Nonculture Diagnosis of Coccidioidomycosis

Background. Coccidioidomycosis, also known as Valley Fever, is a disease caused by the fungus *Coccidioides.* Coccidioidomycosis is endemic in the southwestern United States, Mexico, and parts of Central and South America. It is estimated that about 150,000 new infections occur each year in the United States alone [1] but the disease is greatly underdiagnosed.

The IDSA coccidioidomycosis practice guideline recommends antibody testing for acute coccidioidomycosis [2]. For diagnosing disseminated disease, the guideline states that anti-coccidioidal antibodies are nearly always present, except for in immunocompromised patients. The guideline further indicates that "coccidioidal antigen in urine or serum is typically only positive in patients with extensive infections" but does not describe a role for its use in diagnosis, except for CSF in suspected *Coccidioides* meningitis.

The *Coccidioides* antigen assay in urine was described in 2008 [3] followed by serum in 2009 [4]. Sensitivity was higher in immunocompromised (83%) than in non-immunocompromised patients (50%). Both studies were small. Antigen was detected in CSF in 93% of patients with meningitis [5].

Findings. Most clinicians are unaware that the greatest sensitivity for antigen detection requires **simultaneous testing of urine and serum**. The highest sensitivity was achieved by testing both: 50% were positive in urine alone and 71% if urine and serum were tested [4]. In analysis of *Coccidioides* antigen results at MiraVista in over 5000 patients tested in the last 18 months, urine alone was tested in 46%, serum alone in 36%, and **both in only 18%**. Among 52 patients in whom both specimen types were tested and at least one was positive, 21% to 23% of positive cases would have been missed by testing only serum or only urine (Table 1).

Table 1. 18 Months Survey

Antigen [4]	% positive
Serum only	21%
Urine only	23%
Both	66%

Several studies indicate that antibody detection alone is not sufficient for diagnosis of coccidioidomycosis. In an early study, antibodies were detected by immunodiffusion (ID) in 53% of immunocompromised and 73% of non-immunocompromised patients [7]. Data from a recent study reporting a new IgG and IgM enzyme immunoassay (EIA) is shown in Table 2. The sensitivity of ID was 63% in immunocompetent patients and 50% in immunocompromised patients compared to 90% and 83%, respectively by EIA [6]. Complement fixation (CF) was positive in 64% of cases. A recent study that evaluated two commercially available EIAs reported that 30% of cases diagnosed based on **clinical findings and positive ID or CF** were negative by EIA [8].

Table 2. Malo Study

Antibody [6]	% positive
EIA IgG or IgM	88%
ID IgG or IgM	60%
CF IgG	64%

What about molecular methods? Two recent studies reported encouraging findings [9, 10]. Both evaluated respiratory specimens obtained by bronchoscopy that were classified as cases or controls based on culture. Sensitivity and specificity were 100%. However, both studies were small and did not include subjects in which the diagnosis was based on nonculture methods, potentially overestimating sensitivity.

Summary. These findings suggest that combined testing for antigen in urine and serum together with antibody detection are likely to improve diagnosis of coccidioidomycosis. Additionally, the IgG and IgM antibody EIA [6] is more sensitive than ID, CF and commercial EIAs used at reference laboratories [8].

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