Valley Fever: What Every Clinician Needs to Know

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9/25/18

Coccidioidomycosis

- Coccidioidomycosis is the infection caused by the dimorphic fungi of the genus *Coccidioides* (*Coccidioides immitis* and *Coccidioides posadasii*)
- Most infections are caused by inhalation of spores
- The clinical expression of disease ranges from self-limited acute pneumonia (Valley Fever) to disseminated disease
- Cases of coccidioidomycosis in the United States are concentrated in the southwestern part of the country

Coccidioidomycosis

- *Coccidioides* species grow as mold a few inches below the surface of the soil
- With dry conditions, the mold becomes very fragile (easily fractured by even slight air turbulence) into single-cell spores (arthroconidia)
- These are tiny (~3 to 5 microns in size)
- Can remain suspended for prolonged periods of time in the air

Coccidioidomycosis: Epidemiology

- There's been a substantial increase in the incidence of coccidioidomycosis in endemic regions
  - Climate change, population growth, better tests
- 2017 had the highest annual incidence reported in California since coccidioidomycosis became individually reportable in 1995
  - From January through December 2017, **7,466** new cases of Valley Fever were reported to California Department of Public Health
- It was also the second consecutive record year for reported Valley Fever cases

Coccidioidomycosis: Risk of Infection

- Estimates of the risk of endemic exposure to *Coccidioides* species are approximately 3 percent per year
  - Even persons who have lived in endemic regions for many years may still be susceptible to a new infection
- The risk of exposure within endemic regions is seasonal, typically being highest in dry periods following a rainy season
- It is estimated that approximately 30% of all US coccidioidal infections occur within Kern, Tulare, and San Luis Obispo counties of California

Coccidioidomycosis: Pathogenesis

- Infection is virtually always acquired by inhalation of a **single spore**
- Once in the lung, the spore changes from a barrel-shaped cell to a spherule and then greatly enlarges, sometimes becoming 70 microns or more in diameter
- After several days, mature spherules rupture, releasing endospores into the infected tissue
  - Each endospore is potentially capable of producing another spherule

Coccidioidomycosis: Clinical Manifestations

- It's estimated that less than one-half of all infections come to medical attention because illness is often subclinical
- The proportion of infections that become clinically significant increases in outbreaks with more intensive dust exposure
  - Constructions workers, prisoners who work outdoors, soldiers
- Presumed that this represents higher arthroconidial inoculum

Primary Coccidioidomycosis

- For those who develop symptoms, a wide spectrum of manifestations are possible
- Primary infection due to *Coccidioides* species most frequently manifests as a community-acquired pneumonia (CAP) approximately 7 to 21 days after exposure
- The most common presenting symptoms are chest pain, cough, and fever
  - Some with hemoptysis = > pulmonary cavity

Primary Coccidioidomycosis

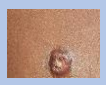
- Some patients also develop systemic complaints, often lasting for weeks to months
- Patients can experience constitutional symptoms, such as fever, drenching night sweats, and weight loss
- Patients can also develop extreme fatigue that can interfere with activities of daily living, and may last for many months

Primary Coccidioidomycosis

- Patients with early coccidioidal infection can also present with dermatologic or rheumatologic complaints
- Cutaneous manifestations of primary coccidioidal infection include erythema nodosum and erythema multiforme
- Erythema nodosum is much more common in women than in men, and often is the symptom prompting evaluation for Valley Fever

Later Coccidioidomycosis Presentations

- Extrapulmonary infection can be found at any site, but skin, bones and joints, and central nervous system localization are the most common
- Any focal abnormality of this sort that has developed since the onset of the primary infection should be a source of concern.

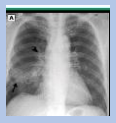


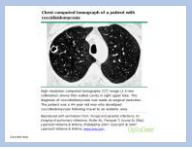
Coccidioidomycosis: Clinical Findings

- Most routine laboratory findings are unremarkable
- Can see eosinophilia (>5 percent) in approximately one-quarter of patients

Coccidioidomycosis: Radiographic Findings

- Although initial infections usually have a respiratory component, CXR can be normal
- Common CXR findings are unilateral infiltrate with ipsilateral hilar adenopathy
- Peripheral thin-walled pulmonary cavities or nodules are detected in 4 to 8% of all patients





Coccidioidomycosis: Laboratory Testing

- Serologic antibody tests using enzyme-linked immunoassays (EIA) for IgM and IgG should be ordered first
  - Can take 7-21 days to develop
- If either IgG or IgM is positive, a confirmatory immunodiffusion test is automatically sent off to UC Davis for confirmation
  - ~50% of IgM + do not confirm out on immunodiffusion testing
- If IgG is +, additional testing (complement fixation) is automatically performed, too

Coccidioidomycosis: Laboratory Testing

- Complement fixing (CF) antibodies can be detected in body fluids other than serum, and their detection in the CSF is an especially important aid to the diagnosis of coccidioidal meningitis
- The CF test also provides a quantitative measure of antibody concentrations, and serial determinations of CF are used to follow response to treatment and to determine initial extent of disease
- Higher CF titers usually equal worse infection
  - If initial CF is > 1:16, worry for a patient having disseminated Cocci

Coccidioidomycosis: Laboratory Testing

- Cocci can be seen in tissues via microscopy by direct examination or by growing it in culture
- If cultures are obtained, the clinician caring for the patient should alert the microbiology laboratory since appropriate biocontainment procedures are needed to prevent infection in laboratory staff

Coccidioidomycosis: Pathology

- **Since *Coccidioides* spp are never normal flora, identifying this fungus in respiratory secretions, tissue, or other patient specimens is definitive evidence of a coccidioidal infection**

Coccidioidomycosis: Who to Treat for Primary Infection

- Greater than 10% loss of body weight
- Night sweats > three weeks
- Infiltrates involving more than half of one lung or portions of both lungs
- Prominent or persistent hilar adenopathy
- CF > 1:16
- Inability to work
- Symptoms persisting for longer than two months
- Immunocompromised (HIV, CA, pregnant)
- African or Filipino ethnicity

Coccidioidomycosis: How to Treat for Primary Infection

- For most nonpregnant patients, start Fluconazole 400 mg PO daily
- There is no consensus regarding the duration of therapy, but most treat non-immunocompromised patients for three to six months
- Patients with primary coccidioidal infection should be monitored for evidence of pulmonary complications and disseminated disease (skin lesions, severe or persistent headaches, or new joint effusions)

Coccidioidomycosis: How to Monitor Primary Infection

- Initially, these patients should be seen every 2-4 weeks
  - Improvement in sx should be seen during this time
- Once they are better, intervals between clinic visits are usually extended to every three to six months
  - For patients not treated with antifungal drugs, follow-up is usually complete by one year
- Those who receive antifungal therapy should be followed annually for at least two years after the completion of treatment because later recurrences have been noted occasionally in such patients

Coccidioidomycosis: How to Monitor Primary Infection

- Laboratory monitoring: Serial CF blood tests should be done after one month of treatment
  - Want to ensure where Cocci CF titer is (e.g. is it suddenly going much higher)
- Testing should be repeated every 3 months to ensure the CF titer is decreasing
  - Timing of stopping treatment is complicated and has to be tailored to the patient
- Radiographic abnormalities should be rechecked once in the first two to three months and again 6 months to a year later to determine if the findings resolved or if there is a residual nodule or cavity

Severe Pulmonary and Extrapulmonary Cocci

- Can see various severe pulmonary manifestations
  - Diffuse fibronodular disease and ruptured Cocci cavities most common
- Extrapulmonary manifestations commonly seen are skin lesions and bone infections (ankle especially prone)

CSF Cocci Infection

- Cocci meningitis is perhaps the most dangerous manifestation of extrapulmonary Cocci infection
  - Comes with the pulmonary Cocci infection, but patient develops a persistent headache
  - Cocci CF can be elevated on first check (> 1:16; usually > 1:64)
- Patient with suspected Cocci meningitis need MRI of brain and then an LP
  - Check Cocci CF on CSF; use to monitor future response as well

Treatment of Severe Pulmonary and Extrapulmonary Cocci Infection: Challenging!!

- Patients start on higher doses of Fluconazole (800 mg PO QD) if they have evidence of a diffuse reticulonodular pulmonary Cocci
  - Some of these patients require IV Ampho B and transition to Fluconazole
- Asymptomatic cocci cavities in immunocompetent patients do not need treatment
- CSF Cocci can require treatment with Ampho B and then Fluconazole or high dose Fluconazole (800-1000mg QD)
  - Some require CSF shunts with Ampho B directly infused
  - Require repeat LPs to check Cocci CF titer
- **Treatment of CSF Cocci is lifelong!**

Sequalae of Primary Infection: Prolonged Fatigue

- Fatigue and lethargy associated with coccidioidal pneumonia may persist for many weeks or months, far beyond the resolution of all other symptoms and laboratory abnormalities
- The protracted duration of these symptoms is from the disease and inactivity due to illness
  - Antifungal drug therapy for this symptom is unlikely to be of any value
  - Exercise is helpful
- Future respiratory exposure to arthroconidia rarely, if ever, results in clinical illness.

Coccidioidomycosis: When to suspect infection

- Consider the diagnosis of coccidioidomycosis in patients with an endemic exposure and a respiratory illness of more than a week's duration, especially if it appears to involve the lower respiratory tract
- Primary coccidioidal infection should also be suspected in patients with an endemic exposure who present with the new onset of diffuse, symmetrical arthralgias and the rash of either erythema nodosum or erythema multiforme

Coccidioidomycosis: Initial Work-Up Pearls

- Ensure you perform Cocci IgG and IgM titers in these patients
  - Lab is sent to UC Davis for reflex CF testing if these titers come back positive
- Initial CF titer can give an idea of extent of infection
- Ensure these patients are referred to ID in a timely fashion so treatment can be initiated quickly
- Cocci takes a long time to treat and fatigue can last for months

Questions?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HAS A RENDEZVOUS WITH DESTINY