ARE YOU UP TO DATE ON COCCIDIOIDOMYCOIS DIAGNOSIS AND TREATMENT?

Images courtesy of Dr. Stanley Rubin, DVM, MS, Diplomate ACVIM

Increasing incidence of coccidiodomycosis and expansion north and east into new territories is documented in human medicine, but similar data is not readily available for animals. As it spreads geographically, it is important for those in non-endemic areas to recognize signs of infection. However, diagnosis of coccidiodomycosis is challenging because clinical presentation resembles other conditions, often delaying suspicion of fungal infection, diagnosis, and treatment. Early recognition and treatment improve outcomes. Read to learn more about current guidelines for coccidiodomycosis.
When will I receive my results?  

**ANSWER**

- The specimen must be received by 10:30am on the day of test set-up. Otherwise, the report will be delayed until the next available test set-up. This can affect turn-around time by up to 7 days for tests not run frequently.
- Exceptions to 10:30 cutoff:
  - Histo/Blasto/Crypto Antigen: 4:00pm for Tues-Friday
  - Crypto Antigen: 2:00pm for Sat

<table>
<thead>
<tr>
<th>Test</th>
<th>Test set up</th>
<th>Report, typically</th>
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<tbody>
<tr>
<td>Antigen (histo, blasto, crypto)</td>
<td>Mon-Sat</td>
<td>same or next day</td>
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<tr>
<td>Antigen (asper, cocci,)</td>
<td>Mon-Fri</td>
<td>same or next day</td>
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<td>Histoplasma IgG and IgM EIA (Human Only)</td>
<td>Mon, Th</td>
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<tr>
<td>Coccidioides IgG and IgM EIA (Human Only)</td>
<td>Mon, Th</td>
<td>same or next day</td>
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<tr>
<td>Histoplasma IgG EIA (Feline Only)</td>
<td>Tu, Th</td>
<td>same or next day</td>
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<tr>
<td>Histoplasma IgG EIA (Canine Only)</td>
<td>Wed, Fri</td>
<td>same or next day</td>
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<tr>
<td>Coccidioides IgG EIA (Canine Only)</td>
<td>Wed, Fri</td>
<td>same or next day</td>
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<td>Blastomyces IgG EIA (Canine Only)</td>
<td>Wed, Fri</td>
<td>same or next day</td>
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<td>Antibody ID (FID)</td>
<td>Tues</td>
<td>Friday</td>
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<td>Beta D Glucan (Fungitell)</td>
<td>Mon-Fri</td>
<td>Same or next day</td>
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<tr>
<td>Itraconazole (VET ONLY)</td>
<td>Wed</td>
<td>Thursday</td>
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How does shipping method affect time to results?  

**ANSWER**

**Shipping methods:** shipping methods affect turnaround time.

- We suggest obtaining a tracking number from your courier to ensure delivery of your shipment.
- Effect of different shipping methods.
  - Overnight: Specimen will be tested in listed turn-around times in chart
  - 2 Day shipping: Add 2 days to listed turn-around time in chart
  - Regular mail: Add 3-5 days to listed turn-around time in chart

How do I ship the specimen?  

**ANSWER**

Place the specimen and requisition in a leak-proof bag. Ship refrigerated or frozen with a cold pack in a styrofoam container inside a shipping box.

Do you accept Saturday delivery?  

**ANSWER**

Yes! The specimen must be received by 10:30am on Saturday. Ship overnight and specify for Saturday delivery.

Do you have a results portal?  

**ANSWER**

Not yet, but it’s on our to-do list for veterinary clients.

Did you know we offer therapeutic drug monitoring?  

**ANSWER**

MVista® Itraconazole by Bioassay, Test Code 312, $43.00
Coccidioidomycosis

Joe Wheat MD, Janelle Renschler DVM, PhD, Heather Largura DDS, MS

See Sykes, J.E. for more detailed information [1].

1) Background
   a. Causative agents: Dimorphic fungi *Coccidioides immitis* and *Coccidioides posadasii*.
   b. Route of infection: inhalation of spores, rarely cutaneous inoculation.
   c. At risk: large breed young adult dogs, although dogs of any breed, age, or gender affected [2, 3]. Risk factors for dogs from AZ are being housed outdoors, roaming areas more than 1 acre, and walking in the desert [4]. Coccidioidomycosis occurs less frequently in cats; a recent study demonstrated a high percentage of cats (66%) with coccidioidomycosis had indoor only lifestyle [5, 6]. Exposure to spores can occur through open doors, windows, air conditioners, or fomites that enter the residence.
   d. Endemic distribution: southwestern United States (California, Arizona, Utah, Texas, Nevada, New Mexico), Mexico, Central and South America. Endemic maps demonstrate evidence of coccidioidomycosis in new areas such as the state of Washington and Oregon [7, 8].

2) Clinical Findings in Dogs: most infections are subclinical ~70% [9, 10].
   a. Pulmonary: most common form of coccidioidomycosis, and often accompanied by disseminated findings.
      i. Signs: tachypnea, cough, dyspnea, exercise intolerance, lethargy, weight loss, anorexia [2, 10]. Cough can be associated with gagging or retching [1].
      ii. Imaging: unremarkable, most common finding is slight to extensive hilar lymphadenomegaly, sometimes with interstitial pulmonary infiltrates, nodular interstitial, interstitial-alveolar, broncho-interstitial infiltrates and/or sternal lymphadenomegaly [2].
   b. Disseminated (extrapulmonary): 25%, may be accompanied by pulmonary involvement [2, 10]
      i. General/systemic:
      ii. Cutaneous lesions:
         Signs: ulcerations with drainage, granulomas, subcutaneous abscesses, may overlie osteomyelitis [1, 3]
   iii. Peripheral Lymphadenomegaly
   iv. Ocular involvement:
         1. Signs: uveitis, keratitis, conjunctivitis, chorioretinitis, optic neuritis, retinal detachment, and endophthalmitis [2, 12, 13]
   v. Bone lesions: most common site of dissemination in dogs [1, 10]
      1. Signs: lameness, firm swellings, swollen joints, draining lesions, sinus tracts
      2. Imaging: osteolytic lesions with periosteal proliferation, can resemble osteosarcomas [3, 5]
   vi. CNS involvement:

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**Areas Endemic for Coccidioidomycosis**

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MiraVista VETERINARY DIAGNOSTICS

HEADQUARTERS
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1. Signs: Seizures are most common [10]. Additional signs are obtundation, blindness, nystagmus, absent menace reflexes, diminished gag response, ataxia, abnormal placing reactions, pacing, circling, cervical pain, tetraparesis, [2, 10, 14, 15].

2. Imaging: Plain radiography is not diagnostic for lesions of brain or spinal cord. [10]. Advanced imaging is primary means of differentiating CNS coccidioidomycosis from other neurological diseases, but definitive diagnosis cannot be made on MRI alone [10]. Half of CNS cases have meningoencephalitis [10], brain lesions, ependymitis.

3) Clinical findings in cats:
   a. Pulmonary
      i. Signs: tachypnea 25-40% [1, 6]
      ii. Imaging: bronchial, interstitial and/or alveolar pattern or consolidation of one or more lung lobes 41% [6], hilar lymphadenopathy 27% [5, 6], solitary lung masses or nodules 18% [6], and pleural effusion 24% [6].
   b. Disseminated (extrapulmonary): 60% present with disseminated infection, perhaps due to delay in seeking care or recognition of infection [6].
      i. General/Systemic: Fever present in 31-50% [1, 6], inappetence 52% [6]
      ii. Cutaneous lesions: present in 50-56%, draining skin lesions, subcutaneous granulomas, abscesses [5, 6]. Coccidioidomycosis should be considered in cats from endemic region that present with chronic dermal lesions not responsive to empirical treatment [5, 6].
      iii. Bone lesions: lameness in 20-50% [1, 6]
         1. Imaging: periosteal proliferation, osteolysis, soft tissue swelling; can resemble osteosarcoma [1, 3, 5]
      iv. Ocular involvement: 13%; conjunctival masses, peri orbital swelling, chorioretinitis, retinal detachment, endophthalmitis, anterior uveitis [12, 16].
      v. CNS involvement: hyperesthesia, posterior paresis, seizures, ataxia [1].
      vi. Other: abdominal organs such as spleen [17].

4) Laboratory abnormalities
   a. CBC: normocytic, normochromic nonregenerative anemia, mild leukocytosis from neutrophilia, monocytosis; lymphopenia.
   b. Serum chemistry profile: mild to moderate hyperglobulinemia (50%) [1], hypoalbuminemia, uncommonly mild hypercalcemia; increased serum alkaline phosphatase (ALP) with bony involvement [1, 2, 18]. Cats may have no abnormalities (20%), neutrophilia with or without monocytosis with normal serum chemistries (33%), or hyperglobulinemia (43%) [6].
   c. Urinalysis: occasional proteinuria.
   d. CSF analysis: increased total nucleated cell counts, increased CSF protein and reduced glucose concentration.

5) Diagnosis
   a. Histology and cytology:
      i. Advantage: FNA or biopsy easy to perform if cutaneous lesions or lymphadenopathy present and most rapid method for diagnosis. Dermatologic dissemination is frequent in cats, allowing for ease of obtaining sample [5, 19, 20].
      ii. Disadvantage: risk and higher cost if more invasive procedure required in the absence of skin lesions or enlarged lymph nodes (i.e., respiratory specimens or surgical or ultrasound-guided biopsy).
   b. Antigen Detection
      i. Advantage: easy to collect specimens, results available in a few days. Combined serum and urine antigen testing, AGID, and antibody EIA yields highest sensitivity (99%) [21].
      ii. Disadvantage: low sensitivity: 20-34% [1, 21, 22] in dogs due to low fungal burden compared to other endemic mycoses, cross reactivity with histoplasmosis (7.7%) and blastomycosis (6.4%) [21]. Sensitivity for antigen test was higher in cats in an unpublished study at MVD (100%: 7/7 cats with proven coccidioidomycosis based on organism ID).
   c. Antibody Detection:
      i. Advantage: most sensitive method for diagnosis [23].
         a. MVista® Coccidioides Canine IgG Antibody Enzyme immunoassay (EIA): high sensitivity/specificity (89.2% / 97%) [21], results same day
         b. Immunodiffusion (AGID): high sensitivity (90-92%) [2, 21], but 3 days to result and additional 3 day for titer.
      c. Complement fixation test is positive in most cats with coccidioidomycosis [5]. It is not routinely used in dogs due to anticomplementary antibody presence [1].
      ii. Disadvantage: No commercially available feline-specific assay.
         a. Titer does not reflect severity of disease [9, 24] due to overlap in titer with clinical and subclinical disease [18]. Negative serology does not rule out coccidioidomycosis [18, 25, 26]. Titers 1:8 may be found in 5-20% of healthy dogs.
   d. Culture:
      i. Advantage: only way to prove the diagnosis. Rarely performed.
      ii. Disadvantages: Rarely performed in vet med. Some
risk to laboratory personnel, so appropriate facilities are required. Cultures require 1 to 3 weeks incubation, up to 5 weeks occasionally; only used for basis of diagnosis in 12% of cases [9].

e. Molecular: inadequate information to determine usefulness
i. Advantage: fast turnaround time, although no peer-reviewed publications available to assess sensitivity and specificity (making interpretation of the results difficult).
ii. Disadvantage: low incidence of fungemia so whole blood unlikely a desirable specimen, invasive procedure to obtain respiratory or tissue specimens, expensive.

6) Treatment
a. General
i. Prognosis depends on severity of infection and extent of dissemination [1]. Initial hospitalization for intravenous amphotericin B and respiratory assistance may reduce mortality in severe cases.
ii. Outcome good to excellent in cases with CNS involvement that show resolution of clinical signs in first few weeks of treatment, but poor if deterioration or signs of static encephalopathy, or severe respiratory insufficiency [10].
b. Amphotericin B: 1 – 3mg/kg every other day, 3 times weekly. Deoxycholate or lipid formulation of amphotericin B are recommended as initial treatment for 3-7 days for cases with severe disease followed by itraconazole to complete therapy. Risk of nephrotoxicity.
c. Fluconazole: 10mg/kg q24h or 5mg/kg q12h. Fluconazole is the first drug of choice for coccidioidomycosis, with high bioavailability and low toxicity; however, resistance to fluconazole has developed in humans and cats with histoplasmosis [10, 27].
d. Itraconazole: 5mg/kg PO q 12 hours for 3 days (loading dose) then q 24 hours for dogs; higher doses may be required for cats.
i. Uncomplicated cases: at least six to twelve months and resolution of signs, resolution or marked improvement of radiographic lesions and resolution of antigen [10].
ii. Complicated cases (bone, joints, CNS) or relapse despite appropriate therapy. At least 12 months and resolution of signs, radiographic lesions and antigen. In humans with CNS involvement, anti-fungal therapy is lifelong [28]. Human studies show Itraconazole more effective than fluconazole in treating skeletal infections [29].
iii. Use only FDA approved generic itraconazole or brand named Sporanox. Compound non-FDA approved preparations have poor bioavailability [30]. The effectiveness of the non-FDA approved preparations for treatment of coccidioidomycosis is unknown.
iv. Verify blood levels of itraconazole of at least 2 µg/ml after reaching steady-state (2 weeks in dogs and 3 weeks in cats) is highly recommended [30].
e. Terbinafine: no published canine studies to support terbinafine, not recommended in humans. A rabbit model comparing terbinafine and fluconazole showed terbinafine to be ineffective in survival, histology and reduction in numbers of colony forming units 28; no information on whether adequate tissue concentration achieved [10, 28].
f. Ancillary therapy: glucocorticoids at anti-inflammatory doses for animals with respiratory distress or severe inflammation; however, for short duration [10]. Nonsteroidal anti-inflammatory drugs, tramadol or gabapentin when NSAIDS insufficient, cough suppressants or short-term bronchodilator therapy, antiepileptics for dogs with seizures. Caution should be used with combination of phenobarbital, prednisone, and fluconazole [10]. Drugs metabolized by cytochrome P450 such as phenobarbital will have increased blood levels when used concomitantly with azoles, and glucocorticosteroids can have suppressive effects to the immune system and contribute to hepatopathy in conjunction with azoles.
g. Surgical management: amputation for persistent osteomyelitis, pericardectomy in tamponade, and enucleation may be required for endophthalmitis [1].

7) Monitoring response to treatment
a. Resolution of clinical signs and reduction in serological titers, though decision to terminate treatment should not be based on titer alone since titers may plateau or decrease slightly after recovery [23, 31].
b. Coccidioides antibody testing at 3-month intervals during and at 3, 6- and 12-months following discontinuation of treatment, until negative.
c. If Coccidioides antigen in serum or urine was initially positive, may be useful as a monitoring tool (treat until negative).
d. Imaging: resolution or marked improvement in radiographs, CT or MRI scans. Antifungal susceptibility testing may be performed on cultured isolates. Services available at UT Health San Antonio Fungus Testing Lab.

8) Relapse: up to 25% of dogs relapse [23].
a. Diagnosis: recurrent signs and increase in antibody titer or antigen concentration.
b. Causes: use of non-FDA approved itraconazole, subtherapeutic levels of itraconazole, development of resistance to fluconazole and inadequate duration of treatment [30, 32, 33].
c. Treatment:
i. Repeat itraconazole adhering to guidelines above.
ii. Chronic suppression with itraconazole 5mg/kg administered 3 times weekly may prevent relapse.
REFERENCES

24. LF, B.C.a.S. A RETROSPECTIVE REVIEW OF CANINE COCCIDIOIDOMYCOSIS CASES AT A TERTIARY CARE CENTER IN TUCSON. In 62nd Annual Coccidioidomycosis Study Group Meeting. 2018. Flagstaff, AZ.
Construction Updates:
The builders have moved inside, and spaces are beginning to take shape. To our new research wing, we’ve added 5 rooms to accommodate our plans to offer PCR panels in the future.
We’ve been busy this year. See our 2019 publications:

Characterization of an Uncinocarpus reesii-expressed recombinant tube precipitin antigen of Coccidioides posadasii for serodiagnosis.


Central Nervous System Infection with Histoplasma capsulatum.


Peripheral blood smear findings in a kidney transplant recipient with disseminated histoplasmosis and elevated Aspergillus galactomannan.


Rabbit Antithymocyte Globulin Causes Blastomyces and Histoplasma Antigenemia.


Novel canine anti-Coccidioides immunoglobulin G enzyme immunoassay aids in diagnosis of coccidioidomycosis in dogs.


Cryptococcal meningitis is a cause for cross-reactivity in cerebrospinal fluid assays for anti-Histoplasma, anti-Coccidioides and anti-Blastomyces antibodies.


Accuracy of a Novel Histoplasmosis Enzyme Immunoassay to Evaluate Suspicious Lung Nodules.