The Re-Emergence and Changing Epidemiology of Coccidioidomycosis, United States, 1998 – 2011

Benjamin Park, MD

Mycotic Diseases Branch
Centers for Disease Control and Prevention
Atlanta, GA
Financial Disclosures

- Nothing to disclose
Take Home Points

- Cocci can be a serious infection
- It is common
- It is increasing
Coccidiodes 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. posadasi* elsewhere
- **Persist in soil of endemic areas, typically warm, arid regions with low annual rainfall**
Coccidioidomycosis

- 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
History of Cocci

- First discovered in 1892 by Alejandro Posadas in Buenos Aires
- Mistaken as a protozoan in 1896 at JHU
  - Called *Coccidioides* ("resembling coccidia") *immitis* ("not mild")
- Incubation period determined when medical student at Stanford inhaled a plate of cocci spores
Old Epidemiology Studies

- Many studies done in 1930s-40s in CA by Charles E. Smith using coccidioidin skin test
  - Migrant farm workers
  - Rail workers (Filipinos)
  - Military- bases in San Joaquin Valley and AZ
  - Japanese internment camps
  - POWs

- First recorded outbreak of cocci
  - Stanford U biology field trip
  - Student dug into a squirrel hole to chase a rattlesnake
  - Seven of 14 students became ill with cocci; *C. immitis* recovered four months later from soil around squirrel hole
CLINICAL ASPECTS
Of 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, community-acquired pneumonia, or TB
  - 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
Risk factors for dissemination

- Race/ethnicity
  - Black, some Asians (Filipinos)
- 3rd trimester of pregnancy
- Immunosuppression (T-cell depression)
  - HIV
  - Corticosteroids
  - Organ transplantation
Diagnosis of disease

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

• Most patients with uncomplicated infection will recover eventually with or without treatment
  – Approach varies; some treat all
• IDSA guidelines (2005) recommend 200-400 mg/d azole for:
  – Persons with severe symptoms
  – Persons at risk for dissemination (African or Filipino, immunosuppressed)
• Amphotericin B may be used with respiratory failure, rapidly progressive infections
But, best treatment for pulmonary disease is unclear

- No clinical trials of treatment for cocci pneumonia
  - Some analyses using retrospective data
  - Found no difference between treated and untreated groups

- Many agents are worthy of study
  - Posaconazole
  - Fluconazole/itraconazole
  - Nikkomycin Z
Treatment of Disseminated Disease

- **Disseminated non-meningeal**
  - Azole or Amphotericin B, depending on clinical picture
- **Disseminated meningeal**
  - Fluconazole
  - Some clinicians start with high dose (800-1000 mg/day)
- Voriconazole, posaconazole may also be beneficial
- Surgical interventions may be needed (pulmonary cavities, shunts)
EPIDEMIOLOGY
How common is cocci?
Cocci is a common cause of CAP

• 55 outpatients presenting to primary care centers in Phoenix and Tucson (2003-2004) with:
  – Lower respiratory disease >1 month
  – 1+ of: pleuritic chest pain, dyspnea on exertion, CXR, multiple visits for same problem, or antibacterial drug for presumed CAP

• Sera at baseline, follow-up (immunodiffusion, EIA)

• 29% (95% CI 16-44%) positive for cocci

• Limitation: patient population likely biased
  – Patients with severe illness selected

• Another study: 25-30% of CAP caused by cocci (Tucson)

Valdivia, Emerg Infect Dis 2006; Campion, AZ Geriatrics Soc J, 2003; Chang DC et al, EID 2008
Cocci also resembles TB

- No good studies in US
- Mexico:
  - TB and cocci coinfection common
- Preliminary data from testing in TB clinics in Sonora
  - $\frac{1}{4}$ of smear-negative TB are cocci +

Large Unmeasured Burden?

• 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 are patients with CAP tested for cocci?

• Objective:
  – Estimate the proportion of patients presenting to clinics with pneumonia who are tested for cocci

• Two primary care health systems
  – Private insurance
  – Most without private insurance

*Chang, DC et al, EID 2008
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 coccic 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>
Large “Diagnostic Gap”

- 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
Benefits of Diagnosis

• Why is testing necessary?
• Guidelines do not recommend universal treatment
• Many reasons:
  – Determine if treatment is necessary (high risk)
  – Follow patients for severe sequelae
  – Avoid unnecessary procedures, visits
  – Provide a diagnosis for patients

• BOTTOM LINE: Test your patients for cocci!
If cocci is common, what is its impact?
Enhanced surveillance for cocci, AZ

Objective:
- To understand more about the public health burden of cocci
  - Morbidity
  - Costs

Contacted every 10th cocci case by mail, interviewed by telephone
- Interviewed 493 patients
- Asked about symptoms, treatment, outcomes
- How cocci affected their everyday lives

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%)
Delays in diagnosis, impact on patients

- Healthcare sought median of 11 days after onset
  - A mean of two provider visits occurred before cocci diagnostic testing ordered
  - Patients who knew about cocci were diagnosed earlier (20 d) than patients who did not know (25 d)

- 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 was Substantial

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

- Coccidioidomycosis has been nationally notifiable in the US since 1995
- Reporting of nationally notifiable diseases is mandatory at the state level, but state reporting to CDC is voluntary
- Reports are lab-based (not physician dependent)
- Complied in National Notifiable Disease Surveillance System (NNDSS)
US coccidioidomycosis cases reported to NNDSS 1998 – 2011 (n=112,099)

- Arizona: 64%
- California: 34%
- Other endemic states: 2%
- Non-endemic states: <1%
## Yearly US coccidioidomycosis case-count

<table>
<thead>
<tr>
<th>Year</th>
<th>Arizona</th>
<th>California</th>
<th>Other endemic states</th>
<th>Non-endemic states</th>
<th>Total US</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>1,474</td>
<td>719</td>
<td>74</td>
<td>8</td>
<td>2,275</td>
</tr>
<tr>
<td>1999</td>
<td>1,812</td>
<td>939</td>
<td>55</td>
<td>21</td>
<td>2,827</td>
</tr>
<tr>
<td>2000</td>
<td>1,917</td>
<td>840</td>
<td>67</td>
<td>43</td>
<td>2,867</td>
</tr>
<tr>
<td>2001</td>
<td>2,301</td>
<td>1,538</td>
<td>63</td>
<td>31</td>
<td>3,933</td>
</tr>
<tr>
<td>2002</td>
<td>3,133</td>
<td>1,727</td>
<td>78</td>
<td>32</td>
<td>4,970</td>
</tr>
<tr>
<td>2003</td>
<td>2,695</td>
<td>2,091</td>
<td>65</td>
<td>21</td>
<td>4,872</td>
</tr>
<tr>
<td>2004</td>
<td>3,668</td>
<td>2,641</td>
<td>112</td>
<td>44</td>
<td>6,465</td>
</tr>
<tr>
<td>2005</td>
<td>3,516</td>
<td>2,885</td>
<td>109</td>
<td>45</td>
<td>6,555</td>
</tr>
<tr>
<td>2006</td>
<td>5,535</td>
<td>3,131</td>
<td>140</td>
<td>127</td>
<td>8,933</td>
</tr>
<tr>
<td>2007</td>
<td>4,832</td>
<td>2,991</td>
<td>164</td>
<td>154</td>
<td>8,141</td>
</tr>
<tr>
<td>2008</td>
<td>4,768</td>
<td>2,597</td>
<td>144</td>
<td>80</td>
<td>7,589</td>
</tr>
<tr>
<td>2009</td>
<td>10,233</td>
<td>2,488</td>
<td>148</td>
<td>81</td>
<td>12,950</td>
</tr>
<tr>
<td>2010</td>
<td>11,887</td>
<td>4,630</td>
<td>159</td>
<td>134</td>
<td>16,810</td>
</tr>
<tr>
<td>2011</td>
<td>16,452</td>
<td>5,985</td>
<td>239</td>
<td>236</td>
<td>22,912</td>
</tr>
<tr>
<td>total</td>
<td>74,223</td>
<td>35,202</td>
<td>1,617</td>
<td>1,057</td>
<td>112,099</td>
</tr>
</tbody>
</table>
Coccidioidomycosis age-adjusted incidence rates, other endemic and non-endemic states, 1998 – 2011

Incidence per 100,000

Other endemic age-adjusted IR
Non endemic age-adjusted IR
Coccidioidomycosis incidence rates by age group, all endemic U.S. states, 1998 – 2011

- Incidence increasing in all age groups
- Largest increases in younger populations
Why has cocci increased?

- **Artifact of surveillance or testing?**
  - Increased testing
  - New diagnostics (EIA)

- **Is there actually more disease?**
  - Difficult to determine
  - Subject of ongoing investigation

- **A number of hypotheses:**
  - Climate?
  - Construction?
FUTURE DIRECTIONS
Is it possible to prevent infection?

- Risky activities exist (digging, etc.)
- Some common-sense prevention measures may help
  - Avoid risky activities (e.g., digging) if immunosuppressed
  - Avoid dust storms
  - Wear a mask
  - Roll up windows in your car
The reality is…

• Cocci spores can travel for miles
• Very few cases associated with particular activity
• Most acquire disease simply by breathing
• Cases have even occurred after only minimal exposure to endemic areas (short trips with minimal outdoor time)

• Since exposure can’t be eliminated, only measure available to prevent infection is a vaccine
Vaccine?

- **Rationale:** immunity from cocci is lifelong
- **Initial human trials did not show benefit**
  - Focus now on live attenuated, recombinant vaccines
- **Cost-effectiveness uncertain**
  - Who would get vaccinated?
  - Focus on high-risk groups
    - Construction, miners, landscapers, immunocompromised patients
    - Military (training recruits who are temporary residents)
If cocci not preventable, what then?

- Because cocci is not currently preventable, focus should be on reducing morbidity/mortality associated with disease
- Improving diagnosis
- Best treatment strategies, especially for primary pulmonary cocci
  - Antifungal trial?
Take Home Points

- Cocci can be a serious infection
- It is common
- It is increasing
- Test your patients for cocci!!
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 Coccidioidomycosis serology on CAP cases
- Manage Valley Fever cases
  - Inform patient of diagnosis
  - Report the case to public health
- Consider treatment with antifungal drugs if the patient is at risk for severe disease

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

Valley Fever Mimics Community Acquired Pneumonia (CAP)

29% of Ambulatory CAP cases in Tucson, Arizona had diagnosis of Valley Fever.


Resources

Arizona Department of Health Services
Office of Infectious Disease Services
1901 N 4th Ave, Suite 140
Phoenix, Arizona 85013
(602) 547-4505
www.valleyfeverarizona.org

Valley Fever Center for Excellence
401 E. Mission Blvd
Tucson, Arizona 85719
(520) 744-4237
http://www.vfco.arizona.edu/
Acknowledgements

CDC
NNDSS
Kaitlin Benedict, MPH
Julie R. Harris, PhD, MPH
Gordana Derado, PhD
Arizona
Shoana Anderson
Ken Komatsu

California
Deb Gilliss
Farzaneh Tabnak
Duc Vugia

For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA  30333
Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov    Web: http://www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.