Updates in coccidioidomycosis

Tucson Medical Center
Health Medical education Program

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Disclosures

No conflicts of interest to disclose
Objectives

• Overview of clinical presentation and challenges involved with the diagnosis and treatment of Valley fever.
• Methods to improve Valley fever early diagnosis.
• Management of CM patients on BRMs.
What Is Valley Fever?

- Caused by soil fungi
  - *Coccidioides immitis*
  - *Coccidioides posadasii*
- Other names:
  - Coccidioidomycosis
  - “COCCI”
- Infection:
  - About 150,000 per year
  - Caused by single spore
- Spectrum of disease
  - Sub-Clinical: 60%
  - “Mild”: 30%
  - Complicated: 10%
- After infection, most persons develop life-long immunity to a second infection
Biology of Coccidioidomycosis

Environmental Form

Host-associated Form

Estimated Areas with Coccidioidomycosis

https://www.cdc.gov/fungal/diseases/coccidioidomycosis/causes.html
The Valley Fever Corridor: 2/3 of all U.S. disease occurs here
Common “Mild” Self-Limited Valley Fever

Signs and Symptoms, < 1 months from exposure:
– 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
– 25% of college students are sick for > 4 months
– 50% of workers lose > 2 weeks
Current Clinical Practice for Valley Fever

Arizona CAP
- ~ 25% - 30% due to Coccidioides
  BUT
- < 15% are tested for Coccidioides

~ 1,000 new AZ medical licenses/year
- 12% received MD in AZ
- 40% no AZ GME

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

40% of clinicians are not confident to treat VF
Only 247 out of 1,812 unique patients (13.6%) who were newly diagnosed as Cocci in primary care clinics (yellow bar)
Delay of Valley Fever Diagnosis

BUMC-P
45% of Diagnoses Delayed > 1 month

Ginn et al. EID, 2019
Delay of Valley Fever Diagnosis

Figure 1.

- Acute Pulm
- Chron Pulm
- Asymptomatic
- Dissemin

BUMC-T
43% of Diagnoses Delayed > 1 month

Donovan et al. EID, 2019
What Do Weeks of Delayed Diagnosis Mean?

- 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
## Summary of Patients with CAP BMG and BUMG, total 2017-2019YTD

<table>
<thead>
<tr>
<th>Measure Year</th>
<th>Patients With Initial Diagnosis of Pneumonia</th>
<th>25% Of Patients With Initial Diagnosis of Pneumonia</th>
<th>Patients With Diagnosis Of Cocci</th>
<th>Patients With Cocci Tests</th>
<th>Patients With Positive Cocci Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>837</td>
<td>209</td>
<td>26</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>2018</td>
<td>851</td>
<td>213</td>
<td>19</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>2019</td>
<td>629</td>
<td>157</td>
<td>12</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Grand Total</td>
<td>2,268</td>
<td>567</td>
<td>57</td>
<td>57</td>
<td>43</td>
</tr>
</tbody>
</table>
Objectives

• Overview of clinical presentation and challenges involved with the diagnosis and treatment of Valley fever.
• Methods to improve Valley fever early diagnosis.
• Management of CM patients on BRMs.
Valley Fever
(Coccidioidomycosis)

Tutorial for
Primary Care Professionals

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

1. **Consider** the diagnosis
2. **Order** the right tests
3. **Check** for risk factors
4. **Check** for complications
5. **Initiate** management
Consider the diagnosis

Respiratory: Previous visit, needs X-ray or antibacterial Rx? 
Musc/Skel: More than one week, associated with fever or fatigue. 
Rashes: *E. nodosum* or *E. multiforme*

Clinician reviews chief complaint(s) and medical history, examines patient, and documents findings (HPI, ROS, PE)

Syndrome: respiratory? musculoskel? rashes?

Endemic Exposure? residence or recent travel

Go to:

2. Order the right tests

Yes

Valley Fever Process Completed

Yes

Add Valley Fever to the Differential

No

No

Yes

No
Consider the diagnosis in Arizona

• 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.
2. Order the right tests

EIA screen for coccidioidal antibodies with reflex to immunodiffusion and quantitative CF.

- Test Negative
  - Illness resolved in 3 weeks

- Test Positive
  - Go to: 3 & 4 Check for risks and complications

Yes

Valley Fever Process Completed

No
Enzyme Immunoassay (EIA) test

– A positive test is very specific and usually is diagnostic.

– A negative test never rules out Valley Fever. Repeated testing improves diagnostic sensitivity.
Check for Risk Factors

Immunosuppression (HIV, organ recipient, Rheum/GI/Derm response modifier Rx, renal failure)
Diabetes, major cardiac or pulmonary comorbidities, pregnancy

3 Check for Risk Factors

Risk factors present?

No → Go to: 5 Management, Uncomplicated infect.

Yes → Complicated VF: Refer to Specialist (ID or Pulmonary)
Risk Factors

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

Disseminated Infection
– Major and critical
  • Cell immunodeficiency
  • Pregnancy
– Minor and small effect
  • Males > Females
  • Racial background
  • Adults > Children
Check for complications evident by physical exam or imaging
Focal ulceration or skin/soft tissue inflammation.
Asymmetric skeletal pain, joint effusions.
Progressive or unusual headache.

Risk factors present? No
Complications present? No
Go to: Management, Uncomplicated infect.

Complicated VF: Refer to Specialist (ID or Pulmonary)
Detecting Complications of Coccidioidomycosis

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

- Physical Examination:
  - Skin lesions
  - Subcutaneous fluctuation
  - Joint effusions
Fibro-cavitary Coccidioidomycosis

Complex

Thin-walled
Widely Disseminated Coccidioidomycosis
Disseminated Coccidioidomycosis
Disseminated Coccidioidomycosis
Disseminated Coccidioidomycosis
Disseminated Coccidioidomycosis
Disseminated Coccidioidomycosis
Check for Complications

• Most complications are focal
• A review of systems and physical examination will usually detect or exclude the possibility of complications.
• New focal findings warrant either evaluation or referral for Infectious Diseases or Pulmonary consultation.
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 Coccidioidial Pneumonia
Primary Coccidioidal Pneumonia
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
Comparison of a Novel Rapid Lateral Flow Assay to Enzyme Immunoassay Results for Early Diagnosis of Coccidioidomycosis

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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 O₂ utilization (VO₂ 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.
Management Strategies for fatigue

• 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? May or May Not be Helpful
2016 Infectious Diseases Society of America (IDSA) Clinical Practice Guideline for the Treatment of Coccidioidomycosis

John N. Galgiani,¹ Neil M. Ampel,² Janis E. Blair,³ Antonino Catanzaro,⁴ Francesca Geertsma,⁵ Susan E. Hoover,⁶ Royce H. Johnson,⁷ Shimon Kusne,³ Jeffrey Lisse,⁸ Joel D. MacDonald,⁹ Shari L. Meyerson,¹⁰ Patricia B. Rakson,¹¹ John Siever,¹² David A. Stevens,¹³ Rebecca Sunenshine,¹⁴,¹⁵ and Nicholas Theodore¹⁵

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2016 IDSA Guidelines
Treatment of Coccidioidomycosis

“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 $\geq 50\%$ 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
The Valley Fever Tool Kit
www.vfce.arizona.edu

Support Resources

- Process Flow pocket guide.
- Wall posters and patient educational brochures
- Nurse Practitioner referral support? (proposed)
- EMR alerts? (only if wanted by the clinicians)

Training Resources

- Webinar Overview
- Primary Care Tutorial
- Powerpoint presentation online
- CME presentations at individual clinical practices.
Potential impact of the Banner Training on Arizona cocci surveillance data
Arizona Department of Health Services Preliminary Analysis, 7/30/19.

Reported cases have been elevated for most of 2019 year-to-date compared to 2018.

Monthly percent change from 2018 to 2019 in cases from Banner and non-Banner facilities.
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• Overview of clinical presentation and challenges involved with the diagnosis and treatment of Valley fever.
• Methods to improve Valley fever early diagnosis.
• Management of CM patients on BRMs.
An increasing number of BRMs used for autoimmune diseases such as RA pose further risk for endemic mycosis.

Some patients on BRMs handle CM poorly.

The risk of DCM rises as much as 150-fold in some immunosuppressed patients (Cohen, 1982).

Clinical question: Is it safe to use BRMs in CM-endemic regions?
Early TNFα blockade has deleterious effect on mice survival
Evaluating the CM risk in patients on BRMs:

Donovan et al, OFID, 2022
Evaluating the CM risk in patients on BRMs:

- Male sex was associated with more CM ($P = 0.003$)
- African ancestry were 3 times more likely than those with European ancestry to develop DCM ($P < .001$).
- Comparing CM+/AI+ ($n = 138$) with CM+/AI− ($n = 449$) patients, there were no significant differences in CM clinical presentations.
- Patients receiving BRMs had 2.4 times more DCM compared to pulmonary CM (PCM).

Donovan et al, OFID, 2022
Evaluating the CM risk in patients on BRMs

Table 4. Comparison of Biologic Response Modifier Used in Pulmonary and Disseminated Coccidioidomycosis Among Patients With Autoimmune Disease

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>BRM</th>
<th>No BRM</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td>PCM</td>
<td>17 (65.4)</td>
<td>58 (85.3)</td>
<td>.045**</td>
</tr>
<tr>
<td>DCM</td>
<td>9 (34.6)</td>
<td>10 (14.7)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>26 (100)</td>
<td>68 (100)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BRM, biologic response modifier; DCM, disseminated coccidioidomycosis; PCM, pulmonary coccidioidomycosis.

*Total of 94 patients identified with both PCM/DCM presentation and autoimmune syndrome.

**Fisher exact test was used to evaluate categorical groups.
**Statistically significant difference between coccidioidomycosis-positive groups.
Summary

• Banner Health and the UA Valley Fever Center for Excellence are changing the way Arizona clinicians recognize and manages patients with Valley Fever.

• Central to this change will be the expanded roll of primary care clinicians in earlier diagnosis and management of uncomplicated Valley Fever.
Thank-You

For more information:
http://vfce.arizona.edu/toolkit