MiraVista (MVD) Fungal Diagnostic Tests
by L. Joseph Wheat, M.D.

I’m often contacted for advice on diagnosis of the endemic mycoses. Many physicians are unaware of these tests and publications describing their use for diagnosis.

For example, some believe the *Histoplasma* antigen test is performed only on urine. Others believe that antigen testing on serum is unnecessary. In fact, nearly half of the cases of acute pulmonary histoplasmosis would have been missed if only urine were tested (sensitivity 83% for combined serum and urine testing; 45% with urine alone (1)). At least 5% of disseminated cases would be missed if only urine were tested (unpublished). Both urine and serum should be tested for maximum sensitivity. Antigen testing of CSF is the most sensitive method for diagnosis of *Histoplasma* meningitis (2,3). Detection of antigen in the bronchoalveolar lavage fluid (BAL) is useful for diagnosing pulmonary histoplasmosis (4).

Some also believe that *Histoplasma* antibody detection is not useful for diagnosis because most individuals from endemic areas have had histoplasmosis, and antibody tests would not differentiate active infection from previous exposure. Studies in Indianapolis, where 50% of residents are histoplasmin skin test positive, reported positive antibody results by immunodiffusion (ID) in 0.5% and by complement fixation (CF) in 5% (5). Skin test reactivity persists for life in most individuals while antibodies clear over a few years.

> READ MORE ON PG. 4
FREQUENTLY ASKED QUESTION FROM CLIENTS
How should we ship the specimen?

ANSWER
Please ship specimens in a sterile leak proof container. All specimens should be labeled with each patient’s unique identifiers and should be shipped at a stable temperature for the specific test being ordered. Please refer to our Test Menu for detailed shipping information by visiting www.miravistalabs.com.

WE’VE ADDED NEW HOURS
We have added evening and Saturday hours. This allows us to maintain same day TAT and confirmatory testing.

NEW HOURS LABORATORY
Monday, 8am – 5pm, Tuesday – Friday, 8am – 11pm, Saturday, 8:30am – 5pm
Business hours and Clinical Consultation: Monday – Friday 8am – 5pm

MEETINGS OF INTEREST

> Coccidioidomycosis Study Group, CSG
  4/5 – 4/6, Sacramento, CA
  Dr. Wheat attending – http://coccistudygroup.com/

> Infectious Disease Society of America, ID Week
  10/2 – 10/6, Washington, DC

> AACC
  8/4 – 8/8, Anaheim, CA
  http://www.2019aacc.org/

COMPANY NEWS

Construction is underway for our 24,000 square foot building expansion. We will be hiring new team members in the coming year with expertise in molecular biology and ASCP certified medical technicians. Please check out website for opportunities to join our team.
EXECUTIVE BIOGRAPHY

Dr. Lawrence Joseph Wheat, Founder of MiraVista Diagnostics

Lawrence Joseph Wheat, MD (Dr. Joe Wheat) is an accomplished and widely published scientist with more than 40 years of focused expertise in the area of infectious diseases. He is recognized by the academic, medical and professional communities as the leading authority on serious fungal infections. In 2002, Dr. Wheat founded MiraVista Diagnostics and currently serves as its Medical Director and President. As a result of Dr. Wheat’s scientific developments, visionary leadership, high quality standards and dedication to excellent client service, MiraVista has earned the reputation as the industry’s premier reference laboratory for fungal diagnostics.

Prior to establishing MiraVista Diagnostics, Dr. Wheat served as a professor at the Indiana University Medical Center’s Infectious Diseases Division for more than 25 years. In addition to teaching medicine, Dr. Wheat was a prolific medical research scientist during his tenure. From 1976-2014, he published more than 300 scientific articles specifically related to fungal infection, hundreds more articles on broader infectious disease topics and authored chapters about histoplasmosis in several leading infectious disease and internal medicine books. Dr. Wheat’s groundbreaking research findings contributed to the development of the first histoplasmosis antigen test in 1986. Since then, he has continued to develop new generations of diagnostic tests for coccidioides (also known as valley fever fungus), histoplasma capsulatum and blastomyces dermatitidis.

Dr. Wheat received his medical degree from Indiana University Medical School where he also completed his internship, residency and fellowship in infectious diseases. He served on the editorial board of the Journal of Infectious Disease from 2002-2013 and is an active member of many professional organizations including the Infectious Disease Society of America, American Society of Microbiology, International Society for Human and Animal Mycology and Medical Mycology Society of the Americas. Dr. Wheat also served in the United States Air Force.
I’m often contacted for advice on diagnosis of the endemic mycoses. Many physicians are unaware of these tests and publications describing their use for diagnosis.

For example, some believe the *Histoplasma* antigen test is performed only on urine. Others believe that antigen testing on serum is unnecessary. In fact, nearly half of the cases of acute pulmonary histoplasmosis would have been missed if only urine were tested (sensitivity 83% for combined serum and urine testing; 45% with urine alone) (1). At least 5% of disseminated cases would be missed if only urine were tested (unpublished). **Both urine and serum** should be tested for maximum sensitivity. Antigen testing of CSF is the most sensitive method for diagnosis of *Histoplasma* meningitis (2;3). Detection of antigen in the bronchoalveolar lavage fluid (BAL) is useful for diagnosing pulmonary histoplasmosis (4).

Some also believe that *Histoplasma* antibody detection is not useful for diagnosis because most individuals from endemic areas have had histoplasmosis, and antibody tests would not differentiate active infection from previous exposure. Studies in Indianapolis, where 50% of residents are histoplasmin skin test positive, reported positive antibody results by immunodiffusion (ID) in 0.5% and by complement fixation (CF) in 5% (5). Skin test reactivity persists for life in most individuals while antibodies clear over a few years.

The newly described MVD IgG and IgM enzyme immunoassay (EIA), combined with antigen detection, improves the sensitivity for diagnosis of acute pulmonary histoplasmosis over antigen and antibody detection by ID or CF (6). The assay is quantitative and was useful for detecting seroconversion in these cases. Similarly, sensitivity for diagnosing *Histoplasma* meningitis by testing CSF increased from 78% to 98% by combining antigen and IgG/IgM antibody testing (2). **Both antigen and MVD antibody EIA** should be tested for maximum sensitivity.

Many are unaware of the MVD *Coccidioides* antigen detection assay or believe that its sensitivity is low. The limit of detection is the same in our *Coccidioides* and *Histoplasma* antigen assays, <0.2ng/mL. The clinical sensitivity in disseminated cases is somewhat lower, about 70% in coccidioidomycosis (7;8) and 90% in histoplasmosis (9). The reason for the lower clinical sensitivity in coccidioidomycosis is the lower fungal burden. For example, the lungs, liver, spleen, bone marrow, other tissues are often involved in disseminated histoplasmosis and fungemia is common. Isolated sites of dissemination to skin, bone, or CNS are more common in coccidioidomycosis and fungemia is rare. Larger unpublished studies indicate the sensitivity was 80% in disseminated cases, most of whom were immunocompromised, if **both urine and serum** were tested. Antigen detection in CSF is the most sensitive method (91%) for diagnosing *Coccidioides* meningitis (10).

The MVD *Coccidioides* IgG and IgM antibody EIA was introduced in 2017 (11). MVD EIA is more sensitive than ID or CF and is not impacted by immunocompromise (11). The assay is quantitative and useful for monitoring changes in antibody concentrations (unpublished). Sensitivity in CSF in *Coccidioides* meningitis is 73% (unpublished).

The MVD *Blastomyces* antigen EIA is the most sensitive method for diagnosing disseminated and pulmonary blastomycosis (12). Antigen also may be detected in CSF (13) in patients with meningitis and BAL fluid in patients with pneumonia (9). We have developed an IgG *Blastomyces* antibody EIA that is more sensitive than immunodiffusion (14). **Combined antigen and MVD EIA antibody** testing increased the sensitivity from 88% to 98%. This IgG test is available as “research use only (RUO)” pending completion of validation and requires preapproval by the laboratory director. The MVD *Blastomyces* antibody EIA is projected to be validated and offered routinely in mid-2019.
<table>
<thead>
<tr>
<th>MVD Test</th>
<th>Specimen</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histoplasma antigen</strong>¹</td>
<td>Urine-disseminated, AIDS</td>
<td>97%</td>
<td>99%</td>
<td>(15)</td>
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<tr>
<td></td>
<td>Serum-disseminated, AIDS</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CSF-meningitis</td>
<td>78%</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BAL-pulmonary</td>
<td>94%</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td><strong>Histoplasma IgG and IgM antibody</strong></td>
<td>Serum-pulmonary, acute</td>
<td>89%</td>
<td>95%</td>
<td>(2;6)</td>
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<tr>
<td></td>
<td>CSF-meningitis</td>
<td>82%</td>
<td>93%</td>
<td></td>
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<tr>
<td><strong>Coccidioides antigen</strong>¹</td>
<td>Urine-disseminated³</td>
<td>51%</td>
<td>98%</td>
<td>(10)</td>
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<tr>
<td></td>
<td>Serum-disseminated³</td>
<td>72%</td>
<td>100%</td>
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<tr>
<td></td>
<td>Urine or serum, disseminated³</td>
<td>80%</td>
<td>ND</td>
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<tr>
<td></td>
<td>CSF-meningitis</td>
<td>91%</td>
<td>100%</td>
<td></td>
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<tr>
<td></td>
<td>BAL-pulmonary</td>
<td>ND2</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td><strong>Coccidioides IgG and IgM antibody</strong></td>
<td>Serum-pulmonary, disseminatedCSF-meningitis³</td>
<td>88%</td>
<td>90%</td>
<td>(11)</td>
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<tr>
<td></td>
<td></td>
<td>73%</td>
<td>88%</td>
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<tr>
<td><strong>Blastomyces antigen</strong></td>
<td>Urine-pulmonary or disseminated</td>
<td>90%</td>
<td>99%</td>
<td>(4;12)</td>
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<tr>
<td></td>
<td>Serum-pulmonary or disseminated</td>
<td>57%</td>
<td>ND²</td>
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<tr>
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<td>CSF-meningitis³</td>
<td>86%</td>
<td>ND</td>
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<td></td>
<td>BAL</td>
<td>80%</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td><strong>Blastomyces IgG antibody (RUO)⁴</strong></td>
<td>Serum, pulmonary or disseminated</td>
<td>88%</td>
<td>99%</td>
<td>(14)</td>
</tr>
</tbody>
</table>

¹ Disseminated only. ² ND-not determined. ³ unpublished; ⁴ RUO, research use only

Reference List