Coccidioidomycosis: clinical issues and conundrums

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Areas of concern that clinicians in Arizona face about coccidioidomycosis

- Epidemiology
- Diagnosis
- Management
- Knowledge
Cases of symptomatic disease: impact of Arizona

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Epidemiology

- While monitoring active cases is important, it does not indicate prevalence or overall incidence of infection.
- Coccidioidal prevalence can be determined by measuring the specific cellular immune response to coccidioidal antigens.
  - The spherulin and coccidioidin skin tests are no longer available.
  - An in vitro blood test is available experimentally.
- The current prevalence of infection is not known.
  - Previously estimated at between 20-40%.
Coccidioidal prevalence in the United States, circa 1952

adapted from Edwards & Palmer, Dis Chest 1957; 31:35.
Estimates of coccidioidal prevalence in Arizona using skin-testing

- **Aronson et al., Arch Pathol 1942; 34:31**
  - skin-tested Native Americans using coccidioidin
    - for those living in south-central Arizona, rates >80% & increased with age

- **Edwards and Palmer, Dis Chest 1957; 31:35**
  - ≥50% in Arizona among U.S. naval recruits (1949-1951) & nursing students (1945-49)
    - highest rates in counties in the south

- **Emmett et al., Am J Publ Health 1952; 42:241**
  - 42% of 1869 school-age children in Phoenix were positive in response to 1:00 coccidioidin

- **Doto et al., Am J Epidemiol 1972; 95:464**
  - 32% of 7982 school-age children in Maricopa County positive
    - annual conversions 3.2% in Phoenix but 10.7% in outlying areas

- **Dodge et al., Am J Publ Health 1985; 75:863**
  - 1977-9 tested non-hispanic Americans >3 years old in Tucson
    - Coccidioidin 1:100 (33.4%) vs Spherulin 1.4 µg (29.6%)
    - rates lower in those >54 years
Current status of coccidioidal skin tests

• Coccidioidin is no longer commercially available in the United States

• A commercial preparation of spherulin (Spherusol®) is FDA approved but not marketed
  - 1.27 µg elicited a response of 23.5 ± 2.3 mm of induration at 48 hr
  - similar to the U.S. reference

A Reformulated Spherule-Derived Coccidioidin (Spherusol) to Detect Delayed-Type Hypersensitivity in Coccidioidomycosis

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Mycopathologia
DOI 10.1007/s11046-012-9555-6
In vitro testing for coccidioidal immunity

• My laboratory has developed several assays to determine coccidioidal cellular immune response
  - all currently use T27K as the antigen
    • complex glycosylated antigen mixture
    • appears to be highly specific and correlates with coccidioidin skin-test positivity

• Whole blood vs peripheral blood mononuclear cells

• Methods
  - flow cytometry
    • surface CD69
    • intracellular cytokine (IL-2 or IFN-γ)
  - cytokine release (IL-2 or IFN-γ)

• Advantages
  - avoids having subject return
  - not susceptible to operator reading variance

• Disadvantages
  - requires 18 hr incubation step
  - methods not widely available in clinical laboratories
  - antigens not standardized
In vitro testing for coccidioidal immunity

Ampel et al., Mycopathologia 2006; 161:67
Ampel et al., Coccidioidomycosis Study Group 2013;
If coccidioidal cellular immunity could be ascertained

• Epidemiologically
  - Determine the overall prevalence of coccidioidomycosis in Arizona
  - Serial studies could determine incidence
  - Determine if there are geographic, climatic, chronologic, or other differences in the risk of infection
  - Relate the incidence of symptomatic disease to prevalence

• Clinically
  - establish if a patient was previously infected and therefore not a risk for new infection
  - monitor efficacy of therapy
    • especially regarding relapse
Diagnosis

• The diagnosis in most instances depends on a serologic response
  - the sensitivity of current tests is not known
    • there is no “gold standard”
  - EIA appears to be more sensitive than standard or immunodiffusion TP/CF
    • EIA may not be as specific as TP/CF
  - usefulness in immunocompromised patients is limited
• Culture and histology demonstrating a spherule are pathonomonic
  - sensitivities may be low
  - may require invasive procedure
• Newer tests include antigen detection and PCR
  - do not appear to be more sensitive than culture
Management issues

• Should all patients with primary pulmonary coccidioidomycosis be treated with an antifungal?
  - if not, who should be treated?
• What is the best therapy?
  - for pulmonary disease
  - for non-meningeal disseminated coccidioidomycosis
  - for meningitis
• What are the roles of the newer antifungals?
  - posaconazole, voriconazole
    • newer agents: isavuconazole, efinaconazole, iodiconazole
  - echinocandins
  - Nikkomycin Z
• There have been no recent randomized, double-blind, controlled studies of any antifungal for coccidioidomycosis
Should all cases of primary pulmonary coccidioidomycosis be treated?

- We performed a prospective/retrospective, non-randomized study
- Compared 51 patients who did not receive antifungal therapy to 54 who did
- Clinical resolution was equivalent in the two groups
- No complications occurred in the untreated group
- 8 of those treated either relapsed or disseminated

Factors and Outcomes Associated with the Decision to Treat Primary Pulmonary Coccidioidomycosis

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Clinical Infectious Diseases 2009;48:172–8
Physician knowledge

• ADHS has shown limited knowledge of coccidioidomycosis among Arizona physicians

• VFCE with ADHS has sponsored a course for primary care physicians

• Medical school courses are limited
Recommendations

• Promote epidemiological & clinical assays of cellular immune response to determine prevalence, incidence and outcome of coccidioidal infection
• Develop more sensitive and specific diagnostic tests
• Promote studies of the best management strategies
  - Need randomized controlled studies of newer antifungals
• Continue and continue educating Arizona physicians about coccidioidomycosis
  - expand medical school curriculum