Clinical Infectious Diseases

IDSA GUIDELINE

2016 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for the Treatment of Coccidioidomycosis

John N. Galgiani,[1] Neil M. Ampel,[2] Janis E. Blair,[3] Antonino Catanzaro,[4] Francesca Geertsma,[5] Susan E. Hoover,[6] Royce H. Johnson,[7] Shimon Kusne,[3] Jeffrey Lisse,[8] Joel D. MacDonald,[9] Shari L. Meyerson,[10] Patricia B. Raksin,[11] John Siever,[12] David A. Stevens,[13] Rebecca Sunenshine,[14,15] and Nicholas Theodore[16]

[1]Valley Fever Center for Excellence, and [2]Division of Infectious Diseases, University of Arizona, Tucson, and [3]Division of Infectious Diseases, Mayo Clinic, Scottsdale, Arizona; [4]Division of Pulmonary and Critical Care, University of California, San Diego, and [5]Department of Pediatrics, Infectious Diseases, Stanford University School of Medicine, California; [6]Division of Sanford Health, Sioux Falls, South Dakota; [7]David Geffen School of Medicine at UCLA, Department of Medicine, Kern Medical Center, Bakersfield, California; [8]Department of Rheumatology, University of Arizona, Tucson; [9]Department of Neurosurgery School of Medicine, University of Utah, Salt Lake City; [10]Division of Thoracic Surgery, Northwestern University, Feinberg School of Medicine, and [11]Division of Neurosurgery, John H. Stroger Jr Hospital of Cook County, Chicago, Illinois; [12]Arizona Pulmonary Specialists, Ltd, Phoenix; [13]Division of Infectious Diseases, Stanford University School of Medicine, California; [14]Career Epidemiology Field Officer Program, Division of State and Local Readiness, Office of Public Health Preparedness and Response, Centers for Disease Control and Prevention; [15]Maricopa County Department of Public Health, and [16]Department of Neurosurgery, Barrow Neurological Institute, Phoenix, Arizona

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. Infectious Diseases Society of America considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

Coccidioidomycosis, also known as San Joaquin Valley fever, is a systemic infection endemic to parts of the southwestern United States and elsewhere in the Western Hemisphere. Residence in and recent travel to these areas are critical elements for the accurate recognition of patients who develop this infection. In this practice guideline, we have organized our recommendations to address actionable questions concerning the entire spectrum of clinical syndromes. These can range from initial pulmonary infection, which eventually resolves whether or not antifungal therapy is administered, to a variety of pulmonary and extrapulmonary complications. Additional recommendations address management of coccidioidomycosis occurring for special at-risk populations. Finally, preemptive management strategies are outlined in certain at-risk populations and after unintentional laboratory exposure.

Keywords. coccidioidomycosis; antifungal treatment; community acquired pneumonia; travel history; immunocompromised patients.

EXECUTIVE SUMMARY

In these revised guidelines, we expanded recommendations for diagnosing and managing early coccidioidal infections, which are more common clinical presentations than the various pulmonary and extrapulmonary complications. We also expanded the management of coccidioidal meningitis (CM) as a sequence of actionable recommendations. In this revision, recommendations were made regarding both cardiothoracic surgical and neurosurgical approach for complications that benefit from surgical support. Management of coccidioidomycosis in specific at-risk groups such as those with human immunodeficiency virus (HIV)/AIDS, solid organ transplants, and pregnancy are addressed specifically. Finally, there is a section that provides guidance on managing laboratory accidents. The panel followed a process used in the development of other Infectious Diseases Society of America (IDSA) guidelines, which included a systematic weighting of the strength of recommendation and quality of evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system (Figure 1) [1–4]. A detailed description of the methods, background, and evidence summaries that support each of the recommendations can be found in the full text of the guidelines.

RECOMMENDATIONS FOR MANAGEMENT OF COCCIDIOIDOMYCOSIS IN PATIENTS WITHOUT OVERT IMMUNOSUPPRESSING CONDITIONS

I. In Which Patients With Newly Diagnosed, Uncomplicated Coccidioidal Pneumonia Should Antifungal Drug Therapy Be Started?

Recommendations

1. We recommend patient education, close observation, and supportive measures such as reconditioning physical therapy for patients who appear to have mild or nondebilitating symptoms, or who have substantially improved or resolved their clinical illness by the time of diagnosis *(strong, low)*.

Received 25 May 2016; accepted 26 May 2016.

Correspondence: J. N. Galgiani, University of Arizona College of Medicine, Valley Fever Center for Excellence, PO Box 245215, Tucson, AZ 85724 (spherule@u.arizona.edu).

Clinical Infectious Diseases® 2016;63(6):717–22

DOI: 10.1093/cid/ciw538

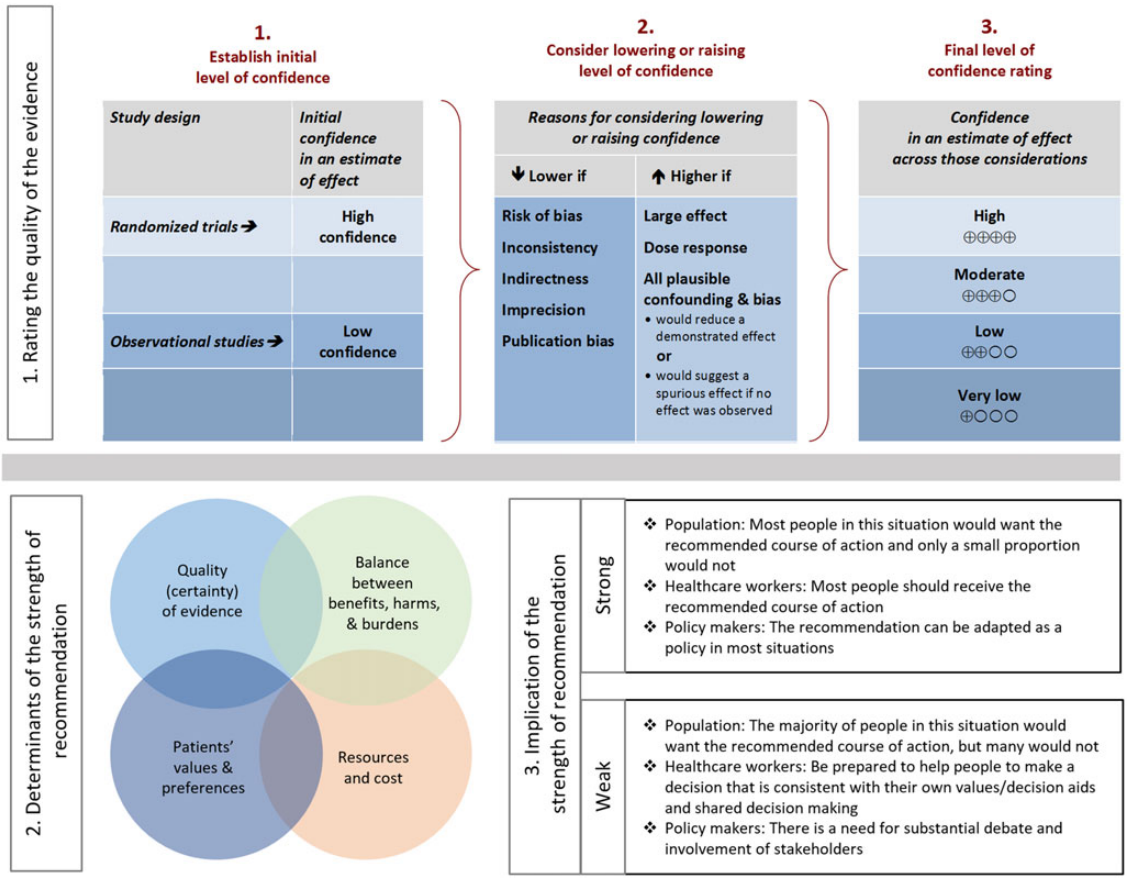

Figure 1. Approach and implications to rating the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (unrestricted use of the figure granted by the US GRADE Network).

2. We recommend initiating antifungal treatment for patients who, at the time of diagnosis, have significantly debilitating illness *(strong, low)*.
3. For patients at the time of diagnosis with extensive pulmonary involvement, with concurrent diabetes, or who are otherwise frail because of age or comorbidities, we recommend initiating antifungal treatment. Some experts would also include African or Filipino ancestry as indications for treatment *(strong, low)*.
4. If treatment is begun in nonpregnant adults, the treatment should be an orally absorbed azole antifungal (eg, fluconazole) at a daily dose of ≥400 mg *(strong, low)*.

II. In Patients With Newly Diagnosed, Uncomplicated Coccidioidal Pneumonia, How Should Health Education and Physical Therapy Reconditioning Programs Be Incorporated Into the Management Program of Uncomplicated Coccidioidal Pneumonia?

Recommendation

5. Patients with uncomplicated pulmonary coccidioidomycosis should have a management plan that incorporates regular medical follow-up, health education, and a plan for physical reconditioning *(strong, low)*.

III. For Patients With Primary Pulmonary Coccidioidomycosis With an Asymptomatic Pulmonary Nodule, and No Overt Immunosuppressing Conditions, Which Treatment Strategy Is Preferred: Antifungal Treatment With Oral Azole, or Observation Without Antifungal Treatment?

Recommendation

6. Once there is confirmation that a pulmonary nodule is due to coccidioidomycosis, we recommend no antifungal treatment for an asymptomatic pulmonary nodule due to coccidioidomycosis *(strong, very low)*.

IV. For Patients Who Have an Asymptomatic Coccidioidal Cavity and Without an Immunosuppressing Condition, Should an Antifungal Drug Be Used?

Recommendation

7. We recommend against the use of antifungal therapy for patients with an asymptomatic cavity *(strong, low)*.

V. For Patients With Symptomatic Chronic Cavitary Coccidioidal Pneumonia, Should an Oral Azole Such as Fluconazole or Intravenous Amphotericin B (AmB) Be Used?

Recommendation

8. We recommend that patients with symptomatic chronic cavitary coccidioidal pneumonia be treated with an

oral agent such as fluconazole or itraconazole *(strong, moderate)*.

VI. In Patients With Symptomatic Cavitary Coccidioidal Pneumonia, Should the Infection Be Removed Surgically?

Recommendation

9. We recommend that surgical options be explored when the cavities are persistently symptomatic despite antifungal treatment. We recommend that surgical options be considered when cavities have been present for more than 2 years and if symptoms recur whenever antifungal treatment is stopped *(strong, very low)*.

VII. In Patients for Whom Cavitary Coccidioidal Pneumonia Is Going to Be Surgically Managed, Should This Be Done by Video-Assisted Thoracoscopic Surgery or Open Thoracotomy?

Recommendation

10. We recommend that when surgical management of cavitary coccidioidal pneumonia is undertaken, a video-assisted thoracoscopic surgery (VATS) approach be attempted if the surgeon has significant expertise in VATS *(strong, low)*.

VIII. In Patients With a Ruptured Coccidioidal Cavity, Should This Be Managed With Chest Tubes or With Surgical Excision of the Ruptured Cavity?

Recommendation

11. For patients with ruptured coccidioidal cavity, we recommend prompt decortication and resection of the cavity, if possible *(strong, very low)*. If the pleural space is massively contaminated, decortications combined with prolonged chest tube drainage may be more appropriate *(weak, very low)*.

IX. For Patients With Ruptured Coccidioidal Cavities, Is an Oral Azole or Intravenous AmB the Preferred Method of Antifungal Treatment?

Recommendation

12. For patients with ruptured coccidioidal cavities, oral azole therapy is recommended. For patients who do not tolerate oral azole therapy or patients whose disease requires 2 or more surgical procedures for control, intravenous AmB is recommended *(strong, very low)*.

X. For Patients With Extrapulmonary Soft Tissue Coccidioidomycosis, Not Associated With Bone Infection, Is Antifungal Therapy Indicated?

Recommendations

13. We recommend antifungal therapy in all cases of extrapulmonary soft tissue coccidioidomycosis *(strong, moderate)*.
14. We recommend oral azoles, in particular fluconazole or itraconazole, for first-line therapy of extrapulmonary soft tissue coccidioidomycosis *(strong, moderate)*.
15. We recommend intravenous AmB in cases of azole failure, particularly in coccidioidal synovitis *(strong, moderate)*.

XI. For Patients With Bone and/or Joint Coccidioidomycosis, Which Therapy Is Preferred: Intravenous AmB or an Oral Azole?

Recommendations

16. We recommend azole therapy for bone and joint coccidioidomycosis, unless the patient has extensive or limb-threatening skeletal or vertebral disease causing imminent cord compromise *(strong, low)*.
17. For severe osseous disease, we recommend AmB as initial therapy, with eventual change to azole therapy for the long term *(strong, low)*.

XII. In Patients With Vertebral Coccidioidomycosis, Should Lesions Be Managed With Surgery?

Recommendations

18. We recommend surgical consultation for all patients with vertebral coccidioidal infection to assist in assessing the need for surgical intervention *(strong, low)*.
19. Surgical procedures are recommended in addition to antifungal drugs for patients with bony lesions that produce spinal instability, spinal cord or nerve root compression, or significant sequestered paraspinal abscess [5] *(strong, low)*.
20. We recommend that surgical consultation be obtained periodically during the course of medical treatment *(strong, low)*.

XIII. In Patients With Newly Diagnosed Coccidioidal Infection, Should a Lumbar Puncture Be Performed?

Recommendation

21. In patients with recently diagnosed coccidioidal infection, we recommend lumbar puncture with cerebrospinal fluid analysis only in patients with unusual, worsening, or persistent headache, with altered mental status, unexplained nausea or vomiting, or new focal neurologic deficit after adequate imaging of the central nervous system (CNS) *(strong, moderate)*.

XIV. For Patients With Newly Diagnosed CM, What Is the Primary Treatment?

Recommendation

22. For CM, we recommend fluconazole 400–1200 mg orally daily as initial therapy for most patients with normal renal function *(strong, moderate)*. There is no role for a dose <400 mg daily in the adult patient without substantial renal impairment. Some experts prefer to use itraconazole 200 mg 2–4 times daily, but this requires closer monitoring to assure adequate absorption, and there are more drug–drug interactions than with fluconazole.

XV. For Patients With CM Who Improve or Become Asymptomatic on Initial Therapy, When Can Treatment be Stopped?

Recommendation

23. For CM, we recommend azole treatment for life *(strong, moderate)*.

XVI. In Patients With CM Who Do Not Have a Satisfactory Response to Initial Antifungal Therapy, What Modifications Can Be Considered?

Recommendation

24. In patients who clinically fail initial therapy with fluconazole, higher doses are a first option *(strong, moderate)*. Alternative options are to change therapy to another orally administered azole, or to initiate intrathecal AmB therapy.

XVII. For Patients Who Develop Hydrocephalus, Which Patients Should Be Referred for Neurosurgical Procedures to Relieve Intracranial Pressure (ICP)?

Recommendations

25. For patients with increased ICP at the time of diagnosis, we recommend medical therapy and repeated lumbar punctures as initial management *(strong, low)*.
26. Because most patients who develop ICP will not resolve this problem without placement of a permanent shunt, we recommend early magnetic resonance imaging (MRI) of the brain and neurosurgical consultation *(strong, moderate)*.

XVIII. In Patients With CM and in Whom a Ventriculoperitoneal Shunt Has Been Placed, Should Shunt Malfunction or Superinfection Be Managed With a Single- or Double-Staged Surgical Revision?

Recommendation

27. We recommend that patients with ventriculoperitoneal shunt malfunction have the revision performed in a single procedure *(strong, low)*. When the shunt has developed a bacterial or other superinfection, we recommend that the infected shunt be removed and a replacement be placed at a subsequent time as a second procedure *(strong, low)*.

XIX. In Patients With CM Who Initially Respond to a Treatment Plan and While on Therapy Develop Acute or Chronic Neurologic Changes, What Assessments Are Needed to Reevaluate and Modify Therapy?

Recommendation

28. We recommend that repeat MRI of the brain and possibly the spinal cord, with and without contrast, as well as spinal fluid analysis be obtained either from a lumbar or cisternal aspiration *(strong, low)*.

RECOMMENDATIONS FOR MANAGEMENT OF PATIENTS WITH COCCIDIOIDOMYCOSIS IN SPECIAL AT-RISK POPULATIONS

XX. For Allogeneic or Autologous Hematopoietic Stem Cell Transplant (HSCT) or Solid Organ Transplant Recipients With Active Coccidioidomycosis, Which Initial Treatment Strategy Is Preferred: Oral Azole or Intravenous AmB?

Recommendations

29. For the treatment of autologous or allogeneic HSCT or solid organ transplant recipients with acute or chronic pulmonary coccidioidomycosis who are clinically stable and have normal renal function, we recommend initiating treatment with fluconazole 400 mg daily or the equivalent dose based upon renal function *(strong, low)*.
30. For the treatment of patients with very severe and/or rapidly progressing acute pulmonary or disseminated coccidioidomycosis, we recommend the use of AmB until the patient has stabilized, followed by fluconazole *(strong, low)*.
31. For autologous or allogeneic HSCT or solid organ transplant recipients with extrapulmonary coccidioidomycosis, we recommend the same treatment as for non–transplant recipients *(strong, very low)*.

XXI. In Such Patients, Should Antirejection Treatment Be Modified or Continued Without Change?

Recommendation

32. For allogeneic HSCT or solid organ transplant recipients with severe or rapidly progressing coccidioidomycosis, we recommend reduction of immunosuppression (without risking graft-vs-host disease or organ rejection, respectively, whenever possible) until the infection has begun to improve *(strong, very low)*.

XXII. In HSCT or Solid Organ Transplant Recipients With Active Coccidioidomycosis, Should Antifungal Treatment Be Modified Following Initial Treatment?

Recommendation

33. Following initial treatment of active coccidioidomycosis, we recommend that suppressive treatment be continued to prevent relapsed infection *(strong, very low)*.

XXIII. For Recipients of Biological Response Modifiers With Active Coccidioidomycosis, Which Treatment Is Preferred: Oral Azole or Intravenous AmB?

Recommendation

34. We recommend oral azole therapy for these patients unless their coccidioidomycosis is severe enough that intravenous AmB would otherwise be recommended (refer to sections on pneumonia, soft tissue dissemination, skeletal dissemination, and meningitis) *(strong, low)*.

XXIV. What Is the Preferred Method for Management of Pregnant Women With Coccidioidomycosis and Their Neonates?

Recommendations During Pregnancy

35. The development of symptomatic coccidioidomycosis during pregnancy should prompt consideration of starting administration of antifungal therapy *(strong, moderate)*. For women who develop initial nonmeningeal coccidioidal infection during pregnancy, their management depends on fetal maturity.
36. For women who develop initial nonmeningeal coccidioidal infection during their first trimester of pregnancy, intravenous AmB is recommended *(strong, moderate)*. Other options include no therapy with close monitoring *(weak, low)*, or an azole antifungal after educating the mother regarding potential teratogenicity *(weak, low)*. After the first trimester of pregnancy, an azole antifungal, such fluconazole or itraconazole, can be considered *(strong, low)*. A final alternative would be to administer intravenous AmB throughout pregnancy *(weak, moderate)*.
37. For women who develop CM during the first trimester of pregnancy, intrathecal AmB is recommended *(strong, moderate)*. After the first trimester and in cases where disease is diagnosed after the first trimester, an azole antifungal, such as fluconazole or itraconazole, can be prescribed *(strong, low)*.
38. Among women with a history of prior coccidioidomycosis who are not currently on therapy, the risk of reactivation is low and antifungal therapy is not recommended *(strong, moderate)*. For such women, close follow-up, including obtaining coccidioidal serologic testing at the initial visit and every 6–12 weeks throughout pregnancy, should be performed *(strong, moderate)*.
39. For women with nonmeningeal coccidioidomycosis on antifungal therapy who become pregnant while infection is in remission, azole antifungal therapy may be discontinued with clinical and serological monitoring every 4–6 weeks to assess for reactivation *(weak, low)*. An alternative to this, especially if the coccidioidal infection is not clearly in remission, is to stop azole antifungal therapy and start intravenous AmB during the first trimester, changing back to an azole antifungal after the first trimester *(strong, low)*.
40. For the pregnant woman with CM who is on azole antifungal therapy at the time of pregnancy, azole therapy should be stopped for the first trimester to avoid the risk of teratogenicity *(strong, moderate)*. During this period, one approach is to initiate intrathecal AmB, especially if meningeal signs and symptoms are present *(strong, moderate)*. Azole antifungal therapy may then be restarted during the second trimester *(weak, low)* or intrathecal AmB continued throughout gestation *(weak, low)*. An alternative is to continue azole antifungal therapy throughout gestation provided that the mother agrees to this approach after being educated regarding the risks and benefits of this strategy *(weak, low)*. A final alternative for the pregnant woman with CM is to stop the azole antifungal, monitor the patient closely during the first trimester, and restart azole antifungal therapy during the second or third trimester *(weak, very low)*. Because of the risk of relapse with this approach, some experts do not recommend it.
41. The development of a febrile pulmonary illness during pregnancy in a woman residing in the coccidioidal endemic region or with an appropriate travel history should be evaluated for active coccidioidomycosis, including obtaining a chest radiograph and coccidioidal serology and cultures *(strong, moderate)*.

Recommendations for Neonates

42. We recommend against coccidioidal serologic tests for infants during the first 3 months of life. Positive tests should be interpreted with caution during the first year of life *(strong, moderate)*.
43. Empiric therapy with fluconazole at 6–12 mg/kg daily is recommended for infants suspected of having coccidioidomycosis and should be continued until the diagnosis has been ruled out *(strong, low)*.
44. Breastfeeding is not recommended for mothers on azole antifungals other than fluconazole *(strong, moderate)*.

XXV. What Is the Best Way to Manage Coccidioidomycosis in Patients Infected With HIV?

Recommendations

45. Antifungal prophylaxis is not recommended to prevent coccidioidomycosis in patients infected with HIV living in coccidioidal-endemic regions *(strong, moderate)*.
46. Antifungal therapy is recommended for all patients with HIV infection with clinical evidence of coccidioidomycosis and a peripheral blood $CD4^+$ T-lymphocyte count <250 cells/μL *(strong, moderate)*.
47. Antifungal therapy should be continued as long as the peripheral $CD4^+$ T-lymphocyte count remains <250 cells/μL *(strong, low)*.
48. For patients with peripheral $CD4^+$ T-lymphocyte counts ≥250 cells/μL, clinical management of coccidioidomycosis should occur in the same manner as for patients without HIV infection, including discontinuing antifungal therapy in appropriate situations *(strong, moderate)*.
49. Within coccidioidal-endemic regions, patients should receive yearly serologic screening and chest radiography for coccidioidomycosis *(strong, low)*.
50. Outside coccidioidal-endemic regions, serologic screening is not recommended *(strong, moderate)*.
51. Although data are lacking, pediatric patients with HIV infection and coccidioidomycosis should be managed in a manner similar to adult patients *(strong, very low)*.

52. Initiation of potent antiretroviral therapy (ART) should not be delayed because of the concern about coccidioidal immune reconstitution inflammatory syndrome *(strong, low)*.

RECOMMENDATIONS FOR PREEMPTIVE STRATEGIES FOR COCCIDIOIDOMYCOSIS IN SPECIAL AT-RISK POPULATIONS

XXVI. For Organ Transplant Recipients Without Active Coccidioidomycosis, Which Primary Prevention Strategy Is Preferred: Observation or Oral Azole?

Recommendation

53. For all patients undergoing organ transplantation in the endemic area without active coccidioidomycosis, we recommend the use of an oral azole (eg, fluconazole 200 mg) for 6–12 months *(strong, low)*.

XXVII. For Recipients of Biological Response Modifiers Without Active Coccidioidomycosis, Which Primary Prevention Strategy Is Preferred: Observation or Prophylactic Antifungal Therapy?

Recommendation

54. For patients in the endemic area, we recommend screening with *Coccidioides* serology prior to initiation of biologic response modifier therapy, as well as regular clinical follow-up for new signs and symptoms *(strong, very low)*. We do not recommend regular serologic screening or antifungal prophylaxis in asymptomatic patients taking biologic response modifiers (BRMs) *(strong, very low)*.

Notes

Acknowledgments. The expert panel expresses its gratitude for thoughtful reviews of an earlier version by Drs Joshua Fierer, Laura Proia, and George Thompson. The panel thanks Vita Washington for her administrative organization, guidance, and preparation of the manuscript.

Financial support. Support for these guidelines was provided by the Infectious Diseases Society of America (IDSA).

Potential conflicts of interest. The following list is a reflection of what has been reported to the IDSA. To provide thorough transparency, the IDSA requires full disclosure of all relationships, regardless of relevancy to the guideline topic. Evaluation of such relationships as potential conflicts of interest (COI) is determined by a review process which includes assessment by the Standards and Practice Guidelines Committee (SPGC) Chair, the SPGC liaison to the development panel and the Board of Directors' liaison to the SPGC, and if necessary, the COI Task Force of the Board. This assessment of disclosed relationships for possible COI will be based on the relative weight of the financial relationship (ie, monetary amount) and the relevance of the relationship (ie, the degree to which an association might reasonably be interpreted by an independent observer as related to the topic or recommendation of consideration). The reader of these guidelines should be mindful of this when the list of disclosures is reviewed. J. N. G. has received research grants from Valley Fever Solutions, P. B. R. has received research grants from BHR Pharmaceuticals LLC. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. BMJ **2008**; 336:1049–51.
2. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians? BMJ **2008**; 336:995–8.
3. Jaeschke R, Guyatt GH, Dellinger P, et al. Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. BMJ **2008**; 337:a744.
4. Guyatt GH; US GRADE Network. Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE methodology. Available at: http://www.gradeworkinggroup.org/. Accessed 15 July 2015.
5. Szeyko LA, Taljanovic MS, Dzioba RB, Rapiejko JL, Adam RD. Vertebral coccidioidomycosis: presentation and multidisciplinary management. Am J Med **2012**; 125:304–14.