Overview of human coccidioidomycosis

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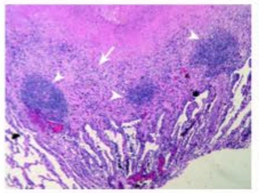
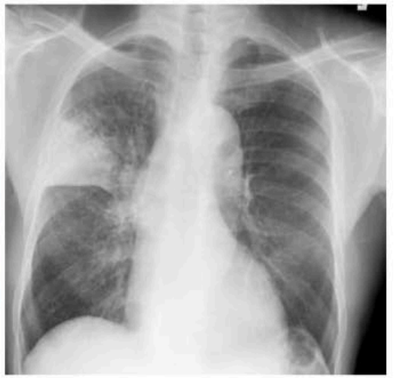
I have no conflicts of interest

The Dimorphic Life-Cycle of *Coccidioides*

Stochastic



Li et al Infect Immun 2005; 73:700

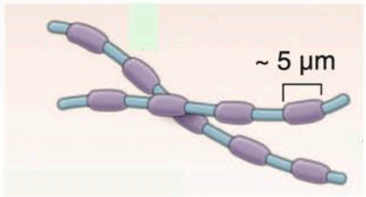


Primary pulmonary disease

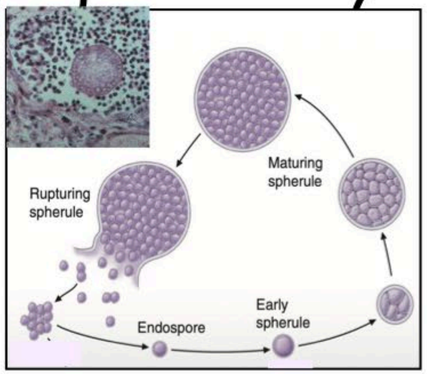
1. Necrotizing granulomata
2. Fungus persists, part of mycobiome
3. Life-long immunity
4. Cellular immune response
5. Local lung complicaitons

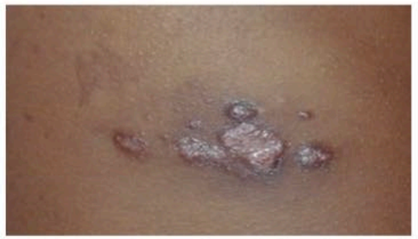
Extrathoracic dissemination

1. Weeks to months after initial infection
2. Infection outside of thoracic cavity
3. Poor cellular immune response
4. Persistent and recurrent after antifungal therapy



Harrison's Textbook of Medicine 21st ed.

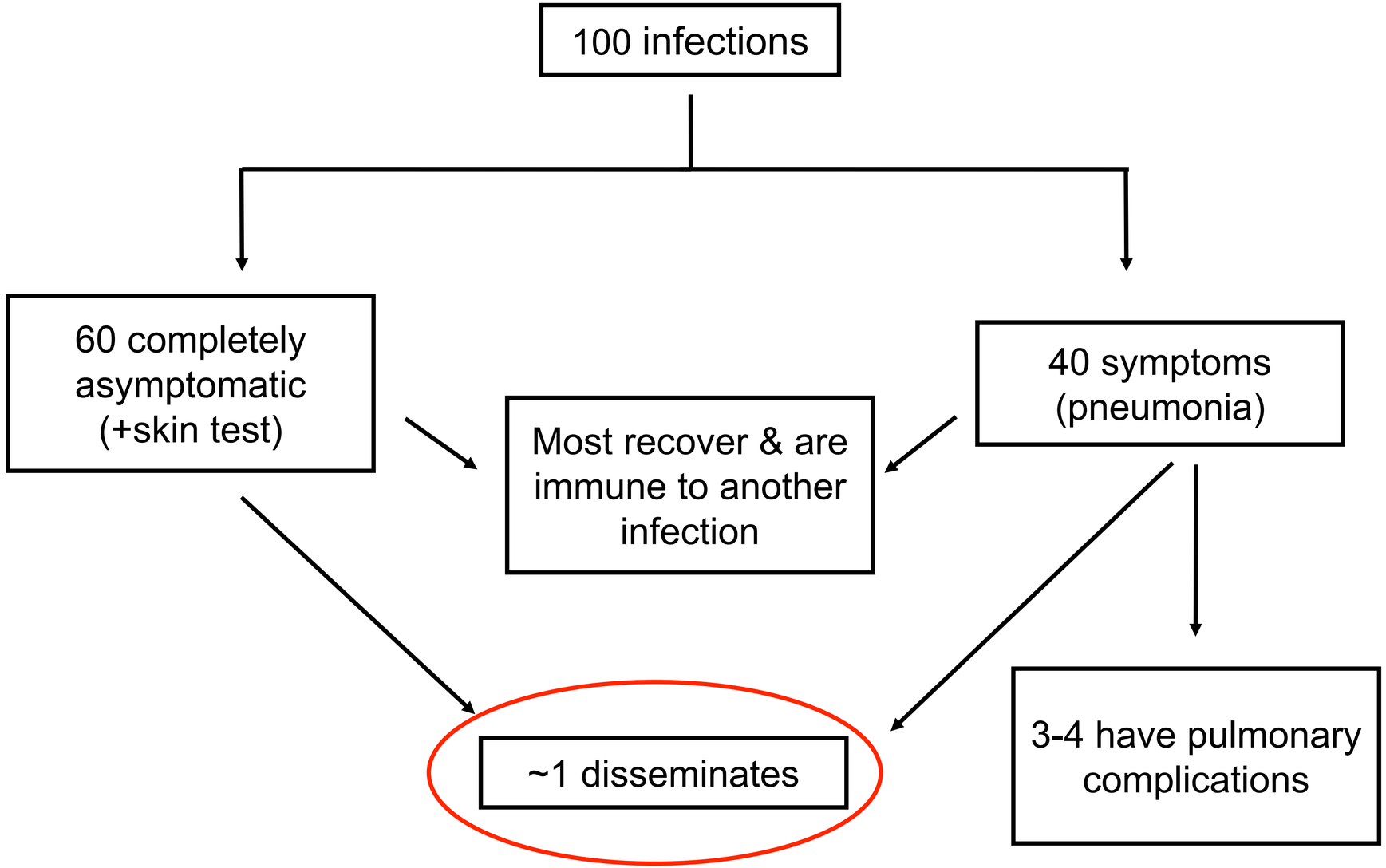




Clinical Expression

- Estimated that 60% of cases of infection are asymptomatic
- 40% will present with a pneumonia syndrome
- 3-4% of these will be complicated
- 1% will develop extrathoracic dissemination

What happens in most cases of coccidioidal infection?



The potential impact of coccidioidomycosis

- A ~5% complication rate appears small
- However, current estimates are that there are approximately **150,000** symptomatic coccidioidal infections annually in the United States*
  - **~375,000** total infections annually
    - **~19,000** complicated cases of complicated infection annually
    - **~3,750** of extrathoracic dissemination
      - require long-term follow-up and antifungal therapy

*Freedman, M et al. 7th International Symposium on Coccidioidomycosis, 2017

Risk of severe disease

- **Certain groups are at risk for severe and disseminated disease**
  - Those with **underlying cellular immune suppression**
    - Untreated HIV-1 infection with CD4 cell count <250/μL
    - Solid organ and hematopoietic stem cell transplants
    - Those on immune suppressive therapies
      - Corticosteroids
      - Anticytokine therapies
        - anti-TNF-α
      - Janus kinase inhibitors (ruxolitinib)

        Kusne Y, et al. Open Forum Infect Dis 2020
      - Other biological response modifying therapy
    - Those receiving cancer chemotherapy
  - Certain **racial groups**
    - Those with African ancestry

      Spendlove S, et al. UCLA, CSG abstract 2022

      Hsu, et al. JCI Insight 2022
    - Possibly those of Filipino ancestry
  - Acquisition of infection **during and after the 2nd trimester of pregnancy**

Clinical Presentations

- Asymptomatic infection
- Primary pulmonary Infection
- Sequelae of pulmonary infection
  - Nodules
  - Cavities
- Extrathoracic dissemination
  - Non-meningeal
  - Meningeal

Asymptomatic or subclinical infection

- Estimated to represent 60% of infections
- Results in cellular immune response (delayed-type hypersensitivity)
- Life-long immunity
  - Likely due to persistence of fungi in mycobiome causing continued maintenance of T-cell memory
  - “Natural vaccination”
- Occasional cases, usually within 6 months of infection, may present with extrathoracic dissemination
  - May occur later during immunosuppression

Primary pulmonary infection

- **Approximately 40% of infections**
- **Presents with cough, chest pain, fever**
  - Confused with bacterial community-acquired pneumonia (CAP)
    - Results in delays in diagnosis, inappropriate use of antibacterial therapy

      Donovan F, et al. Emerg Infect Dis 2019
- **Unique findings**
  - Night sweats, fatigue, rashes, prolonged course
  - Pulmonary opacities often upper lobe with hilar and/or mediastinal adenopathy
  - Peripheral and tissue eosinophilia
- **Immunological events may cause considerable morbidity**
  - Severe rashes (erythema nodosum, erythema multiforme, toxic erythroderma, Sweet's syndrome)
  - Diffuse arthralgias ("Desert rheumatism")
  - Prolonged fatigue

Complicated pulmonary infection

- **Nodules**
  - Common end-result of primary pulmonary infection
  - Difficult to distinguish from pulmonary malignancy
    - Positive coccidioidal serology may not be reliable
    - PET/CT does not distinguish

      Reyes N, et al. Lung 2014
    - If initial pneumonia diagnosis not established, either invasive procedures or prolonged follow-up is required
- **Cavities**
  - Presumed to occur from extrusion of nodule contents into bronchial tree
  - Asymptomatic or associated with persistent cough, chest pain, hemoptysis
  - May remain stable or increase in size
  - Antifungal therapy appears to decrease size

    Panicker RR, et al. Med Mycol 2021
  - May require surgical resection
- **Pyopneumothorax**
  - Rupture of cavity that abuts pleural wall creating bronchopleural fistula
  - Requires surgical intervention

Non-meningeal extrathoracic dissemination

- Generally occurs within 6 months of initial infection
  - May occur much later in those who have received a course of triazole antifungal therapy

    Ampel NM, et al. Clin Infect Dis 2009
- Pathogenesis and immunology unclear
  - Is there early sub-clinical dissemination in everyone?
  - Is there a later loss of cellular immunity after primary infection?

    Cox RA, et al. Infect Immun 1981
- Almost always requires prolonged antifungal therapy
  - Occasionally requires surgical intervention
- Recurrences after antifungal therapy is discontinued are common (15-30%)
  - Occurs at site of initial area of dissemination

Meningeal dissemination

- Often presents subtly with headache and cognitive defects
- Mortal if untreated

  Vincent T, et al. Clin Infect Dis 1993

- Preserved systemic cellular immunity
- Therapy difficult and life-long
  - Triazole therapies may fail
  - Intrathecal amphotericin B associated with arachnoiditis, technical difficulties
- May be complicated by hydrocephalus
  - Blocks often at multiple sites of CSF circulation
  - Often occurs on appropriate antifungal therapy
  - Permanent and requires shunting

Thompson GR III, et al. Clin Infect Dis 2022

Conclusion

- While the majority of individuals who acquired coccidioidal infection will do well and develop life-long immunity to further infection, many will not.
- These latter individuals may be at risk for prolonged illness with complications that require close clinical follow-up, antifungal therapy, and surgical intervention.
- Current therapy is frequently prolonged and associated with a high-rate of relapse after discontinuation.