Top Questions in the Diagnosis and Treatment of Coccidioidomycosis

Fariba M. Donovan, Tirdad T. Zangeneh, Joshua Malo, and John N. Galgiani

The Valley Fever Center for Excellence and Department of Medicine, University of Arizona College of Medicine, Tucson, Arizona

Revised and greatly expanded treatment guidelines for coccidioidomycosis were published last year by the Infectious Diseases Society of America. We have selected 4 questions that commonly arise in the management of patients suspected of this disease and for which there remain divided opinions.

Keywords. antibody tests; antifungal drugs; lung nodule; organ transplantation; preemptive treatment.

Coccidioidomycosis (San Joaquin Valley Fever) is an endemic systemic fungal infection throughout the Western Hemisphere [1]. Although in the United States endemic regions are primarily in the Southwest, there are exceptions in northern California, Washington, northeastern Utah, and perhaps others yet to be discovered [2–4]. With tourism and business travel, coccidioidal infections may be diagnosed literally anywhere in the world [5–8]. Revised and greatly expanded treatment guidelines for coccidioidomycosis were published last year by the Infectious Diseases Society of America (IDSA) [9]. For this brief report, we selected 4 questions that commonly arise in the management of patients suspected of this disease and for which there remain divided opinions.

WHICH TESTS FOR COCCIDIOIDAL ANTIBODIES ARE BEST FOR DIAGNOSIS AND MANAGEMENT?

Most diagnoses of coccidioidomycosis are based upon the detection of anticoccidioidal antibodies. Exceptions include biopsy of pulmonary nodules (see below) and extrapulmonary lesions to diagnose hematogenous spread beyond the lungs. There is a large, now classic, literature describing the original test methodology and its relationship to various coccidioidal disease manifestations [10]. These tests are the qualitative immunodiffusion (ID) tests for IgM and IgG antibodies and the quantitative test for complement-fixing (CF) antibodies. Of note, most of the reports were based upon the results from a single laboratory directed by the tests' originator, Dr. Charles Smith, and one of his students,

Dr. Demosthenes Pappagianis. In current medical practice, tests for coccidioidal antibodies are now done at a variety of laboratories throughout the country, and it has not been established to what extent lab-to-lab variation exists, especially with respect to the quantitative CF antibody test results. An enzyme-linked immunoassay (EIA) to detect anticoccidioidal IgM and IgG antibodies was introduced as a commercial kit in the 1990s, and currently there are several on the market produced by different manufacturers [11–13]. These appear more sensitive than the older methods as conventionally performed [14]. However, there is little published documentation of this. Moreover, all of the EIA tests are proprietary, and the antigens used by different manufacturers as the basis of antibody detection are trade secrets. The Clinical Laboratory Improvement Amendments mandates laboratory sharing of samples for quality assurance. However, since there is no publically available reference EIA method, this is the only way to assess quality other than to rely upon the manufacturers' own instructions.

Given this background, the revised IDSA guidelines recommend in patients who manifest a syndrome consistent with coccidioidomycosis that EIA tests be done for both IgM and IgG antibodies. For the purposes of interpretation, an "indeterminate" EIA result should be considered the same as nonreactive. If either is reactive, an active infection is likely to be present since both tests usually revert to nonreactive as illness resolves. If only the EIA IgM is reactive, there is some possibility that it constitutes a false-positive result, and repeated testing at later times may clarify the situation [12, 15, 16]. Also, if both EIA tests are nonreactive, this never completely excludes the diagnosis of coccidioidomycosis, and repeat testing may subsequently be helpful.

Serum from patients with either EIA test reactive should also be submitted for qualitative ID tests for both IgM and IgG. Because of the uncertainty as to which antibodies the EIA tests detect, it is possible that EIA IgM reactive sera will demonstrate ID IgG reactivity or vice versa. The ID IgG was configured to more sensitively detect the same antibodies that produce a positive CF antibody test [17, 18], and a negative ID IgG test

result should make further testing for CF antibodies unnecessary. However, this relationship depends on the training and experience of laboratory staff in reading ID plates, and, for this reason, some authorities recommend CF antibody testing in all sera that are EIA reactive. Once a diagnosis of coccidioidomycosis has been established, only the CF antibody test should be used for ongoing management since none of the other tests have been shown to have prognostic value.

WHICH NEWLY DIAGNOSED COCCIDIOIDAL INFECTIONS SHOULD BE TREATED?

Of the estimated 50 000 patients who seek medical attention each year because of newly acquired coccidioidomycosis, their symptoms of pneumonia, arthralgias, and especially debilitating fatigue may persist for many weeks to many months. However, for most, the illness is eventually self-limited, and life-long immunity results without the complications of chronic fibrocavitary pneumonia or hematogenous dissemination [19, 20]. Moreover, there is no evidence that early treatment improves outcome or prevents complications [21, 22]. Thompson et al. [23] have shown that early treatment with fluconazole may reduce the chance of developing IgG antibodies, but the clinical importance of this is unclear. There is an NIH study underway to address the value of early treatment (https://clinicaltrials.gov/ct2/show/NCT02663674?cond=Coccidioidomycosis&draw=1&rank=6). In the absence of results from that study and for patients without immunodeficiencies, other risk factors, or already established pulmonary or extrapulmonary complications, there is considerable uncertainty as to whether to always initiate antifungal therapy or reserve it for selected patients.

The revised IDSA guidelines for managing newly diagnosed, uncomplicated coccidioidal infections recommend always including supportive measures [9]. Patients with mild or non-debilitating symptoms who improved or resolved their clinical illness by the time of diagnosis will benefit from education, close observation, and other supportive measures such as physical therapy. However, in those patients with significant debilitating illness at the time of diagnosis, initiation of antifungal treatment is recommended. The antifungal treatment is also recommended in patients with extensive pulmonary involvement or concurrent risk factors such as immunodeficiencies (ie, untreated HIV/AIDS, organ transplantation (see below), biologic response modifier therapies), diabetes mellitus, or severe cardiopulmonary dysfunction. Some authorities would also include African or Filipino ancestry as indication for early treatment. For such patients, the treatment is an oral azole antifungal, usually fluconazole, at a daily dose of 400 mg per day, and this is continued for 3 to 6 months.

HOW TO MINIMIZE THE RISK OF COCCIDIOIDOMYCOSIS IN SOLID ORGAN TRANSPLANTATION?

The incidence of coccidioidomycosis is estimated at 3.8% to 6.9% in solid-organ transplant (SOT) recipients during the early transplantation period, based on published reports of kidney and heart transplant recipients at 3 medical centers in Arizona from 1960 to 2000 [24, 25]. In addition, the incidence of coccidioidal infection during the first year was reported at 4.2% after liver transplantation [26] and as 5.8% among lung transplant recipients [27]. In addition, there have been recent reports of an overall increase in the incidence of coccidioidomycosis that may be due to several factors such as an increase in the number of immunosuppressed patients, including organ transplant recipients living in the endemic area [28]. However, at the same time, lower rates of infection have been reported among SOT recipients who have received antifungal prophylaxis [29].

The revised IDSA guidelines recommend prophylaxis (eg, 200 mg of fluconazole daily) for 6–12 months for all SOT recipients who have no history of a past coccidioidal infection, whose coccidioidal serologies are nonreactive, and who are without evidence of active coccidioidal infection [9]. However, this recommendation leaves several important questions unaddressed. For one thing, it is unclear whether prophylaxis should be continued beyond 1 year. For another, it is clear that some patients who are serologically positive at the time of transplantation have been successfully managed with prophylaxis [30]. However, what dose and what duration of antifungal prophylaxis are appropriate for this group remain unsettled. Finally, occasional coccidioidal infections in SOT recipients occur outside of the endemic region, suggesting that coccidioidal serologies should be routinely done prior to SOT anywhere in the country.

Although not common, donor-derived coccidioidomycosis has occurred in SOT recipients [31–35] and has received increasing attention. The transmission rate of coccidioidomycosis from donors with active infection to recipients has been reported to be 43% (median of 30 days post-transplant), with a mortality rate of 28.5% [36]. Therefore, screening of living donors from the endemic areas is recommended [37]. Donors with active infection should be excluded, and donation should be delayed until resolution of infection [37]. In the cases of deceased donors with postmortem identification of *Coccidioides* spp. infection, testing including serology of stored serum or histologic examination of tissue samples should be pursued. Furthermore, the Organ Procurement Organizations and the United Network for Organ Sharing should be notified, and recipients should undergo evaluation for infection and receive antifungal prophylaxis [37]. Duration of antifungal prophylaxis varies by the organ transplanted and the severity of disease in the donor. Serological monitoring of donor-positive recipients is recommended if antifungal prophylaxis is discontinued and is performed every 2–3 months in the first 12 months, followed by every 6–12 months [37].

SHOULD LUNG CANCER SCREENING PRACTICES BE DIFFERENT IN *COCCIDIOIDES*-ENDEMIC AREAS?

Several professional societies, including the US Preventive Services Task Force [38–40], have endorsed the use of low-dose

computed tomography (CT) of the chest for lung cancer screening in response to the results of the National Lung Screening Trial (NLST), which demonstrated a reduction in lung cancer mortality with targeted screening [41]. For patients and practitioners living in areas with endemic mycoses, these recommendations present potential challenges as the burden of false-positive screening tests is likely to be higher. In areas endemic for coccidioidomycosis, prior pulmonary infection may account for 25–50% of solitary pulmonary nodules [42–44].

As patients undergoing CT screening all have an increased risk for lung cancer, any identified nodules would typically undergo further diagnostic workup. Serologic testing for coccidioidomycosis is often negative, as these nodules represent residua of past infection. The features of these nodules on CT do not allow easy distinction from malignancy, as they may be spiculated, have irregular margins, and typically do not calcify [45]. Chronic cavitary disease may also be mistaken for cavitary malignancy. Coccidioidal nodules tend to have a lower SUV_{max} on Fludeoxyglucose PET/CT imaging than malignant nodules but frequently have values in a range suspicious for malignancy [46, 47]. Tissue assessment of such nodules, typically done by CT-guided transthoracic needle biopsy, is generally safe and has been demonstrated to have sensitivity and specificity for the diagnosis of coccidioidomycosis of 83% and 100%, respectively [48]. However, a series of cytologic specimens from known coccidioidal nodules demonstrated immature or sparse spherules often on a necrotic background, increasing the risk for misdiagnosis of malignancy or nondiagnostic procedures [49]. Surgical intervention may be required for cases in which the diagnosis remains in question. Video-assisted thoracoscopic surgery has a low risk of complications [50], although the risk of complications increases with cavitary rather than nodular disease [51].

The exact burden of false-positive results of lung cancer screening due to coccidioidomycosis is not yet known and should be an area of further study as screening becomes more common. It is also important to consider the cost and stress burden of such screening in endemic areas. Over the 3-year study period in the NLST, 39% of patients screened with CT had at least 1 positive result, an incidence that could be expected to be higher in coccidioidal endemic regions. Furthermore, preventing 1 cancer-related death over the course of 3 years required the performance of 985 CT scans, 18 PET scans, 8 bronchoscopies, and 9 surgical procedures [52]. The number of procedures and the potential risk to patients would be expected to be higher in areas with a high prevalence of coccidioidomycosis.

In summary, a definitive statement regarding lung cancer screening with CT in coccidioidal endemic regions cannot be made. However, practitioners in these areas should be aware of the likelihood of false-positive screening, the limits of available diagnostic modalities, and the potential risk to patients of multiple diagnostic procedures. Further study is warranted to demonstrate the safety and cost-effectiveness of this screening strategy in these areas.

References

1. Nguyen C, Barker BM, Hoover S, et al. Recent advances in our understanding of the environmental, epidemiological, immunological, and clinical dimensions of coccidioidomycosis. Clin Microbiol Rev **2013**; 26:505–25.
2. Litvintseva AP, Marsden-Haug N, Hurst S, et al. Valley fever: finding new places for an old disease: *Coccidioides immitis* found in Washington State soil associated with recent human infection. Clin Infect Dis **2015**; 60:e1–3.
3. Johnson SM, Carlson EL, Fisher FS, Pappagianis D. Demonstration of *Coccidioides immitis* and *Coccidioides posadasii* DNA in soil samples collected from Dinosaur National Monument, Utah. Med Mycol **2014**; 52:610–7.
4. Werner SB, Pappagianis D, Heindl I, Mickel A. An epidemic of coccidioidomycosis among archeology students in northern California. N Engl J Med **1972**; 286:507–12.
5. Corpolongo A, Giancola ML, Ghirga P, et al. An imported case of acute pulmonary coccidioidomycosis in an Italian traveller. Infection **2014**; 42:921–4.
6. Subedi S, Broom J, Caffery M, et al. Coccidioidomycosis in returned Australian travellers. Intern Med J **2012**; 42:940–3.
7. Indhirajanti S, Maartense E, Posthuma EF, et al. Pulmonary coccidioidomycosis: import illness and the importance of travel history. Neth J Med **2009**; 67:353–5.
8. Panackal AA, Hajjeh RA, Cetron MS, Warnock DW. Fungal infections among returning travelers. Clin Infect Dis **2002**; 35:1088–95.
9. Galgiani JN, Ampel NM, Blair JE, et al. 2016 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for the treatment of coccidioidomycosis. Clin Infect Dis **2016**; 63:e112–46.
10. Pappagianis D, Zimmer BL. Serology of coccidioidomycosis. Clin Microbiol Rev **1990**; 3:247–68.
11. Kaufman L, Sekhon AS, Moledina N, et al. Comparative evaluation of commercial Premier EIA and microimmunodiffusion and complement fixation tests for *Coccidioides immitis* antibodies. J Clin Microbiol **1995**; 33:618–9.
12. Lindsley MD, Ahn Y, McCotter O, et al. Evaluation of the specificity of two enzyme immunoassays for coccidioidomycosis by using sera from a region of endemicity and a region of nonendemicity. Clin Vaccine Immunol **2015**; 22:1090–5.
13. Malo J, Holbrook E, Zangeneh T, et al. Enhanced antibody detection and diagnosis of coccidioidomycosis with the miravista IgG and IgM detection enzyme immunoassay. J Clin Microbiol **2017**; 55:893–901.
14. Wieden MA, Lundergan LL, Blum J, et al. Detection of coccidioidal antibodies by 33-kDa spherule antigen, coccidioides EIA, and standard serologic tests in sera from patients evaluated for coccidioidomycosis. J Infect Dis **1996**; 173:1273–7.
15. Kuberski T, Herrig J, Pappagianis D. False-positive IgM serology in coccidioidomycosis. J Clin Microbiol **2010**; 48:2047–9.
16. Blair JE, Mendoza N, Force S, et al. Clinical specificity of the enzyme immunoassay test for coccidioidomycosis varies according to the reason for its performance. Clin Vaccine Immunol **2013**; 20:95–8.
17. Huppert M, Bailey JW. The use of immunodiffusion tests in coccicioidomycosis. I. The accuracy and reproducibility of the immunodiffusion test which correlates with complement fixation. AmJClinPathol **1965**; 44:364–8.
18. Huppert M, Bailey JW. Immunodiffusion as a screening test for coccidioidomycosis serology. Sabouraudia **1963**; 2:284–91.
19. Willett FM, Weiss A. Coccidioidomycosis in Southern California; report of a new endemic area with a review of 100 cases. Ann Intern Med **1945**; 23: 349–75.
20. Goldstein DM, McDonald JB. Primary pulmonary coccidioidomycosis; follow-up of 75 cases, with 10 more cases from a new endemic area. JAMA **1944**; 124: 557–61.
21. Ampel NM, Giblin A, Mourani JP, Galgiani JN. Factors and outcomes associated with the decision to treat primary pulmonary coccidioidomycosis. Clin Infect Dis **2009**; 48:172–8.
22. Blair JE, Chang YH, Cheng MR, et al. Characteristics of patients with mild to moderate primary pulmonary coccidioidomycosis. Emerg Infect Dis **2014**; 20:983–90.
23. Thompson GR III, Lunetta JM, Johnson SM, et al. Early treatment with fluconazole may abrogate the development of IgG antibodies in coccidioidomycosis. Clin Infect Dis **2011**; 53:e20–4.
24. Cohen IM, Galgiani JN, Potter D, Ogden DA. Coccidioidomycosis in renal replacement therapy. Arch Intern Med **1982**; 142:489–94.
25. Hall KA, Sethi GK, Rosado LJ, et al. Coccidioidomycosis and heart transplantation. J Heart Lung Transplant **1993**; 12:525–6. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8329432
26. Blair JE, Balan V, Douglas DD, Hentz JG. Incidence and prevalence of coccidioidomycosis in patients with end-stage liver disease. Liver Transpl **2003**; 9:843–50.

27. Chaudhary S, Meinke L, Ateeli H, et al. Coccidioidomycosis among persons undergoing lung transplantation in the coccidioidal endemic region. Transpl Infect Dis **2017**; 19:e12713.

28. Arizona Department of Health Services. Valley Fever. 2015 Annual Report. **2015**. Available at: http://www.azdhs.gov/documents/preparedness/epidemiology-disease-control/valley-fever/reports/valley-fever-2015.pdf

29. Kahn A, Carey EJ, Blair JE. Universal fungal prophylaxis and risk of coccidioidomycosis in liver transplant recipients living in an endemic area. Liver Transpl **2015**; 21:353–61.

30. Hall KA, Copeland JG, Zukoski CF, et al. Markers of coccidioidomycosis before cardiac or renal transplantation and the risk of recurrent infection. Transplantation **1993**; 55:1422–4.

31. Vucicevic D, Carey EJ, Blair JE. Coccidioidomycosis in liver transplant recipients in an endemic area. Am J Transplant **2011**; 11:111–9.

32. Miller MB, Hendren R, Gilligan PH. Posttransplantation disseminated coccidioidomycosis acquired from donor lungs. J Clin Microbiol **2004**; 42:2347–9.

33. Tripathy U, Yung GL, Kriett JM, et al. Donor transfer of pulmonary coccidioidomycosis in lung transplantation. Ann Thorac Surg **2002**; 73:306–8.

34. Wright PW, Pappagianis D, Wilson M, et al. Donor-related coccidioidomycosis in organ transplant recipients. Clin Infect Dis **2003**; 37:1265–9.

35. Carvalho C, Ferreira I, Gaião S, et al. Cerebral coccidioidomycosis after renal transplantation in a non-endemic area. Transpl Infect Dis **2010**; 12:151–4.

36. Kusne S, Taranto S, Covington S, et al. Coccidioidomycosis transmission through organ transplantation: a report of the OPTN Ad Hoc disease transmission advisory committee. Am J Transplant **2016**; 16:3562–7.

37. Singh N, Huprikar S, Burdette SD, et al; American Society of Transplantation, Infectious Diseases Community of Practice, Donor-Derived Fungal Infection Working Group. Donor-derived fungal infections in organ transplant recipients: guidelines of the American Society of Transplantation, infectious diseases community of practice. Am J Transplant **2012**; 12:2414–28.

38. Moyer VA; US Preventive Services Task Force. Screening for lung cancer: US Preventive Services Task Force recommendation statement. Ann Intern Med **2014**; 160:330–8.

39. Detterbeck FC, Mazzone PJ, Naidich DP, Bach PB. Screening for lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest **2013**; 143(5 Suppl): e78S–92S.

40. Bach PB, Mirkin JN, Oliver TK, et al. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA **2012**; 307:2418–29.

41. Aberle DR, Adams AM, Berg CD, et al; National Lung Screening Trial Research Team. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med **2011**; 365:395–409.

42. Read CT. Coin lesion, pulmonary: in the Southwest. (Solitary pulmonary nodules). Ariz Med **1972**; 29:775–81.

43. Forseth J, Rohwedder JJ, Levine BE, Saubolle MA. Experience with needle biopsy for coccidioidal lung nodules. Arch Intern Med **1986**; 146:319–20.

44. Chitkara YK. Evaluation of cultures of percutaneous core needle biopsy specimens in the diagnosis of pulmonary nodules. Am J Clin Pathol **1997**; 107:224–8.

45. Jude CM, Nayak NB, Patel MK, et al. Pulmonary coccidioidomycosis: pictorial review of chest radiographic and CT findings. Radiographics **2014**; 34:912–25.

46. Reyes N, Onadeko OO, Luraschi-Monjagatta Mdel C, et al. Positron emission tomography in the evaluation of pulmonary nodules among patients living in a coccidioidal endemic region. Lung **2014**; 192:589–93.

47. Pasha AK, Walsh TK, Ampel NM. Dual-time-point FDG PET/CT to distinguish coccidioidal pulmonary nodules from those due to malignancy. Lung **2015**; 193:863–4.

48. Sachdeva M, Ronaghi R, Mills PK, Peterson MW. Complications and yield of computed tomography-guided transthoracic core needle biopsy of lung nodules at a high-volume academic center in an endemic coccidioidomycosis area. Lung **2016**; 194:379–85.

49. Aly FZ, Millius R, Sobonya R, et al. Cytologic diagnosis of coccidioidomycosis: spectrum of findings in southern Arizona patients over a 10 year period. Diagn Cytopathol **2016**; 44:195–200.

50. Ashfaq A, Vikram HR, Blair JE, Jaroszewski DE. Video-assisted thoracoscopic surgery for patients with pulmonary coccidioidomycosis. J Thorac Cardiovasc Surg **2014**; 148:1217–23.

51. Jaroszewski DE, Halabi WJ, Blair JE, et al. Surgery for pulmonary coccidioidomycosis: a 10-year experience. Ann Thorac Surg **2009**; 88:1765–72.

52. Gross CP. ACP Journal Club. Screening with low-dose computed tomography reduced lung cancer mortality in high-risk patients. Ann Intern Med **2011**; 155:JC5–06.