The National Epidemiology of Coccidioidomycosis and Public Health Goals and Strategies

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Nov 3, 2015
Indian Health Service
Four Corners meeting
Durango, CO

National Center for Emerging and Zoonotic Infectious Diseases
Division of Foodborne, Waterborne, and Environmental Diseases
Disclosures

• No financial disclosures

• The views and opinions expressed in this presentation are not necessarily that of the Centers for Disease Control and Prevention
Overview

• Background
• Clinical presentation
• Diagnosis
• High risk groups
• Treatment
• National epidemiology
• Current Updates & MDB Strategy
Coccidioides

- Dimorphic fungus
- Two species
  - *C. immitis*: CA, WA
  - *C. posadasii*: AZ and elsewhere
- Most infections result from inhalation of *Coccidioides* from the environment (not contagious)

* Citations, references, and credits
In the environment, *Coccidioides spp.* exists as a mold (1) with septate hyphae. The hyphae fragment into arthroconidia (2), which measure only 2–4 μm in diameter and are easily aerosolized when disturbed (3). Arthroconidia are inhaled by a susceptible host (4) and settle into the lungs. The new environment signals a morphologic change, and the arthroconidia become spherules (5). Spherules divide internally until they are filled with endospores (6). When a spherule ruptures (7) the endospores are released and disseminate within surrounding tissue. Endospores are then able to develop into new spherules (6) and repeat the cycle.
CLINICAL PRESENTATION
Coccidioidomycosis

- Also called “Valley Fever” or “cocci”
- Ranges from asymptomatic to life-threatening
  - 60% asymptomatic
  - 40% primary pulmonary disease. Of those,
    - 5 to 10% develop pulmonary complications
    - 1% develop disseminated disease
- Incubation period = 1 to 3 weeks
- Unknown if antifungal treatment improves outcomes for primary pulmonary disease
- No proven prevention methods

* Citations, references, and credits
Primary pulmonary disease

- Can be acute and self-limiting, or chronic/progressive
- Acute disease:
  - Cough, fatigue, fever, infiltrate on chest x-ray, rash
  - Usually self-resolves in 2-3 mos.
  - Resembles influenza, TB, or community-acquired pneumonia!

Musil et al, 2008
Disseminated disease

- Meningitis: 30-50% of disseminated cases
  - Mortality rate >90% if untreated

- Osteomyelitis: ~40% of disseminated cases
  - Spine, ribs, cranial bones, long bone ends
  - Persistent, dull pain
  - Fractures
Cocci is associated with substantial morbidity

- Interviews with 493 cocci patients in AZ found:
  - Fatigue (84%), cough (67%), shortness of breath (59%), fever (54%)
  - Symptoms lasted a median of 3 months
  - 26% saw their doctor ≥10 times; 41% hospitalized
  - Delays in diagnosis were common (median 55, mean 209 days)
  - 75% were unable to do activities of daily living
- Median cost $33,000 per hospital visit

DIAGNOSIS
Serological tests for IgG and IgM

• Immunodiffusion (ID) - usually IgM
  – Positive = recent, recurrent, or active infection

• Complement fixation (CF) for IgG
  – Positive = late or chronic disease
  – Titer changes mirror progression

• Enzyme immunoassay (EIA) – Meridian or Immy
  – Higher sensitivity than ID and CF; detects infection earlier
  – Sensitivity increases with CF titers
  – Specificity, false + rates, affected by technique
Other tests

- Culture or histopathology
  - Definitive diagnosis
  - Difficult with sputum because patients’ coughs often nonproductive

- Urine antigen test (MiraVista)
  - Potential cross-reactivity with histoplasma

- Real-time PCR of sputum to detect cocci DNA
  - More validation needed
Cocci skin test

Spherusol® skin test (Nielsen BioSciences)
• FDA-approved in 2011
• *C. immitis* spherule-derived antigen (vs. mycelial)
• Preservative = phenol (vs. thimerosal)
• ↓ adverse effects and cross-reactivity with histo
• *Only assesses immunity*, not stage of disease
• Was commercially launched in early 2015
RISK FACTORS
Risk groups

- Anyone can get Valley fever, but it’s most common in adults aged 60 and older
- Some groups are at higher risk for the severe forms:
  - People with weakened immune systems
  - Pregnant women
  - People with diabetes
  - People who are Black or Filipino, …other race/ethnicity?
Medical risk factors

- **Immunosuppressive conditions are a major risk factor for more severe disease**
  - HIV/AIDS
  - Chemotherapy/malignancy
  - Transplant
  - TNF-α blockers, etc

- **Pregnancy**
  - Women are at risk for severe disease especially late in pregnancy

- **Diabetes**
  - Patients with diabetes have an increased risk of pulmonary complications
Blacks / African Americans

- Many studies suggest higher rates of severe / disseminated
- 1940s: rate of disseminated cocci in blacks was 10 times higher than whites among Army population\(^1\)
- 1977: massive dust storm → rate of disseminated cocci was 24/100,000 in blacks vs. 2.5/100,000 in whites\(^2\)
- 1991: Tulare County, CA – black race was an independent risk factor for hospitalization\(^3\)
- 1995-1996: Kern County, CA – after controlling for SES and other factors, black race was a risk factor for disseminated cocci

1. Smith et al. Varieties of coccidioidal infection in relation to the epidemiology and control of the diseases. AJPH 1946
Filipinos

- Historically singled out as having a higher risk for disseminated disease, but limited data
- 1930s Kern County report: a disproportionate number of cases and deaths due to cocci occurred among Filipinos
- Analysis of Naval Medical Center data 1994–2002: Filipinos were 10 times more likely than whites to develop disseminated disease

American Indians

- Many reside in historically highly-endemic areas
- 1972: Skin-test reactivity among children was 60% in AIs vs. 30% in whites\(^1\)
- Retrospective analysis 1959-1972: AIs were 3 times more likely to develop disseminated disease and 5 times more likely to die than whites\(^2\)
  - Suspect differential environmental exposures rather than genetics
- Few studies specifically in AIs since the 1980s
  - Studies in the general population limited by small numbers of AIs
  - Study of infectious disease mortality in AI/ANs 1999-2009 found that mortality rates for mycoses were 3.2 times higher than whites\(^3\)

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TREATMENT
Treatment of pulmonary disease

• Most patients with uncomplicated infection will recover eventually with or without treatment
• Some providers always treat, some rarely treat
• IDSA guidelines (2005) recommend 200-400 mg/d azole for:
  – Persons with severe symptoms
  – Persons at risk for dissemination
  – Amphotericin B for those with respiratory failure, rapidly progressive infections
Randomized Control Trial (RCT) of early treatment
National Institutes of Health

- A controlled clinical trial of antifungal treatment for community acquired pneumonia would provide stronger evidence than observational studies
- NIH finalizing protocol for a two arm, double-blinded, RCT of outpatients with CAP
  - All treated with antibiotic for bacterial pneumonia
  - \( \frac{1}{2} \) receive antifungal and \( \frac{1}{2} \) a placebo
  - Monitor cocci serology, clinical sx, outcomes
- Trial set to begin in late 2015
NATIONAL EPIDEMIOLOGY
National Coccidioidomycosis Surveillance

- CDC receives case counts from states through the National Notifiable Diseases Surveillance System (NNDSS)
- Reportable in 20 states
- Case definition:
  - Culture, histopathologic, or molecular evidence, OR
  - Detection of coccidioidal IgM by immunodiffusion, EIA, latex agglutination, or tube precipitin, OR
  - Detection of coccidioidal IgG by immunodiffusion, EIA, or complement fixation, OR
  - Coccidioidal skin-test conversion after onset of signs or symptoms, AND
  - Clinical signs or symptoms? (criteria may be unclear)
Reported cases have decreased... but the numbers are still substantial

As reported in the National Notifiable Diseases Surveillance System
Reported cases have recently decreased... but numbers remain substantial.

In 2009, a major commercial laboratory in AZ changed its laboratory-reportable statewide in CA reporting practices to conform to the 2008 change in CSTE case definition.

In 2008, laboratory component of CSTE case definition was revised to include cases with a single positive test result.

In late 2012, changes in testing practices at a major AZ commercial lab.

CDC. Summary of Notifiable Diseases, United States, 2012
Rates are highest in older adults
Surveillance only captures the tip of the iceberg

- Arizona: small studies identified cocci as an important cause of community-acquired pneumonia (CAP)
  - Proportion of CAP tested can vary greatly by facility, 2-13% ¹
  - Among patients tested, 15-29% were positive¹,²,³
  - Varies by CAP and cocci diagnostic criteria

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  - Varies by CAP and cocci diagnostic criteria

- **California**: Kaiser Permanente Southern California retrospectively reviewed all CAP cases in 2011
  - Only 2,023 (5.7%) of 35,567 CAP patients tested for cocci
  - Among patients tested, 19% were positive\(^4\)

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- **Every where else? NO DATA!**

ENDEMIC AREAS AND EXPANDING GEOGRAPHY
Historical endemic area for coccidioidomycosis in the US

- Based on skin testing of military recruits from the 1940s

Discovering Coccidioidomycosis in Washington: summary of first known locally-acquired cases

- 3 acute, unrelated cases during 2010 – 2011
  - 12-year-old male with coccidioidal pneumonia
  - 15-year-old male with knee wound infection
  - 58-year-old male with pneumonia → meningitis
- Diagnostic delays
- All had culture-confirmed infection
- Patients resided in SE Washington
- Each had distant travel to known endemic areas
  - But not recent and very short

Coccidioides identified in soil

- **2010**: soil was collected from two locations in WA where patients reported potential exposures
  - No reliable test for identifying *Coccidioides* in soil existed at the time

- **2013**: a novel, real-time PCR assay developed by Translational Genomics
  - Detected DNA in 6/22 samples
  - CDC improved ability to isolate from soil
  - *C. immitis* isolated from 4/6 positive samples

New Tools for Epidemiologic Surveillance
Whole genome sequence typing of isolates

Clinical isolate was genetically indistinguishable from environmental isolates
Continuing Surveillance in Washington State

**Washington Cases with Suspected Local Acquisition**

*Cases of Locally Acquired Coccidioidomycosis, WA State, 2010-2014*

**Figure 4: Counties Reporting Coccidioidomycosis Cases, 2014**

- Travel associated case
- Locally acquired case

Locally acquired cases reported
Endemic areas for coccidioidomycosis in the US

- Based on skin test data from the 1940s and outbreak locations

http://www.cdc.gov/fungal/diseases/coccidioidomycosis/causes.html
Engelthaler et al. bioRxiv, 2015
doi: http://dx.doi.org/10.1101/024778)
What’s the true geographic distribution? Something more like this

http://www.cdc.gov/fungal/diseases/coccidioidomycosis/causes.html
Public Health Goals: Coccidioidomycosis

1. Increase awareness among healthcare providers and public
2. Refine understanding of “endemic areas”
3. Conduct surveillance and research
4. Develop risk stratification strategies
5. Further strengthen domestic and international public health partnerships

* Citations, references, and credits
1. Increase awareness

**Importance**

- Even in highly-endemic areas, healthcare providers and the public may not be familiar, resulting in delayed or missed diagnoses
- Increased awareness $\rightarrow$ increased testing $\rightarrow$ better outcomes

**Strategies**

- Support state-based public awareness materials and assessments of provider knowledge, attitudes, and practices
- Work with public and private health organizations and academic SMEs to develop and disseminate clinical education materials

* Citations, references, and credits
Clinical Education

- State and local health departments leading the charge
- Valley Fever Center for Excellence (University of Arizona) Tutorial for Primary Care Professionals
  - Original version released in the late 1990s, recently updated
  - Addition of CDC logo strengthens credibility outside of AZ and helps achieve a wider distribution
- Working with Medscape to develop online CME
  - 0.5 credits, for physicians and nurses
  - Will feature experts from AZ and CA
2. Refine understanding of “endemic areas”

**Importance**
- Maps based on data that are > 60 years old
- Improved understanding of cocci endemic areas → inform surveillance and educational efforts

**Strategies**
- Continue to develop methods to detect *Coccidioides* in environmental samples and animals
- Work with state and local HDs, veterinarians, academic SMEs, private industry, etc. on human and animal testing

* Citations, references, and credits
Development of a cocci EIA for IgG detection in dogs

- Collaboration with WA State Department of Health to collect sera from 23 vet clinics
- Continue to collect and test dog sera and establish specificity
- Could adapt to a variety of animal species (rodents?)

<table>
<thead>
<tr>
<th>A/G result</th>
<th>West</th>
<th>East</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>1 (0.55%)</td>
<td>7 (2.7%)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Negative</td>
<td>175</td>
<td>245</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>181</strong></td>
<td><strong>261</strong></td>
</tr>
</tbody>
</table>
3. Conduct surveillance and research

**Importance**
- Many unanswered questions about cocci’s epidemiology and natural history

**Strategies**
- Continue to monitor national trends through NNDSS
- Estimate the true burden of disease
- Conduct enhanced surveillance projects
- Collaborate with the CDC National Center for Environmental Health to explore associations with environmental conditions such as drought and soil characteristics
- Support the NIH’s Randomized Controlled Trial
- Support NIOSH-funded studies of occupational risk factors

* Citations, references, and credits
Analysis of HCUP and IHS data

- **Healthcare Cost and Utilization Project (HCUP) data**
  - Family of databases sponsored by AHRQ
  - Largest collection of publicly-available all-payer healthcare data
  - National Inpatient Sample is a 20% sample of discharges from ~1,000 community hospitals; estimates >36 million discharges/year

- **Indian Health Services (IHS) data**
  - Direct and contract health services data
  - Inpatient and outpatient
**IHS and HCUP data, 2001–2012**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IHS (AI/ANs)</th>
<th></th>
<th></th>
<th>HCUP (entire US)</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>Rate</td>
<td>RR</td>
<td>N (SE)</td>
<td>Rate (95% CI)</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>113</td>
<td>15.6</td>
<td>Ref</td>
<td>16,754 (1,011)</td>
<td>9.5 (8.4, 10.6)</td>
<td>Ref</td>
</tr>
<tr>
<td>Female</td>
<td>50</td>
<td>6.3</td>
<td>0.4</td>
<td>9,659 (683)</td>
<td>5.3 (4.6, 6.0)</td>
<td>0.6 (0.5, 0.7)</td>
</tr>
<tr>
<td><strong>Age Group (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>17</td>
<td>2.3</td>
<td>Ref</td>
<td>3,009 (298)</td>
<td>2.4 (2.0, 2.9)</td>
<td>Ref</td>
</tr>
<tr>
<td>25-64</td>
<td>129</td>
<td>19.0</td>
<td>8.2</td>
<td>17,652 (1,129)</td>
<td>9.3 (8.1, 10.5)</td>
<td>3.8 (2.9, 4.7)</td>
</tr>
<tr>
<td>65+</td>
<td>17</td>
<td>16.7</td>
<td>7.2</td>
<td>5,957 (464)</td>
<td>13.0 (11.0, 15.0)</td>
<td>5.4 (4.0, 6.7)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>12,908 (969)</td>
<td>5.4 (4.6, 6.2)</td>
<td>Ref</td>
</tr>
<tr>
<td>Black</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3,009 (244)</td>
<td>6.6 (5.6, 7.7)</td>
<td>1.2 (1.0, 1.5)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>6,595 (524)</td>
<td>12.1 (10.2, 14.0)</td>
<td>2.2 (1.8, 2.7)</td>
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<tr>
<td>A/PI</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1,324 (120)</td>
<td>7.6 (6.2, 8.9)</td>
<td>1.4 (1.1, 1.7)</td>
</tr>
<tr>
<td>AI/AN</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>450 (82)</td>
<td>15.1 (9.7, 20.4)</td>
<td>2.8 (1.7, 3.9)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>163</td>
<td>10.7</td>
<td></td>
<td>26,735 (1,645)</td>
<td>7.4 (6.5, 8.3)</td>
<td></td>
</tr>
</tbody>
</table>

First-listed coccidioidomycosis hospitalization rates per 1,000,000 population, 2001–2012
AI/AN, American Indian/Alaska Native; A/PI, Asian/Pacific Islander; RR, rate ratio; SE, standard error; CI, confidence interval
4. Develop risk stratification strategies

**Importance**
- Identification of highest-risk persons is needed to develop targeted risk reduction methods
- Evaluating the newly-available skin test to determine immunity is a critical aspect of assessing risk

**Strategies**
- Ongoing collaboration with state and local HDs and NIOSH to better describe and address cocci occupational health issues and explore skin testing for specific groups
- Pursue opportunities to evaluate approaches to primary prevention

* Citations, references, and credits
5. Further strengthen public health partnerships

✦ Importance
  • Regular communications with state and local HDs, academic SMEs, and other CDC groups are essential for
    o Ensuring coordinated and complementary efforts
    o Sharing preliminary findings; exploring new opportunities to collaborate

✦ Strategies
  • Quarterly Cocci Public Health Working Group calls: information sharing
    o Surveillance Sub-Working Group
    o Skin Testing Sub-Working Group
    o Environmental and Animal Testing Sub-Working Group
  • Continue working with state and national labs in Mexico
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Acknowledgments

Ron Wohrle
David Kangiser
Wayne Clifford
Hanna Oltean

Bridget Barker
Chandler Roe
Elizabeth Driebe
David Engelthaler
Paul Keim

Nancy Chow
Steven Hurst
Lalitha Gade
Mark Lindsley
Ana Litventseva
Kaitlin Benedict
Raj Mody
Tom Chiller
Mary Brandt

Dale Griffin
Geoff Plumlee
THANK YOU!
THINK AND CONSIDER COCCI!!!!
Questions?

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Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
Visit: www.cdc.gov | Contact CDC at: 1-800-CDC-INFO or www.cdc.gov/info

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.
Older adults

- **Case-control study among persons ≥60 years old in AZ:**
  - Risk for acquiring symptomatic cocci declined by 5% for each year lived in the endemic area.
  - Controlling for duration of residence, CHF, corticosteroid use, smoking, cancer, and male gender were independently associated with developing cocci.
  - Suggests that cocci among the elderly in AZ may be partly related to the large number of retirement-age persons (many of whom have underlying medical conditions) who seasonally or permanently relocate to AZ from non-endemic areas.

Sex

- Historically, cocci has been more common among men
- Surveillance data show:
  - In AZ, 55-66% of cases occurred in men until 2009
  - In CA, rates consistently higher in men
- Men more likely to participate in high-risk activities?
- Sex hormones have been shown to stimulate growth of *Coccidioides* in vitro
- Some studies show males more likely to develop severe or disseminated disease, others do not

Mexico

- Collaborative work with Mexico to enhance laboratory capacity and epidemiologic capabilities for Valley fever
- Laboratory Training and Technology Exchange, 2011
- Development of bilingual clinical educational materials
- Pilot study among Tuberculosis Syndromic Surveillance System in Sonora, MX and Chihuahua, MX
  - Preliminary results 17% patients were serologically positive for Valley fever