Management of Coccidioidomycosis in Rheumatic Patients on Biologic Response Modifiers

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Objectives

• Discuss the risk of Coccidioidomycosis infection in the rheumatic population.
• Discuss the treatment and management of infected patients.
• Discuss screening habits and how they relate to the 2016 IDSA guidelines.
• Discuss research since 2016 relating to screening and treatment.
I have nothing to disclose.
Coccidioides immitis / Coccidioides posadasii

Mycelia

www.idimages.org

Spherule
Endemic Areas for Coccidioidomycosis

- Arizona
- California
- Nevada
- New Mexico
- Texas
- Utah
- Washington

- Mexico: the north (near the US border), the Pacific coast, and the central valley.
- Guatemala: the Motagua River valley
- Honduras: the Comaya valley
- Argentina: the Sierras Pampeanas
- Colombia: the Magdalena, Guajira, and Cesar provinces
- Paraguay: the Great Chaco
- Venezuela: the Departments of Falcon, Lara, and Zulia
- Brazil: the Piaui and Ceará districts
Reported Cases of Coccidioidomycosis (Valley Fever) in the US 1998-2015

[Diagram showing the number of cases reported annually from 1998 to 2015 for Arizona, California, and all other states where Coccidioidomycosis is reportable.]


The case numbers reported here are those reported in the annual Summary of Notifiable Infectious Diseases, published in CDC’s Morbidity and Mortality Weekly Report.
Coccidioidomycosis Infections in the US

- 150,000 infections occur annually
  - 50,000 illness warrant medical attention
  - 10,000–20,000 diagnosed and reported
  - 2,000–3,000 pulmonary symptoms
  - 600–1000 spread from lungs hematogenously resulting in disseminated disease
  - 160 result in death

- Considerable yr-to-yr variation associated with seasonal precipitation

Symptoms of *Coccidioidomycosis*

- **Systemic**
  - Fatigue, headache
  - Weight loss, night sweats
- **Pulmonary**
  - Cough, Shortness of breath
- **Myalgias, arthralgias, arthritis**
  - “Desert Rheumatism”
- **Rash on upper body or legs**

https://www.cdc.gov/fungal/diseases/coccidioidomycosis/symptoms.html
Coccidioidomycosis and Community-acquired Pneumonia

• CAP most common reason patients get medical attention
  • Two studies demonstrated Cocci infection in 24% cases of CAP
  • Inhalation of arthroconidia
  • Develop within month of endemic exposure

Pulmonary Coccidioidomycosis
Disseminated *Coccidioidomycosis*
Diagnosing *Coccidioidomycosis*

- Direct isolation in culture
- Spherules identified in tissue specimens
- Serum enzyme immunoassays (EIAs) for anticoccidioidal IgM and IgG.
  - Positive test must be confirmed with positive immunodiffusion
  - IDC (complement fixation) or IDTP (tube precipitin)
- Positive Cocci tests ASSUMED to be associated with recent or active infection
  - IgG, IgM titers normalize as infection resolves
Types of *Coccidioidomycosis* Infection

- **“Asymptomatic”** - positive serology on routine surveillance not ordered in response to symptoms
- **“Pulmonary”** - positive serology plus new X-ray findings, lower respiratory symptoms, erythema nodosum, fever, or night sweats
- **“Disseminated”** - positive culture or histology from an extra-pulmonary site

- 60% remain asymptomatic
- 50% of symptomatic patients develop abnormal chest radiographs
  - Symptoms clear in 2-3 weeks or may last for months
  - 5% develop residual lung lesions
- <1% develop disseminated disease
Risk for Disseminated *Coccidioidomycosis*

- **Skin**, bone, joint, meninges, larynx, eye, peritoneum
- **3rd trimester pregnancy**
- HIV infection or other illnesses impairing cellular immunity
- Use of immunosuppressing medication
  - High-dose corticosteroids
  - Antirejection treatment for organ transplantation
  - Tumor necrosis factor inhibitors
- **Biologic response modifiers (BRMs) shown to increase risk of serious infection**
- **Limited information on the risk of coccidioidomycosis in patients treated with BRMs and/or corticosteroids**

Singh JA Current Rheumatology Reports 2016; 18:61
Singh JA et al Lancet 2015; 386:258-265
• TNF alpha important for host defense
• TNF alpha antagonist therapy associated with increased risk of infections
• With respect to coccidioidomycosis
  • Serologic testing and chest x-ray unproven to identify patients at risk for reactivation
  • Not enough data to warrant primary prophylaxis in seropositive patients
Increased Risk of Coccidioidomycosis in Patients Treated with Tumor Necrosis Factor alpha Antagonists

- Charts from 5 practices in endemic areas (AZ, CA, NV) reviewed January 2000 – February 2003
- Total of 985 patients with inflammatory arthritis
  - 845 RA, 50 JRA, 70 PsA, 20 ReA
- 13 patients with cocci were identified while receiving anti-TNF therapy
  - Infliximab: 12, Etanercept: 1
- Logistic regression modeling showed infliximab associated with presence of symptomatic coccidioidomycosis
  - 7/247 infliximab vs. 4/738 other meds (MTX, prednisone)
  - Risk ratio 5.23 (1.54-17.71)

- Patients with inflammatory arthritis receiving TNF alpha antagonist therapy are at higher risk for developing symptomatic cocci.

Management of Coccidioidomycosis in Patients Receiving Biologic Response Modifiers or Disease-Modifying Antirheumatic Drugs

• 44 patients with cocci were identified
  • 11 BRM, 8 DMARD, 25 combo
• Pulmonary (29), Disseminated (9), Asymptomatic (6)
• DMARD and BRM stopped (26), BRM only (8), no change (10)
• Antifungal for at least 1 month (41)
• BRM and/or DMARD resumed in 33
  • 16 were continued on antifungal, 17 were not
  • Median follow up 30 months

Management of Coccidioidomycosis in Patients Receiving Biologic Response Modifiers or Disease-Modifying Antirheumatic Drugs

• Re-treating with a BRM and/or DMARD after cocci infection safe in some patients

• All patients should receive initial antifungal therapy
  • Concomitant antifungal when resuming BRM/DMARD must be individualized

• Larger, longer studies needed to characterize relationship with BRM/DMARD therapy and fungal infection

Asymptomatic Coccidioidomycosis
- Consider continuing BRM if rheumatic disease is active
- Antifungal therapy 6-12 months

Pulmonary Coccidioidomycosis
- Hold BRM
- Antifungal therapy at least 6-12 months or until resolved

Disseminated coccidioidomycosis
- Hold BRM
- Antifungal therapy indefinitely

Repeat serology in 1-3 months

NEGATIVE
- Consider restarting BRM if rheumatic disease active

POSITIVE
- Is coccidioidomycosis active? Consider Infectious Disease consultation
  - NO
    - Consider restarting BRM
  - YES
    - Hold BRM
Update in the Management of Biologic Response Modifiers and Disease-Modifying Antirheumatic Drugs Following Coccidioidomycosis

- ACR 2015 abstract presentation
- 71 patients with cocci were followed
  - Included many of original 44
  - 19 BRM, 16 DMARD, 36 Combo
- Pulmonary (42), Disseminated (10), Asymptomatic (19)
- Follow-up data for 64/71 (90%) patients
- 50/64 (78%) patients had resumed or continued BRM and/or DMARD
  - Time to restart:
    - DMARD: 1 month (0-48 months)
    - BRM: 10 months (0-72 months)
- Median follow-up: 29 months (Range 2-141 months)
Biologic response modifiers at diagnosis

<table>
<thead>
<tr>
<th>Biologic Response Modifier</th>
<th>Total</th>
<th>BRM alone</th>
<th>BRM in combination with DMARD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>26</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>Etanercept</td>
<td>10</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>10</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Abatacept</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Rituximab</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Golimumab</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

No particular agent seemed to be associated with dissemination.
Update in the Management of Biologic Response Modifiers and Disease-Modifying Antirheumatic Drugs Following Coccidioidomycosis

- Retreating with DMARD and/or BRM after cocci infection safe
- If asymptomatic, continuation of DMARD and/or BRM can be considered.
  - Algorithm revised: Monitor asymptomatic patients rather than treat with fluconazole
- Severe Pulmonary or Disseminated Coccidioidomycosis:
  - Immunosuppressive therapy should be stopped
  - Antifungal therapy continued until no evidence of active infection

Usman Ajaz, Neil M. Ampel, Varun Bhalla, Jeffrey R. Lisse and Dominick Sudano
**Initial Management**

**Asymptomatic**
- Continue BRM/DMARD if rheumatic disease active
- Closely monitor

**Pulmonary**
- Hold BRM
- Consider continue DMARD if mild infection and rheumatic disease active
- Antifungal therapy at least 6-12 months or until resolved
- Closely monitor

**Disseminated**
- Hold DMARD & BRM
- Antifungal therapy indefinitely
- Closely monitor

**TRIAGE!**
Initial Management

Asymptomatic Cocci
- Continue BRM/DMARD if rheumatic disease active
- Closely monitor

Pulmonary Cocci
- Hold BRM
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- Hold DMARD & BRM
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- Closely monitor

Initial Management

Disseminated Cocci

- Hold DMARD & BRM
- Antifungal therapy indefinitely
- Closely monitor
Subsequent Management

Assess for active infection every 1-3 months

Persistent Symptoms?

OR

Imaging not resolved/stable?

NO

Serology NEGATIVE

Infection Resolved
• Consider restart BRM
• Antifungal therapy 6-12 months
• Closely monitor

Serology POSITIVE

Low Titer Serology (IDCF < 1:16)
• Consider restarting BRM after consultation with ID
• Risk vs Benefit
• Continue antifungal
• Closely monitor

High Titer Serology
• Do not restart BRM
• Continue antifungal
• Reevaluate every 1-3 months

YES

Serology POSITIVE

• Do not restart BRM
• Continue antifungal tx
• Reevaluate every 1-3 months
Subsequent Management

Assess for active infection every 1-3 months
Persistent Symptoms? OR Imaging not resolved/stable?

**NO**

**Serology NEGATIVE**
- Infection Resolved
  - Consider restart BRM
  - Antifungal therapy 6-12 months
  - Closely monitor

**Serology POSITIVE**
- Low Titer Serology (IDCF < 1:16)
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**YES**

Serology POSITIVE
- Do not restart BRM
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Infection Resolved
- Consider restart BRM
- Antifungal therapy 6-12 months
- Closely monitor
Subsequent Management

Assess for active infection every 1-3 months
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OR
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• Consider restart BRM
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Subsequent Management

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  • Reevaluate every 1-3 months

YES

Serology POSITIVE

• Do not restart BRM
• Continue antifungal tx
• Reevaluate every 1-3 months
Subsequent Management

Assess for active infection every 1-3 months
Persistent Symptoms? OR Imaging not resolved/stable?

NO
Serology NEGATIVE

Infection Resolved
• Consider restart BRM
• Antifungal therapy 6-12 months
• Closely monitor

Serology POSITIVE

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• Closely monitor

High Titer Serology
• Do not restart BRM
• Continue antifungal
• Reevaluate every 1-3 months

YES

• Do not restart BRM
• Continue antifungal tx
• Reevaluate every 1-3 months
2016 IDSA Clinical Practice Guideline for the Treatment of *Coccidioidomycosis*

XXIII. For Recipients of Biological Response Modifiers With Active Coccidioidomycosis, Which Treatment Is Preferred: Oral Azole or Intravenous AmB? Recommendation

34. We recommend oral azole therapy for these patients unless their coccidioidomycosis is severe enough that intravenous AmB would otherwise be recommended (refer to sections on pneumonia, soft tissue dissemination, skeletal dissemination, and meningitis) (*strong*, *low*).

XXVII. For Recipients of Biological Response Modifiers Without Active Coccidioidomycosis, Which Primary Prevention Strategy Is Preferred: Observation or Prophylactic Antifungal Therapy? Recommendation

54. For patients in the endemic area, we recommend screening with *Coccidioides* serology prior to initiation of biologic response modifier therapy, as well as regular clinical follow-up for new signs and symptoms (*strong*, *very low*). We do not recommend regular serologic screening or antifungal prophylaxis in asymptomatic patients taking biologic response modifiers (BRMs) (*strong*, *very low*).
34. For recipients of BRMs with active Coccidioidomycosis, which treatment is preferred: oral azole or intravenous AmB?

- Oral azole preferred
- AmB for serious infections
- Additional evidence needed for this population, particularly asymptomatic patients with positive serologies
54. For recipients of BRMs without active Coccidioidomycosis, which primary prevention strategy is preferred: observation or prophylactic antifungal therapy?

• For patients in the endemic area
  • Recommend screening with Coccidioides serology prior to initiation of BRM therapy
  • Regular clinical follow up for new signs and symptoms

• Do not recommend regular serologic screening or antifungal prophylaxis in asymptomatic patients taking BRMs.
  • Some rheumatologists in endemic area obtain Coccidioides serologies regularly on patients taking BRMs, value not evaluated
  • No studies of primary prevention with antifungal therapy have been published
  • Some evidence suggest that patients with asymptomatic positive serologies do well
Asymptomatic Coccidioidomycosis in Patients with Rheumatic Disease: 8 years of experience.

- ACR 2016 abstract
- 19 patients with asymptomatic cocci were followed
  - 17 RA, 1 PsA, 1 dermatomyositis
  - 8 BRM alone, 2 DMARD along, 9 Combo
  - Median follow: 43 months
- 10 patients neither reduced antirheumatic therapy, nor started antifungal treatment.
- No patients have developed symptomatic Cocci illness

In the past 8 years there have been no complications in the asymptomatic cocci patients who continued BRM and DMARD.
Use of Disease-Modifying Antirheumatic Drugs, Biologic Response Modifiers and Corticosteroids, and Subsequent Risk of Coccidioidomycosis Infection Among Medicare Beneficiaries

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Meeting: 2017 ACR/ARHP Annual Meeting
Objective

• Estimate and compare the risk of coccidioidomycosis infection among Medicare beneficiaries with rheumatic diseases or autoimmune diseases treated by:
  • Disease Modifying Anti-Rheumatic Drugs (DMARDs)
  • Biologic Response Modifiers (BRMs)
  • Corticosteroids
Methods

• Retrospective cohort study using 2011-2013 Medicare claims data (5% representative sample)
• Seven endemic states - Arizona, California, New Mexico, Nevada, Texas, Utah, and Washington
• Beneficiaries with any of ten autoimmune diseases
  • Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis
  • Systemic Lupus Erythematosus, Reactive Arthritis, Polymyositis
  • Dermatomyositis, Systemic sclerosis, Psoriasis
  • Inflammatory Bowel Disease
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMARDs</td>
<td>azathioprine, cyclophosphamide, cyclosporine, hydroxychloroquine, leflunomide, methotrexate, minocycline, penicillamine, sulfasalazine</td>
</tr>
</tbody>
</table>
| BRMs and small molecule | • TNF-α Inhibitors: adalimumab, certolizumab, etanercept, golimumab, infliximab;  
                          • Non-TNFi Biologics: abatacept, anakinra, tocilizumab, belimumab, rituximab  
                          • Janus kinase (JAK) inhibitor: tofacitinib                              |
| Corticosteroids (oral, intramuscular, intra-articular) | • Dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone, triamcinolone, |
Statistical Methods

• Estimate hazard ratios (HRs) with 95% confidence intervals (CI) to compare DMARD, BRM, and corticosteroid use and risk of subsequent coccidioidomycosis infection

• Adjusted for age, sex, race, Medicaid eligibility, low income subsidy, CMS prescription drug hierarchical condition categories risk score (RxHCC), Elixhauser comorbidity index, disability status, metropolitan area, opioid use, and NSAID use within 3 months of the index date
Results

<table>
<thead>
<tr>
<th>Table 1. Selected Characteristics of Study Cohort (n=14,931)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), years</td>
</tr>
<tr>
<td>Female, %</td>
</tr>
<tr>
<td>Whites, %</td>
</tr>
<tr>
<td>African-Americans, %</td>
</tr>
<tr>
<td>With 1 rheumatic/autoimmune disease, %</td>
</tr>
<tr>
<td>Rheumatic arthritis</td>
</tr>
<tr>
<td>Psoriasis</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
</tr>
<tr>
<td>Others (polymyositis, dermatomyositis, reactive arthritis)</td>
</tr>
<tr>
<td>With ≥2 rheumatic/autoimmune diseases, %</td>
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</tbody>
</table>
### Results

- 51 Cocci cases (1.6 cases per 1,000 person-years)

<table>
<thead>
<tr>
<th></th>
<th>No. Cocci Cases</th>
<th>Person-years</th>
<th>Crude rate (per 1,000 person-years)</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)</th>
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<tbody>
<tr>
<td><strong>DMARDs</strong></td>
<td></td>
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<tr>
<td>No</td>
<td>35</td>
<td>23,218</td>
<td>1.5</td>
<td>Reference</td>
<td>Reference</td>
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<tr>
<td>Yes</td>
<td>16</td>
<td>9,036</td>
<td>1.8</td>
<td>1.05 (0.56, 1.94)</td>
<td>1.02 (0.54, 1.91)</td>
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<tr>
<td><strong>BRMs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>43</td>
<td>29,662</td>
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<tr>
<td>Yes</td>
<td>8</td>
<td>2,592</td>
<td>3.1</td>
<td>2.20 (1.01, 4.83)</td>
<td>2.25 (1.02, 4.95)</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
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<td></td>
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<tr>
<td>No</td>
<td>29</td>
<td>23,539</td>
<td>1.2</td>
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<tr>
<td>Yes</td>
<td>22</td>
<td>8,715</td>
<td>2.5</td>
<td>1.95 (1.11, 3.42)</td>
<td>1.94 (1.10, 3.42)</td>
</tr>
</tbody>
</table>

*Adjusted HRs were estimated by including sociodemographic and health status covariates and indicator variables for corticosteroids, DMARD, and BRM, simultaneously.

For example, the HR for BRMs compares the risk of Cocci for beneficiaries exposed to BRMs to those not exposed to BRMs, adjusted for concurrent corticosteroid exposure and/or DMARD exposure.
Limitations

• Medicare database represent older population
• Rheumatologic diseases first diagnosed prior to Medicare eligibility
  • New medication users rare
  • Predominantly prevalent users
• Due to limited number of cases, we were unable to evaluate risk:
  • Combinations of therapeutic classes
  • Medications based on mechanism of action
Conclusion

• Overall incidence from 2011 to 2013 among Medicare beneficiaries with rheumatic or autoimmune diseases was higher than rates reported for the general population in the southwestern US (1.6 vs 0.43 per 1,000 person-years) [MMWR]

• Use of BRM and corticosteroids was associated with higher risk of Coccidioidomycosis compared to non-users

• No association between DMARD use and risk of Coccidioidomycosis was observed
Management of Coccidioidomycosis - Summary

• Now have a guideline regarding management of Cocci in BRM or disease-modifying antirheumatic drug (DMARD) users:
  • Use fluconazole if there is an active infection (AmB if serious)
  • Asymptomatic patients should be closely monitored
  • Serologic screening at initiation
  • Annual serologic screening has not been evaluated

• Can you resume BRM or DMARD therapy?
  • Yes, once the infection has improved

• Should corticosteroids be treated the same as BRMs?
  • Probably?
Management of Coccidioidomycosis - Summary

• How do you manage these patients during and after cocci infection?

• Do all the BRMs/DMARDs confer the same risk?
  • This has not been addressed

• Areas of need:
  • Management of asymptomatic patients, value of annual screening, antifungal primary prophylaxis
Questions?

Thank you!