Endemic Mycoses: Update on *Coccidioides* spp

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**Key Questions**

- Expanding geographic range
  - New locations or simply newly recognized?
- New diagnostic methods
  - Development of rapid diagnostics
- New treatment options and trials?
  - New azoles and new formulations
- Unanswered questions
  - Genomics, other diagnostic modalities and advances

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**Coccidioides: Life Cycle**

- Environmental Form
  - Environmental form as alternate host following mycelial growth

- Host-associated Form
  - Endospores
  - Spherules

- Subpopulation (~15%) of endospores that do NOT induce chemotaxis or undergo phagocytosis
- Size likely to be major virulence factor for *Coccidioides* spp

Ecology

- Predominance of cases in Fall and Winter
- Seasonal rainfall patterns play large role
- Difficult to predict in past models
- Current drought conditions in CA...

"Grow and Blow" hypothesis:
Year 1 (blue): Oct-Dec precipitation
Year 2 (orange): Aug-Mar drought...

Stay tuned!!!


What is the Natural Habitat?

- Saprophytic soil phase (presumed)
- More easily isolated from pocket mice (Perognathus spp.) and kangaroo rats (Dipodomyces spp.) and their burrows
- Coccidioides spp lack genes for several enzymes necessary for plant cell wall digestion:
  - (lack of cellulases, cutinases, tannases, pectinesterases, etc)
- Keratinophilic nature of Coccidioides spp


Expanding geographic range

- Highly endemic
- Established endemic
- Suspected endemic

Affects approximately 150,000 yearly
- ½ to 1/3 are subclinical
- Almost universal protection from reinfection

Cause of CAP in 17-29% of patients in endemic areas!

No definitive recommendations for Coccidioidomycosis testing in IDSA or IDSA/ATS CAP guidelines

U.S. Medicaid data:

- Up to 10% of cases diagnosed outside endemic region

Clues to diagnosis:

- Travel History
- “Persistent” pneumonia
- CAP (with eosinophilia) unresponsive to antibacterials
- Development of rash


Risk Factors

- Men > Women (6:1)
- Anthroponic disruption of soil
- Immunosuppressed
  - HIV/AIDS
  - Chemotherapy/malignancy
  - Transplant
  - TNF-α blockers, etc
  - Pregnancy
- Ethnicity – suggests genetic predisposition
  - Filipino (17xX risk)
  - African-American (10X risk)
  - Asian and Hispanics?


Pattern of Valley Fever Progression

- Only one-third of patients with coccidioidal infection have clinical illness:
  - Most have CAP, which improves over time
  - A small percentage develop serious complications.

60 without symptoms
40 with symptoms
37 Recover
2-4 progress to dissemination
100 Infections

Life-long immunity

Mouse models: Dectin-1, TLR2 and TLR4, CARD9, MyD88

Human patients: IFNγ/IL-12 and MR?

Differential Host Susceptibility

- Selected patients with defects in IFNγ/IL-12 pathway
- Targeted analysis of TLR2/4, MR, Dectin-1 and several other regions has been mostly unrevealing

Mouse models: Dectin-1, TLR2 and TLR4, CARD9, MyD88

Human patients: IFNγ/IL-12 and MR?

- Large scale, whole exome sequencing project in collaboration with Broad Institute and NIH.
  - Database of >4000 patients
  - >2000 excluded due to lack of follow-up
  - Those included had > 2 years of follow-up after diagnosis
  - “Immunocompetent” and > 18 years of age, nonpregnant
  - All treated with fluconazole or other triazole
  - Cases: dissemination (pleuropulmonary or mediastinal LAD not include).
  - All with proven disease
  - Controls: proven or probable disease with no dissemination after 2 years

Diagnostics

Culture/Histology
- Culture: definitive, laboratory hazard
- Histopath dx: characteristic forms in tissue

Serological diagnosis
- ID/CF: used to establish diagnosis
  ▪ May be negative early or immunocompromised
  ▪ CSF ab: meningoencephalitis
  ▪ Impact of early fluconazole on development of CF ab
- EIA: sensitivity, potential false +; cross react w/ other endemic fungi
- Dissem. infection: ID/CF titers ≥ 1:16
- Adenosine deaminase (ADA)
- Ossseous involvement of ankle

New Diagnostics

Antigen testing – detects Coccidioides GM
- Timing of disease and host factors
  ▪ Useful in acute disease
  ▪ Highly immunocompromised
- CSF
  ▪ Response to therapy? – 7 patients reported
    ▪ Helpful in those with IT ampho?
    ▪ Post-operative/CVA?
  ▪ More helpful than CSF Ab?


Emerging Diagnostics

Biomarkers in Coccidioidomycosis

(1→3)-β-D-glucan
- 188 pts: 47 with acute pulmonary coccidiodomycosis
- +BDG 3/47 prior to IgM
- Overall: limited utility for early dx

Adenosine deaminase (ADA)
- 15 patients with pleuropulmonary cocci
  ▪ ADA >40 IU/L: 0/15
  ▪ Serology pos 15/15
  ▪ PCR pos: 3/14

Proven Probable Other

Collaborations with Immy – Unpublished data

Example patient serum positive for IgM and IgG antibodies


Collaborations with Immy – Unpublished data
Emerging Diagnostics

**Immunosignature**
- Pattern of antibodies, allows for pathogen specific “signature”
- Advantages: not hypothesis driven
  - Able to detect multiple different pathogens
- Questions:
  - Over time? Sequential samples?
  - Acute vs Immune?
  - Those at risk for chronic infection?
  - Immunosuppressed?
  - Coinfections?

Collaborations with Phillip Stafford and Stephen Johnston; ASU and Dept Homeland Security

Aspects of Management

Immunosignature profile of different Coccidioides spp. Unpublished data

Treatment Guidelines

Treatment of primary infection:
- Immunosuppressed
- Diabetes mellitus
- Frail due to comorbidities or age
- Some treat all if Filipino or African-American
  - “Treatment does not prevent dissemination!!”
- “Exceptionally severe primary infection”

Guidelines acknowledge debate:
- “unsettled issue because of the lack of prospective controlled trials.”

Decision to Treat?

- Unsettle – debated issue!!!
  - **Always Treat:** Immunosuppressed

**TO TREAT?**
- Not treating is historical rec based on AMB as only option
- May decrease intensity, duration of symptoms?
- Prevent chronic disease?

**NOT TO TREAT?**
- Meds patient may not need...
- >95% of patients resolve infection regardless of treatment (eventually)


NIH funded prospective study:
- Patients with CAP
- Endemic region
- Randomized 1:1
  - Antibiotics
  - Antibiotics/flucon
- Primary endpoint:
  - Symptoms day 21
- Secondary EP:
  - Symptoms day 42


Susceptibility

- Large scale susceptibility testing
  - >400 isolates
- >1/3 of isolates with FLC MICs > 16 µg/mL
- 22 isolates with FLC MICs > 64
  - Variable MIC to ITC, POS, VOR – MICs > 2 rare

Biased? – isolates sent to reference lab

Prior literature – animal models and one clinical trial suggest mold active azoles more favorable response – has this played a role in prior studies of disease?

Thompson, Barker, Wiederhold. *Microbe* 2017

Abrogate Immune Response?

- Patients treated early did not develop IgG antibodies.
- Precedent in: Lyme, Syphilis, streptococcal pharyngitis – rheum fever
- Clinical sequela?


Symptoms after initiation of antifungal therapy

Week 20
- Increase in: fatigue, fever, chills, night sweats, arthralgia, rash

- Are these side effects secondary to azoles?
- Altered natural history of disease?
- Aberrant immune response?
- Study Underpowered

Prospective observational study – 20 treated fluconazole 400mg/day (dotted line); 16 not treated (solid line)

Follow Primary Infection to Resolution

- Following to resolution potentially avoids later work-up/resection of nodules

Does this patient need a LP?

- Although routinely done – no data on routine CSF analysis.
- Examination in patients with active coccidioidomycosis and high CF titers or other risk factors for disseminated infection.
- In our review 100% of patients diagnosed with coccidioidal meningitis had at least one sign or symptom consistent with infection of the CNS.
- Routine lumbar puncture is unnecessary

Meningitis

Severe consequences:
- Stroke
- Hydrocephalus
- Space-occupying lesions (edema)

Pathophysiology of CM-vasculitis:
- Inflammatory reaction involving walls of small/medium sized vessels
- Increase in: IL-1, IL-2, IL-6, IL-10, TNF-α, IFN-γ, MMP-9 (Rabbit model)
- Human studies: CSF ↑ TNF-α and IL-1β

Table 1. Baseline characteristics of 221 patients with coccidioidal meningitis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No CVA (n=203)</th>
<th>CVA (n=18)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years (range)</td>
<td>46 (5-89)</td>
<td>41 (25-84)</td>
<td>0.8641</td>
</tr>
<tr>
<td>Male sex</td>
<td>151 (74%)</td>
<td>15 (83%)</td>
<td>0.5718</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>0.7580</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>71 (35%)</td>
<td>7 (39%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>71 (35%)</td>
<td>7 (39%)</td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>33 (16%)</td>
<td>3 (17%)</td>
<td></td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>17 (8%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>11 (5%)</td>
<td>1 (6%)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities</td>
<td>0.2708</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>22 (11%)</td>
<td>2 (11%)</td>
<td></td>
</tr>
<tr>
<td>CD4 &lt;200 cells/µL</td>
<td>18 (9%)</td>
<td>2 (11%)</td>
<td></td>
</tr>
<tr>
<td>Transplant</td>
<td>1 (0.5%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Immunocompromised patients</td>
<td>2 (1%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 (5%)</td>
<td>1 (6%)</td>
<td></td>
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<tr>
<td>CSF parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opening pressure, median</td>
<td>19 (11-56)</td>
<td>28 (13-45)</td>
<td>0.6152</td>
</tr>
<tr>
<td>CSF WBC</td>
<td>5 (0-170)</td>
<td>21 (5-36)</td>
<td>0.3279</td>
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<tr>
<td>CSF protein</td>
<td>36 (15-184)</td>
<td>171 (10-136)</td>
<td>0.0880</td>
</tr>
<tr>
<td>CSF glucose</td>
<td>58 (13-58)</td>
<td>28 (13-45)</td>
<td>0.9853</td>
</tr>
</tbody>
</table>

Vasculitis Incidence: 18/221 = 8%

Prior studies examining incidence:
- Autopsy study: 52% - patients who died of CM and were treated with AMB-d
- No other “incidence” study for CM-vasculitis

Corticosteroid therapy:
- Dexamethasone (14 pts)
  - 8-40 mg/day x 10-21 days
  - Most received 10mg followed by 4mg four times daily (9/14).
- Hydrocortisone (1 pt)
  - 50 mg q 6 hours x 10 days
- Tapers ranged from 2-6 weeks
- Odds ratio 0.01
- 95% [CI] 0.00 – 0.45
- P=0.0049**
- No patient with a stroke underwent an LP after the initial (diagnostic LP).

<table>
<thead>
<tr>
<th>Table 2. Clinical variables by receipt of corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receipt of corticosteroids</td>
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<tr>
<td>Age</td>
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<tr>
<td>Sex, male</td>
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<tr>
<td>Ethnicity</td>
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<td>Caucasian</td>
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<tr>
<td>African-American</td>
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<tr>
<td>Other</td>
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<tr>
<td>Second CVA</td>
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<tr>
<td>Tapered to steroids</td>
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<tr>
<td>Clinical worsening of coccidioidal meningitis attributed to corticosteroids</td>
</tr>
<tr>
<td>3* NA</td>
</tr>
<tr>
<td>Clinical worsening of coccidioidal meningitis</td>
</tr>
<tr>
<td>attributed to corticosteroids</td>
</tr>
<tr>
<td>0 NA</td>
</tr>
</tbody>
</table>

*1 case each of hyperglycemia, AV necrosis of tibia, superimposed bacterial infection

All three patients without adjunctive therapy experienced a second CVA, while only 1/15 (7%) receiving adjunctive treatment experienced a second CVA.

New Agents

- Isavuconazole
  - Mould active triazole
  - Clinical data for 1st pulmonary Coccidioides
  - Limited experience with disseminated disease
  - Clinical trials planned
  - Astellas

- Nikkomycin Z
  - Chitinase inhibitor
  - Prior animal studies encouraging
  - "Cidal" agent
  - Toxicity not seen in preclinical studies
  - Phase II trials planned in next year
  - Owned by Univ of AZ

VT-1598
- CYP51 inhibitor
- Orphan Drug designation for Coccidioidomycosis
- Oral formulation
- Viamet compound

Conclusions
- Expanding area of endemicity
  - Coccidioidomycosis in "new" areas; life cycle?
  - Travel has increased number of practitioners seeing these patients
- New diagnostic tools
  - Lateral flow assays, Antigen Assay, ADA, (1→3)-β-D-glucan, emerging technology
- New treatment options and trials?
  - Primary therapy of cocci, most efficacious agent?
- Unanswered questions
  - Genomics, new diagnostic modalities, best agent?

Thank You!

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- Bridget Barker PhD

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