

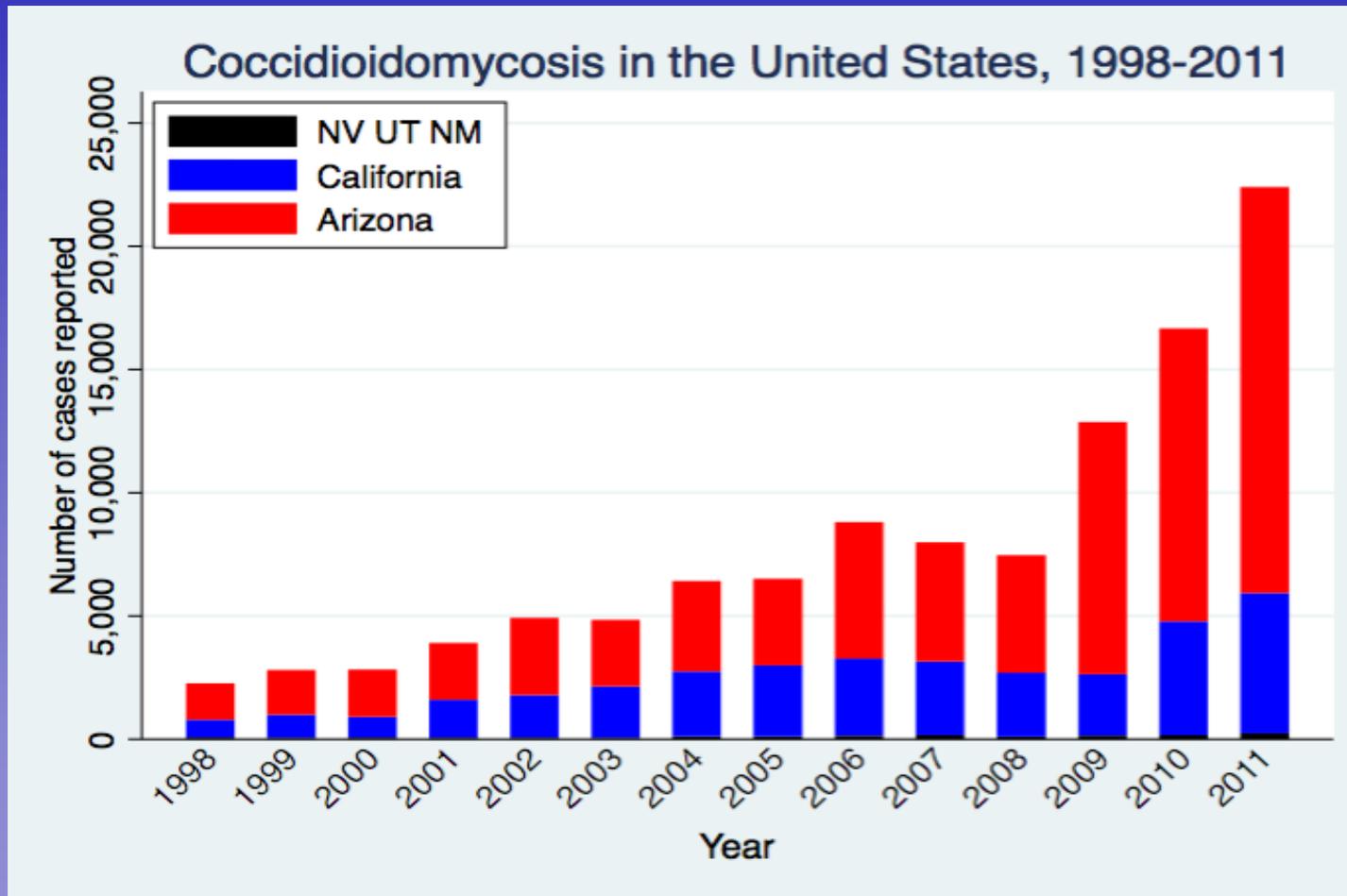
Coccidioidomycosis: clinical issues and conundrums

Neil M. Ampel, M.D.
Professor of Medicine
University of Arizona
Staff Physician, SAVAHCS
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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

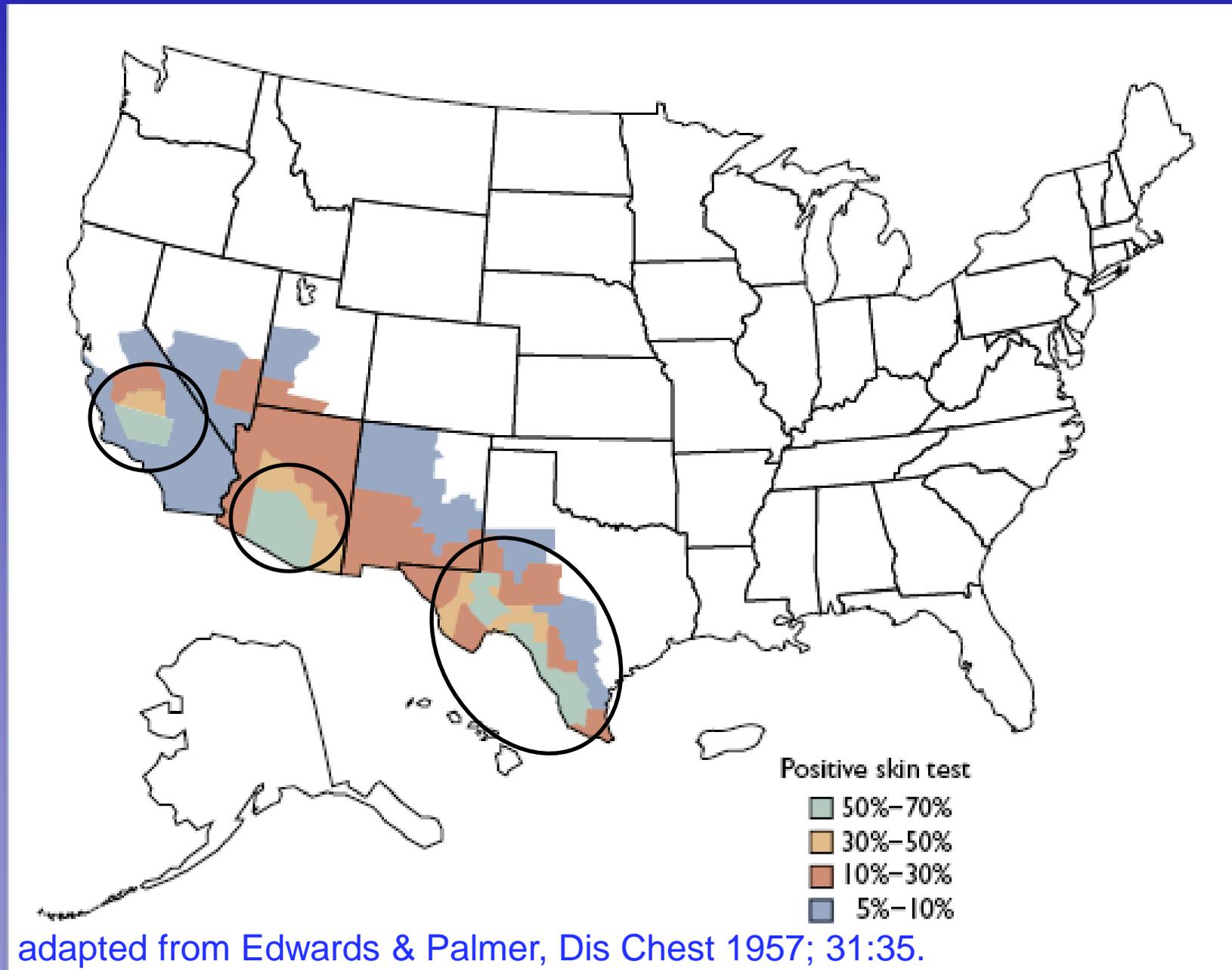


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Epidemiology

- 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



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

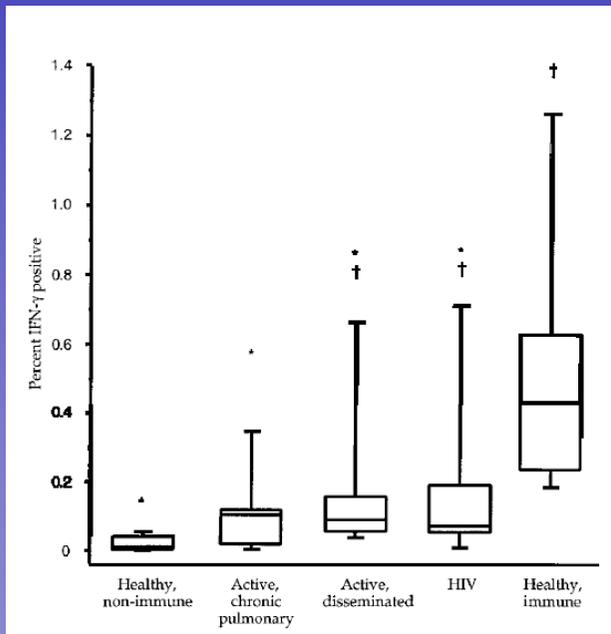
Royce Johnson • Steven M. Kernerman •
Bradley G. Sawtelle • Suresh C. Rastogi •
H. Stewart Nielsen • Neil M. Ampel

Mycopathologia
DOI 10.1007/s11046-012-9555-6

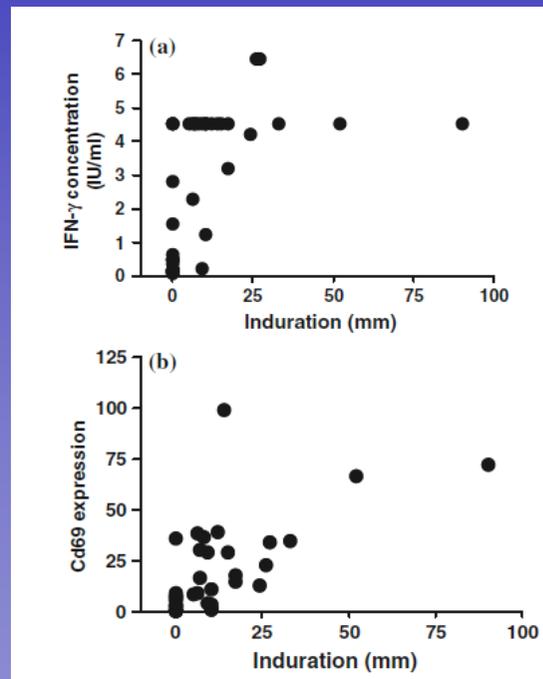
In vitro testing for coccidioidal immunity

- 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

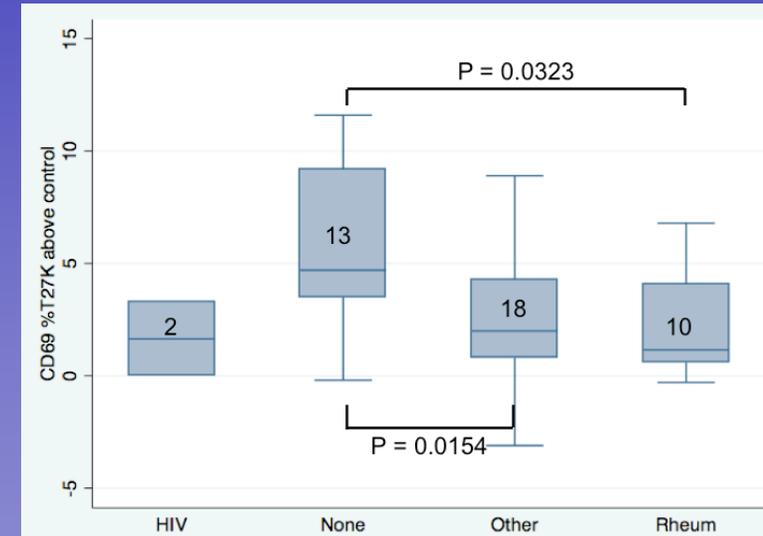
In vitro testing for coccidioidal immunity



Ampel et al., Med Mycol 2000; 39:315



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 pathognomonic
 - 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

Neil M. Ampel, Andrea Giblin, John P. Mourani, and John N. Galgiani

Department of Medicine, Section of Infectious Diseases, University of Arizona, and the Southern Arizona Veterans Affairs Health Care System, Tucson

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

