Coccidioidomycosis (Valley Fever) FAQs for Clinicians

- **When should I consider coccidioidomycosis in my patient?**

In patients who reside in or have traveled to endemic regions (including south-central Washington), consider testing for coccidioidomycosis if <u>any</u> of the following are present:
Respiratory symptoms associated with at least one: • More than one office visit • Chest x-ray ordered • Antibiotic prescribed but failed to improve
Two of the following for a prolonged period: • Fever • Fatigue • Arthralgia
Unexplained peripheral blood eosinophilia
Skin lesions of: • Erythema nodosum • Erythema multiforme

From the Valley Fever Center for Excellence Tutorial for Primary Care Physicians

  - When present, symptoms (~40% of cases) include fatigue, night sweats, and respiratory symptoms (cough, shortness of breath, chest pain); other symptoms can include fever, headache, myalgias, arthralgias, weight loss, and rash. Some patients fail to recover and develop complications or chronic pulmonary disease.
  - Symptoms generally start one to three weeks after inhaling fungal spores from dust or disturbed soil in an endemic area. *Coccidioides* is endemic in the Southwestern US, parts of Mexico, and Central and South America; it has also recently been recognized in the soil of south-central Washington.

- **What laboratory tests are available to assist in the diagnosis of coccidioidomycosis?**
  - Recommended commercially available tests to aid in the diagnosis of cocci include:
    - **Serology** (testing for IgM and IgG antibodies) – Serum, CSF for patients with suspected or proven meningitis, less frequently: pleural, synovial, or ascitic fluid. (NOTE: offered at UC Davis Coccidioidomycosis Lab; consult with laboratory about case prior to submitting).
    - **Microscopy/Histopathology** – Tissue or respiratory secretions; detect spherules with cytology stains such as are performed on bronchoscopy specimens, by hematoxylin and eosin stains of tissue sections, and with other specialized stains.
    - **Fungal culture** - Respiratory secretions (sputum, BAL), normally sterile fluids (pleural, peritoneal), tissues (fine needle aspirates or biopsies of lung, brain, skin), or abscesses. Isolating *Coccidioides sp.* from a clinical specimen is definitive evidence of infection.
  - Other tests that are not widely available and may have issues with reproducibility include:
    - Urine antigen (available at MiraVista Labs only)
    - PCR testing - available in some institutions (including University of Washington) as a research test; one FDA-approved (Gene-probe) but not widely available; only use on sputum or tissue
  - Other:

- Spherulin skin test (indicates prior infection, reactivity is lifelong)

- **What are the differences in the serologic assays?**
  - Serology is a tool to aid in diagnosing infection. Results should not be interpreted without considering the full clinical presentation and exposure information.
  - In most circumstances, a positive serologic test for coccidioidal antibodies is highly presumptive of a current infection (although false positives can occur).
  - A negative serologic test never excludes the presence of a coccidioidal infection.

Test type	Description	Pros	Cons
Enzyme Immunoassay (EIA)	Semi-quantitative test for detecting IgM and IgG antibodies	• High sensitivity • Same day results • Objective interpretation of results	• Lower specificity (especially with IgM), so confirmation with immunodiffusion is recommended for positives
Latex agglutination (LA)	Qualitative test for detecting IgM	• Rapid and highly sensitive • Same-day results	• Low specificity, so confirmation with immunodiffusion is recommended for positives • Subjective interpretation of results
Immunodiffusion (ID)	Qualitative test for detecting IgM (ID tube precipitin [IDTP]) and IgG (ID complement fixation [IDCF])	• More specific than EIA, LA, or CF • Simple to perform • IDTP is positive early in the course of infection • IDCF later in course of illness	• Lower sensitivity • Subjective interpretation of results • Requires 2-3 days for results • May not be positive late in infection
Complement Fixation (CF)	Quantitative test for antibody detection. Repeat at the same lab to avoid inter-lab variability	• More sensitive than ID • Useful for measuring disease severity and progression • Macrodilution titers correlate with patient symptoms/burden of disease	• Technically demanding • Less specific than ID • Requires two days for results • Useful in prognosis and management of disease but less for diagnosis.

Note: Lower **specificity** means there may be more false positives. Lower **sensitivity** means may be more false negatives among people who truly have the disease.

- **When are antibodies detectable by serology?**
  - Immunoglobulin M (IgM) antibodies are detectable in ~50% of patients by 1 week after symptom onset, and ~90% by 3 weeks after symptom onset
  - Immunoglobulin G (IgG) antibodies are generally detectable by 4-6 weeks post symptom onset, and ~85-90% of patients have detectable IgG by 3 months
  - Antibodies (both IgM and IgG) can be transient, and generally do not persist for longer than several months to a year, occasionally longer, especially in association with disseminated disease.

- **I suspect my patient has cocci, but all the tests I've ordered are negative. My patient is responding to antifungals. What can I do to determine if the infection is due to cocci?**

- Keep in mind that some serologic assays don't have great sensitivity (i.e., may be falsely negative), so a negative result does not exclude the diagnosis of coccidioidomycosis.
- Keep in mind that tests are less reliable in patients who are immunocompromised.
- Continue to follow and re-test patient in 2-3 weeks; repeat again if necessary. Some laboratories will hold and save serum for several months so that repeat samples can be tested in tandem.
- Consider imaging, e.g., chest radiography or CT.

- **I've received discrepant results between an EIA and ID test. What should I do?**
  - The EIA assays are more sensitive (i.e., most people with the disease will test positive and there will be few false negatives). The ID assay is more specific (i.e., most people who do not have the disease will test negative, and there will be few false positives).
  - If the EIA is positive and ID is negative, it is possible that the EIA was falsely positive or the ID may be falsely negative early in infection. If patient has consistent symptoms and exposure history, consider obtaining a second serum 3-4 weeks later for acute/convalescent comparison at the same laboratory.
  - If the EIA is negative, ID is not needed. If EIA is negative with ID positive on the same serum specimen, then consider asking about quality control (QC) results. In the absence of another explanation, repeat testing. It is likely the EIA was a false negative. This is not a common occurrence.

- **I suspect my patient has primary pulmonary cocci. What should I do to confirm this?**
  - Obtain chest radiograph, serology, and sputum for fungal culture.
    - Many clinical laboratories offer a coccidioidomycosis panel but these differ slightly. The testing algorithm often includes an EIA screen (IgM and IgG); if positive, then confirm with ID. If ID positive, also get CF titer to indicate severity of infection and follow a patient.
    - Chest radiographs often disclose abnormalities; pulmonary infiltrates are usually one-sided and are typically patchy and not as consolidated as seen with bacterial infections. Nodules are common. Often there is associated ipsilateral hilar adenopathy. Peripneumonic pleural effusions may also occur.
  - Follow patient and continue testing.

- **I suspect my patient has cocci meningitis. What should I do to confirm this?**
  - Do a lumbar puncture and send CSF for culture and serology.
  - Consider ordering an MRI of the brain to evaluate for ischemia, infarction, hemorrhage or hydrocephalus.
  - Consider consultation with those experienced in the treatment of cocci meningitis.

Other resources:

- CDC Information for Healthcare Professionals: http://www.cdc.gov/fungal/diseases/coccidioidomycosis/health-professionals.html

- Valley Fever Center for Excellence Tutorial for Primary Care Professionals: https://vfce.arizona.edu/sites/default/files/valleyfever_training_manual_2019_mar_final-references_different_colors_3.pdf

- IDSA Guidelines: https://www.idsociety.org/practice-guideline/coccidioidomycosis/