Coccidioidomycosis Update for Primary Care

SW Conference on Medicine
April 26, 2018

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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
Morphology of *Coccidioides* spp.

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

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

www.vfce.arizona.edu
Arthroconidia (transmission & scanning EM)
Valley Fever in the U.S.

% Positive Skin Test

- 50-70%
- 30-50%
- 10-30%
- 5-10%
- <5%

www.vfce.arizona.edu
Reported Valley Fever

*Extrapolated from week 13
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>
</tr>
</thead>
<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>
</tr>
<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>
</tr>
</tbody>
</table>

117/100,000
UA Campus Health

N Stern Emerg. Inf. Dis. 2010
### Valley Fever at UA Campus Health 1998-2006

<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>
</tr>
<tr>
<td></td>
<td></td>
<td>79-103</td>
</tr>
</tbody>
</table>

Chi square, p < 0.00001
<table>
<thead>
<tr>
<th>Patient group</th>
<th>Tested</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Athletes:</td>
<td>197 tests</td>
<td>4.6%</td>
</tr>
<tr>
<td>Non-Athletes:</td>
<td>2,558 tests</td>
<td>0.8%</td>
</tr>
</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

22nd Anniversary of the UA VFCE

- Education
  - 2002 Valley Fever Awareness Program
  - 2016 Primary Care Tutorial, 2nd Edition
  - CME Programs: Live and Online
- Research
  - $25-35 million in funding: Epi., Immunol., Genetics, Diagnostics, Drugs, Vaccines
- Clinical Care
  - 15th Annual Valley Fever Awareness Week
    - November 11th – 19th 2017
  - CME Programs: Live and Online
How bad is it?

Ariz CAP

- ~25%-30% due to *Coccidioides* BUT
- <15% are tested for *Coccidioides*.

~1,000 new Az medical licenses/yr

- 12% received MD in Az; 40% no Az GME

80% didn’t know: VF is reportable;
Vaccine does not exist

40% of clinicians not confident to treat VF

• Chang, 2008; Chen, 2011
Consequences of Current Standard Practices

• Delays in diagnosis of early coccidioidal infections: In BUMC-T, 30% > 1 month*
  – Unnecessary anti-bacterial drug use
  – Protracted patient anxiety and fear
  – Over-utilization CT scans and bronchoscopies, even thoracotomies

• Hypothesis: Earlier diagnosis would improve outcomes and reduce cost.

*Donovan et al, unpublished 2018
Valley Fever
(Coccidioidomycosis)

Tutorial for
Primary Care Professionals

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

- Consider the diagnosis
- Order the right tests
- Check for risk factors
- Check for complications
- Initiate management
When to think of Valley Fever

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
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<tbody>
<tr>
<td>Pulmonary</td>
<td>• Fever</td>
</tr>
<tr>
<td>– Cough</td>
<td>• Weight loss</td>
</tr>
<tr>
<td>– Chest pain</td>
<td>• Skin rashes</td>
</tr>
<tr>
<td>– Dyspnea</td>
<td>– Maculopapular rash</td>
</tr>
<tr>
<td>– Hemoptysis</td>
<td>– <em>Erythema nodosum</em></td>
</tr>
<tr>
<td>Arthralgias/Myalgias</td>
<td>– <em>Erythema multiforme</em></td>
</tr>
<tr>
<td>Headache (20%)</td>
<td>Pulmonary symptoms may not be prominent</td>
</tr>
<tr>
<td>Systemic</td>
<td></td>
</tr>
<tr>
<td>– Fatigue</td>
<td></td>
</tr>
<tr>
<td>– Night sweats</td>
<td></td>
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Symptoms: 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.
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
Primary Care of Coccidioidomycosis

- Consider the diagnosis
- Order the right tests
- Check for risk factors
- Check for complications
- Initiate management
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
• Disseminated Coccidioidomycosis
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

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<td>Initiate</td>
<td>management</td>
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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
Primary Coccidioidal Pneumonia
Primary Coccidioidal Pneumonia
Primary Coccidioidal Pneumonia

Study date: 12.15.2011
Study time: 14:38.55

Series number: 1
Image number: 2

KVP: kv
X-ray tube current: mA
Exposure: mAs
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

• In some, striking deficit in O$_2$ utilization (VO$_2$ peak <10% of predicted)*

• Physical deconditioning because of decreased activity.

• Lack of experience by the patient with subacute or chronic disability.

• Patient with excessive expectations of own performance.

*Ganley, Open Forum Infectious Diseases 2017
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
2016 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for the Treatment of Coccidioidomycosis

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IDSociety.org Downloads thru Sept 2017
Full-text, Exec. summary, Online flipbook, Pocket card
>21,000 total

Clin Infect Dis, Sept 15th, 2016
“It should be emphasized that no randomized trials exist to assess whether antifungal treatment either shortens the illness of early uncomplicated coccidioidal infections or prevents later complications.”
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
Seroology or Cultures

Risk Factors Present?

- Yes

Focal Signs or Symptoms?

- No

Observe

- Yes

Retest

Specialty Referral and/or Treatment

Start Anti-fungal?
Questions?

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