



## CLINICAL TREATMENT & MONITORING

### When to Stop Antifungal Medication(s)

Invasive fungal infections (IFI) can be challenging to diagnose. In some cases, however, the biggest challenge is treatment. More specifically, how to monitor treatment and when to discontinue antifungal drug(s) is most difficult. Biomarkers (fungal antigens and antibodies) are useful for treatment monitoring. MVD recommends a multi-modal approach to treatment monitoring that includes clinical signs, physical examination, imaging studies and repeat biomarker testing. Below is a table for each common IFI – systemic aspergillosis, blastomycosis, coccidioidomycosis (Valley Fever), cryptococcosis, and histoplasmosis (Tables 4-8). In addition, a common fungal-like oomycosis, pythiosis, is included. Beforehand, there is a brief review of treatment recommendations (Tables 1 & 2) and diagnostic performance of common fungal biomarker tests (Table 3). It is important to check itraconazole blood levels (MVista Itra Bioassay, test code 312) after 3 weeks of treatment ideally within 4-hours of the next dose (near-trough level).

**Table 1.** Recommended antifungal drug(s) for select invasive fungal infections in cats and dogs.

Disease	Mild-Moderate (outpatient)	Life-threatening (hospitalized)	Salvage (failed initial therapy)
<b>Aspergillosis</b> (other molds)*	Posa + Terb OR Vori + Terb	Amp-b + Terb	Amp-b + Azole +/- Echinocandin
<b>Blastomycosis</b>	Itra > Flu	Amp-b	Posa > Vori
<b>Coccidioidomycosis</b> (Valley Fever)	Itra = Flu	Amp-b	Posa = Vori
<b>Cryptococcosis</b>	Flu > Itra	Amp-b	Posa = Vori
<b>Histoplasmosis</b>	Itra > Flu	Amp-b	Posa > Vori
<b>Pythiosis</b> (GI form)	Itra + Terb + Pred	NA	NA

Itra, itraconazole; Flu, fluconazole; Posa, posaconazole; Vori, voriconazole; Amp-b, lipid or liposomal encapsulated amphotericin b; Terb, terbinafine; Pred, prednisone or prednisolone.

\*Antifungal sensitivity of invasive molds varies and culture and sensitivity testing is recommended.



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**Table 2.** Recommended dosage of select antifungal drugs in cats and dogs.

Drug	Host	Formulation	Dose	Route
Itraconazole*	Dog	Capsule or Solution	5 mg/kg/day	PO
	Cat	Capsule	10 mg/kg/day	
		Solution	4 mg/kg/day	
Fluconazole	Dog	Tablet or Solution	20 mg/kg/day	PO
	Cat	Tablet or Solution	20 mg/kg/day	
Posaconazole	Dog	Tablet ER	5 mg/kg EOD	PO
		Solution	5 mg/kg BID	
	Cat	Solution	15 mg/kg once then 7.5 mg/kg/day	
Voriconazole	Dog	Tablet or Solution	5 mg/kg BID	PO
	Cat	Solution	12.5 mg (total dose) q 72 h	
Terbinafine	Dog	Tablet	30 mg/kg/day	PO
	Cat	Tablet	125 mg (total dose) / day	
Amphotericin B (lipid or liposomal)	Dog	Solution	1-2 mg/kg EOD (cumulative 24 mg/kg)	IV
	Cat	Solution	0.5-1 mg/kg EOD (cumulative 12 mg/kg)	
Caspofungin	Dog	Solution	1 mg/kg/day	IV
	Cat	Solution	1 mg/kg once then 0.75 mg/kg/day	
Micafungin	Dog	Solution	2 mg/kg/day	IV
	Cat	Solution	NA	
Prednisolone#	Dog	Tablet	1 mg/kg BID x 1 week, then 1 mg/kg SID x 1 month, then 0.5 mg/kg SID x 1 month pending clinical response	PO

ER, extended release.

\*Starting dose only. Individualized dose should be determined based on itraconazole blood levels.

#As part of the treatment of GI pythiosis in dogs. Prednisone is also sufficient.



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**Table 3.** Diagnostic performance of common fungal biomarkers to establish diagnosis of mycosis or oomycosis in cats and dogs.

Pathogen	Test	Host	Sample	Sensitivity	Specificity	Ref
<i>Blastomyces</i>	GM Antigen EIA	<b>K9</b>	<b>Urine</b>	<b>93</b>	<b>98</b>	2-5
		K9	Serum	91	100	3,4,6
		<b>Feline</b>	<b>Urine</b>	<b>100</b>	<b>NA</b>	7,8
	IgG Antibody EIA	K9	Serum	82	97	3,4
		Antibody ID	K9	Serum	54	100
<i>Histoplasma</i>	GM Antigen EIA	<b>K9</b>	<b>Urine</b>	<b>92</b>	<b>99</b>	11,12
		<b>Feline</b>	<b>Urine</b>	<b>94</b>	<b>98</b>	13,14
		Feline	Serum	73	NA	15
	IgG Antibody EIA	K9	Serum	76	93	MVD
		Feline	Serum	83	95	MVD
	Antibody ID	K9	Serum	14	100	MVD
		Feline	Serum	0	100	MVD
<i>Coccidioides</i> (Valley Fever)	GM Antigen EIA	K9	Urine	8	100	16,17
		K9	Serum	27	97	16,17
	IgG Antibody EIA	<b>K9</b>	<b>Serum</b>	<b>89</b>	<b>94</b>	16
		K9	Serum	87	92	16,18,19
		<b>Feline</b>	<b>Serum</b>	<b>99</b>	<b>NA</b>	20,21
<i>Cryptococcus</i>	GXM Antigen LA	<b>K9</b>	<b>Serum</b>	<b>91</b>	<b>100</b>	22-24
		<b>Feline</b>	<b>Serum</b>	<b>98</b>	<b>NA</b>	22,24,25
<i>Aspergillus</i> (systemic)	GM Antigen EIA	K9	Urine	88	92	26
		<b>K9</b>	<b>Serum</b>	<b>92</b>	<b>84</b>	26
<i>Aspergillus</i> (sinonasal)	GM Antigen EIA	K9	Serum	24	82	27
		Feline	Serum	23	78	28
	Antibody ID	<b>K9</b>	<b>Serum</b>	<b>77</b>	<b>100</b>	27
		<b>Feline</b>	<b>Serum</b>	<b>43</b>	<b>100</b>	29
<i>Pythium</i>	IgG Antibody EIA	<b>K9</b>	<b>Serum</b>	<b>99</b>	<b>98</b>	MVD
		<b>Feline</b>	<b>Serum</b>	<b>99</b>	<b>98</b>	MVD

**Bolded** biomarker tests are the primary test used for diagnosis and treatment monitoring. The one exception is antibody ID for sinonasal aspergillosis which is only used for diagnosis.

NA, not available; EIA, enzyme immunoassay; ID, immunodiffusion; GM, galactomannan; GXM, glucuronoxylomannan.

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**Table 4. Systemic aspergillosis treatment monitoring.** All of the following should be met before discontinuing treatment.

Monitoring Tool	Criteria	Notes
Minimum Treatment Duration	Minimum 12-month duration	<ul style="list-style-type: none"> <li>Required duration is often longer, or even indefinite.</li> </ul>
History	≥1-month past resolution of clinical signs	<ul style="list-style-type: none"> <li>Skin lesions, lymphadenopathy, bone pain, lameness, ocular lesions, CNS deficits, etc.</li> </ul>
Physical Examination	≥1-month past resolution of physical exam abnormalities	<ul style="list-style-type: none"> <li>Same as above</li> </ul>
Imaging Studies	≥1-month past resolution of imaging abnormalities	<ul style="list-style-type: none"> <li>Bone, spine, or chest radiographs; abdominal ultrasound</li> </ul>
Aspergillus GM Antigen EIA (test code 309)	≥1-month past negative GM antigen.	<ul style="list-style-type: none"> <li>Use whichever sample type was positive at baseline. If both were positive, use serum to monitor.</li> <li>Submit GM antigen EIA at diagnosis, then every 3 months during treatment. After treatment GM EIA should be done at 6 months then every 12 months.</li> </ul>

GM, galactomannan; EIA, enzyme immunoassay

**Table 5. Blastomycosis treatment monitoring.** All of the following should be met before discontinuing treatment.

Monitoring Tool	Criteria	Notes
Minimum Treatment Duration	Minimum of 6 months	<ul style="list-style-type: none"> <li>Required duration is often much longer.</li> </ul>
History	≥1-month past resolution of clinical signs	<ul style="list-style-type: none"> <li>Mild exercise intolerance might persist, most notable in working or performance animals.</li> <li>Persistent tracheobronchial lymphadenopathy can cause cough, requiring concurrent corticosteroid treatment.</li> </ul>
Physical Examination	≥1-month past resolution of physical exam abnormalities	<ul style="list-style-type: none"> <li>Differentiating active ocular disease from permanent inactive change is important.</li> </ul>
Imaging Studies	≥1-month past resolution of imaging abnormalities	<ul style="list-style-type: none"> <li>Pulmonary scarring can be permanent and can cause static focal unstructured interstitial lung disease.</li> <li>Radiographic bone lesions should improve but might never return to normal.</li> </ul>
MVista® Blastomyces GM Antigen EIA (test code 316)	≥1-month past no detectable antigen  OR  Antigen ≤0.4 ng/ml on 2 consecutive rechecks at least 3 months apart	<ul style="list-style-type: none"> <li>Urine is the ideal sample</li> <li>Most dogs, and essentially all cats, have no detectable antigen at the time of remission.</li> <li>Submit antigen test at diagnosis, every 3 months during treatment, and at 6 months then every 12 months after treatment.</li> </ul>

GM, galactomannan; EIA, enzyme immunoassay

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**Table 6. Coccidioidomycosis (Valley Fever) treatment monitoring.** All of the following should be met before discontinuing treatment.

Monitoring Tool	Criteria	Notes
Minimum Treatment Duration	Minimum of 6 months	<ul style="list-style-type: none"> <li>Required duration is often much longer.</li> </ul>
History	≥1-month past resolution of clinical signs	<ul style="list-style-type: none"> <li>Mild exercise intolerance might persist, most notable in working or performance animals.</li> <li>Persistent tracheobronchial lymphadenopathy can cause cough, requiring concurrent corticosteroid treatment.</li> </ul>
Physical Examination	≥1-month past resolution of physical exam abnormalities	<ul style="list-style-type: none"> <li>Differentiating active ocular disease from permanent inactive change is important.</li> </ul>
Imaging Studies	≥1-month past resolution of imaging abnormalities	<ul style="list-style-type: none"> <li>Pulmonary scarring can be permanent and can cause static focal unstructured interstitial lung disease</li> <li>Radiographic bone lesions should improve but might never return to normal.</li> </ul>
MVista® Coccidioides IgG EIA (test code 329) OR Coccidioides antibody ID (test code 320)	≥1-month past no detectable antibody  OR After 12-months of treatment:  EIA <20 EU or ID ≤1:4	<ul style="list-style-type: none"> <li>Serum is the required sample</li> <li>Most animals, have negative antibody testing at time of remission</li> <li>EIA is only available for dogs</li> <li>Submit IgG EIA or ID test at diagnosis, every 3 months during treatment, and at 6 months then every 12 months after treatment.</li> </ul>

ID, immunodiffusion; EIA, enzyme immunoassay

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**Table 7. Cryptococcosis treatment monitoring.** All of the following should be met before discontinuing treatment.

Monitoring Tool	Criteria	Notes
Minimum Treatment Duration	Minimum of 6 months	<ul style="list-style-type: none"> <li>Required duration is often much longer.</li> </ul>
History	≥1-month past resolution of clinical signs	<ul style="list-style-type: none"> <li>Nasal discharge, CNS deficits, other signs case specific</li> </ul>
Physical Examination	≥1-month past resolution of physical exam abnormalities	<ul style="list-style-type: none"> <li>Differentiating active ocular disease from permanent inactive change is important.</li> </ul>
Imaging Studies	≥1-month past resolution of imaging abnormalities	<ul style="list-style-type: none"> <li>Radiographic/CT bone or nasal lesions should improve but might never return to normal.</li> <li>Imaging studies are case specific</li> </ul>
Cryptococcus GXM Antigen LA (test code 319)	≥1-month past no detectable antigen	<ul style="list-style-type: none"> <li>Serum is the required sample</li> <li>Most animals, have no detectable antigen at the time of remission.</li> <li>Submit GXM antigen LA test at diagnosis, every 3 months during treatment, and at 6 months then every 12 months after treatment.</li> </ul>

GXM, glucuronoxylomannan; LA, latex agglutination



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**Table 8. Histoplasmosis treatment monitoring.** All of the following should be met before discontinuing treatment.

Monitoring Tool	Criteria	Notes
Minimum Treatment Duration	Minimum of 6 months	<ul style="list-style-type: none"> <li>Required duration is often much longer.</li> </ul>
History	≥1-month past resolution of clinical signs	<ul style="list-style-type: none"> <li>Mild exercise intolerance might persist, most notable in working or performance animals.</li> <li>Persistent tracheobronchial lymphadenopathy can cause cough, requiring concurrent corticosteroid treatment.</li> </ul>
Physical Examination	≥1-month past resolution of physical exam abnormalities	<ul style="list-style-type: none"> <li>Differentiating active ocular disease from permanent inactive change is important.</li> </ul>
Imaging Studies	≥1-month past resolution of imaging abnormalities	<ul style="list-style-type: none"> <li>Pulmonary scarring can be permanent and can cause static focal unstructured interstitial lung disease.</li> <li>Radiographic bone lesions should improve but might never return to normal.</li> </ul>
MVista® Histoplasma GM Antigen EIA (test code 310)	<p>≥1-month past no detectable antigen</p> <p>OR</p> <p>Antigen ≤0.4 ng/ml on 2 consecutive rechecks at least 3 months apart</p>	<ul style="list-style-type: none"> <li>Urine is the ideal sample</li> <li>Most dogs, and essentially all cats, have no detectable antigen at the time of remission.</li> <li>Submit antigen test at diagnosis, every 3 months during treatment, and at 6 months then every 12 months after treatment.</li> </ul>

GM, galactomannan; EIA, enzyme immunoassay



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**Table 9. Pythiosis treatment monitoring.** All of the following should be met before discontinuing treatment in dogs and cats with pythiosis.

Monitoring Tool	Criteria	Notes
Minimum Treatment Duration	Minimum 12-month duration	<ul style="list-style-type: none"> <li>Required duration can be longer.</li> </ul>
History	≥1-month past resolution of clinical signs	<ul style="list-style-type: none"> <li>Vomiting, diarrhea, and weight loss for GI pythiosis</li> <li>Cutaneous/SQ lesions</li> </ul>
Physical Examination	≥1-month past resolution of physical exam abnormalities	<ul style="list-style-type: none"> <li>Examination of cutaneous/SQ lesions and abdominal and peripheral lymph node palpation.</li> </ul>
Imaging Studies	≥1-month past resolution of imaging abnormalities	<ul style="list-style-type: none"> <li>Abdominal US: GI masses, wall thickening, and lymphadenopathy should resolve with successful treatment.</li> </ul>
MVista® Pythium IgG EIA (test code 332)	≥1-month past negative IgG	<ul style="list-style-type: none"> <li>Serum is the required sample</li> <li>IgG levels decrease and normalize with successful treatment.</li> <li>Submit IgG test at diagnosis, monthly for 3 months, then every 3 months during treatment. After treatment IgG test should be done at 6 months then every 12 months.</li> </ul>

EIA, enzyme immunoassay





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