# Endemic Mycoses: Update on *Coccidioides* spp

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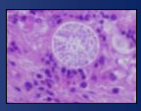
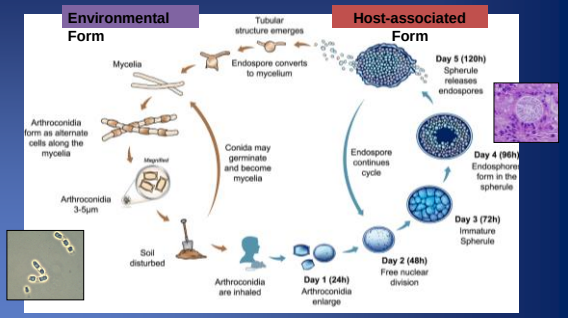
## Key Questions

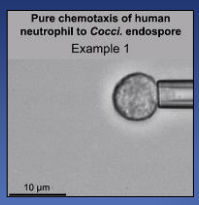
- **Expanding geographic range**
  - New locations or simply newly recognized?
- **New diagnostic methods**
  - Development of rapid diagnostics
- **New treatment options and trials?**
  - New azoles and new formulations
- **Unanswered questions**
  - Genomics, other diagnostic modalities and advances



## *Coccidioides*: Life Cycle




Lewis and Barker. ***PLoS Pathog***. 2015 11(5):e1004762. Brown J, et al. ***Clin Epidemiol***. 2013 Jun 25;5:185-97.



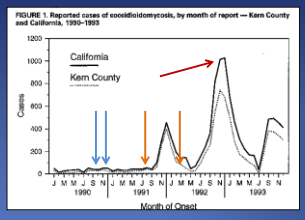

Endospores and human neutrophil

Spherule and human neutrophil

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

Lee CY, et al. ***PLoS One***. 2015 10(6):e0129522.

# 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…

**Stay tuned!!!!**

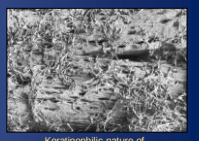
*"Grow and Blow" hypothesis:*
Year 1 (blue): Oct-Dec precipitation
Year 2 (orange): Aug-March drought….

Comrie AC. ***Environ Health Perspect***. 2005 Jun;113(6):688-92.

# 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)
  - Saprozoic? (dead or decaying animal matter)
    - Keratinophilic

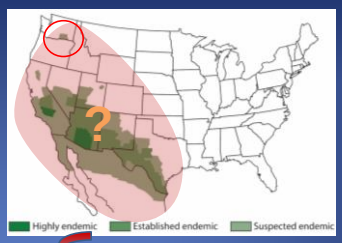
*Coccidioides* more frequently isolated in/near burrows



Keratinophilic nature of *Coccidioides* spp

Sharpton TJ, et al. ***Genome Res***. 2009;19(10): 1722–31. Barker – Unpublished data

# Expanding geographic range




Endemic, Hyper- and Hypoendemic
Transiently endemic

AZ pocket mouse

Kangaroo Rat

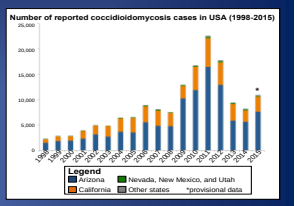
Marsden-Haug N, et al. ***Clin Infect Dis***. 2013 Mar;56(6):847-50. Benedict K, et al. ***Emerg Infect Dis***. 2015 Nov;21(11):1935-1941.

# Epidemiology

**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!**

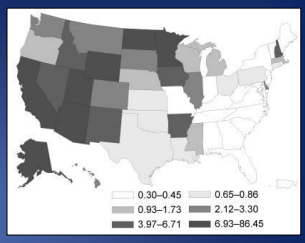



**No definitive recommendations for Coccidioidomycosis testing in IDSA or IDSA/ATS CAP guidelines**

Vugia DJ,et al. ***MMWR Morb Mortal Wkly Rep***. 2009;58:105–9
Brown J, et al. ***Clin Epidemiol***. 2013 Jun 25;5:185-97.

**Clues to diagnosis:**

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



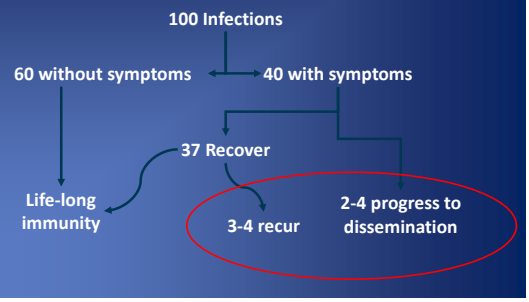

**U.S. Medicaid data:**

- Up to 10% of cases diagnosed outside endemic region

Baddley JW, et al. ***Emerg Infect Dis***. 2011; 17:1664-69.

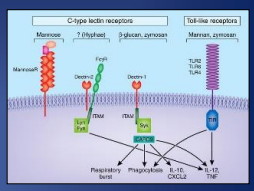
## Pattern of Valley Fever Progression

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




## Risk Factors

- Men > Women (6:1)
- Anthropogenic disruption of soil
- Immunosuppressed
  - HIV/AIDS
  - Chemotherapy/malignancy
  - Transplant
  - TNF-α blockers, etc
  - Pregnancy
- Ethnicity – suggests genetic predisposition
  - Filipino (175X risk)
  - African-Americans (10X risk)
  - Asian and Hispanics?




Mouse models: Dectin-1, TLR2 and TLR4, CARD9, MyD88
Human patients: IFNγ/IL-12 and MR?

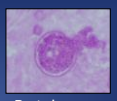
Thompson GR et al. ***Med Mycol***. 2013 Apr:51(3):319-23. Crum et al. ***Medicine***. 2004;83:149-75.

## Differential Host Susceptibility

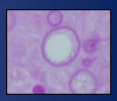
- Selected patients with defects in IFNγ/IL-12 pathway
- Targeted analysis of TLR2/4, MR, Dectin-1 and several other regions has been mostly unrevealing
- Large scale, whole exome sequencing project in collaboration with Broad Institute and NIH.
  - Database of >4000 patients
  - >2000 excluded due to 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



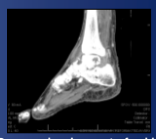
Rupturing spherule releasing endospores



Empty spherule

**Serological diagnosis**
- ID/CF: used to establish diagnosis
  - May be negative early or immunocompromised
  - Dissem. infection: IDCF titers ≥ 1:16
  - + CSF ab: meningeal infection
  - Impact of early fluconazole in reducing development of CF ab
- EIA: ↑sensitivity, potential false +; cross react w/ other endemic fungi – good for rapid screen

**Alternative methods: investigational**
- Antigen testing: varies widely -timing and host/site
- PCR (limited sensitivity) – no different than Cx
- (1→3)-β-D-glucan
- Adenosine deaminase (ADA)



Osseous involvement of ankle

Thompson GR et al. ***Clin Infect Dis***. 2011;53:e20-4; Thompson GR, et al. ***J Clin Micro***. 2012; 50(9):3060-2; Thompson GR, et al. ***Chest***. 2012; 143(3):776-81.

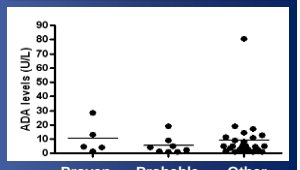
# Biomarkers in Coccidioidomycosis

**(1→3)-β-D-glucan**
- 188 pts; 47 with acute pulmonary cocci
- +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

TABLE 1 Performance of the β-glucan assay in coccidioidomycosis patients using >80 pg/ml as the cutoff for a positive result

| Variable | Value in patients: With acute coccidioidomycosis | Hospitalized with coccidioidomycosis |
|---|---|---|
| Sensitivity (%) | 19.1 | 43.9 |
| Specificity (%) | 91.1 | 91.1 |
| Positive predictive value (%) | 69.2 | 81.8 |
| Negative predictive value (%) | 51.9 | 64.1 |
| Positive likelihood ratio | 2.15 | 6.03 |
| Negative likelihood ratio | 0.89 | 0.62 |




Thompson GR, et al. ***J Clin Micro***. 2012; 50(9):3060-2
Thompson GR, et al. ***Chest***. 2012; 143(3):776-81.

# 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?

Kassis C et al. ***Clin Infect Dis.*** 2015 Nov 15;61(10):1521-6
Bamberger DM, et al. ***Mycoses.*** 2015 Oct;58(10):598-602.

# Emerging Diagnostics

*Lateral Flow Assay*
- Developed specifically to improve turn around time
- Simplicity of use
- Yes or no answer while patient in urgent care/clinic/ER

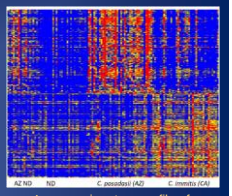
Example patient serum positive for IgM and IgG antibodies

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?




Immunosignature profile of different *Coccidioides* spp. Unpublished data

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

## Aspects of Management

## 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 trails."**

Galgiani JN et al. ***Clin Infect Dis***. 2016 Sep 15;63(6):e112-46.

## Decision to Treat?

- **Unsettled – 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?**

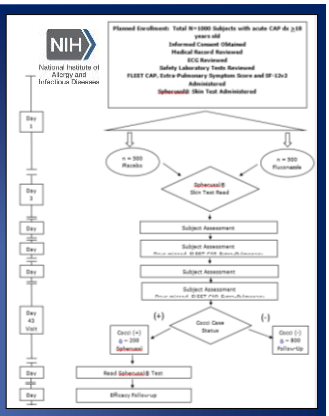
**NOT TO TREAT?**

- **Meds patient may not need…**
- **>95% of patients resolve infection regardless of treatment (eventually)**

Ampel NM. ***Clin Infect Dis***. 2009 ;48(2):172-8.

NIH funded prospective study:

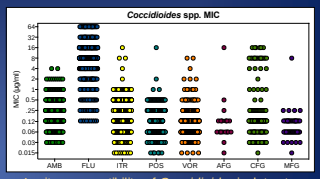
- Patients with CAP
- Endemic region
- Randomized 1:1
  - Antibiotics
  - Antibiotics/flucon
- Primary endpoint:
  - Symptoms day 21
- Secondary EP:
  - Symptoms day 42




Thompson GR ***Clin Infect Dis***. 2011 Sep;53(6):e20-4.

# 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




In vitro susceptibility of *Coccidioides* isolates to AMB, triazoles and echinocandins

ITC ≥ 2, 1.0% VOR ≥2, 1.2%;
POS ≥1, 1.1% AMB ≥ 2, 2.8%

**Biased? – isolates sent to reference lab**
**Prior literature – animal models and one clinical trial suggest mould active azoles more favorable response – has this played a role in prior studies of 1º 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 sequalea?

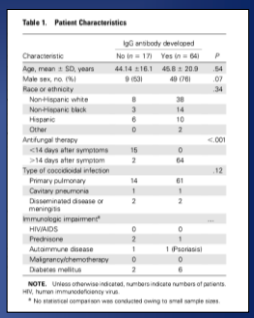
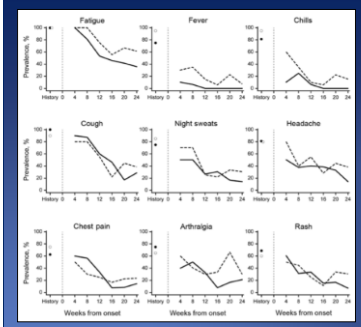


**Table 1. Patient Characteristics**

| Characteristic | IgG antibody developed | | P |
|---|---|---|---|
| | No (n = 17) | Yes (n = 64) | |
| Age, mean ± SD, years | 44.14 ±16.1 | 45.8 ± 20.9 | .54 |
| Male sex, no. (%) | 9 (53) | 49 (76) | .07 |
| Race or ethnicity | | | .34 |
| Non-Hispanic white | 8 | 38 | |
| Non-Hispanic black | 3 | 14 | |
| Hispanic | 6 | 10 | |
| Other | 0 | 2 | |
| Antifungal therapy | | | <.001 |
| <14 days after symptoms | 15 | 0 | |
| >14 days after symptom | 2 | 64 | |
| Type of coccidioidal infection | | | .12 |
| Primary pulmonary | 14 | 61 | |
| Cavitary pneumonia | 1 | 1 | |
| Disseminated disease or meningitis | 2 | 2 | |
| Immunologic impairment[a] | | | … |
| HIV/AIDS | 0 | 0 | |
| Prednisone | 2 | 1 | |
| Autoimmune disease | 1 | 1 (Psoriasis) | |
| Malignancy/chemotherapy | 0 | 0 | |
| Diabetes mellitus | 2 | 6 | |

**NOTE.** Unless otherwise indicated, numbers indicate numbers of patients. HIV, human immunodeficiency virus.
[a] No statistical comparison was conducted owing to small sample sizes.

Thompson GR et al. ***Clin Infect Dis***. 2011 Sep;53(6):e20-4.




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

**Symptoms after initiation of antifungal therapy**

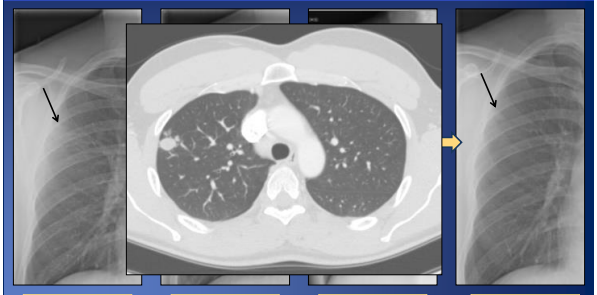
**Week 20**

– 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

Blair JE, et al. ***Emerg Inf Dis***. 2014 20(6): 983-990.

# Follow Primary Infection to Resolution



Initial : Day 0 | Day 32 | Day 71 | Day 299

- 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

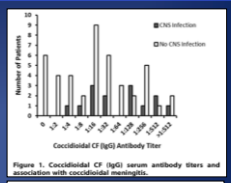



Figure 1. Coccidioidal CF (IgG) serum antibody titers and association with coccidioidal meningitis.

**Table 3.** Pooled estimates (95% confidence limits) for sensitivity, specificity, likelihood ratio positive, likelihood ratio negative for 1) at least 1 CNS disease sign or symptom and 2) headache alone as predictors of meningitis.

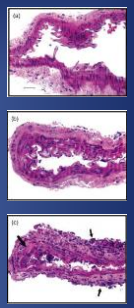
| | At least 1 sign/ symptom | Headache alone |
|---|---|---|
| Sensitivity | 1.00 (0.77, 1.00) | 1.00 (0.77, 1.00) |
| Specificity | 0.25 (0.15, 0.40) | 0.59 (0.45, 0.74) |
| Likelihood Ratio Positive | 1.25 (0.99, 1.59) | 2.40 (1.55, 3.42) |
| Likelihood Ratio Negative | 0.33 (0.07, 1.59) | 0.13 (0.03, 0.68) |

Thompson GR et al. ***PLoS One***. 2013 May 22;8(5):e64249.

# 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↑



Normal (control)

Mild inflammation (day 4)

Severe inflammation (day 9) – neutrophils in all layers

Williams PL, et al. ***Clin Infect Dis***. 1992; 14:673-82.
Zucker KE, et al. ***Clin Exp Immunol***. 2003; 143(3):458-66. Ampel N, et al. ***J Infect Dis*** 1995 171(6):1675-8.

**Table 1. Baseline characteristics of 221 patients with coccidioidal meningitis**

| | No CVA (n=203) | CVA (n=18) | P value |
|---|---|---|---|
| Age, median years (range) | 46 (8-89) | 41 (25-84) | 0.8641 |
| Male sex | 151 (74%) | 15 (83%) | 0.5718 |
| Ethnicity | | | 0.7580 |
| Hispanic | 71 | 7 | |
| Caucasian | 71 | 8 | |
| African-American | 33 | 1 | |
| Asian/Pacific Islander | 17 | 1 | |
| Other/Unknown | 11 | 1 | |
| Comorbidities | | | 0.2708 |
| HIV | 22 | 2 | |
| CD4 <200 cells/μL | 18 | 2 | |
| Transplant | 1 | 0 | |
| Immunosuppressive meds | 2 | 0 | |
| Diabetes | 11 | 1 | |
| CSF parameters | | | NS* |
| Opening pressure, median | 19 (11-53) ↔ | 29 (13-40) | 0.6132 |
| CSF WBC | 5 (0-1375) ↔ | 21 (5-36) | 0.3379 |
| CSF protein | 38 (15-564) ↔ | 210 (117-304) | 0.0583 |
| CSF glucose | 58 (9-135) ↔ | 38 (31-45) | 0.1683 |

**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

Sobel RA, et al. ***Hum Pathol*** 1984; 15:980-95.

**Table 2. Clinical variables by receipt of corticosteroids**

| | Receipt of corticosteroids (n=15) | No corticosteroids (n=3) |
|---|---|---|
| Age | 74 (63-91) | 64 (63-70) |
| Sex, male | 12 (80%) | 3 (100%) |
| Ethnicity | | |
| Caucasian | 6 | 2 |
| African-American | 0 | 1 |
| Other | 9 | 0 |
| Second CVA | 1 | 3 |
| Complications attributed to steroids | 3* | NA |
| Clinical worsening of coccidioidal meningitis attributed to corticosteroids | 0 | NA |

*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

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

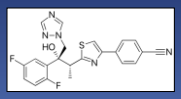
- Odds ratio 0.01
- 95% [CI] 0.00 – 0.45
- P=0.0049**

- No patient with a stroke underwent an LP after the initial (diagnostic LP).

Thompson, et al. Pending Manuscript submission

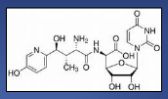
# New Agents

**Isavuconazole**



- Mould active triazole
- Clinical data for 1° pulmonary Cocci
- 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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