Coccidioidomycosis for Primary Care Practitioners

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Valley Fever Center for Excellence
University of Arizona
What Is Valley Fever?

• Caused by soil fungi
  - *Coccidioides immitis*
  - *Coccidioides posadasii*

• 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 to a second infection

Valley Fever Center for Excellence
Morphology of *Coccidioides* spp.

**In the Soil**
- Septate Mycelium
- Free Arthrospores
- Arthrospore Formation
- Disarticulation

**In infected tissue**
- Rupturing Spherule
- Endosporulating Spherule (Mature)
- Free Endospores
- Immature Spherules

www.vfce.arizona.edu
Arthroconidia (transmission & scanning EM)
Reported Valley Fever

- Arizona
- California

* data provisional
The Valley Fever Corridor:
2/3 of all US disease occur here
Age Specific Rates of Reported Coccidioidomycosis in Arizona, 2004*

<table>
<thead>
<tr>
<th>Age Groups in Years</th>
<th>Cases per 100,000</th>
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<tbody>
<tr>
<td>0-9</td>
<td>8.86</td>
</tr>
<tr>
<td>10-19</td>
<td>23.64</td>
</tr>
<tr>
<td>20-29</td>
<td>38.7</td>
</tr>
<tr>
<td>30-39</td>
<td>57.08</td>
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<tr>
<td>40-49</td>
<td>81.76</td>
</tr>
<tr>
<td>50-59</td>
<td>112.95</td>
</tr>
<tr>
<td>60+</td>
<td>125.8</td>
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</tbody>
</table>

*UA Campus Health

N Stern Emerg. Inf. Dis. 2010
<table>
<thead>
<tr>
<th>Patient group</th>
<th>Incidence</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scholarship Athletes:</td>
<td>475 per yr</td>
<td>374</td>
</tr>
<tr>
<td></td>
<td></td>
<td>192-639</td>
</tr>
<tr>
<td>Non-Athletes:</td>
<td>35,525 per yr</td>
<td>90</td>
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<tr>
<td></td>
<td></td>
<td>79-103</td>
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</table>

Chi square, p < 0.00001
## Valley Fever at UA Campus Health 1998-2006

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tested</th>
<th>95% CI</th>
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<tbody>
<tr>
<td><strong>Athletes:</strong></td>
<td></td>
<td></td>
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<tr>
<td>197 tests</td>
<td>4.6%</td>
<td>3.9%-5.4%</td>
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<tr>
<td><strong>Non-Athletes:</strong></td>
<td></td>
<td></td>
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<tr>
<td>2,558 tests</td>
<td>0.8%</td>
<td>.77%-.84%</td>
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</tbody>
</table>

Chi square, \( p < 0.000001 \)
Coccidioidomycosis Spectrum of Disease

100 Infections

60 No Symptoms → 40 Symptoms

37 Recover

Life-Long Immunity

Recover=Mild Or does it?
Common “Mild” Valley Fever

- **Manifestations:**
  - Cough, chest pain, fever, weight loss
  - Fatigue
  - Bone and joint pains (a.k.a. Desert Rheumatism)
  - Skin rashes (painful or intense itching)

- **Course of illness:**
  - Weeks to months
  - 1 of 4 college students are sick for > 4 months
  - 4-fold more drop a semester for Valley Fever than for Mononucleosis
Coccidioidomycosis as Community-Acquired Pneumonia

In Southern Arizona
29% (CI: 16% - 44%) of all CAP is Valley Fever

Tourists to Arizona: average risk is <1:15,000
But
CAP weeks after trip to Arizona,
Risk same as if you live in Arizona

Valley Fever
(Coccidioidomycosis)

Tutorial for
Primary Care Professionals

Prepared by the
VALLEY FEVER CENTER FOR EXCELLENCE
The University of Arizona
## Primary Care of Coccidioidomycosis

<table>
<thead>
<tr>
<th>Consider</th>
<th>Order</th>
<th>Check</th>
<th>Initiate</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>the right tests</td>
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<td></td>
<td></td>
<td>for risk factors</td>
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<td>for complications</td>
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<td></td>
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<td>management</td>
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### When to think of Valley Fever

#### Symptoms
- **Pulmonary**
  - Cough
  - Chest pain
  - Dyspnea
  - Hemoptysis
- **Arthralgias/Myalgias**
- **Headache (20%)**
- **Systemic**
  - Fatigue
  - Night sweats

#### Signs
- **Fever**
- **Weight loss**
- **Skin rashes**
  - Maculopapular rash
  - *Erythema nodosum*
  - *Erythema multiforme*

**Pulmonary symptoms may not be prominent**
What’s causing this Pneumonia?
Consider the diagnosis

- In Arizona, Valley Fever is very common. It should be in the differential often.
- More frequent between the monsoons and the winter rains.
- Syndromes:
  - **Always** in community acquired pneumonia.
  - Rheumatism.
  - Rashes.
Coccidioidomycosis is a Laboratory Diagnosis

- Detection of anti-coccidioidal antibodies
- Histologic identification of spherules
- Culture of *Coccidioides* spp.
- Other tests
  - Detection of coccidioidal antigens
  - PCR detection of coccidioidal DNA
Order the Right Tests
Detecting Coccidioidal Antibodies

– If coccidioidal antibodies are detected, this is a very specific result and usually important.

– A negative test does not eliminate the possibility of Valley Fever. Repeated testing improves diagnostic sensitivity.
Order the Right Tests
Detecting Coccidioidal Antibodies

- Tube Precipitins (TP, IDTP, or “IgM”)
  - only on serum
  - results are positive or negative
- Complement Fixing (CF, IDCF, or “IgG”)
  - Serum or CSF
  - results are quantitated
- EIA kit (Meridian, IMMY) (IgM or IgG)
  - screening test
  - more sensitive, not as specific
Percent Positive

Time (months)
The case took months to diagnose. There’s no cure or vaccine. The D-Back’s centerfielder, who has been too weak for workouts, could spend the season recuperating.”

-June 8, 2009 –

First two blood tests were negative before finally establishing a diagnosis.
KOH Examination
Spherule (Silver stain of BAL fluid)
Spherules (Hematoxylin-Eosin stain)
Coccidioidomycosis
Spectrum of Disease

100 Infections

60 No Symptoms  →  40 Symptoms

37 Recover

Life-Long Immunity

3-4 Recur

2-4 Progress Disseminate

www.vfce.arizona.edu
### Primary Care of Coccidioidomycosis

<table>
<thead>
<tr>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>Consider</td>
<td>the diagnosis</td>
</tr>
<tr>
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Risk Factors for Coccidioidal Complications

Pulmonary
- Diabetes mellitus
- Cardio-pulmonary or other co-morbidities. (Evidence: “common sense”).

Disseminated Infection
- Deficient cellular immunity
- Males > Females
- Racial background
  - African-American
  - Filipino
- Adults > Children
- Pregnancy
Primary Care of Coccidioidomycosis

- Consider the diagnosis
- Order the right tests
- Check for risk factors
- Check for complications
- Initiate management
Detecting Focal Lesions in Coccidioidomycosis

• Review of Systems: Pain or discomfort
  – Headache
  – Back pain
  – Joint pain or loss of function

• Physical Examination:
  – Skin lesions
  – Subcutaneous fluctuation
  – Joint effusions
Widely disseminated Coccidioidomycosis
• Disseminated Coccidioidomycosis
• Disseminated Coccidioidomycosis
Disseminated Coccidioidomycosis
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Disseminated Coccidioidomycosis
Check for Complications Summary

• Most complications are focal

• A careful review of systems and physical examination will usually detect or exclude the possibility of complications.

• If new focal findings are present, further imaging and laboratory studies can determine if they are related to infection.
Primary Care of Coccidioidomycosis

- **Consider** the diagnosis
- **Order** the right tests
- **Check** for risk factors
- **Check** for complications
- **Initiate** management
Management
Low Risk, Simple Early Infection

• Follow-up office visits
• Serial body weights
• Check for new symptoms or signs
• Repeat coccidioidal antibody testing
• Repeat Chest PA and Lateral X-rays
• Most patients do not need therapy
Management
Low Risk, Simple Early Infection

• Follow-up office visits for one year
  2-4 weeks ROS; Exam; Chest X-ray
  2-3 months ROS; Exam; serology
  3-6 months ROS; Exam;
  12 months ROS; Exam; Chest X-ray
Follow-up Chest X-rays
What to order?

Purposes:

– Identify if infiltrate cavitates.
– Determine if there is a residual nodule (could be confused with cancer in later years)

In most patients, these objectives can be accomplished with simple PA and lateral X-rays; CT scans are usually not needed.
Primary Coccidioidal Pneumonia

October 26
Primary Coccidioidal Pneumonia

November 3
Primary Coccidioidal Pneumonia

November 14
Primary Coccidioidal Pneumonia

December 15
Peripheral Coccidioidal nodule
Follow-up Coccidioidal Serology
How do they help?

• As patients improve, titers generally decrease
• The decrease typically occurs over several months, occasionally even slower.
• If titers increase, re-evaluate for possible complications.
• Titers are a marker, not a disease
Fatigue: Often the Last Symptom
Typical Problem

• Primary coccidioidal pneumonia diagnosed serologically in an otherwise healthy active person.
• Over several weeks, weight returns to normal, fever resolves and pulmonary symptoms gone. ESR becomes normal. CF low or neg.
• However, patient complains of profound inability to carry out normal activities.
• How should this be managed?
Potential Causes of Fatigue

- Circulating cytokines? Altered cell receptors? Signal transduction polymorphisms? Other guesses?
- Physical deconditioning because of decreased activity.
- Lack of experience by the patient with subacute or chronic disability.
- Patient with excessive expectations of own performance.
Management Strategies

- Exclude objective evidence of tissue destruction or focal lesions.
- **Patient Education**
  - Prolonged fatigue common and resolves
  - No evidence of permanent damage
  - Deconditioning and unrealistic expectations
- **Patient Actions**
  - Keep a journal
  - Refer patient to Physical Therapist for reconditioning
- **Antifungal drugs?** Usually not helpful
2005 IDSA Guidelines
Treatment of Coccidioidomycosis

“How best to manage primary respiratory coccidioidal infections is an unsettled issue because of the lack of prospective controlled trials.”
Median days to ≥50% decline in total clinical score

\[ P = 0.899 \]

Ampel et al. CID 2009
Outcome of Subjects (> 1 month follow-up)

• 50 not treated
  – Median follow-up: 3.1 years
  – All without complications

• 51 treated
  – Median follow-up: 2.9 years
  – 38 off-therapy and without complications
  – 5 remained on treatment
  – 8 had relapses
    • 5 with pulmonary disease
    • 3 with extrapulmonary dissemination
    • Relapses occurred up to 2 years after stopping treatment

Ampel et al. CID 2009
Primary Care of Coccidioidomycosis

Compatible Symptoms

Diagnostic Studies
Serology or Cultures

Risk Factors Present?

Focal Signs or Symptoms?

Revised evaluations

Observe

Start Anti-fungal?

Specialty Referral and / or Treatment

Retest
Questions?

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