Coccidiodomycosis in the United States

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Coccidioides spp.

- **Dimorphic fungus**
  - In environment: mold with single-celled arthrospores
  - In human body: spherule filled with endospores
- **Two species causing disease:**
  - *C. immitis* in California
  - *C. posadasii* elsewhere
- **Persist in soil of endemic areas, typically warm, arid regions with low annual rainfall**
Coccidiodomycosis

- Commonly referred to as “Valley Fever”
- Disease caused when spores inhaled, frequently after a soil disruption
- NO person-to-person transmission
Endemic Areas

- 150,000 infections in US each year
- 50,000 symptomatic infections
- 60% of all US cases in Arizona

Galgiani, CID 2005
100 persons infected with coccidiodomycosis

~1-3 weeks

~35-50 develop primary pulmonary disease; the rest subclinical (protection from future disease)

~3-12 months (later, if reactivation)

- Chronic pulmonary disease in 5-10 individuals
- Disseminated disease in ~1 individual
- Higher rates of chronic pulmonary, disseminated disease if patients are nonwhite, immunosuppressed (HIV or SOT), or pregnant
Pulmonary disease can be acute and self-limiting, or chronic/progressive

- **Primary pulmonary disease**
  - Resembles influenza or community-acquired pneumonia
  - Cough, fatigue, fever, infiltrate on CXR
  - Usually acute, self-limited

- **Chronic pulmonary disease**
  - Residual nodules, thin-walled cavities
  - Most disappear in ~2 years; hemoptysis may occur in ~25%
  - Chronic symptoms, cavitary lesions with infiltrates, may mimic TB

Musil et al, 2008
Broad spectrum of disseminated disease

- Cutaneous, subcutaneous common
  - Varied appearance
- Joints, soft tissue may be affected (arthritis)
- Osteomyelitis: ~40% with disseminated disease
  - Spine, ribs, cranial bones, long bone ends
  - Persistent, dull pain
- Meninges: 30-50% with disseminated disease
  - Mortality rate >90% if untreated

www.humenhealth.com
Risk factors for dissemination

• Race/ethnicity
  – Black, some Asians (Filipinos)
• 3rd trimester of pregnancy
• Immunosuppression
  – HIV
  – Corticosteroids
  – Organ transplantation
Diagnosis of disease

- **Immunodiffusion (ID) tests**
  - Positive = recent or active infection
  - Sensitivity reduced early in infection
- **EIA test (Meridian)**
  - More sensitive than ID?
  - Performance unproven
- **Complement fixation**
- **Culture of sputum**: difficult because patients’ coughs often nonproductive
- **PCR of sputum?** – may aid early diagnosis
Treatment of Pulmonary Disease

• Most patients with uncomplicated infection will recover **eventually** with or without treatment
• IDSA guidelines recommend 200-400 mg/d azole for:
  – Persons with severe symptoms
  – Persons at risk for dissemination (nonwhite, immunosuppressed, pregnant)
  – For others, no guidance
• Amphotericin B may be used with respiratory failure, rapidly progressive infections
Treatment of Disseminated Disease

- Disseminated non-meningeal
  - Azole or Amphotericin B, depending on clinical picture
- Disseminated meningeal
  - Fluconazole or itraconazole
  - Some clinicians start with high dose (800-1000 mg/day)
- Vorizconazole, posaconazole may also be beneficial
- Surgical interventions may be needed (pulmonary cavities, shunts)
- Patients with disseminated disease should be treated indefinitely due to high relapse rates
Best treatment unclear

- **No data from clinical trials to evaluate symptom relief or prevention of relapse: need for proven treatment strategies**
- **Studies of azole with early cocci pneumonia:**
  - No difference between treated and untreated groups; complications only in treated group, after drug d/c
  - Treatment failure in 20-40%; relapse rates high among those who improved during treatment
  - New treatment? Nikkomycin Z, Phase II trials
Is it possible to prevent infection?

- Risky activities exist (digging, etc.)
- Most acquire disease simply by breathing
- Since exposure can’t be eliminated, only measure available to prevent infection is a vaccine
  - NO VACCINE currently
Vaccine?

- **Rationale:** immunity from cocci is lifelong
- **Initial whole-spherule and whole-mycelial vaccines nonimmunogenic in human trials**
  - Focus now on live attenuated, recombinant vaccines
- **Cost-effectiveness uncertain**
  - Focus on high-risk groups?
    - Construction, miners, landscapers, immunocompromised patients
    - Military (training recruits who are temporary residents)
Surveillance for cocci in California

- Passive surveillance for cases and outbreaks
- Case definition based on CSTE definition
  - Clinical criteria
    - Flu-like illness
    - Pneumonia, other pulmonary lesion, or meningitis
    - Rash
    - Bones, joints, skin involvement
    - Involvement of viscera or lymph nodes
  - Lab evidence of infection
    - Culture, histopathologic, molecular, or immunologic evidence of infection
Rates of reported Valley Fever in California, 2001-2009

Hector, 2011

Rates per 100,000
Reported cocci in California, 2001-2009

- Rates vary widely by county
- 65% male
- Rates highest in 20-50 yo
- Highest rates in Hispanics, Blacks

FIGURE 2. Average annual rate* of reported cases of coccidioidomycosis, by county — California, 2000–2007†

* Per 100,000 population.
Surveillance for cocci in Arizona

- Mandatory reporting from laboratories beginning in 1997
  - ~5,000 cases reported each year using lab-only reporting
- Two major commercial labs report 46% of cases in AZ
  - One lab required both EIA and complement fixation / immunodiffusion for positive results; beginning in 2009, reporting changed to only require EIA
  - As a result, case reports increased in 2009
Rates of reported Valley Fever in Arizona, 1990-2009

Reporting at major commercial lab changed to require only positive EIA

Disease becomes lab-reportable in AZ

Reported cases /100,000 population

AZDHS.gov/phs/oids; Hector, 2011

*2 major commercial labs account for 46% of all cocci reporting to AZ State HD
Reported cocci in AZ, 2009

- 55% female (45% female 2006-8)
- Rates highest in >65 yo
- Highest rates in most populous counties (Maricopa, Pima, Pinal)

Hector, 2011
Enhanced surveillance for cocci, AZ

- **Objectives**
  - To validate the laboratory-based case definition
  - To understand more about the public health burden of cocci
- **Contacted every 10\textsuperscript{th} cocci case by mail, interviewed by telephone (n=493 patients)**

Tsang *et al*, EID 2010; Sunenshine *et al*, Cocci Study Group 2008
Patients (N=493)

• Common symptoms:
  − Fatigue (84%)
  − Cough (67%)
  − Dyspnea (59%)
  − Fever (54%)

• Symptoms lasted median of 120 days
  − 42 days among recovered cases (40%)
  − 157 days among non-recovered cases (60%)

• 469 (95%) met CSTE case definition
Delays in diagnosis, impact on patients

- Healthcare sought median of 11 days after onset
- Among employed, 74% missed work due to cocci
  - Median workdays missed: 14
- 75% unable to do activities of daily living (ADLs) at some point during illness
  - Median days unable to perform ADLs: 47
Impact on Healthcare System

- 46% went to the ER for Valley Fever
- 41% were hospitalized, median of six days
- 26% saw their doctor 10+ times during illness
- 1,093 hospital visits with primary dx of cocci in 2007
  - Over 59 million dollars in hospital charges
  - Median $33K / visit
Cocci is underdiagnosed

- Three separate studies in Arizona have shown that cocci may cause 10-30% of CAP!*
  - If cocci represents a large % of CAP, could be many cases/year (>50,000?)
  - ~5,000 reported to health dept in AZ each year
  - How frequently is CAP tested for cocci?

*Valdivia, Emerg Infect Dis 2006; Campion, AZ Geriatrics Soc J, 2003; Chang DC et al, EID 2008

• Objectives
  – Estimate the proportion of patients presenting to clinics with pneumonia who are tested for cocci
  – Determine predictors of cocci among CAP patients
  – Understand provider testing practices in Maricopa County

• Methods
  – Retrospective cohort studies in two distinct outpatient populations (Healthcare Systems A and B)
    • Chart review to determine % of CAP patients tested for cocci

*Chang, DC et al, EID 2008
## Study locations

<table>
<thead>
<tr>
<th>Service</th>
<th>System A</th>
<th>System B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary care</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Subspecialty care</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Community health centers</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Associated with hospital</td>
<td>Yes (Public)</td>
<td>No</td>
</tr>
<tr>
<td>Racial /ethnic minorities</td>
<td>Majority</td>
<td>N/A</td>
</tr>
<tr>
<td>Insurance</td>
<td>Many without private insurance</td>
<td>Almost exclusively privately insured</td>
</tr>
</tbody>
</table>
Few CAP patients tested for cocci overall… *and* serological testing more likely in private vs public healthcare system

<table>
<thead>
<tr>
<th>Cocci testing</th>
<th>System A (n=66 CAP cases)</th>
<th>System B (n=87 CAP cases)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serology at any CAP visit</td>
<td>1 (2)</td>
<td>11 (13)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diagnosis of cocci</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>NS</td>
</tr>
<tr>
<td>Days until testing (median)</td>
<td>12</td>
<td>27 (1-99)</td>
<td>-</td>
</tr>
<tr>
<td>Symptoms ≥ 14 days before test</td>
<td>0 (0)</td>
<td>7 (64%)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Few clinical differences between CAP patients who test positive vs negative for cocci

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Positive Cocci Serology (n=9)</th>
<th>Negative Cocci Serology (n=134)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range), years</td>
<td>41.4 (20-82)</td>
<td>42.0 (14-91)</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>6 (66.7)</td>
<td>66 (49.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Black/ African-American</td>
<td>3 (33.3)</td>
<td>9 (6.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking Past or Present</td>
<td>3 (33.3)</td>
<td>64 (47.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Cough</td>
<td>8 (88.9)</td>
<td>125 (93.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Fever</td>
<td>5 (55.6)</td>
<td>119 (88.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>2 (22.2)</td>
<td>65 (48.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 (22.2)</td>
<td>46 (34.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (11.1)</td>
<td>18 (13.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Rash</td>
<td>0 (0)</td>
<td>1 (0.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Symptom duration (days)</td>
<td>11.6 (2-35)</td>
<td>10.4 (1-182)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Longer duration of symptoms made testing for cocci more likely

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Tested (n=125)</th>
<th>Not Tested (n=260)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days of sx (mean, range)</td>
<td>11 (1-182)</td>
<td>6 (1-90)</td>
<td>0.01</td>
</tr>
<tr>
<td>Age (mean, range), years</td>
<td>42 (14-91)</td>
<td>40 (13-91)</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>72 (50%)</td>
<td>147 (52%)</td>
<td>NS</td>
</tr>
<tr>
<td>White Non-Hispanic</td>
<td>87 (61%)</td>
<td>153 (54%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hispanic/ Latino</td>
<td>30 (21%)</td>
<td>83 (29%)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking history</td>
<td>67 (47%)</td>
<td>114 (40%)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Conclusions

• Coccidiodomycosis causes a significant health and quality-of-life burden for patients
  – The economic impact of each case on the patient and on the healthcare system is substantial

• High proportion of CAP probably attributable to cocci
  – Low levels of testing in CAP patients (2-13%?)
  – Symptom differences, symptom duration do not help distinguish cocci from other CAP; thus, lab testing is needed for diagnosis

• No vaccine and existing treatment is not optimal; need for proven treatments
Ongoing Physician Education in AZ

VALLEY FEVER CASES ARE INCREASING

Coccidioidomycosis rate per 100,000 population by year, Arizona -1993-2006

WHAT CAN YOU DO?

- Order Cocci serology on CAP cases
- Manage Valley Fever cases
  - Inform patient of diagnosis
  - Report the case to public health
  - Consider treatment with anti-fungal drugs if the patient is at risk for severe disease

For more information on treatment guidelines, visit www.idsocess.org/pg

20% of Ambulatory CAP cases in Tucson, Arizona had diagnosis of Valley Fever.

Valderrama L, No D, Wright H, et al.
Coccidioidomycosis as a Common Cause of Community Acquired Pneumonia. Emerging Infectious Diseases. 2005; 11:198-203

Resources:
Arizona Department of Health Services
Office of Infectious Disease Services
130 N. 4th Ave. Suite 400
Phoenix, Arizona 85003
602-256-4567
www.valleyfeverarizona.org

Valley Fever Center for Excellence
P.O. Box 11116
2601 N. 6th Avenue
Tucson, Arizona 85705
Hotline (877) 398-4277
https://www.vfc.arizona.edu/
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For more information please contact Centers for Disease Control and Prevention
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E-mail: cdcinfo@cdc.gov  Web: www.cdc.gov

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