2014 Update on Coccidioidomycosis

AZDHS Infectious Disease Training & Exercise

July 24, 2014

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Financial Disclosures

Nothing to disclose
Overview

• Background
• Clinical presentation
• Diagnosis
• Treatment
• National and AZ epidemiology
• Preventing, predicting exposure
• Take home points
Take Home Points

• Cocci can be a serious infection
• Case numbers have decreased from their peak in 2011, but are still higher than a decade ago
• Cocci likes to imitate other infections, so be vigilant!
• There is little data about how to prevent exposure
• It is unknown if treatment improves outcomes
BACKGROUND
Coccidioides spp.

- **Dimorphic fungus**
  - In environment: mold with single-celled arthrospores
  - In human body: spherule filled with endospores

- **Two species cause disease:**
  - *C. posadasii* in AZ, NM, NV, TX, UT
  - *C. immitis* in CA, WA

- **Persist in soil of warm, arid regions with low rainfall**
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.
Coccidiodomycosis

• Commonly referred to as “Cocci” or “Valley fever”
  – Spectrum of symptoms

• Causes of infection:
  – Usually from inhaling spores
  – Organ transplants (several cases each year)
  – Abrasion leading to local skin infection (rare)

*No person-to-person transmission
CLINICAL PRESENTATION
Of 100 persons exposed & infected with *Coccidiodes*

~1-3 weeks

~40 → primary pulmonary disease

~60 remain asymptomatic/subclinical (with lifelong immunity)

~3-12 months

5-10 individuals progress to chronic pulmonary disease

~1 develops disseminated disease
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
Few differences between community-acquired pneumonia patients who test + vs - 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><strong>Fever</strong></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>
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<tr>
<td>Symptom duration (days)</td>
<td>11.6 (2-35)</td>
<td>10.4 (1-182)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Chang, DC et al, EID 2008*
Primary pulmonary disease (2)

Chronic pulmonary disease

- Residual nodules, thin-walled cavities
- Hemoptysis may occur in ~25%
- Most findings resolve in ~2 years
- Chronic symptoms, cavitary lesions with infiltrates → mimic TB
Disseminated disease (1)

- 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

www.life-worldwide.org
Disseminated disease

- Joints, soft tissue may be affected (arthritis)
- Cutaneous, subcutaneous common
  - Varied appearance: papules, nodules, erosions
Risk factors for severe disease

• Race/ethnicity
  – Black, Filipino, Pacific Islander
• 3rd trimester of pregnancy
• Male sex
• Immunosuppression (T-cell depression)
  – Corticosteroids
  – HIV
  – Organ transplantation
• Diabetes, if poorly controlled
DIAGNOSIS
Serological tests for IgG and IgM

- **Immunodiffusion (ID)**
  - Positive = recent 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
- Will be commercially launched in **early 2015**
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
But what have studies shown?

Studies to date have yielded different findings

- Limitations: observational, small studies; severity of disease and treatment regimens often not standardized

No strong data on whether antifungals decrease the frequency or severity of symptoms

- May also be worth studying some other regimens
  - Posaconazole, fluconazole/itraconazole
  - Nikkomycin Z
  - Viamet (VT-116)
Randomized controlled trial (RCT)

• 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
  – ½ receive antifungal and ½ a placebo
  – Monitor cocci serology, clinical sx, outcomes

• Trial set to begin in late 2015
Treatment of disseminated disease

- Disseminated non-meningeal
  - Azole or Ampho B, depending on clinical picture
- Disseminated meningeal
  - Fluconazole
  - Some clinicians start with ↑ dose (800-1000 mg/d)
- Voriconazole, posaconazole may also be beneficial
- Surgical interventions may be needed (pulmonary cavities, increased intracranial pressure)
EPIDEMIOLOGY: HOW COMMON IS COCCI?
Public health importance

- Estimated 150,000 infections per year in U.S.
  - ~67% in Arizona
- In 2012: 12,920 new cases of cocci in Arizona
  - 2013 case numbers yet to be finalized but likely to be significantly lower
- 3,089 cocci-associated deaths from 1990 – 2008*
  - Overall age-adjusted mortality rate 0.59/million person-years

* Huang, *EID*, 2012
Cocci is a Notifiable Disease in the U.S.

• 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)
Cocci cases reported to NNDSS*
1998 – 2012 (n= 129,494)

- Arizona: 67%
- California: 30%
- Nevada, New Mexico, Utah: <1%
- Other states: 1%

*NNDS: National Notifiable Disease Surveillance System
Yearly US coccidioidomycosis case-count

<table>
<thead>
<tr>
<th>Year</th>
<th>Arizona</th>
<th>California</th>
<th>Nevada, New Mexico, Utah</th>
<th>Other states</th>
<th>Total US</th>
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<tbody>
<tr>
<td>1998</td>
<td>1,474</td>
<td>719</td>
<td>72</td>
<td>6</td>
<td>2,271</td>
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<tr>
<td>1999</td>
<td>1,812</td>
<td>939</td>
<td>55</td>
<td>20</td>
<td>2,826</td>
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<tr>
<td>2000</td>
<td>1,917</td>
<td>840</td>
<td>67</td>
<td>41</td>
<td>2,865</td>
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<td>2001</td>
<td>2,301</td>
<td>1,538</td>
<td>63</td>
<td>30</td>
<td>3,932</td>
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<td>2002</td>
<td>3,133</td>
<td>1,727</td>
<td>63</td>
<td>32</td>
<td>4,955</td>
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<tr>
<td>2003</td>
<td>2,695</td>
<td>2,091</td>
<td>55</td>
<td>19</td>
<td>4,860</td>
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<tr>
<td>2004</td>
<td>3,667</td>
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<td>110</td>
<td>44</td>
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<tr>
<td>2005</td>
<td>3,516</td>
<td>2,885</td>
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<td>43</td>
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<tr>
<td>2006</td>
<td>5,535</td>
<td>3,131</td>
<td>140</td>
<td>118</td>
<td>8,924</td>
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<td>2007</td>
<td>4,832</td>
<td>2,991</td>
<td>163</td>
<td>149</td>
<td>8,135</td>
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<td>2008</td>
<td>4,768</td>
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<td>7,533</td>
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<td>2009</td>
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<td>2,488</td>
<td>147</td>
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<td>12,943</td>
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<tr>
<td>2010</td>
<td>11,883</td>
<td>4,622</td>
<td>159</td>
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<td>2011</td>
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<td>5,697</td>
<td>237</td>
<td>240</td>
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<tr>
<td>2012</td>
<td>12,920</td>
<td>4,431</td>
<td>211</td>
<td>240</td>
<td>17,802</td>
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<tr>
<td>total</td>
<td>87,153</td>
<td>39,337</td>
<td>1,749</td>
<td>1,255</td>
<td>129,494</td>
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</table>
Coccidioidomycosis incidence rates by age group, all endemic U.S. states, 1998 – 2011

- Incidence increasing in all age groups
- Largest increases in younger populations
Cocci surveillance in Arizona

- AZDHS surveillance system in place since 1995
  - Lab-based
- Cocci has been laboratory-reportable since 1996
Cocci sex-specific incidence rates, Arizona, 1999 – 2011

Incidence per 100,000

Males | Females

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence Rate</th>
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<tbody>
<tr>
<td>1999</td>
<td>40</td>
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<tr>
<td>2000</td>
<td>45</td>
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<tr>
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<tr>
<td>2009</td>
<td>110</td>
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<tr>
<td>2010</td>
<td>120</td>
</tr>
<tr>
<td>2011</td>
<td>130</td>
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</table>
Summary

• Significant increases in U.S. reported cocci cases occurred during 1998 – 2011
  - Average yearly incidence increase of 41% in AZ

• Decrease in rates in 2012 and likely 2013
  - Seen in Arizona and nationally
  - AZDHS, CDC trying to determine why

• Beginning in 2009 there was a shift towards infection among females in AZ…still true in 2011 – 2013?

- Objective:
  - Describe the public health burden of cocci
    - Morbidity, costs
- Methods
  - 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 very common
Impact on patients, healthcare costs

- Among employed, 74% missed work due to cocci
  - Median workdays missed: 14
- 75% unable to do activities of daily living at some point during illness (median: 47 days)
- 26% saw their doctor 10+ times during course of illness
  - 46% went to the ER
  - 41% were hospitalized
  - Estimated cost of $33,000 per hospitalization
Large unmeasured burden

- May cause up to 29% of community-acquired pneumonia (CAP) cases in Arizona*
  - But in highly-endemic areas <15% of healthcare providers test CAP patients for cocci*
- Therefore, if cocci represents a large % of CAP, most cases go undiagnosed
  - Could be >50,000 cases/year

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

**Increased testing can help clarify the true # of cases**
Other benefits of testing

- Although the benefit of antifungal treatment is uncertain for most...still many reasons to test:
  - Determine if treatment is necessary (high risk)
  - Follow patients for severe sequelae
  - Avoid unnecessary procedures, visits (time and $)
  - Provide a diagnosis for patients

BOTTOM LINE: Test your patients for cocci!
PREVENTING AND PREDICTING EXPOSURE
Is it possible to prevent infection?

- Risky activities exist (digging, ATV use, etc.)
- Some common-sense prevention measures may help
  - Avoid risky activities (e.g., digging) if immunosuppressed
  - Wet down soil
  - Avoid dust storms
  - Wear an N95 mask
  - Roll up windows in your car
Is it possible to prevent infection?

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

- Cocci spores can travel for miles
- Some cases associated with particular activity, but most acquire disease simply by breathing
- Cases have even occurred after only small exposure to endemic areas (short trips with minimal outdoor time)
- Since exposure can’t be eliminated, a vaccine may be the only way to prevent infection
- More studies are needed to figure out how exposure can be reduced, prevented
What about a vaccine?

• Rationale:
  – ~60% of infected do not develop symptoms
  – Immunity from cocci is lifelong

• Initial human vaccine trials did not show benefit

• Cost-effectiveness uncertain
  – Who would get vaccinated?
  – Target high-risk groups
    • Construction, miners, landscapers, immunocompromised patients, military
If cocci not preventable, what then?

Since cocci isn’t currently preventable, must focus on:
• Identifying people with disease in a timely manner
• Reducing morbidity and mortality
• Improving diagnosis
• Finding effective treatment strategies, especially for primary pulmonary cocci
TAKE HOME POINTS
Take Home Points

• Cocci can be a serious infection and often mimics other diseases
• It is common in Arizona
• It is unclear if preventive measures work
• Testing is important and can help guide treatment, possibly reduce patient anxiety and healthcare costs
Acknowledgements

Arizona
Mohammed Khan
Clarisse Tang
Shane Brady
Ken Komatsu
Peter Kelly

CDC
Kaitlin Benedict
Rebecca Sunenshine

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