method to treat a fungal infection in birds.

Oral dosing of antifungal drugs is the most common route of administration in systemic fungal diseases. However, oral drug absorption is a complex process affected by numerous factors associated with the drug's formulation characteristics and the GI anatomy and physiology of the target species.[50] Bunting and colleagues[51] demonstrated that the maximum itraconazole and hydroxyitraconazole plasma concentrations after oral administration of the commercially available itraconazole with hydroxypropyl-β-cyclodextrin were much higher compared with generic bulk compounded itraconazole powder in Humboldt penguins (see **Table 1**). In addition, factors such as GI pH and transit time are characterized by considerable variability between and within types of birds. Many azoles are highly lipophilic and poorly water soluble at a neutral pH; however, they are soluble in acidic solutions. The pH of the crop and stomach of birds is considerably less acidic than the mammalian stomach, possibly because of the rapid digestive transit time, which negatively affect antifungal drug solubility and absorption.[52] Further adding to the complexity of absorption is the coadministration of food. Concurrent administration of itraconazole with an intracrop feed bolus and dissolving itraconazole-lactose granules in 0.1 N hydrochloric acid (HCl) before oral administration to pigeons (5 mg/kg BW, once a day for 14 days) increased the maximum plasma concentration of itraconazole and the concentration of its metabolite hydroitraconazole in the lung (see **Table 1**).[53] The relative bioavailability of voriconazole administered orally (20 mg/kg BW, once a day) in mallard ducks with a bolus of liquid feed was slightly higher compared with birds that were not being fed at the time of drug administration (see **Table 2**).[22] In contrast, in falcons, it was observed that, by administering voriconazole in meat, the median peak plasma concentrations were reduced by 21% to 26%.[54]

Several PK studies have reported plasma and lung itraconazole and hydroxyitraconazole concentrations after a single bolus and steady-state PK studies in different bird species (see **Table 1**). Because of the extended time to reach steady state, in cases of acute aspergillosis or in severely diseased birds, itraconazole should initially be combined with amphotericin B (IV) or voriconazole (IV or by mouth) for 3 to 5 days. In the different studies, steady-state concentrations after oral administration were reached within 3 to 14 days.[51,53,55–57] Steady-state plasma concentrations itraconazole plus hydroxyitraconazole above the MIC of 500 to 1000 ng/mL were achieved in pigeons, blue-fronted Amazon parrots, red-tailed hawks, and Humboldt penguins administered itraconazole (see **Table 1**).[28,51,53,55–57] Unfortunately, concentration of itraconazole and its active metabolite in the lung and other target organs were only measured in pigeons and red-tailed hawks.[53,55,56] After oral administration of itraconazole to pigeons and red-tailed hawks in a dosage of 5 mg/kg BW, once a day for 14 days, the sum of the mean lung concentration of itraconazole and hydroxyitraconazole was above the MIC in both species, 3456 to 80,235 ng/g and 4348 ng/g, respectively (see **Table 1**). However, a high interindividual variability of itraconazole and hydroxyitraconazole concentrations was observed in all tissues.[53,56] Based on these studies, the following dosing regimens have been suggested for itraconazole: pigeons, 6 to 26 mg/kg BW twice a day; blue-fronted Amazon parrot, 5 mg/kg BW once a day; red-tailed hawks, 10 mg/kg once a day; and Humboldt penguins, 8.5 mg/kg twice a day or 20 mg/kg once a day.[51,53,56,57] Recently, it was demonstrated in rats that the oral bioavailability of an experimental liposomal formulation of itraconazole-containing sodium deoxycholate was 1.67-fold higher than that of the commercially available itraconazole formulation containing hydroxypropyl-β-cyclodextrin.[58] However, whether this new experimental liposomal formulation can also improve the oral bioavailability of itraconazole in birds, and decrease the high interindividual variability of itraconazole and hydroxyitraconazole concentrations in the target organs, needs further investigation. In addition, an increased oral bioavailability might also lower the GI toxicity of itraconazole; however, systemic toxicity (eg, hepatotoxicity) might increase.

Voriconazole is increasingly used to treat invasive aspergillosis in birds, given the broad antifungal spectrum, which includes molds (fungicidal) and yeasts (fungistatic), and its fast bioavailability.[6,19,22,59] Beernaert and colleagues[45] demonstrated that administering voriconazole (10 mg/kg BW twice a day) orally in pigeons reduced clinical signs and eliminated *A fumigatus* in racing pigeons experimentally infected with *A fumigatus*. Similarly, Tell and colleagues[60] showed that oral administration of voriconazole (20 and 40 mg/kg BW once a day) reduced mortality rate in Japanese quails after experimental *A fumigatus* infection.

The clinical efficacy of voriconazole was also demonstrated in falcons with aspergillosis. Complete clinical resolution occurred in 70% of the birds, partial response in 25%, and 1 bird (5%) died during treatment.[61] However, interspecies and interindividual variability in this drug's PK profile necessitates species-specific PK studies. The average oral voriconazole bioavailability for pigeons and mallard ducks, 44% and 61%, respectively, is much higher compared with chickens, at 16% to 20% (see **Table 2**).[19,22,59] After a single oral voriconazole administration, the $T_{1/2el}$ was longer in pigeons and African penguins, at 10.32 and 10.92 hours, respectively, compared with other bird species (range, 0.90–2.29 hours), which presents the potential for drug accumulation with extended dosing.[18–22,59] In pigeons, the administration of 20 mg voriconazole/kg BW twice daily maintained plasma concentrations of greater than the MIC of 500 ng/mL for 4 days, but induced hepatotoxicity.[19,28] Furthermore, voriconazole concentrations in the lung were only above the MIC in a few pigeons.[19]

In contrast, lung levels were above this MIC value in chickens after oral administration of voriconazole (10 mg/kg BW, once a day) for 20 to 30 days (see **Table 2**).[28,59] Based on these studies, the following dosing regimens have been suggested for voriconazole: pigeons, 10 mg/kg BW twice a day or 20 mg/kg once a day; chicken, 10 mg/kg BW once a day; Hispaniolan Amazon parrot, 18 mg/kg BW 3 times a day; timneh gray parrot, 12 to 18 mg/kg BW twice a day; African penguin, 5 mg/kg once a day; mallard duck, 20 mg/kg BW twice a day-3 times a day; and falcons, 12.5 mg/kg BW once or twice a day.[18–22,54,59]

On contrast with other azoles, fluconazole is highly water soluble. Consequently, the drug can also be administered in the drinking water. Ratzlaff and colleagues[47] demonstrated that, by administering fluconazole-mediated drinking water at a concentration of 100 mg/L for 8 days to cockatiels (*Nymphicus hollandicus*), fluconazole plasma concentrations could be maintained above the MIC for most strains of *C albicans* (based on susceptibility data from humans). After oral administration of 10 mg fluconazole/kg BW to cockatiels and timneh gray parrots, a similar relative bioavailability was observed in both species; the area under the plasma concentration time curve was 149.28 versus 154.55 h·μg/mL, respectively. However, the maximum plasma concentration was lower and the $T_{1/2el}$ longer in the cockatiel compared with timneh African gray parrot (4.94 μg/mL vs 7.45 μg/mL, and 19.01 hours vs 9.22 hours, respectively).[21,47] Based on these studies, the following dosing regimens have been suggested: cockatiels 5 to 10 mg/kg BW orally every 24 to 48 hours, drinking water 100 mg/L, and timneh gray parrots 10 to 20 mg/kg BW orally every 24 to 48 hours. However, clinical studies are needed to verify the efficacy.

Beside the azoles, polyene macrolide antifungal agents are also frequently used in avian medicine. Oral administration of amphotericin B is used widely to treat *Macrorhabdus ornithogaster*, at a recommended dosage of 25 to 100 mg/kg BW twice a day.[2] However, amphotericin B deoxycholate is amphipathic and exhibits low solubility and permeability, resulting in negligible absorption when administered orally. Consequently, oral application to treat systemic aspergillosis is not recommended.[6] Advances in drug delivery systems have overcome some of the solubility issues that prevent oral bioavailability by improving drug stability in the GI tract environment, providing opportunities for targeting specific sites in the GI tract, increasing drug solubility and bioavailability, and providing sustained release in the GI tract. However, unknown in birds, poly(ethylene glycol)ylated PLGA NPs formulation of amphotericin B increased the oral bioavailability of amphotericin B from 1.5% to 10.5% when compared with the commercially available amphotericin B deoxycholate in rats by increasing amphotericin B solubility.[62] Similar to amphotericin, oral administration of nystatin was shown to be effective in the treatment of *M ornithogaster*.[2] A flock of budgerigars was successfully treated with nystatin at 3,500,000 IU/L drinking water for 2 days, followed by 2,000,000 IU/L for 28 days.[63]

Terbinafine hydrochloride, an allylamine, can be given orally or topically. The administration of terbinafine hydrochloride (15 mg/kg, once a day) for 2 days in a multiple-dose PK trial in African penguins provided plasma levels approaching the MIC of 1000 ng/mL against *Aspergillus fumigatus* (**Table 3**).[64] Based on these PK parameters of terbinafine, steady-state trough levels in African penguins are predicted to occur in 2 weeks at 1200 ng/mL, using 15 mg/kg BW once a day.[64] Unfortunately, no PK parameters could be calculated after multiple oral administration of terbinafine in red-tailed hawks (50–120 mg/kg BW; see **Table 3**), because most of the birds regurgitated within a few hours after administration.[25] As a result, additional multiple dose and clinical trials are needed to demonstrate the actual efficacy and safety of long-term treatment with terbinafine against aspergillosis in birds.

Table 3
PK characteristics of terbinafine hydrochloride after single bolus and multiples doses administration in different bird species

	Animal Species	BW (g)	Dosage Terbinafine Hydrochloride (mg/kg BW)	Frequency of Administration	Feed	C_{min} (ng/mL)	T_{max} (h)	C_{max} (ng/mL)	V_d /F (mL/kg)	$T_{1/2}$ (h)	Cl/F (mL/h·kg)	C_{lung} (ng/g)	C_{liver} (ng/g)	Reference
PK oral bolus	African penguins	2700–3300	3	Single	Yes	—	2.70	100	37,000	—	867[a]	—	—	Bechert et al,[64] 2010
			7	Single	Yes	—	1.60	200	37,000	—	633[a]	—	—	
			15	Single	Yes	—	2.40	200	68,000	—	933[a]	—	—	
	Red-tailed hawks	1070–1670	15	Single	No	—	5.40	300	72,000	15.00	2300	—	—	Bechert et al,[25] 2010
			30	Single	No	—	3.40	1200	50,100	18.20	1400	—	—	
			60	Single	No	—	5.10	2000	45,500	13.30	1400	—	—	
	Hispaniolan Amazon parrot	274–329	60	Single	Yes	—	6.40	353	—	8.71	—	—	—	Evans et al,[81] 2013
Multiple doses PK	African penguins	2700–3300	15	SID, 4 d	Yes	400	0.80	2100	—	16.00	500	—	—	Bechert et al,[64] 2010
	Red-tailed hawks	1070–1670	120	SID, 2 d	Yes	—	—	—	—	—	—	—	—	Bechert et al,[25] 2010
			Day 1: 60; d 2: 50	SID, 2 d	Yes	—	—	—	—	—	—	ND	270	

Abbreviations: BW, bodyweight; Cl/F, clearance; C_{liver}, terbinafine concentration in liver; C_{lung}, terbinafine concentration in lung; C_{max}, maximum plasma concentration; C_{min}, minimal plasma terbinafine concentration in multiple doses PK; F, absolute bioavailability; ND, not detected; PK, pharmacokinetic; SID, once a day; $T_{1/2el}$, elimination half-life; T_{max}, time point of maximum plasma concentration; Vd or Vd/F, volume of distribution.

[a] Calculated based on average bodyweight.

Topical Treatment

Inhalation is a very common technique of drug administration to patients with a variety of lung diseases in humans. The treatment of respiratory fungal infections in avian patients requires currently the use of oral or systemic agents; however, aerosolized delivery (**Fig. 1**) is an attractive option because the lag time of the action onset of the drug is short, less drug substance is needed, systemic side effects are reduced, and nebulization is achieved with only minor patient stress.[6,65] Pressurized metered dose inhalers and dry powder inhalers systems might be difficult to use in avian patients because of practical difficulties. In contrast, nebulization is frequently used in avian medicine, and administered to birds in a closed cage, induction chamber, or by means of a face mask.[43] Tell and colleagues[66] showed that, with an increasing time of exposure to aerosolized particles, the degree of particle deposition into the avian respiratory system could be enhanced, until an equilibrium is established with approximately uniform particle deposition/translocation to each of the air sacs of the respiratory system.

Nebulizers convert a liquid in solution or suspension into small droplets. Two basic types of nebulizers are frequently used, that is, the jet and the ultrasonic nebulizer. In jet nebulizers, compressed air/oxygen passes through a capillary tube, trespasses the entrained drug solution, and droplets suitable for inhalation are formed (**Fig. 2**). In an ultrasonic nebulizer, an electronic oscillator generates a high-frequency ultrasonic wave, and an aerosol is generated by the ultrahigh-frequency vibration of a piezoelectric crystal at the bottom of a liquid (**Fig. 3**).[65,67] Particles of the nebulized drug should preferably have a mass median aerodynamic diameter between 1 and 5 μm, to reach the lower respiratory tract, which is needed in case of aspergillosis.[42,65] The newer generation vibrating mesh nebulizers use electricity to vibrate a piezo element that moves liquid formations through a fine mesh to generate aerosol.[67] Mesh nebulizers generate aerosols either passively with a transducer horn vibrating ultrasonically against a static mesh or actively with a mesh mounted in an ultrasonically vibrating piezo ring. These nebulizers have several distinct advantages over jet or ultrasonic

Fig. 1. Aerosol therapy in a cockatiel via a jet nebulizer. Nebulization is a drug delivery method used to administer medication in the form of a mist (*insert*) inhaled into the respiratory tract.

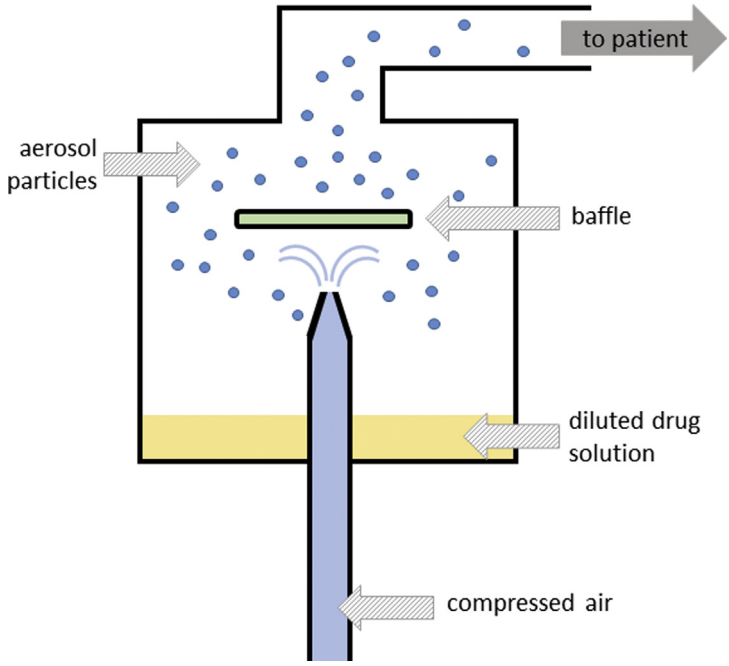

Fig. 2. Jet nebulizer working scheme. Compressed air/oxygen passes through a capillary tube, trespasses the entrained drug solution, and droplets suitable for inhalation are formed.

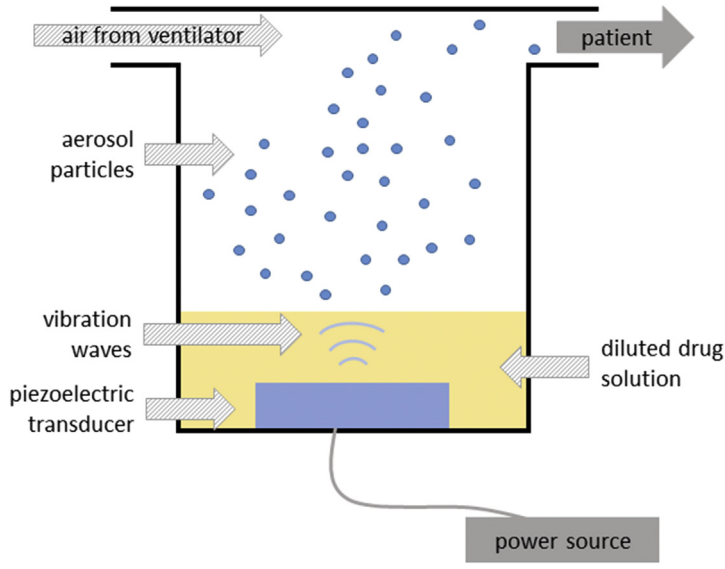

Fig. 3. Ultrasonic nebulizer working scheme. An electronic oscillator generates a high-frequency ultrasonic wave, and an aerosol is generated by the ultrahigh- frequency vibration of a piezoelectric crystal at the bottom of a liquid.

devices, such as having a higher respiratory tract deposition, negligible residual volumes, minimizing drug loss to evaporation, a fast rate of nebulization, and the possibility to nebulize a wider variability of drug compounds.[68] Additionally, liposomes can be delivered using a mesh and jet nebulizer, whereas an ultrasonic nebulizer is less suitable for delivering these particles, because they only deposit a very small proportion of phospholipids in the lower respiratory tract.[67,69]

Currently, there are no antifungal drugs on the market that have been developed specifically to administer by nebulization. Consequently, in different avian studies and clinical cases, birds are nebulized with the off-label use with antifungal drug formulations that were developed for IV or oral administration. Nebulization of a Hispaniolan Amazon parrot with terbinafine (crushed 250 mg terbinafine HCl tablet, Camber Pharmaceuticals Inc, Piscataway, NJ; and raw terbinafine HCl powder) dissolved in sterile water (1 mg/mL) for 15 minutes resulted in therapeutic plasma concentrations (above MIC of *A fumigatus* and *A fluvus*) for 0.5 to 4.0 hours after administration.[70] However, because the lung levels were not assessed in this study, clinical efficacy of this protocol in cases of avian aspergillosis still needs to be elucidated.

After 15 minutes of nebulization of a commercially available IV formulation of voriconazole (Vfend, Pfizer Global Pharmaceuticals, Ixelles, Belgium) dissolved in 0.9% NaCl (10 mg/mL) with a jet nebulizer in pigeons, only low plasma and lung concentrations (below the MIC of 0.5 mg/L) could be achieved for less than 1 hour.[19] In contrast, high and clinically relevant lung and plasma levels were found in mice after nebulization with an aqueous solution of the IV voriconazole formulation (Vfend, 6.25 mg voriconazole/mL in sterile water for injection, for 20 minutes) with an active mesh nebulizer.[71] In this study, the commercially available IV formulation was adjusted to ensure that the osmolality (293.2 mOsm/kg) and pH (6.4–6.8) were within the physiologically acceptable ranges for pulmonary delivery by adding sulfobutylether-β-cyclodextrin up to a concentration of 100 mg/mL.[71,72] The addition of this substance helps to increase the water solubility of voriconazole in the commercial IV formulation via complexation with sulfobutylether-β-cyclodextrin.[73] Inhaled voriconazole significantly improved the severity and survival of invasive pulmonary aspergillosis in mice compared with control and treatment with intraperitoneal amphotericin B.[72] Therefore, the impact of adding extra sulfobutylether-β-cyclodextrin to the commercially available IV voriconazole formulation, and the use of a mesh nebulizer instead of a jet nebulizer, on the PK/pharmacodynamic aspects of voriconazole aerosol therapy in birds needs to be investigated.

In contrast with the older antifungal drug formulations, promising results are observed when nebulizing antifungal NPs. A single intratracheal aerosol administration of liposomal amphotericin B (AmBisome; 3 mg/kg BW) with a jet nebulizer in mallard ducks resulted in drug concentrations above the MIC (1 μg/mL) in lung tissue for up to 9 days after administration. However, the drug distribution was uneven, with the majority of the drug concentrated in 1 lung lobe.[33] Nebulized liposomal amphotericin B showed an improved survival rate of rats with pulmonary aspergillosis compared with animals treated with amphotericin deoxycholate IV.[74] Similarly, once daily nebulization with a 10% itraconazole NP suspension for 30 minutes was capable of alleviating an acute *A fumigatus* infection in quails.[75] High lung itraconazole concentrations, well above the MIC for *A fumigatus*, were achieved after a single-dose inhalation of itraconazole NP suspension (1% and 10% dissolved in distilled water with addition of a 1.4% polysorbate 80 solution) to Japanese quails via a jet nebulizer for 30 minutes. Drug clearance from the lungs was slow, with a $T_{1/2el}$ of 19.7 and 35.8 hours after inhalation of 1% and 10% suspension, respectively. Even after 5-day repeated

administration, no adverse clinical reactions were observed. Moreover, serum concentrations were low (only 0.1% of the lung tissue concentration).[76]

In rare cases of fungal dermatologic infections in birds, the topical application of miconazole, enilconazole, or clotrimazole might be used, whether or not combined with systemic treatment.[3,77] Oral candidiasis, which is most often seen in lorikeets and associated with vitamin A deficiency, responds well to therapy with topical nystatin, ketoconazole, fluconazole, miconazole, or itraconazole.[78,79] Furthermore, wound aspergillosis was successfully treated in a goliath heron (*A goliath*) with topical liposomal amphotericin B, after well-established therapies with surgical debridement followed by topical povidone-iodine in conjunction with oral itraconazole, and also topical miconazole, failed.[34]

In conclusion, because the conventional treatment options have limitations such as restricted efficacy, limited biodistribution, and toxicity, the use of newer antifungal drug delivery methods should be considered by clinicians to overcome these limitations and drawbacks in cases of treatment failure and toxicity.

SUMMARY

This review article aimed to provide insight into the interrelation of antifungal drug formulation, administration route, therapeutic–toxic range, and treatment outcome in fungal diseases, focusing in particular on aspergillosis in birds. The major antifungal agents used in avian medicine are azole derivatives, polyenes, and allylamines, which all owe their antifungal activities to inhibition of synthesis, or direct interaction with ergosterol. Antifungal pharmacokinetics in birds are characterized by a large interspecies and even interindividual variability. Consequently, conventional antifungal therapies in avian medicine are frequently associated with a lack of efficacy and high toxicity. Innovative drug formulations such as NPs can help to reduce the intrinsic toxicity and enhance efficacy of antifungal agents in birds. Because the majority of systemic fungal infections require long-term therapy, oral administration of antifungal drugs is preferred, with IV administration being reserved for the initial phase of treatment in cases of acute aspergillosis or severely debilitated birds. Finally, topical administration of antifungals through nebulization shows promising results in birds; however, because drug formulations and type of nebulizer are found to highly influence the therapeutic output, clinicians are recommended to take these factors into account when considering to use this administration route in their patients.

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