Endemic Mycoses: Update on Diagnostics and Treatment

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Key Questions

▪ Expanding geographic range
  New locations or simply newly recognized?
  10% diagnosed outside of normal range

▪ Taxonomy updates and new species

▪ New diagnostic methods
  Development of rapid diagnostics, kinetics of serology

▪ Prolonged treatment – unique toxicities?
  New azoles and new formulations
Endemic Mycoses

Dimorphic fungal infections Location

- Histoplasmosis Scattered worldwide
- Blastomycosis Scattered worldwide
- Coccidioidomycosis US/Latin America
- Paracoccidioidomycosis Latin America
- Talaromycosis Northern Thailand/China
- Sporotrichosis Worldwide
- Emergomycosis/Emmonsia Scattered

Case 1: 45 y/o with recurrent pneumonia presents for second opinion

- 45 y/o African American male with no prior history
- Presents with severe cough and chest pain.
- Works as long-haul truck driver. Recent project in Bakersfield, CA.
- No headache or MSK complaints
- Exam reveals: tired appearing, course breath sounds, no skin lesions.

What is likely diagnosis? Appropriate workup?
Origin of *Coccidioides* spp?

- Geographic expansion requires further analysis of population structure and evolutionary history
  - Phyllogenetics and population genomics (86 isolates)
    - Additional ~200 added
- *C. posadasii* is the more ancient of the two spp
- Arizona-N. Mexico origin for *C. posadasii*


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!

Definite seasonal increase in early fall

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
  - 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
- Lateral Flow assay

Alternative methods: investigational
- Antigen testing: varies widely - timing and host/site
- PCR (limited sensitivity) – no different than Cx
- Skin test: new test (Spherusol) decreased sensitivity compared to prior (Spherulin)


Mchardy I, Thompson GR. *J Clin Micro*. 2018 In press
Diagnostics

- Significant differences in serology kinetics
- Closely correlate with symptomatic improvement – (symptom scores not shown)
- Minority of patients are serofast even years later

Cohort of 500+ patients with 4 distinct forms of disease followed over 5 years

Sequalae: Peripheral nodules

Low-dose CT screening for current and former smokers (ages 55-80)
No guidance for those in endemic regions

Peripheral pulmonary infiltrates and lesions
- Coccidioides
- Blastomyces
- Histoplasma
- Cryptococcus

✓ PET scan not always reliable
✓ Bronchoscopy 65-88% sens
  ✓ Peripheral<2cm lesions ~34%
✓ Transthoracic biopsy for <6mm nodules:
  ✓ Non-diagnostic ~15%
Case 2: 65 y/o male with hand lesions after fall

- 65 y/o male painter fell off ladder while painting state capital building.
- Fell onto bush and had puncture to dorsum of hand.
- Exam with purulent drainage, no warmth, and no lymphadenopathy.
- Cultures return after ~10 days.
Sporotrichosis

- *S. brasiliensis* (cat), *S. schenckii* (plant), *S. globosa*, *S. luriei*, *S. mexicana*
- Prevalence ~0.1-0.5%
- Cutaneous disease, spread via lymphatics.
- Pulmonary or disseminated in immunosuppressed
- Shift of environmental to zoonotic disease
  - Outbreak in South America
  - Human = feline cases (claws+ in 29%!)
- Human cases
  - Adults: extremity
  - Children: face/neck
- Facial lesions secondary to high-inoculum occupational factors


- *S. brasiliensis* exhibits increased virulence
- Outbreak and expansion over last 2 decades
- Preliminary evidence AMB (>1 µg/mL) and ITZ (>2) MICs are increasing (shift of MIC90 from 2 → 4); TBF MICs remains low (0.1)

What almost was....

- **Sporothrix** spp vs **Ophiostoma** proposed taxonomic changes

- Cause of Dutch Elm disease

Diagnostics

**Culture/Histology**
- Culture: definitive (4-20 days), rosettes
- Histopath dx: “asteroid” bodies (5-13 µm)

**Serological diagnosis**
- Immunodiffusion and western blot
- Latex agglutination – useful in **Sporothrix** meningitis?
- ELISA (cell wall antigen)
  - ScCBF-ELISA – Sens: 90%, useful as response to therapy with decreasing titers over time
  - AUC ROC= 0.9154

**Alternative methods:**
- PCR in tissue (none commercially available)
- Skin test: sporotrichin (not commercially available)
Sporotrichosis: Treatment

- Severe disease/dissemination: Ampho B
- Cutaneous: SSKI, itraconazole, new azoles?
- Long durations of therapy common despite debridement/drainage

Case 3: South American man with chronic cough, weight loss.

- 65 y/o man from Peru
- 3 month history of 20 pound weight loss, fatigue, cough
- Examination: chronically ill man with wasting
- Chest radiograph: bilateral granulomatous disease

Evaluation at this point?
Likely diagnosis?
Paracoccidioidomycosis

*Paracoccidioides brasiliensis* (dimorphic fungus)
- Most common systemic mycosis in Latin America
- Tissue phase: “pilot wheel”
- New spp proposals:
  - *P. lutzii*, *P. americana*, *P. restrepiensis*,
  - *P. venezuelensis*
- **Clinical Presentation & Diagnosis**
  - Granulomatous disease: pulm and disseminated infection

**Diagnosis**
- Double immunodiffusion (gold standard)
- ELISA: More sens, less spec
- CF: More spec, less sens
- Antigen detection: useful in highly immunocompromised


Case 4: Forester returning home from Thailand

- A 52 yo man, with no prior medical history, returned home with extensive pedunculated skin lesion over his face and trunk, some of which had become ulcerated
- His history was significant for extensive world-wide travel in course of his work as a forester
- During the last trip he tripped and fell, injuring forehead in a bamboo thicket.

Likely diagnoses?

Case Courtesy of Dr. Tom Patterson. Thanks!
Talaromycosis (formerly Penicilliosis)

*Talaromyces marneffei*

- Produces red pigment in culture media; may be a laboratory hazard
- Associated with bamboo rats
- Patients with AIDS: Thailand/Southern China, Vietnam, NE India, Hong Kong

**Clinical Presentation & Diagnosis**

- Chronic granulomatous infection: fever, weight loss

**Diagnosis**

- Cultures (~14 days): red diffusible pigment
- Blood culture (+): ~76%
- Bone Marrow (+): ~100%
- Non-invasive:
  - GM cross reactivity (73-80%)
  - Antigen testing: Sens-75-100%; Spec 83-100%


**Treatment**
Treatment: Toxicity (Fluconazole)

- Fluconazole toxicity?
- Alopecia, cheilitis, dry skin
  - Generally well tolerated, even at doses > 800 mg/day; for many life-long therapy
  - Eval of >300 patients on fluconazole for > 30 days: 50% discontinued secondary to toxicity
  - Change to itra/posa/or stop – ~14-21 days to resolution of skin toxicity, ~90 days to resolution of alopecia

![Graph showing percentage of hair on fluconazole treated vs. no fluconazole with statistical significance]

P=0.007  P<0.001

Davis M, Nguyen V, Thompson GR, et al. Pending submission

Treatment: Toxicity (Posaconazole and Itraconazole)

- Tablet formulation has improved serum [conc] (median of 0.74 → 1.92 μg/mL)
  - 10% with levels > 3.5 μg/mL
  - Ceiling for toxicity?

![Graph showing serum levels of posaconazole and itraconazole]

Recognition of 7 patients:
Hypertension, hypokalemia, alkalosis
All had posa level >4 μg/mL
Undetectable renin and aldo
Elevated 11-deoxycortisol, and cortisol/cortisone ratio
Mean posa 5.62 (range 3-9.5 μg/mL)

Treatment: Toxicity (Posaconazole and Itraconazole)

- CNS and peripheral neuropathy
- Hepatotoxicity
- Photopsia
  - Bipolar On-Cells
- Photosensitivity
  - N-oxide metabolite

Long term use:
- Cutaneous malignancy
- Fluoride toxicity

Conclusions

**Update in Endemic Mycoses:**

- Evolutionary biology
- Epidemiology and endemicity
- Taxonomic changes!!
- New Diagnostics are under active evaluation
- Toxicity of current agents – new agents are on the way!

- **Unanswered questions**
  - Genomics, new diagnostic modalities, performance characteristics, best agent(s)? Combination therapy, drug repurposing, New Toxicities?