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Treatment of Histoplasmosis in Dogs and Cats

Summary

1. Generic FDA approved itraconazole capsules or Itrafungol® solution is the treatment of choice.
2. Itraconazole dose is 5 mg/kg BID for 3 days then 5 mg/kg/day for dogs. 10 mg/kg/day (capsule) and 7.5 mg/kg/day (solution) is recommended for cats.
3. Itraconazole capsules should be administered with food and the solution can be given with or without food.
4. Serum should be obtained for trough (just before dosage) itraconazole blood levels 2 weeks after starting treatment in dogs and 3 weeks after starting treatment in cats.
5. Itraconazole dosage should be adjusted to achieve trough levels of 2-7 mcg/mL.
6. Treatment could be stopped if (a) at least 6 months treatment, (b) clinical findings resolved, (c) imaging abnormalities resolved, (d) urine antigen levels are negative (or serum if they are higher than urine).
7. If criteria for stopping treatment are not met, continue treatment for another 3 months and reassess criteria for stopping treatment.
8. Antigen levels in urine (or serum if they are higher than urine) should be tested at 6 and 12 months after stopping or if suspect relapse.
9. Hepatic enzymes and bilirubin should be measured at baseline, periodically during treatment and if hepatotoxicity is suspected.
10. Obtain consultation if these criteria have not been met by 12 months or you have other questions.

Introduction

A retrospective study in dogs reported that 71% responded to itraconazole and 17% relapsed [1]. Combining data from 3 retrospective studies in cats, 68/79 (86%) of those treated with itraconazole survived to hospital discharge [2-4]. Since histoplasmosis is often chronic and requires long term treatment, longer term survival is arguably more important and in one study, 6-month survival with itraconazole was 35/53 (66%) [4]. Relapse rates were reported in 3 studies and occurred in 8/36 (22%) of cats receiving itraconazole [2,3,5]. Retrospective design, small sample size and inclusion of cases spanning over several years were serious limitations of these studies. These limitations preclude determination of the best treatment based on veterinary studies.

Prospective studies in humans with AIDS found itraconazole to be more effective than fluconazole **(Table 1)** [6,7]. 85% of patients responded to itraconazole and none relapsed with at least one year of follow-up. Of the 9 nonresponders,

only 5 (8%) were attributed to progressive histoplasmosis. 74% of patients treated with fluconazole responded, of which 30% relapsed when the dosage was reduced from 800 mg daily during the first 12 weeks to 400 mg daily as maintenance therapy [7]. One-year relapse rate was estimated to be 53%. Fluconazole and itraconazole susceptibility were assessed in *Histoplasma* isolates from patients who failed fluconazole[8]: Resistance developed to fluconazole in 59% of failure isolates and to itraconazole in none.

Treatment

FDA approved itraconazole is recommended for treatment of histoplasmosis in dogs and cats and humans [9,10]. Generic FDA approved itraconazole capsules are less expensive than Sporanox® capsules and achieves similar concentrations in the blood. FDA approved itraconazole solution, Itrafungol®, labelled for dermatophytosis in cats is considered equivalent to Sporanox® solution. Compounded itraconazole powder should not be used as blood levels are undetectable or very low [9,11-13]. Guidance for use of itraconazole for treatment of dogs and cats with histoplasmosis is reviewed below.

Life-Threatening Illness. Euthanasia may be avoided by an aggressive approach to life-threatening illness **(Table 1)**. Lipid or liposomal encapsulated amphotericin B (Abelcet® or Ambisome® is recommended at a dosage of 1.0 mg/kg (dog) or 0.5 mg/kg (cat) three times weekly (or every other day) by intravenous infusion over 4-6 hours for cumulative doses up to 12 mg/kg (cat) or 24 mg/kg (dog) [14,15]. Renal function, electrolytes, and potassium levels should be monitored during treatment. Respiratory failure is the cause of death in most cases and supplemental oxygen is appropriate. Reasons that amphotericin B is more effective than itraconazole include immediate achievement of therapeutic blood levels and its fungicidal mode of action: Itraconazole requires up to a week to reach therapeutic levels and is fungistatic.

Anti-inflammatory treatment with low doses of corticosteroids may be helpful in reducing systemic side effects of amphotericin B (fever, chills, lethargy) and clinical worsening attributed to inflammatory reaction to antigens released from “dying” *Histoplasma* organisms.

Treatment Ocular Disease. While itraconazole is the most effective treatment for histoplasmosis, some veterinary ophthalmologists prefer fluconazole because of higher penetration into ocular tissue and fluid [16]. Itraconazole penetrates aqueous fluid, vitreous fluid and cornea poorly but was effective in cats with ocular histoplasmosis [3,16,17]. Clinical experience suggests that some dogs and cats with ocular histoplasmosis will respond to itraconazole after incomplete response to fluconazole, suggesting that the lower itraconazole concentrations in the eye are offset by the inherent higher sensitivity of *Histoplasma* to itraconazole. Studies are needed to determine the best treatment of ocular histoplasmosis in dogs and cats.

Treatment CNS Disease. There is a paucity of information regarding the treatment of CNS histoplasmosis in veterinary patients. In cats, CNS involvement was found in 3% of histoplasmosis cases and was a negative prognostic indicator for survival at 1 and 6 months after diagnosis [4]. In dogs, CNS involvement was found in 4% of histoplasmosis cases and none of the dogs survived long term (>6 months) [1]. In humans, a lipid formulation of amphotericin B followed by step down therapy with itraconazole is recommended [10]. Itraconazole penetrates CSF poorly but achieves good concentration in brain tissue [16]. Concern has been raised that itraconazole may not be effective because of poor CSF penetration, however CSF penetration may not be important. Itraconazole was equally as effective as amphotericin B and more effective than fluconazole, which penetrates CSF well, in an experimental model of *Histoplasma* meningitis [18]. Itraconazole and fluconazole were equally effective in a rabbit model of *Coccidioides* meningitis, and itraconazole was effective for salvage

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treatment in patients who failed standard therapy for *Coccidioides* meningitis [19,20].

Combined Treatment with Terbinafine. Some veterinarians recommend terbinafine in combination with other antifungal agents in dogs or cats failing treatment. *In vitro* activity has been demonstrated with MICs below 0.39 µg/ml in 90% of strains [21]. Pharmacokinetic studies in dogs demonstrate that blood levels exceed MICs of *Blastomyces dermatitidis*, *Histoplasma capsulatum* and *Coccidioides immitis* [22]. Moreover, *in vivo* animal studies suggest terbinafine may be effective in treating histoplasmosis [23].

Role of anti-inflammatory treatment. A retrospective study showed that cats that received corticosteroids were significantly less likely to survive to hospital discharge or 1 month after diagnosis [4]. This study was likely confounded by the fact that corticosteroids were likely used in cats with more severe respiratory disease, which was also shown to be a negative prognostic indicator. Corticosteroids, mostly in conjunction with antifungals, were effective at resolving tracheobronchial lymphadenopathy in dogs with probable histoplasmosis [24]. Studies in humans with acute respiratory distress syndrome (ARDS) of any cause showed no benefit from use of corticosteroids [25]. The clinical use of anti-inflammatory treatment (low dose corticosteroid) to reduce fever, malaise, and lethargy, potentially hastening clinical improvement, is common in veterinary medicine, but there are no studies to establish benefit. Further research regarding the use of corticosteroids in dogs and cats with histoplasmosis are needed.

Formulation. Generic FDA approved itraconazole, compounded FDA approved itraconazole capsules (see below), and brand name Sporanox® capsules contain “pelletized” drug coated onto spheres and polyethylene glycol, which improves absorption. Itraconazole capsules should be administered with food for better absorption (see Sporanox® capsule package insert). Sporanox® and Itrafungol® oral solutions contain cyclodextrin which improves bioavailability. Blood levels of itraconazole are similar with FDA approved brand name Sporanox® and generic FDA approved itraconazole [11-13]. Compounded itraconazole powder should not be used as blood levels are undetectable or very low [11-13].

Dosage. Itraconazole should be administered at 5 mg/kg twice daily for 3 days and then 5 mg/kg once daily in dogs. In cats receiving capsules, 5 mg/kg twice daily or 10 mg/kg once daily is appropriate, while a lower starting dose with the solution (7.5 mg/kg/day) should be considered [9,13]. Itraconazole blood levels should be measured after 2 weeks in dogs and 3 weeks in cats to verify that blood levels are in the therapeutic range (2-7 mcg/mL). Dosage may need to be increased in puppies or kittens that gain weight during treatment: consider repeating blood levels at 1-2 months intervals until weight stabilizes. Dose also may need to be increased in animals that lost considerable weight before itraconazole was started.

Small dogs and cats pose challenges for use of 100 mg capsules. Alternatives include Itrafungol® or Sporanox® solution (more expensive than generic itraconazole) and compounded pelletized itraconazole capsules. At least two veterinary pharmacies provide that service: (http://www.pethealthpharmacy.com (623-214-2791); https://petapothecary.com/ (414-247-8633). Alternatively, some veterinarians prescribe 100 mg generic FDA approved capsules and instruct the pet owners to empty the capsules onto a hard surface and divide the pellets into roughly equal size piles in dosages appropriate for the weight of the dog. They instruct the owners to coat the pellets onto peanut butter for administration. Finally, findings of a pharmacokinetic study support the use of 100 mg itraconazole capsules once every other day in cats [26].

Therapeutic drug level monitoring. It’s important to obtain serum for trough (just before next dose) itraconazole blood level at the end of 2 weeks in dogs and 3 weeks in cats to verify that concentrations are between 2-7 mcg/mL. A dosage change is recommended if concentrations are outside that range. Blood levels should be determined again following a dosage

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change to verify levels between 2-7 mcg/mL. Itraconazole blood level testing, measured by bioassay, is offered at MiraVista Diagnostics.

Duration. At least 6 months of itraconazole is recommended in humans and dogs and cats.[9,10] Many cases require a year or more of treatment, especially those with bone/joint, ocular, or central nervous system involvement or widespread disseminated disease.[9]

Toxicity and Drug Interactions. Toxicities are usually caused by high blood levels [27,28]. A human study reported 31% of patients with levels below 17 µg/mL experienced toxicity compared to 86% with levels above 17.1 mcg/mL. Toxicity also occurred in 20 to 40% of patients with levels between 5 and 10 µg/mL and may occur with levels between 2-7 µg/mL. Levels above 7 mcg/mL are unnecessary and dose reduction decreases toxicity and cost.

The most common toxicities observed in humans were fluid retention (21%) and gastrointestinal intolerance (21%) [28]. Central nervous system toxicity occurred in 19%. Diffuse nonpruritic maculopapular rash (7%) resolved after stopping treatment and may be caused by hypersensitivity rather than high blood levels. Hepatic toxicity with a bilirubin greater than 3 times the reference limit occurred in 2% of humans. Congestive heart failure occurred in 1%. Itraconazole also can cause hypertension and hypokalemia, although these have not been reported in dogs and cats (see Sporanox® and Itrafungol® package inserts).

Toxicities in dogs resemble those in humans. Median alanine aminotransferase (ALT) levels were higher in dogs receiving 5 mg/kg twice daily (84 IU/L) than once daily (35 IU/L). ALT and alkaline phosphatase (ALP) elevation in the absence of clinical findings of hepatotoxicity can be managed by dose reduction or discontinuation until they have resolved, after which itraconazole could be resumed at a lower dosage [29]. Ulcerative skin lesions (a sign of cutaneous vasculitis) also occurred in approximately 7% of dogs receiving 10 mg/kg/d. Itraconazole is a negative inotrope and should be used with caution in dogs and cats with significant heart disease.

Most toxicities resolve within a week or two after stopping or reducing the dose of itraconazole. Drug levels should be rechecked 2-3 weeks after resuming itraconazole to verify the level is therapeutic, but nontoxic. Itraconazole can be resumed at a lower dose in dogs or cats with clinical evidence of hepatotoxicity once clinical findings have resolved and ALT and ALP levels declined [29,30]. ALT, ALP, bilirubin, and itraconazole blood levels should be monitored closely if itraconazole is resumed.

Itraconazole inhibits cytochrome P450 3A4 isoenzymes and may increase blood levels of drugs cleared by that mechanism. Serious drug interactions, including death, may occur when itraconazole is used with certain drugs that are cleared by CYP450 3A4. Drugs that might be affected include amitriptyline, amlodipine, benzodiazepines, cisapride, corticosteroids, cyclosporine, ivermectin, and macrolides, to name a few.

Inducers of CYP3A4, such as phenobarbital, accelerate metabolism of itraconazole and may cause treatment failure because of subtherapeutic blood levels. Drugs that decrease gastric acid secretion reduce itraconazole blood levels.

Antigen monitoring. Studies in cats showed that antigen elimination was a marker for disease remission during treatment [5]. The sensitivity was 90% and specificity was 65% for elimination of antigen from urine and 90% and 52% for

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elimination from serum. Antigen was negative in all cases at 6 months. Monitoring also assisted in diagnosis of relapse, showing increases in antigen concentration compared to prior results.

Antigen should be tested in urine at 3-month intervals during treatment, at 6 and 12 months after stopping treatment, and any time the clinical findings suggest recurrence. And if the urine antigen is “Above Limit of Quantification, ALQ” serum should be used for treatment monitoring instead. When the serum antigen is negative (or low level, <2 ng/mL) resume monitoring urine antigen until negative. Consultation should be obtained for questions about discontinuation of treatment and if antigen remains positive more than 12 months.

Failure of the antigen concentration to decline also raises concern about the effectiveness of treatment, which may be caused by inadequate itraconazole blood levels or development of resistance to fluconazole. If itraconazole levels are subtherapeutic, the dosage should be increased, and blood levels should be rechecked 14-21 days later. Increase in antigen concentration after stopping treatment suggests relapse. An example of antigen clearance in urine and serum is presented in Figure 1.

Alternatives to itraconazole. Fluconazole is not recommended as a first-line treatment because its activity against *Histoplasma* is low. **(Figure 2 and Table 2)**. The fluconazole MICs, illustrated in Figure 2, are especially noteworthy as a recent population-based fluconazole PK study showed mean maximal blood concentrations of 26.8 and 32.1 µg/ml for dogs and cats, respectively. Collectively these data suggest that some *Histoplasma* isolates infecting dogs and cats have inherent fluconazole resistance. Acquired resistance also has been described in

Figure 1. Example of serum and urine antigen clearance in a dog with histoplasmosis treated successfully.

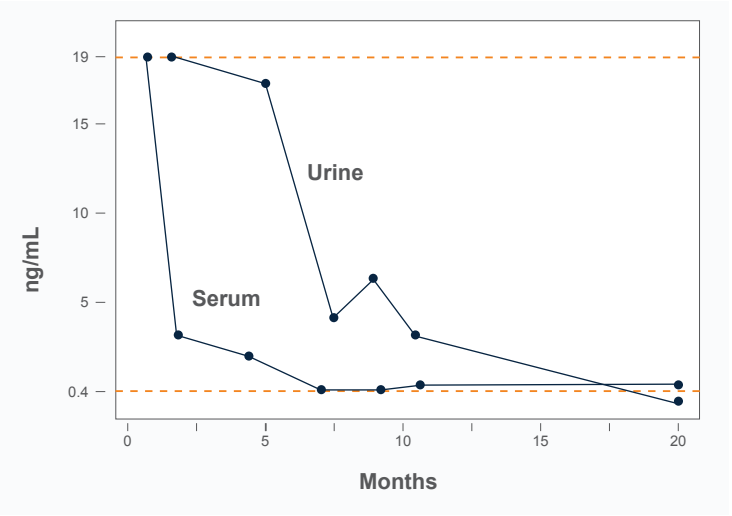
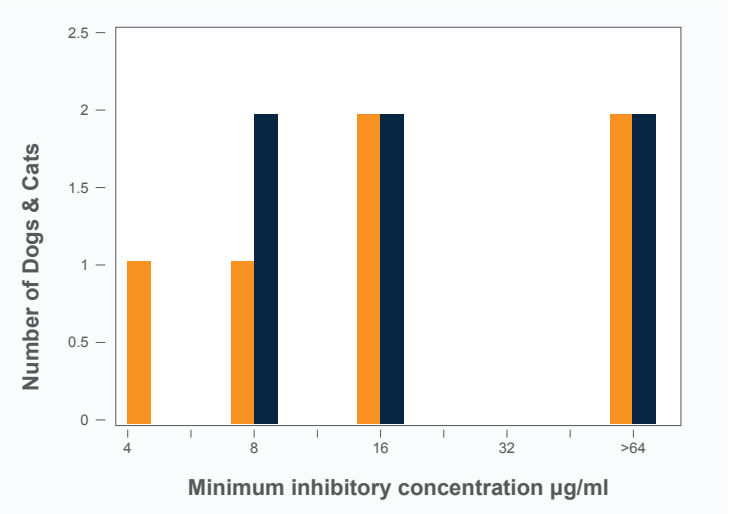


Figure 2. Fluconazole sensitivity in 12 consecutive *Histoplasma* isolates from dogs (blue) and cats (orange) with histoplasmosis.



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a cat with histoplasmosis that failed fluconazole treatment [31]. Lower inherent sensitivity notwithstanding, in situations where itraconazole is not tolerated, or is cost prohibitive, fluconazole could be considered. Appropriate dose (20 mg/kg/day), treatment duration (see below) and use of FDA approved drug are important for maximizing chance of treatment success. MICs to voriconazole are higher than to itraconazole and *Histoplasma* also may develop resistance to voriconazole [32]. *Histoplasma* is highly susceptible to posaconazole (median MIC <0.007 mcg/mL) and isavuconazole (median MIC <0.007 mcg/mL) and resistance has not been reported to these triazoles [33,34].

Posaconazole was more effective than itraconazole in murine models of histoplasmosis and case reports describe successful treatment in patients who failed or could not take other antifungal agents [33,35-38]. Posaconazole may be the best alternative based on MICs and limited clinical experience and isavuconazole should also be effective [39]. Newer triazoles are more expensive than itraconazole.

In small studies posaconazole, voriconazole and isavuconazole have been used successfully in humans [36,39,40]. The voriconazole study evaluated patients who discontinued other treatments because of intolerance or toxicity (8 patients) or increasing urinary antigen (1 patient): 3 patients improved and 6 remained stable [40]. Resistance to voriconazole has been observed in isolates from AIDS patients with histoplasmosis that failed treatment with fluconazole [32,40].

Cost for itraconazole treatment. Prices for FDA approved itraconazole are presented in **Table 3** but should be verified for your location (GoodRx.com).

When to Stop Treatment. Treat for at least 6 months and until the (1) clinical findings have resolved, (2) radiographic findings have resolved or improved significantly and are thought to represent residual scarring, and (3) the antigen is negative. At 6 months if these criteria have not been met, continue treatment for another 3 months and reevaluate to determine if criteria for stopping have been met, and if not continue treatment at 3-month intervals until they have been met.

Table 1. Treatment recommendations

Category	Daily dose	Duration
Mild-Moderate	Itraconazole 5 mg/kg BID for 3 days then SID (dog) Itraconazole 5 mg/kg BID or 10 mg/kg SID (capsule cat) Itraconazole 3.8 mg/kg BID or 7.5 mg/kg SID (solution cat)	6-12 months
Severe disease*	Amphotericin B 0.5 mg/kg (cat) or 1.0 mg/kg (dog) IV 3 times a week or EOD	Up to 24 mg/kg (dog) or 12 mg/kg (cat) cumulative dose
	Itraconazole as above	6-12 months

* Anti-inflammatory doses of corticosteroids may reduce amphotericin B toxicity and inflammatory response to antigens released from dying *Histoplasma* yeast.

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Table 2. MICs (µg/mL) to Triazoles

Itra	Flu	Vori	Posa	Isavu	References
≤ 0.019*	*1.0**	*0.015**	≤0.007*	*≤0.007**	32,38,40,41
	Italics = median or geometric mean MIC, others are MIC[90]; *MiraVista Diagnostics				

Table 3. Cost for one month of treatment for 20 kg dog or 5kg cat (GoodRx.com)

	20 kg dog	20 kg dog	5 kg cat	20 kg dog	5 kg cat	5 kg cat	5 kg cat
Medication	Generic Itraconazole tablet 100 mg	Sporanox® capsule 100 mg	Sporanox®, solution 10 mg/ml	Generic Fluconazole tablet 200 mg	Generic Fluconazole solution 40 mg/ml	Itrafungol®, solution 10 mg/ml	Compounded Itraconazole 25 mg
Costco	$39.36	$841.30	$260.01	$66.88	$45.41		
CVS	$89.84	$891.54	$275.87	$142.02	$77.78		
Walmart	$53.13	$889.84	$274.59	$82.46	$60.97		
Chewy	Pricing unique to Chewy or veterinary compounding pharmacies					$114.72	
Compounding Pharmacy							$72.00 - $260.00
Dose	5 mg/kg/d	5 mg/kg/d	7.5 mg/kg/d	20 mg/kg/d	20 mg/kg/d	7.5 mg/kg/d	10 mg/kg/d
Lowest cost*	$39.36 Costco	$841.30 Costco	$260.01 Costco	$66.88 Costco	$45.41 Costco	$152.97 Chewy	$72.00 compounding pharmacy

** Pricing data provided by https://www.goodrx.com/. Input your location for accurate local pricing which may vary regionally and pricing changes frequently.

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