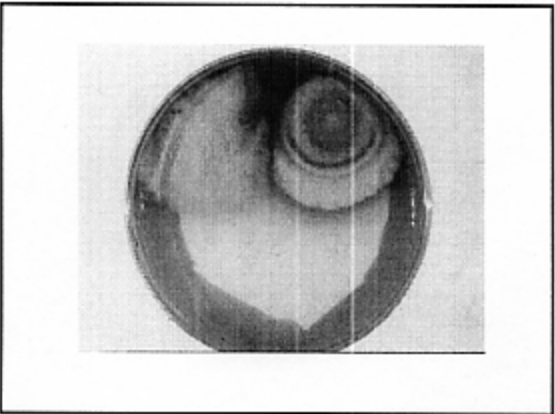


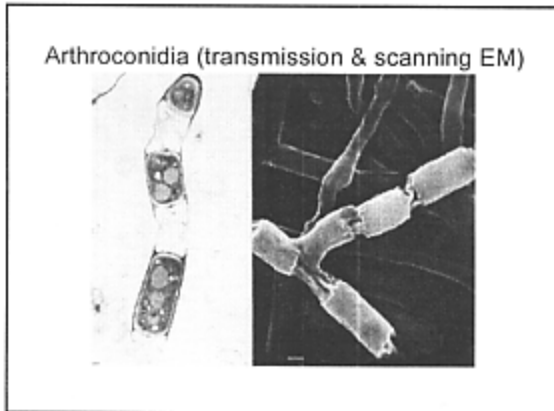
Coccidioidomycosis
Mycology
UT Austen

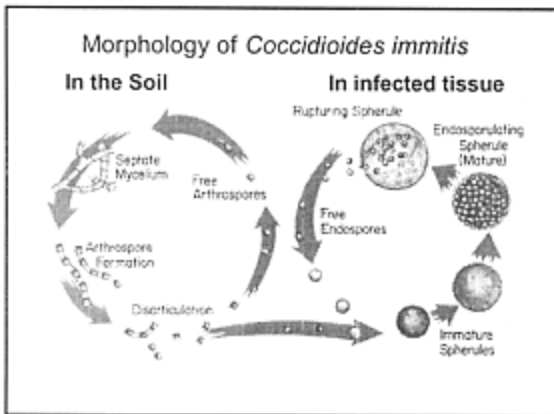
John N Galgiani
Valley Fever Center for Excellence
April 11, 2002

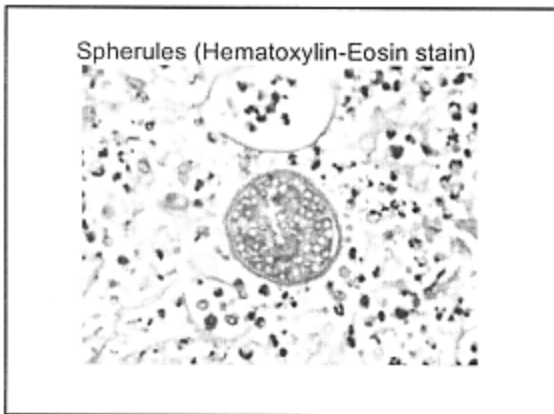
What Is Valley Fever?

- Caused by a soil fungus
Coccidioides immitis
- Other names:
 - Coccidioidomycosis (cocci)
 - Desert Rheumatism
- Infection results from inhaling a spore
- Severity varies
 - Mild: 60%
 - Moderate: 30%
 - Complicated: 10%
- After infection, most persons develop life-long immunity



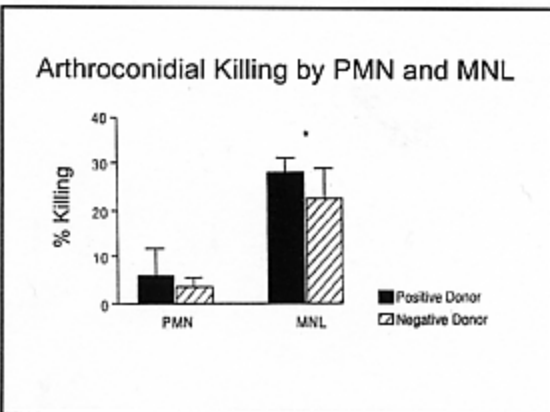


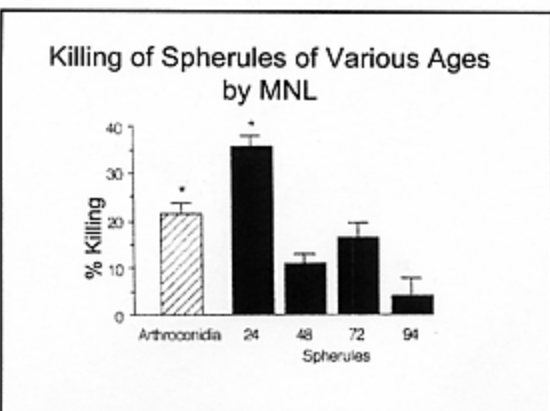




How Do 95% of Patients Recover from Coccidioidomycosis

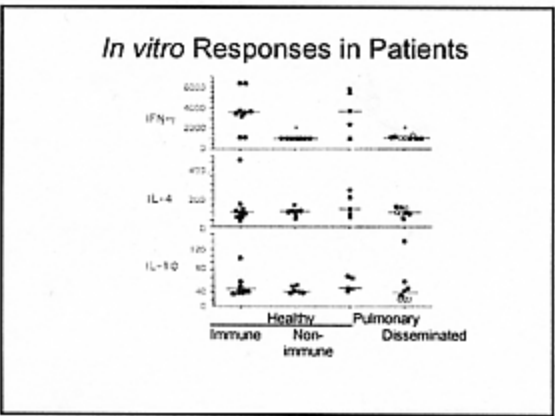
- Innate Immunity
 - Neutrophils
 - Mononuclear/NK cells
- Acquired Immunity
 - Antigen presentation
 - Specific T-cell clones stimulated.
 - Cytokine-mediated effector cell responses.

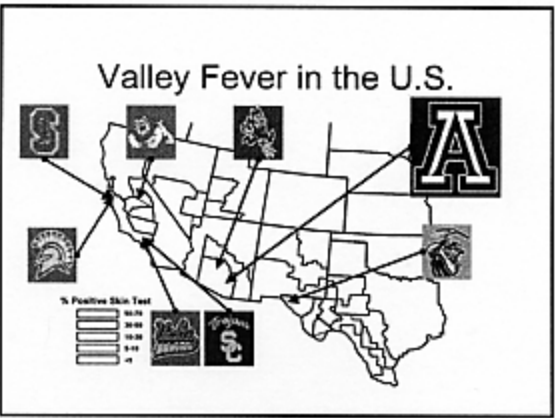


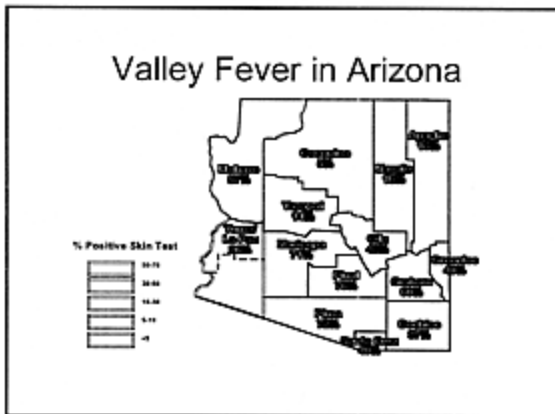


Cellular Immunity against *C. immitis*

- Murine studies
 - Adoptive transfer of immune splenocytes confer protection to naive animals
 - IL-12 or IFN-gamma prolongs survival or reduces fungal growth *in vivo*.
- Human studies
 - LT, IL-2, IFN-gamma response in immune persons but not in non-immune or those with disseminated infections.

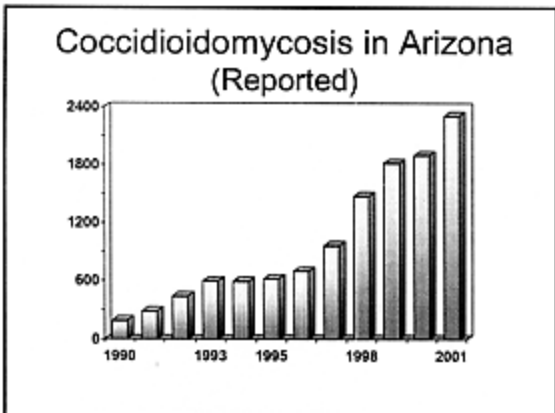






Valley Fever: Arizona's Problem

- Major Problem for Public Health
 - 100,000 infections per year (60,000 in AZ)
 - 30,000 illnesses that last from weeks to many months. Some infections are fatal.
- Potential Problem for State Economy
 - If perceived risk of Valley Fever is not managed by education and research, businesses and tourists may go elsewhere



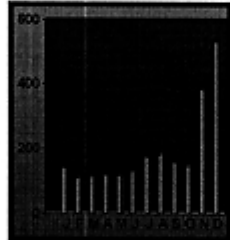
Community-Acquired Pneumonia S Az VA Health Care System

- **Pneumococcus**
 - Bacteremia: 10/year
52 blood isolates in 1997-2001. Evelyn Pugh, Lab Services.
 - Est: 40 pneumonia/yr
25% of *Str. Pneumo* infections are bacteremic. D Musher. In Mandel, PPID, 2000.
- ***Coccidioides immitis***
 - **Pulmonary**
 - + Pneumonia: 16/year
 - + Nodule: 5/year
 - + Fibrocavitary: 7/year
 - **Disseminated:**
 - + Meningitis: 4/year
 - + Soft tissue: 4/year
 - + Skeletal: 2/year

NM Ampel. Valley Fever Clinic, 2001 data.

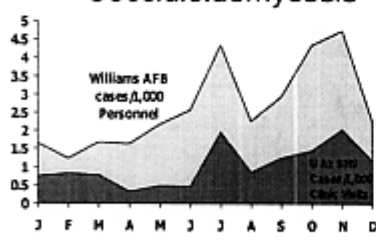
Valley Fever in Arizona: 2001

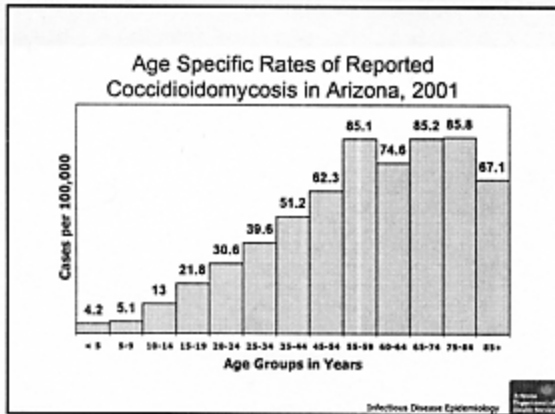
- Maricopa: 74.7%
- Pima: 17.7%
- Pinal: 3.7%
- Mohave: 1.0%
- Gila: 0.6%
- Others: 0.005-0.4%

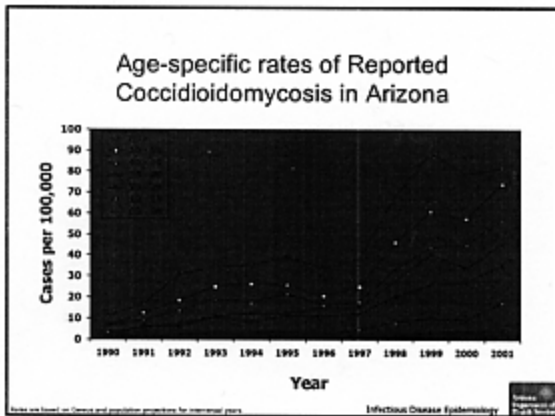


Provisional data, AzDHS
February 1, 2002

Seasonality of Coccidioidomycosis







The Increase in Reported Infections is Unexplained

- Increased awareness?
- Population growth?
 - Average age increasing and case rates higher for older persons.
- Climatic effects?
 - Not well understood: studies underway by Andrew Comrie and Mary Kay O'Rourke
- Bioterrorist attack?

**Coccidioidomycosis in Arizona
(Estimated)**

- Endemic populations (Phoenix, Tucson)
~ 3.5 million
- Population at risk (no prior infection)
~ 2.3 million
- Risk of exposure (3% conversion rate)
~ 70,000 / year
- Estimated illness(1/3 of all exposures)
~ 23,000 / year

Common "Mild" Valley Fever

- Manifestations:
 - Cough, chest pain, fever, weight loss (5-10%)
 - Fatigue
 - Bone and joint pains
 - Skin rashes (painful or intense itching)
- Course of illness
 - Weeks to months
 - 1 of 4 college students were sick for > 4 months

**Problems with Managing
Common Valley Fever**

- Sensitivity of tests needs improvement
 - Example: Serology negative in 1/3-2/3 of first tests
- Agreement of results between laboratories is poor.
- All aspects of management are woefully under-studied for optimal outcome.

Approaches to Earlier Diagnosis

- Heightened clinical awareness
 - Order standard serologic tests
 - Submit fungal cultures
- More sensitive antibody assays
- DNA probe to determine species
- PCR directly from clinical specimens
- Detection of coccidioidal antigens

Detecting Coccidioidal Antibodies

Standard Tests

- Tube Precipitins:
 - TP
 - IDTP
 - "IgM"
- Complement Fixing:
 - CF
 - IDCF
 - "IgG"

Newer Tests

- EIA kit (Meridian)
 - IgM
 - IgG
- Research ELISA based on purified antigens
 - Proline Rich Antigen (Ag2)
 - chitinase (CF Antigen)

Suspected Coccidioidal Pneumonia

n = 138, first specimens only

Wieden et al. JID May '96

Rapid Culture Diagnosis of Coccidioidomycosis

- Growth of *C. immitis* is usually evident within 4-5 days.
- Additional time to determine species
 - Mouse inoculation: 20 days
 - Exoantigen test: 10 days
 - in vitro* spherulation: 3 days
 - C. immitis*-specific probe: 3 hours

Specificity of Commercial Probe (Gen-Probe)

Probe Result	<i>C. immitis</i>	Other Fungi
Pos.	121	0
Neg.	1	164

Sensitivity: 99.2%
Specificity: 100.

Stockman et al. JCM Apr '93

Direct PCR of Clinical Specimens

- Benefits
 - Theoretical sensitivity < 1 fungal cell per specimen
 - Specific primers exist for *C. immitis rRNA gene*
 - Results could be obtained quickly
- Problems
 - Not available commercially
 - Gap between theoretical and actual sensitivity

PCR Sensitivity ($\times 10^3$ RLU)
(*in vitro* titration)

9,000.	endospores	1,458.1
650.		1,347.3
9.		1,163.2
6.5		1,339.7
0.9		360.9
.7		533.6
.1		3.7
<u>Negative Control</u>		<u>1.5</u>

Clark et al. 1994 Coccidioidomycosis Symp.

PCR Sensitivity
(Clinical Specimens)

Specimen	Result ($\times 10^3$ RLU)
Pleural tissue	941.2
Lung abscess	176.2
Lung mass	1,475.2
Lung fluid	1,315.5
Sputum	1,010.0
Bronchial wash	1,342.6
Chest fluid	87.0
Leg abscess	570.0

Clark et al. 1994 Coccidioidomycosis Symp.

- Detection of Coccidioidal Antigens**
- Chronic infections:
 - Immune complexes in 73% of patients (Yoshinoya et al., 1980)
 - Antigenemia in 56% of patients (Weiner, 1983)
 - Acute infections:
 - Antigenemia transiently in mice (Cox et al., 1988)
 - Antigenemia in more than half of patients during first two weeks of self-limited pneumonia (Galgiani et al., 1991)

**Antigenemia during
Acute Coccidioidal Pneumonia**

- 290 sera from 233 university students
- Diagnosis by detection of IDTP or IDCF antibodies
- Specimens also assayed for:
 - Anti-spherule (TSL) IgM or IgG
 - Antigenemia detected by competitive ELISA

Galgiani et al. JID 1991

**The Detection of Antigen in
relation to the presence of
Antibodies**

Antigen	Anti-TSL Antibodies	
	Yes	No
Yes	3	30
No	51	117

Galgiani et al. JID 1991

**Detection of Coccidioidal
Antigens**

- Benefits
 - Evidence indicates that circulating antigens exist
 - In early infections, antigen detection precedes antibody detection
- Problems
 - Nature of antigen uncharacterized
 - More specific antisera are needed to produce assays with acceptable performance

Galgiani et al. JID 1991

Complications of Coccidioidomycosis

- Pulmonary
 - Respiratory Failure
 - Pleural effusions
 - Nodules
 - Cavities
 - Bleeding
 - Chest pain
 - Rupture
 - Chronic pneumonia (years)
- Disseminated Infection
 - Skin
 - Subcutaneous abscesses
 - Arthritis
 - Osteomyelitis
 - Meningitis

Institute Management Progressive, Complicated Infections

- Indications for therapy
 - Pulmonary symptoms > 3 mos
 - Diffuse reticulonodular pneumonia
 - Extrapulmonary Lesions
- Current Therapies
 - Amphotericin B
 - Azoles: ketoconazole, fluconazole, Itraconazole
- Multidisciplinary approach

Current Therapy: Good News

- Most infections (>95%) need no treatment
- Azole antifungals are safe and effective
 - Fluconazole: ~50%
 - Itraconazole: ~63%
 - Ketoconazole: similar
- Fluconazole a major advance for CNS infections

Current Therapy: Bad News

- Not everyone responds to treatment
- Relapses when therapy stopped
 - non-CNS: ~30%
 - Meningitis: ~75%
- Indefinite therapy is expensive
 - Example: median for CNS:30 years old
 - 800 mg/d fluconazole per yr:\$20,000
 - Life-time therapy: \$2/3 million per case

Strategies for the Future

- **National** awareness of coccidioidomycosis
- New treatments
 - Newer azoles
 - Lipid formulations of amphotericin B
 - Cell wall-active antifungals
 - Cytokines as adjunctive therapy
- Prevention
 - Risk reduction
 - Vaccines

Lipid Formulations of Polyenes

- Formulations
 - Amphotericin B lipid complex (Abelcet)
 - Amphotericin B liposomes (Ambisome)
 - Amphotericin B colloidal dispersion
 - Nystatin liposomes
- Virtually no information with respect to Coccidioidomycosis

Cell Wall-Active Antifungals

- Chitin synthase inhibitors
 - Nikkomycin Z Excellent Efficacy
- Glucan synthesis inhibitors
 - Cilofungin (Eli Lilly) No Efficacy
 - LY-121,019 (Eli Lilly) ???
 - Cancidas (Merck) Moderate Efficacy

New therapies: Nikkomycin Z

- Bayer transferred rights to Shaman.
- Purchased at online auction by California State Bakersfield University Research Foundation (includes 2.5 kg of drug).
- Letter of Understanding between UAz and CSBURF.
- Partner(s) or grant needed to proceed.

Prevention

- > Predictive Models based upon desert and environmental factors
 - Climatology
 - Soil, Geology
 - Microbial ecology
 - Anthroprogenic Factors
 - Construction, urbanization, agriculture
- > Vaccines
