ORIGINAL ARTICLE

Peter D. Yorgin · Mona Rewari · Amira Y. Al-Uzri
Andreas A. Theodorou · Katherine M. Scott
Leslie L. Barton

Coccidioidomycosis in adolescents with lupus nephritis

Abstract Coccidioidomycosis, a fungal infection endemic in the southwestern United States, can cause life-threatening infections in immunosuppressed patients. We report the contrasting cases of two adolescents with lupus nephritis, treated with intravenous pulse cyclophosphamide and daily oral corticosteroids, who developed pulmonary coccidioidomycosis. One patient developed a fatal form of fulminant disseminated coccidioidomycosis, while the other patient developed a solitary pulmonary *Coccidioides immitis* abscess which was responsive to intravenous liposomal amphotericin and fluconazole therapy. Because serologies and initial X-ray studies can be negative, definitive diagnostic studies including bronchioaveolar lavage and needle aspiration should be performed when there is clinical suspicion of coccidioidomycosis in an immunocompromised patient. Immunosuppressed patients with coccidioidomycosis should receive early intravenous amphotericin therapy and may benefit from long-term suppressive antifungal therapy to prevent relapse.

Keywords Coccidioidomycosis · Amphotericin · Liposomal amphotericin · Fluconazole · Systemic lupus erythematosus · Adolescent

P.D. Yorgin
Department of Pediatrics, Stanford University,
Stanford, California, USA

M. Rewari · A.A. Theodorou · L.L. Barton
Department of Pediatrics,
Steele Memorial Children's Research Center,
University of Arizona, Tucson, Arizona, USA

A.Y. Al-Uzri
Department of Pediatrics,
University of Virginia Health Sciences Center,
Charlottesville, Virginia, USA

K.M. Scott
Department of Pathology, University of Arizona,
Tucson, Arizona, USA

P.D. Yorgin (✉)
Department of Pediatrics, Section of Pediatric Nephrology,
Stanford University, 703 Welch Road, Suite H5,
Palo Alto, CA 94305, USA
e-mail: pyorgin@stanford.edu
Tel.: +1-650-4985480, Fax: +1-650-4978718

Introduction

Intravenous pulse cyclophosphamide (IPC) in combination with oral daily corticosteroids is thought to be effective therapy for diffuse proliferative glomerulonephritis (DPGN) in patients with systemic lupus erythematosus (SLE) [1, 2]. Yet, the immunosuppression required to control lupus nephritis impairs T-cell function, B-cell activity and antibody formation [2, 3] and, as a consequence, increases the risk of life-threatening bacterial, viral and fungal infections [1, 4].

Coccidioidomycosis, a fungal infection endemic in the southwestern United States, Mexico and Central and South America, most frequently causes a pulmonary infection with a wide spectrum of clinical illness. In healthy individuals, symptomatic infection is most commonly a subacute, self-limited pulmonary illness, which occasionally may mimic bacterial pneumonia or sepsis. Immunocompromised patients, in endemic areas, are at risk of developing disseminated coccidioidomycosis [5, 6], since their normal immune response to *Coccidioides immitis* is blunted [7, 8]. Coccidioidomycosis has become a national health concern due to the increased travel of immunosuppressed patients to and from the southwestern United States [9].

We report two adolescent patients with lupus nephritis who demonstrate the diverse presentation of coccidioidomycosis in immunosuppressed individuals. Both patients lived in Tucson, Arizona, an endemic area for coccidioidomycosis. To our knowledge, this is the first case report of coccidioidomycosis in adolescent patients with SLE. The diagnostic and therapeutic dilemmas encountered in these cases are discussed.

Case reports

Case 1

A 13-year-old female with recently diagnosed lupus nephritis (DPGN) presented with fever, rhinorrhea and cough 15 days after
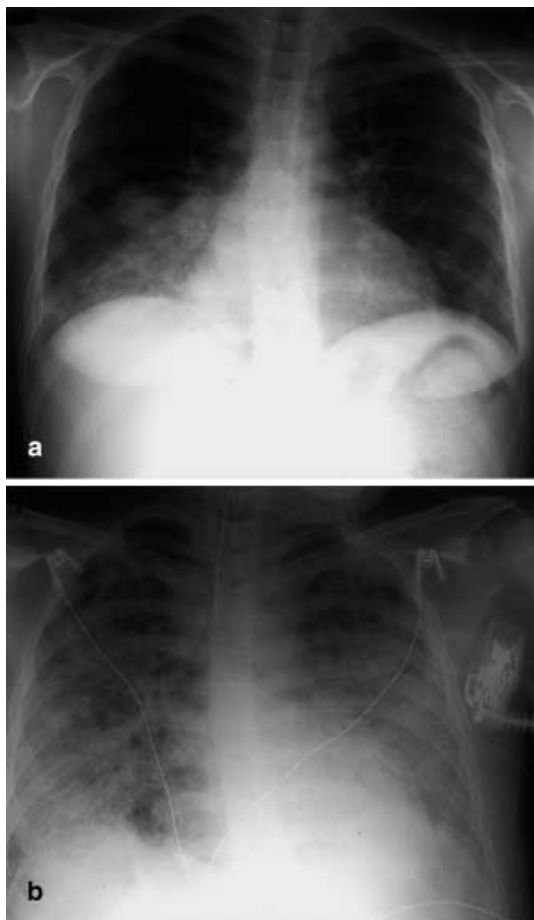
Fig. 1 a Posterior-anterior chest radiograph revealing a right lower lobe infiltrate consistent with right basal pneumonia. b Anterior-posterior chest radiograph demonstrating progression of air space disease with severe bilateral consolidation and areas of well-defined rounded lucency within the right lung consistent with pneumatoceles

Fig. 2 Giant cells are shown engulfing spherules. ×140

her first intravenous pulse cyclophosphamide dose (500 mg/m^2). Admission physical examination was significant for a temperature of 39.9°C, a blood pressure of 145/81 mmHg and a pulse of 137 bpm. A chest radiograph obtained on admission demonstrated clear lung fields. Intravenous erythromycin and ceftazidime were started on the 3rd hospital day, after a chest radiograph revealed a right lower lobe infiltrate consistent with right basal pneumonia (Fig. 1a). The next day the patient developed increasing respiratory distress with oxygen saturations in the low 80s. Oxygen by nasal cannula was initiated at 3 l/min. There was progression of the right lower lobe consolidation with left-sided patchy infiltrates. Intradermal coccidiodin and tuberculin skin tests were negative with a positive mumps control. Coccidioidomycosis serologies (tube precipitins and complement fixation antibodies by immunodiffusion) were negative. During the 5th hospital day, the patient was transferred to the pediatric intensive care unit for mechanical ventilation. Bronchoalveolar lavage demonstrated coccidioidal spherules. Antibiotic therapy was discontinued and intravenous amphotericin B (1 mg/kg/day) and fluconazole (7 mg/kg/day) therapy were initiated. By the 6th hospital day there was generalized involvement of both lungs consistent with acute respiratory distress syndrome (ARDS). High ventilatory parameters (FiO$_2$ 100%, R 20, PC 38, PEEP 14) were required to maintain hemoglobin oxygen saturations >80%. Left and right pneumothoraces requiring thoracostomy developed and a pleural fluid viral culture was positive for adenovirus. On the 11th hospital day, amphotericin B was
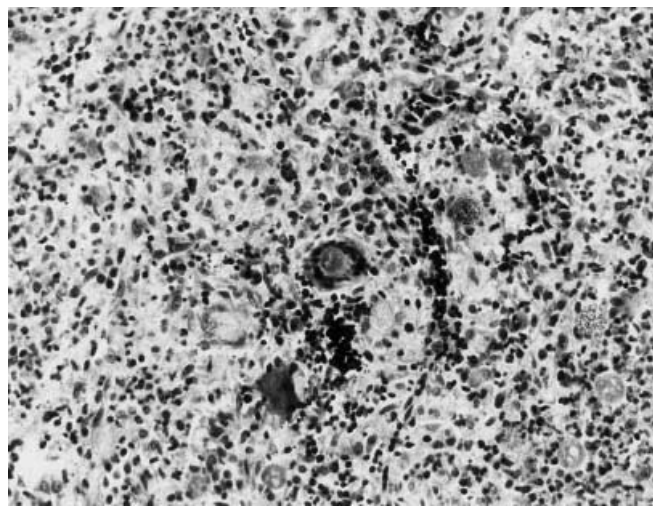
discontinued and liposomal amphotericin (2.5 mg/kg) was initiated to minimize nephrotoxicity. The patient's pulmonary status worsened despite maximal ventilatory support (FiO$_2$ 100%, R 30, PC 50, PEEP 14). On the 18th hospital day there was progression of air space disease with severe bilateral consolidation and areas of well-defined rounded lucency within the right lung consistent with pneumatoceles (Fig. 1b). Because of progressive respiratory acidosis, hypoxemia, and hypotension due to overwhelming sepsis, ventilatory support was withdrawn on the 27th day of her hospitalization.

On postmortem examination, disseminated coccidioidomycosis involving the lungs, lymph nodes, liver, spleen, thyroid, parathyroids, myocardium, and brain was found. Severe and diffuse lung injury was noted, characterized by consolidation, inflammation, necrosis and microabscess formation with an overwhelming number of fungal organisms scattered throughout the pulmonary parenchyma (Fig. 2). *Coccidioides immitis* and *Staphylococcus aureus* were isolated from lung tissue.

Case 2

A 10-year-old girl with a 4-year history of lupus nephritis was admitted with a 1-day history of back pain, dyspnea and fever. The patient had received a course of intravenous pulse cyclophosphamide (monthly ×6 and quarterly doses ×4) for treatment of DPGN. Three months prior to her admission, she had an episode of SLE-mediated acute renal failure which responded to pulse methylprednisolone, a 2-week course of plasmapheresis, monthly intravenous pulse cyclophosphamide and an increase in oral corticosteroids. Admission physical examination revealed a female who appeared acutely ill with a temperature of 38.9°C and a pulse of 115 bpm. Lungs were clear to auscultation and percussion. Her back was tender to palpation in the mid-lumbar spine but there was no bruising, erythema or swelling. Initial laboratory studies included a WBC of 11,500/mm^3 and no evidence of serologic activity attributable to SLE. The initial chest radiograph was unremarkable; blood and urine cultures were negative. Empiric vancomycin and tobramycin treatment were started on admission and one dose of intravenous immune globulin was given due to low serum IgG levels. The patient had back pain that localized to her left lower thoracic spine. A chest radiograph on the second hospital day revealed a round density in the left lower lobe (Fig. 3a) and computerized tomography (CT) scans of the chest and abdomen demonstrated a pleural based density measuring 3.5×2 cm in the left lower lung with a necrotic center (Fig. 3b). Antibiotic therapy was changed to ceftazidime and clindamycin, but fevers (39.4°C) per-
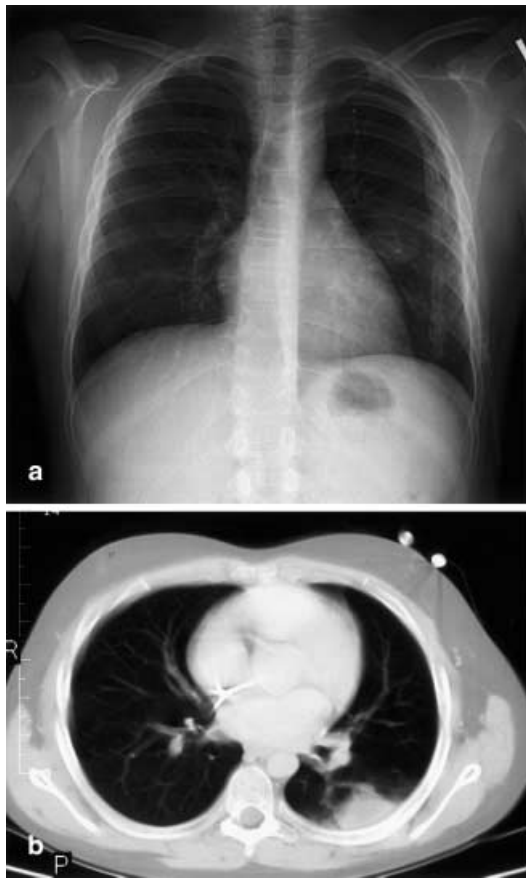
Fig. 3 a Posterior-anterior chest radiograph showing a round density in the left lower lobe. **b** Computerized tomography (CT) scans of the chest and abdomen demonstrating a pleural based density measuring 3.5×2 cm in the left lower lung with a necrotic center

sisted. On the 6th hospital day, needle aspiration of the abscess was performed when the CT scan showed an increase in the size of the lung lesion to 3.8×2.5 cm. Cultures from the aspirate were positive for *C. immitis*. Antibiotics were stopped and intravenous amphotericin B (1 mg/kg/day) was started. Serum coccidioidomycosis serologies obtained from pre-IVIG serum were negative. However, repeat serologies (tube precipitins and complement fixation antibodies by immunodiffusion) on the 16th hospital day were positive. Intravenous liposomal amphotericin was substituted due to amphotericin B induced mild acute renal failure. Although the patient felt better and was afebrile without back pain, there was no change in the lung density detectable by CT scan. The prednisone dose was tapered to 0.8 mg/kg/day to lessen her immunosuppression. The patient was discharged on oral fluconazole (200 mg/day) for 1 year duration. Yearly chest radiographs and CT scans have shown complete resolution of her lung abscess; there has been no evidence of relapse with a 2-year follow-up.

Discussion

In patients with SLE, the risk of death from infection is proportional to the intensity of immunosuppressive therapy. Individuals with lupus nephritis receiving immunosuppressive therapy, with exposure to *C. immitis*, are at risk for fulminant coccidioidomycosis [7, 10–12]. Although early recognition and treatment of the disease is

critical to improve the chances of patient survival, the diagnosis of coccidioidomycosis may be difficult, particularly if the patient presents for medical care outside endemic areas [13]. The clinical presentation of coccidioidomycosis in the immunocompromised patient is varied, sometimes presenting as in normal individuals, mimicking bacterial pneumonia, influenza, reactivation of lupus or sepsis [14]. The pulmonary disease may present with focal alveolar infiltrates, hilar adenopathy, or pleural effusions [15]. Pulmonary alveolar infiltrates may undergo excavation leaving a residual peripheral coccidioidal cavity or a coccidioidal nodule on chest radiograph [16]. Occasionally, in immunocompromised individuals, pulmonary coccidioidomycosis may also cause a chronic persistent and progressive pneumonia with pulmonary scarring and cavitation [16, 17]. Patients with chronic progressive coccidioidal pneumonia may have recurrent or persistent low-grade fever, productive cough, and weight loss. Our cases demonstrate that variable presentation and a normal chest radiograph on presentation do not exclude the diagnosis of coccidioidomycosis.

In less than 1% of cases, *C. immitis* can disseminate from the lungs and thoracic cavity to involve other organs through hematogenous spread [15, 18]. Spread of infection may occur within a few weeks to a few months after the initial infection. In disseminated coccidioidomycosis, the lesions are granulomatous with giant cells and histiocytes. Spherules can be identified in the lesions and within macrophages. The most common extrapulmonary sites of infection are bone, skin, muscle, lymph nodes, and the meninges. In case 1, lymph nodes, liver, spleen, thyroid, parathyroids, myocardium, and brain were involved.

At this time the best diagnostic tools are direct *C. immitis* culture from blood, bronchoalveolar lavage, cerebrospinal fluid, and serologic testing. Skin testing for *C. immitis* is likely to be unreliable in immunosuppressed patients due to an impairment in the delayed hypersensitivity response [19]. *C. immitis* can be cultured from the sputum; yet in our patients coccidioidomycosis was diagnosed by identification of *C. immitis* in samples obtained by needle aspiration and bronchoalveolar lavage. Serum complement fixation (CF) antibody titers (IgG) are typically high in patients with disseminated coccidioidomycosis; however, both of our patients had negative serologies at the time of presentation. Immunodiffusion testing for anti-coccidioidomycosis IgG and IgM was also negative. The initial immune response to a coccidioidomycosis infection is a detectable rise in IgM antibody with 50% of immunocompetent patients positive in the 1st week and 90% positive by 2–3 weeks. IgG antibodies appear later and are present in 50–90% of immunocompetent patients by 3 months after the onset symptoms. Together, 90% of infected immunocompetent patients will be either IgM or IgG positive [20]. However, immunocompromised patients, including those with SLE treated with IPC and corticosteroids, may have no detectable antibody even in the context of disseminated

coccidioidomycosis [17, 21, 22]. There are some newer approaches to diagnosing coccidioidomycosis. Enzyme immunoassay testing for coccidioidomycosis antibodies compares favorably with older techniques [19]. Recently, a proline-rich antigen (PRA), isolated from the spherules of *C. immitis*, was reported to be sensitive and specific in the detection of *C. immitis* antibodies [23]. A reliable PCR useful in detecting coccidioidomycosis is not available at this time.

Practice guidelines for the treatment of coccidioidomycosis in adults have been recently published [24]. All immunosuppressed patients with symptoms or radiographic evidence of progressive disease should be treated. *C. immitis* has been shown to be uniformly susceptible to amphotericin B in vitro; therefore, amphotericin B, at a dose of 0.1–1 mg/kg/day [25], is the drug of first choice in patients with invasive coccidioidal infections as well as fulminant infections. Lipid formulations of amphotericin B have been reserved for patients with amphotericin-induced progressive renal dysfunction or with fungal infections unresponsive to conventional amphotericin B therapy. For patients with diffuse pneumonia, amphotericin B therapy is continued for several weeks, until there is significant improvement, then discontinued in favor of oral azole therapy [24]. The total duration of the combined therapy is 1 year if the patient is immunocompetent; a longer course of therapy should be used for patients with disseminated coccidioidomycosis. Because amphotericin B and itraconazole do not cross the blood-brain barrier well, patients with meningeal involvement should be treated with intrathecal amphotericin or oral fluconazole (3–12 mg/kg/day) [25]. Our patient (case 1) was treated with intravenous fluconazole to treat her central nervous system disease. Relapses of coccidioidomycosis can occur after treatment [26, 27]. Patients who are symptomatic with pulmonary coccidioidal cavities should be treated with an oral azole [24] and may benefit from lobectomy [18, 24]. In patients with meningeal disease, concurrent use of fluconazole with amphotericin has been shown to be beneficial [28]. Amphotericin can be used until the disease becomes inactive, but acute treatment must be followed by long-term suppressive therapy with an oral azole to prevent relapse in immunosuppressed patients [24]. The appropriate duration of secondary prophylaxis is unknown.

The long-term management of lupus nephritis patients with coccidioidomycosis poses a unique challenge; achieving control of the lupus nephritis may induce worsening of the coccidioidomycosis. Even relatively low doses (500 mg/m^2) of intravenous pulse cyclophosphamide may increase the risk of fulminant coccidioidomycosis (case 1). The use of potentially less immunosuppressive drugs during the maintenance phase of lupus nephritis, or the use of prophylactic therapy (fluconazole or itraconazole) concomitantly with periodic administration of immunosuppressive agents, could be beneficial.

At present, there is no effective means available for prevention of human coccidioidomycosis in immunosuppressed individuals in endemic areas besides avoidance of outdoor activities [19]. In the cases presented, it is unclear whether the patients had preexisting latent coccidioidomycosis infections that worsened with immunosuppression therapy or if they became infected after immunosuppression therapy began. In endemic areas, serologic screening prior to immunosuppressive therapy to identify preexisting coccidioidomycosis infection should be considered, given the possibility of reactivation [13, 29–33]. Reactivation has been described in pregnant women [29, 30], patients with human immunodeficiency virus [32, 33], renal transplant patients treated with immunosuppressive agents [31] and even in apparently healthy individuals [13]. Fluconazole antifungal prophylaxis should be considered in immunosuppressed patients with positive coccidioidomycosis serologies. However, there is controversy over chemoprophylaxis due to the substantial cost of azole antifungal drugs and induction of antifungal resistance. Studies of coccidioidomycosis in patients with human immunodeficiency virus revealed that acquired immunodeficiency syndrome [34], low CD4 counts [34, 35], black race [35] and a history of oral candidiasis [35] were variables that were predictive of active infection, where prior coccidioidal infection, length of residence in the endemic area and even a prior history of coccidioidomycosis were not [34]. Woods et al. concluded that azole chemoprophylaxis was warranted for HIV-infected individuals with any of the risks listed above [35]. We speculate that the overall risks-benefit ratio of chemoprophylaxis can be improved by treating immunosuppressed children/adolescents that have low CD4 counts or patients receiving intense immunosuppressive therapy, including renal transplant recipients and patients receiving intravenous pulse cyclophosphamide therapy.

Pediatric nephrologists need to be aware of the early signs of coccidioidomycosis infection in children/adolescents with lupus nephritis, renal transplants or human immunodeficiency virus-mediated glomerular diseases, as these patients may present in non-endemic areas.

References

1. Austin HA III, Klippel JH, Balow JE, le Riche NG, Steinberg AD, Plotz PH, Decker JL (1986) Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Engl J Med 314:614–619
2. McCune WJ, Golbus J, Zeldes W, Bohlke P, Dunne R, Fox DA (1988) Clinical and immunologic effects of monthly administration of intravenous cyclophosphamide in severe systemic lupus erythematosus. N Engl J Med 318:1423–1431
3. Hurd ER, Giuliano VJ (1975) The effect of cyclophosphamide on B and T lymphocytes in patients with connective tissue diseases. Arthritis Rheum 18:67–75
4. Pryor BD, Bologna SG, Kahl LE (1996) Risk factors for serious infection during treatment with cyclophosphamide and high-dose corticosteroids for systemic lupus erythematosus. Arthritis Rheum 39:1475–1482
5. Deresinski SC, Stevens DA (1975) Coccidioidomycosis in compromised hosts. Experience at Stanford University Hospital. Medicine 54:377–395
6. Rutala PJ, Smith JW (1978) Coccidioidomycosis in potentially compromised hosts: the effect of immunosuppressive therapy in dissemination. Am J Med Sci 275:283–295

7. Conger J, Farrell T, Douglas S (1973) Lupus nephritis complicated by fatal disseminated coccidioidomycosis. Calif Med 118:60–65

8. Cox RA, Vivas JR, Gross A, Lecara G, Miller E, Brummer E (1976) In vivo and in vitro cell-mediated responses in coccidioidomycosis. I. Immunologic responses of persons with primary, asymptomatic infections. Am Rev Respir Dis 114:937–943

9. Galgiani JN (1999) Coccidioidomycosis: a regional disease of national importance. Rethinking approaches for control. Ann Intern Med 130:293–300

10. Andersen FG, Guckian JC (1968) Systemic lupus erythematosus associated with fatal pulmonary coccidioidomycosis. Texas Rep Biol Med 26:93–99

11. Berry CZ, Goldberg LC, Shepard WL (1968) Systemic lupus erythematosus complicated by coccidioidomycosis. JAMA 206:1083–1085

12. Sieving RR, Kauffman CA, Watanakunakorn C (1975) Deep fungal infection in systemic lupus erythematosus – three cases reported, literature reviewed. J Rheumatol 2:61–72

13. Williams FM, Markides V, Edgeworth J, Williams AJ (1998) Reactivation of coccidioidomycosis in a fit American visitor. Thorax 53:811–812

14. Lopez AM, Williams PL, Ampel NM (1993) Acute pulmonary coccidioidomycosis mimicking bacterial pneumonia and septic shock: a report of two cases. Am J Med 95:236–239

15. Stevens DA (1995) Coccidioidomycosis. N Engl J Med 332:1077–1082

16. Bayer AS (1981) Fungal pneumonias; pulmonary coccidioidal syndromes, part I. Primary and progressive primary coccidioidal pneumonias – diagnostic, therapeutic, and prognostic considerations. Chest 79:575–583

17. Ampel NM, Wieden MA, Galgiani JN (1989) Coccidioidomycosis: clinical update. Rev Infect Dis 11:897–911

18. Bayer AS (1981) Fungal pneumonias: pulmonary coccidioidal syndromes, part 2. Miliary, nodular, and cavitary pulmonary coccidioidomycosis; chemotherapeutic and surgical considerations. Chest 79:686–691

19. Shehab ZM (1998) Textbook of pediatric infectious diseases, vol 2, 4th edn. Edited by JDC Ralph D Feigin. Saunders, Philadelphia, pp 2314–2345

20. Smith CE, Saito MT, Simons SA (1956) Pattern of 39,500 serologic tests in coccidioidomycosis. JAMA 160:546–552

21. Pappagianis D, Zimmer BL (1990) Serology of coccidioidomycosis. Clin Microbiol Rev 3:247–268

22. Singh VR, Smith DK, Lawrence J, Kelly PC, Thomas AR, Spitz B, Sarosi GA (1996) Coccidioidomycosis in patients infected with human immunodeficiency virus: review of 91 cases at a single institution. Clin Infect Dis 23:563–568

23. Orsborn KI, Galgiani JN (1998) Detecting serum antibodies to a purified recombinant proline-rich antigen of *Coccidioides immitis* in patients with coccidioidomycosis. Clin Infect Dis 27:1475–1478

24. Galgiani JN, Ampel NM, Catanzano A, Johnson RH, Stevens DA, Williams PL (2000) Practice guidelines for the treatment of coccidiodomycosis. Clin Infect Dis 30:658–661

25. Pappagianis D (2000) Nelson textbook of pediatrics, 16th edn. Edited by RMK Richard E Behrman and HB Jenson. Saunders, Philadelphia, pp 942–944

26. Oldfield EC III, Bone WD, Martin CR, Gray GC, Olson P, Schillaci RF (1997) Prediction of relapse after treatment of coccidioidomycosis. Clin Infect Dis 25:1205–1210

27. Catanzaro A, Galgiani JN, Levine BE, Sharkey-Mathis PK, Fierer J, Stevens DA, Chapman SW, Cloud G (1995) Fluconazole in the treatment of chronic pulmonary and nonmeningeal disseminated coccidioidomycosis. NIAID Mycoses Study Group. Am J Med 98:249–256

28. Galgiani JN, Catanzaro A, Cloud GA, Higgs J, Friedman BA, Larsen RA, Graybill JR (1993) Fluconazole therapy for coccidioidal meningitis. The NIAID-Mycoses Study Group. Ann Intern Med 119:28–35

29. Peterson CM, Schuppert K, Kelly PC, Pappagianis D (1993) Coccidioidomycosis and pregnancy. Obstet Gynecol Surv 48:149–156

30. Walker MP, Brody CZ, Resnik R (1992) Reactivation of coccidioidomycosis in pregnancy. Obstet Gynecol 79:815–817

31. Seltzer J, Broaddus VC, Jacobs R, Golden JA (1986) Reactivation of coccidioides infection. West J Med 145:96–98

32. Minamoto G, Armstrong D (1988) Fungal infections in AIDS. Histoplasmosis and coccidioidomycosis. Infect Dis Clin North Am 2:447–456

33. Galgiani JN, Ampel NM (1990) Coccidioides immitis in patients with human immunodeficiency virus infections. Semin Respir Infect 5:151–154

34. Ampel NM, Dols CL, Galgiani JN (1993) Coccidioidomycosis during human immunodeficiency virus infection: results of a prospective study in a coccidioidal endemic area. Am J Med 94:235–240

35. Woods CW, McRill C, Plikaytis BD, Rosenstein NE, Mosley D, Boyd D, England B, Perkins BA, Ampel NM, Hajjeh RA (2000) Coccidioidomycosis in human immunodeficiency virus-infected persons in Arizona, 1994–1997: incidence, risk factors, and prevention. J Infect Dis 181:1428–1434