THE UNIVERSITY OF ARIZONA
COLLEGE OF MEDICINE TUCSON
Pediatrics

Banner Children's
Diamond Children's Medical Center

Pediatric Coccidioidomycosis

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Disclosures

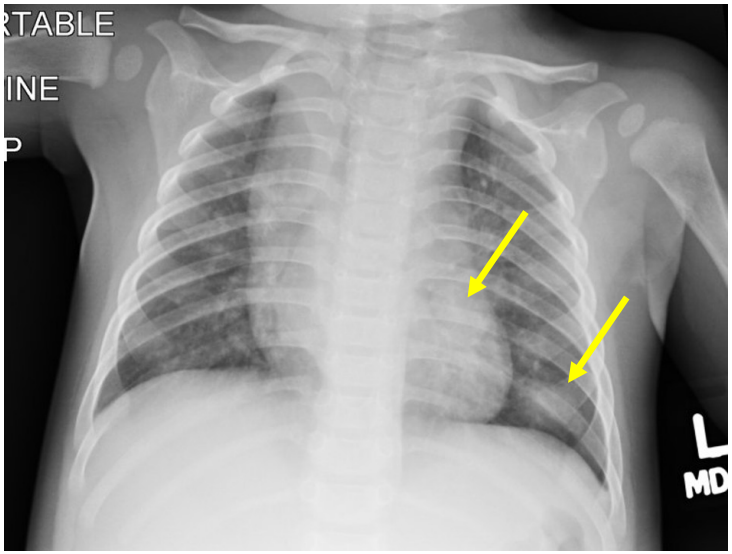
- I have no conflicts of interest to disclose

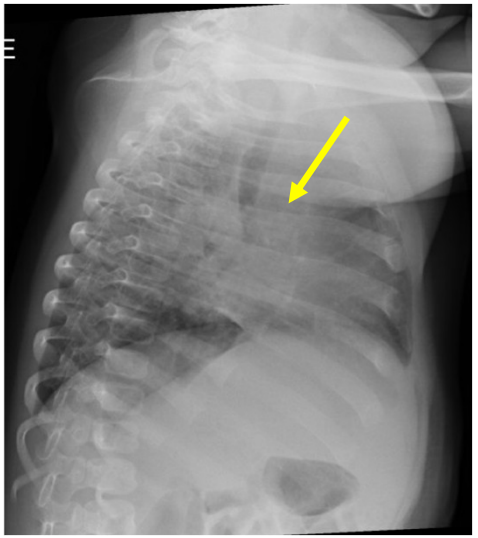
Objectives

- Describe the epidemiology of Coccidioides
- Choose and interpret the appropriate diagnostic tests
- Decide when and how pediatric Cocci infection needs to be treated

9 month-old with cough and fever

- Term, some URIs in the past
- 2 weeks of cough, now some fever for a few days and increased work of breathing <1d
- Wheezing on exam
- Infiltrates on CXR
- What are the chances that this is Cocci?





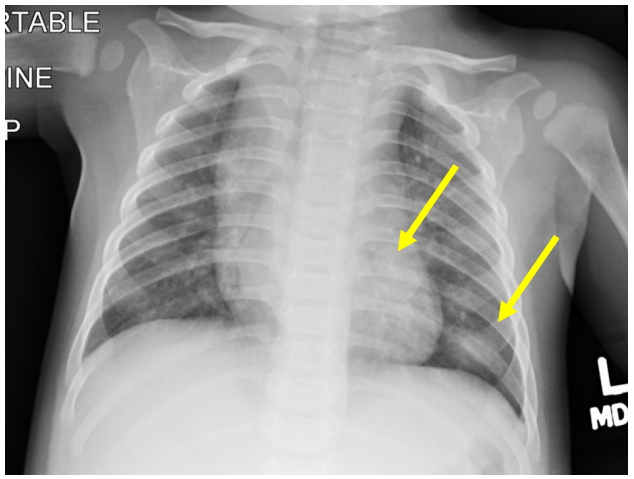
Community Acquired Pneumonia (CAP) and Coccidioides

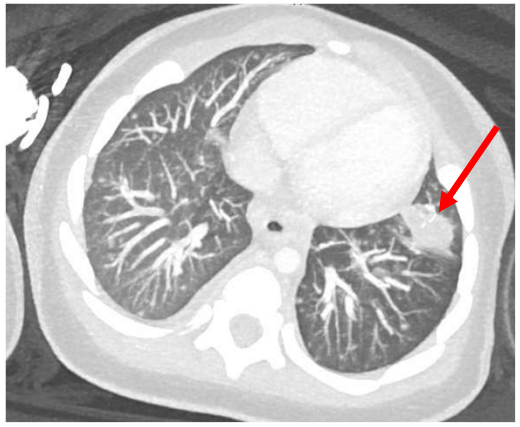
- 2 small prospective studies in adults who presented with CAP in the early 2000's
  - Outpatient, ED, UC
  - 1st study: 35 patients, 17% seropositive for Cocci
  - 2nd study: 55 patients, 29% seropositive
    - 81% received antibiotics for bacterial infection
- Pediatric series of 108 patients
  - 83% CAP symptoms
    - 82% received antibiotics prior to diagnosis of Cocci

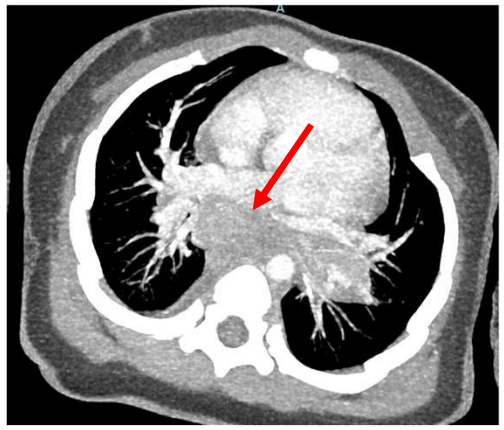
EID 2006, EID 2009, PIDJ 2019

Our 9 month-old

- Cough, fever, increased work of breathing and wheezing with abn CXR
- Elevated WBC and CRP
- Doesn’t respond to amox and then ceftriaxone
- CT shows infiltrate and adenopathy
- Testing for Cocci is positive





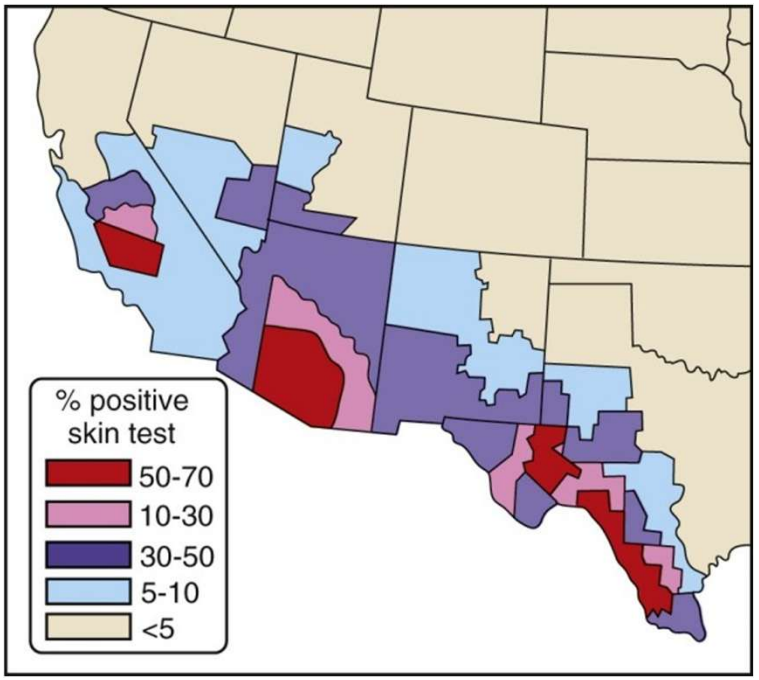


Coccidioides immitis/posadasii

- Originally described by Alejandro Posadas in Argentina, 1892
  - Skin biopsy of a soldier with cauliflower-like fungating lesion
    - Organism resembled the protozoan Coccidia
- 1896 San Joaquin Valley
  - Patient with fungating cutaneous lesions
  - Culture grew mold, initially thought to be contaminant
    - Coccidioides (resembling Coccidia), immitis (not mild)
  - Valley that lends its name to Valley Fever
- 1929 Harold Chope accidentally inhales spores from the lab
  - Developed pneumonia and erythema nodosum
  - Spherules are seen on sputum culture

Cocci History

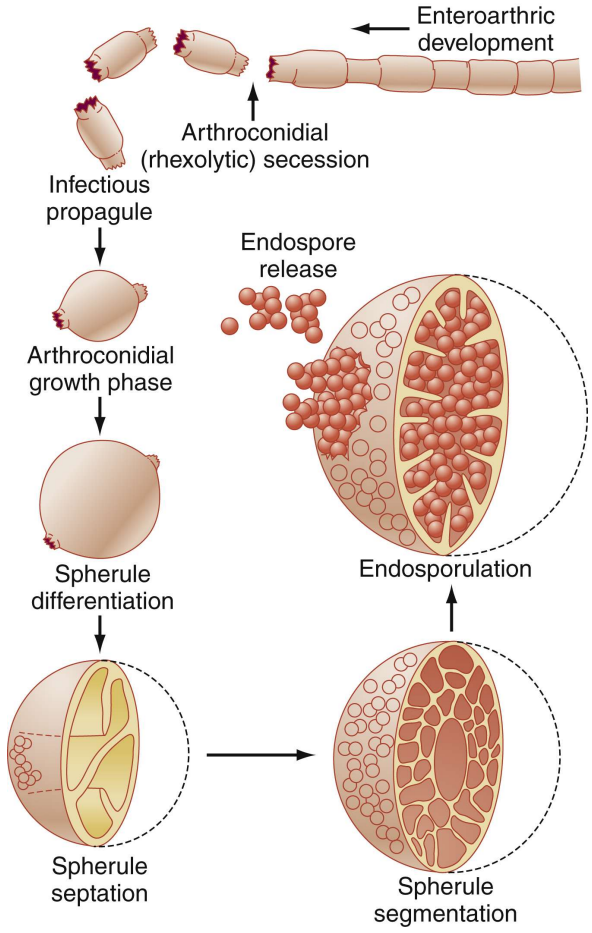
- Skin testing (similar to PPD) 1930's and later
  - 100% of members of the Pima tribe tested positive
  - Up to 50% of military recruits
  - 17% of children after 1 year, 77% after 10 years
- Related to dust exposure
  - Increased incidence after Northridge, CA earthquake in the 1990's
- Organisms found in hot, dry regions with alkaline soil
- Concentrations around animal burrows

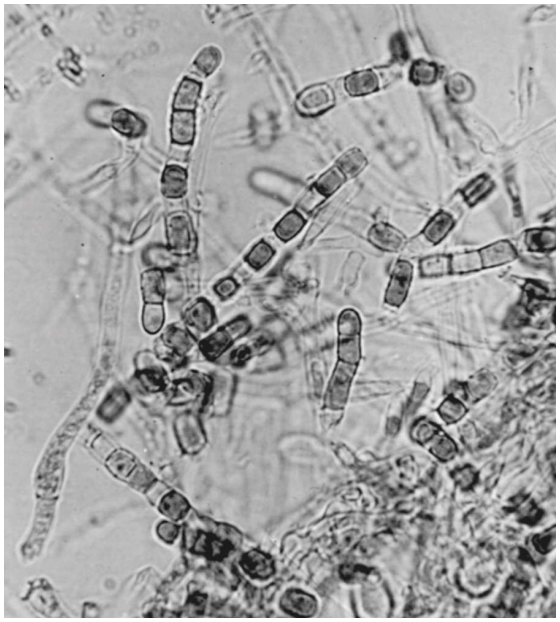


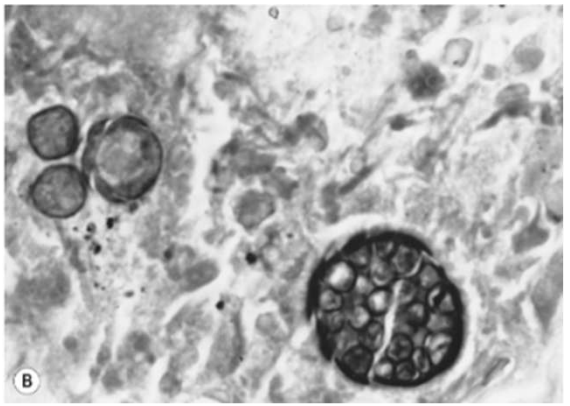
DC 1957, JAMA 1997

The Organism

- Dimorphic: mold on the outside, yeast on the inside
  - Mold produces arthroconidia that can aerosolize
  - Yeast-like form can invade tissues
    - Spherules and endospores







Feigin and Cherry 2025, Long 2023

A Question

A 12-year-old girl with ALL presents with cough for 5 days, fever to 103 and RLL infiltrate on chest xray. Testing for coccidioides is positive. A medical student asks what should be done to prevent transmission of the infection to others. You answer

A) Airborne precautions (N95 and negative pressure room)

B) Droplet precautions (simple mask)

C) Contact precautions (gown and gloves)

D) No precautions are needed

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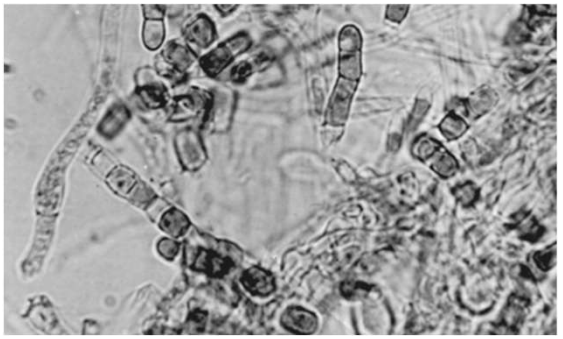
Transmission



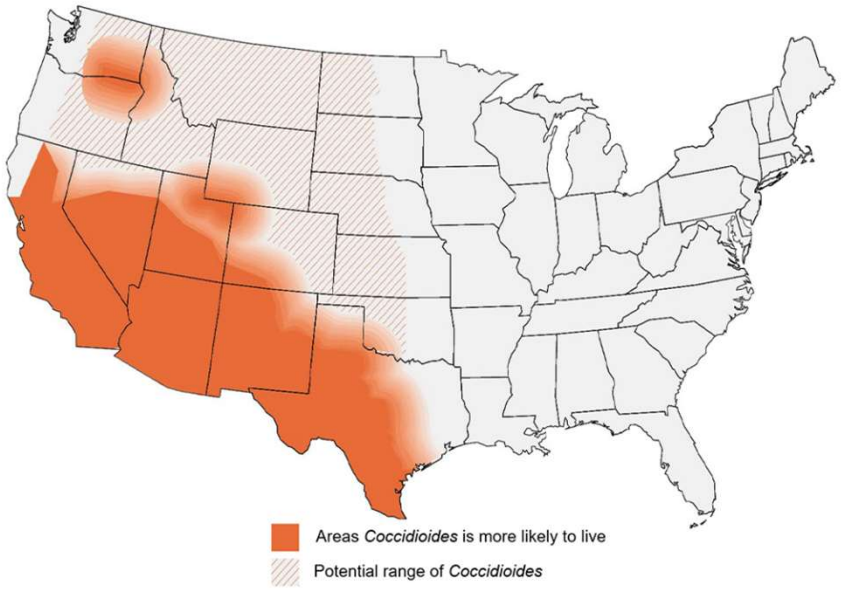
- Inhalation of spores
- In vivo changes to yeast like phase that isn't contagious to others
- Certain risks
  - Lab personnel can inhale spores from mold on culture
  - Case of inhalation from a chronic osteomyelitis that caused sinus tract and became mold on the cast
    - Aerosolized when cast cut off
- Don't have to be in the endemic area for a prolonged period of time
  - Layover in Phoenix airport
- May not even have to be in the area
  - Child that helped unpack his grandparent's dusty shoes from their trip to the SW

What about this patient?

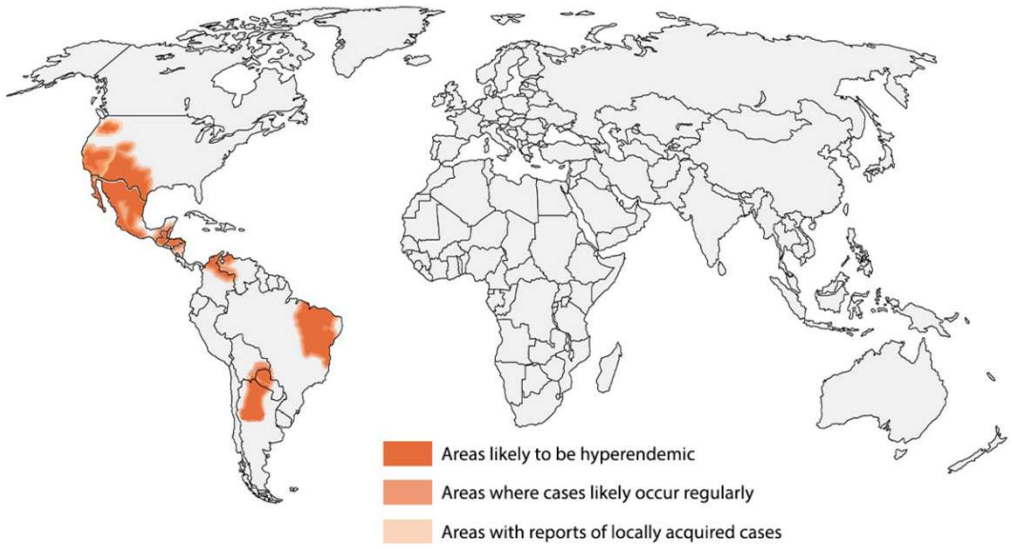
- A 12-year-old boy in Washington state with no travel history to the SW develops fever, chest pain and RLL infiltrate on CXR and has erythema multiforme on exam
- No improvement with antibiotics targeting bacterial causes of CAP
- Could this be Cocci?
  - Didn't unpack anyone's dusty shoes from AZ
  - Testing was positive
  - Is it cross reacting with other endemic fungi?
- Additional patients in the area developed Cocci over a period of time
  - The organism was found in local soil samples

CID 2013, EID 2019

Geographic Distribution of Coccidioides spp



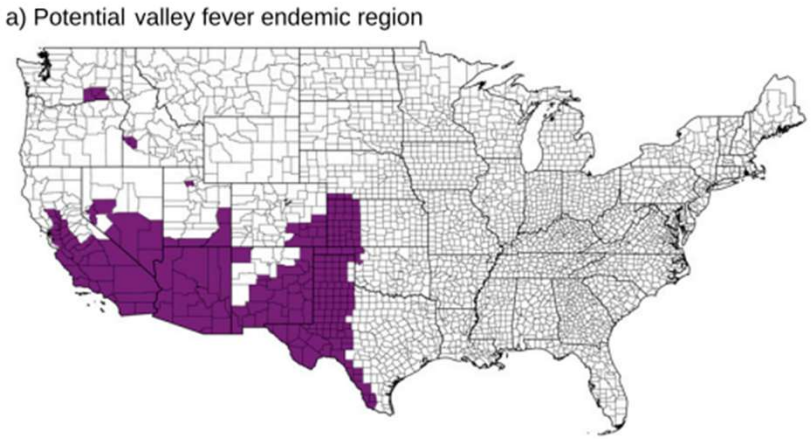
Approximate area with *Coccidioidomycoses* in the US

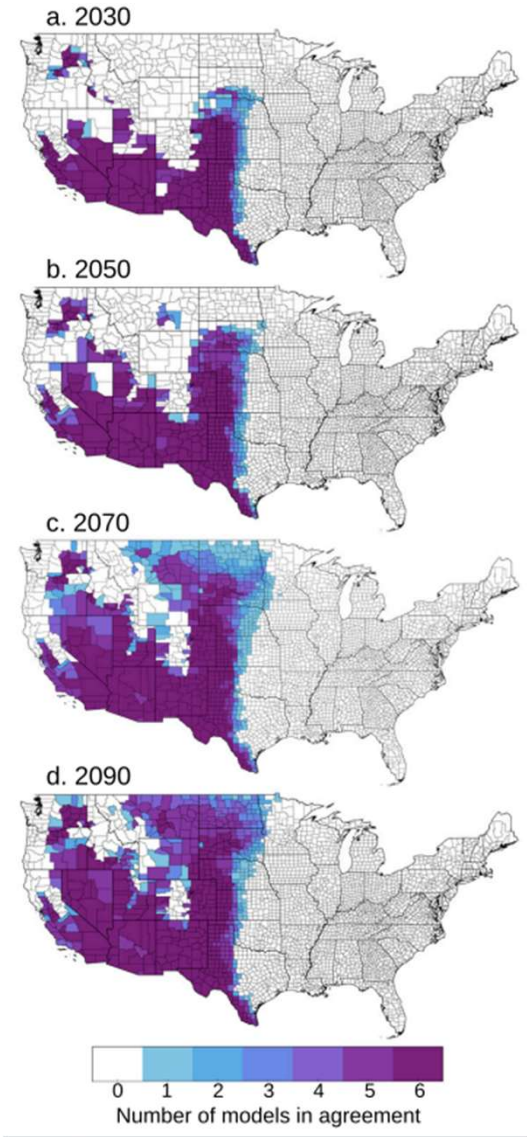


Approximate area with *Coccidioidomycoses* in the world

https://www.cdc.gov/valley-fever/hcp/testing-algorithm/index.html

Projected Cocci Expansion





Gorris 2021

Coccidioides Infection

- Estimated 150,000 cases/year in the US
  - Most are asymptomatic/mildly symptomatic
- Pulmonary infection
  - Usually self limiting
  - Any range of xray/CT findings
    - Nothing, lobar, multifocal, nodular, cavitary, granulomas (with or without calcification), miliary, hilar adenopathy, effusion, pneumothorax, etc
    - Cavities can rupture, bleed, get superinfected, cause pain, etc
      - Thick walled with initial infection, thin walled later on
        - May resolve over time
      - Many are asymptomatic

Extrapulmonary/Disseminated Infection

- Occurs in about 1% of cases
  - Usually present weeks/months after pulmonary infection
    - Often don't recall any pulmonary symptoms
    - CXR is often normal
- Can be life threatening
- Can affect most any organ system (usually spares the GI tract)
  - Osteomyelitis
    - Can be multifocal
    - Often involves bones that aren't typical for bacterial osteo
      - Skull, hand, ribs, vertebrae
  - Arthritis
    - Can also be direct invasion from a thorn
  - Skin: verrucous lesions
  - Lymph nodes
  - Meningitis: often basilar

Extrapulmonary/Disseminated Infection

- Higher risk
  - Immune compromise
    - Malignancy, transplant, primary immune deficiencies, diabetes
    - TNF alpha inhibitors and some biologics
    - Steroids?
      - Short course for asthma, inhaled steroids OK
  - Ethnicity?
    - Described higher rates of severe/disseminated disease in people of African descent, Philippines, (Marshallese?)

Coccidioides Infection

- Parainfectious manifestations
  - Desert rheumatism: symmetric joint pain with or without swelling
    - Self limiting
  - Erythema nodosum and erythema multiforme

AAP Red Book

Signs and Symptoms

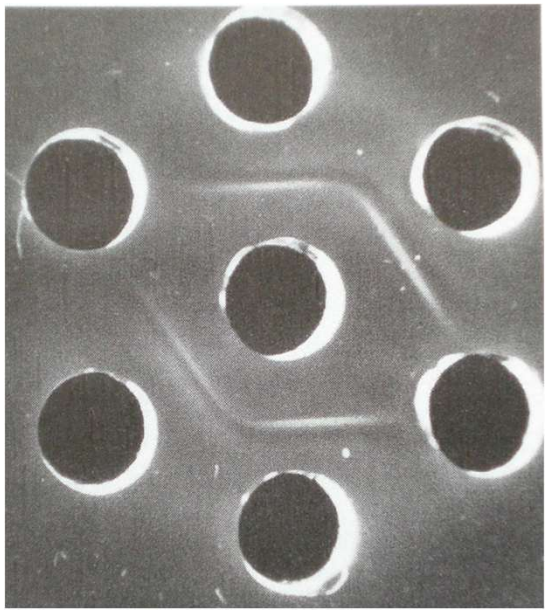
- Generally start within 1-3 weeks of inhaling the arthroconidia
  - Fever
  - Cough (often non-productive of sputum)
  - Weight loss
  - Night sweats
  - Headaches
    - common with acute disease, but may be concern for CNS infection
- Chronic and/or progressive
  - Headaches, MSK pain/swelling, fungating skin lesions, adenopathy, etc
- Some of the most severe cases I've seen had minimal symptoms for a long time
- Lots of overlap with TB signs/symptoms

Diagnosis

- Serology (blood and CSF)
- Antigen (blood, urine, CSF): poor sensitivity
- DNA detection?
- Culture
  - Rare fungemia
  - Often grows on bacterial specimen cultures for tissue samples
- Pathology findings
  - Spherules
  - Granulomas
- Other hints: eosinophilia on CBC, in pleural fluid or CSF

Serology: welcome to the alphabet soup confusion

- EIA
  - IgM and IgG
- Immunodiffusion (IMDF)
  - IgM (TP)
  - IgG (CF)
- Complement fixation (CF)
  - Titer
    - Possibly prognostic if >1:16???
  - Often decreases with symptom/infection resolution
- ImmunoChromogenic Assay (ICA):
  - Point of care lateral flow assay to detect IgM/IgG
  - Scant data, 31% Sensitivity, 92% specificity

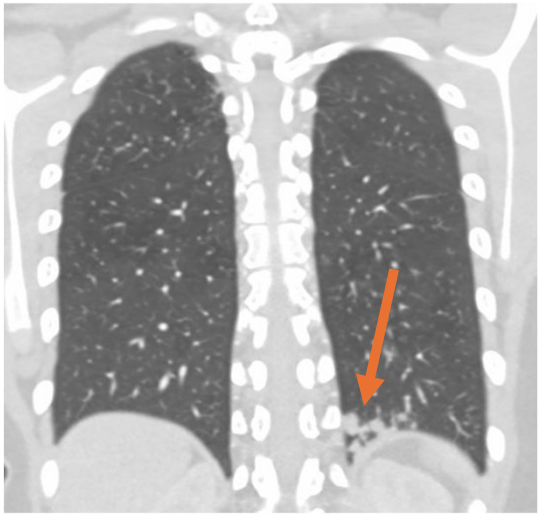


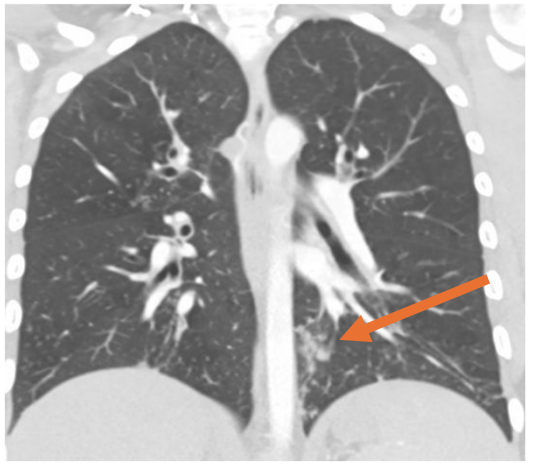
Serology

- EIA is easier to do and may be more sensitive compared to IMDF
  - False positive IgM
  - Indeterminate results
- ICA is easiest to do, but not very sensitive
- Serologies tend to wane over time and usually eventually become negative within months to years
  - Can cross react with other endemic fungi (ie histo)
- Infection can be present in the setting of any serologic result

12 y/o girl with cystic fibrosis and cough

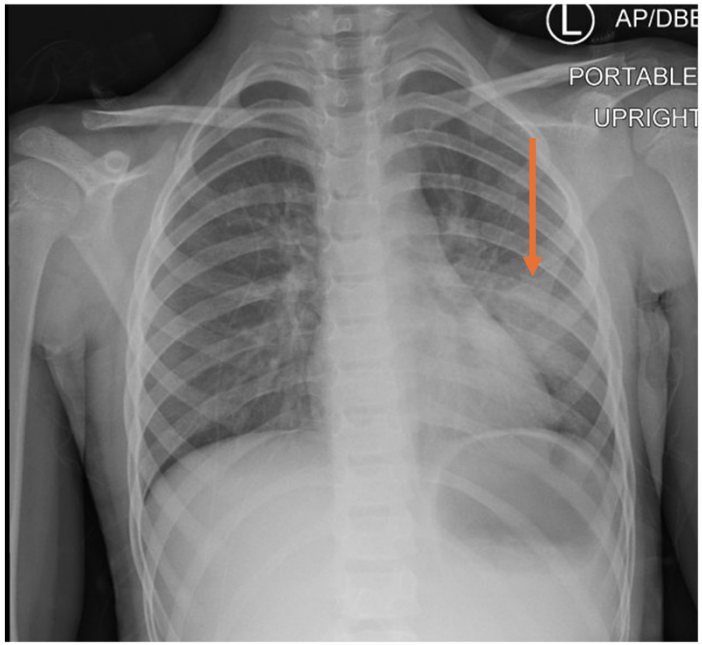
- Months of dry cough, fatigue, off and on headaches
  - Afebrile
  - Hasn't changed with empiric antibiotic course
- Decreasing PFTs
- Cocci EIA IgM and IgG negative, CF titer <1:2
- CT scan shows pulmonary nodules, tree in bud opacity
- Is this Cocci?
  - Negative serology, broad differential
  - Cocci grows from BAL cultures
- Serology stayed negative every other time I tested her over the next few years





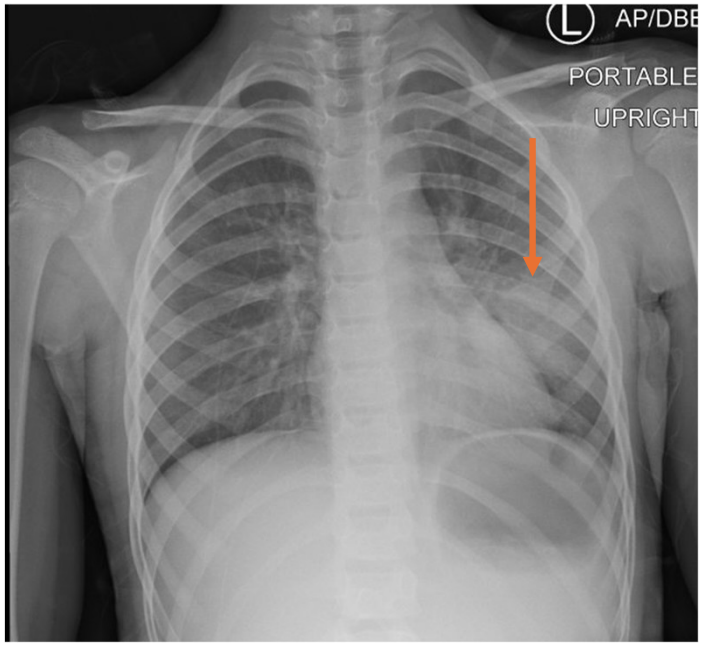
6 y/o girl with fever, cough and rash

- Dry cough x1 month, 5 d fever, bilateral arthralgias, LLL infiltrate on CXR
- Rash somewhat pruritic/painful. Has an oral ulcer
  - What rash is this?
    - Erythema multiforme
- Cocci EIA IgM and IgG negative
- Is this Cocci?



6 y/o girl with fever, cough and rash

- EIA IgM and IgG positive 3 weeks later
- Do you treat her with fluconazole?



Treatment

- Pulmonary disease almost always self limiting
  - Can take weeks for fever and cough to resolve
    - Sometimes months for the fatigue to resolve
    - Can be difficult to differentiate between cocci symptoms and asthma or new infections
  - Treatment reserved for severe, progressive cases
    - Lack of good data to show benefit to treating pulmonary infection
    - Length of therapy 3-6 months?

Treatment

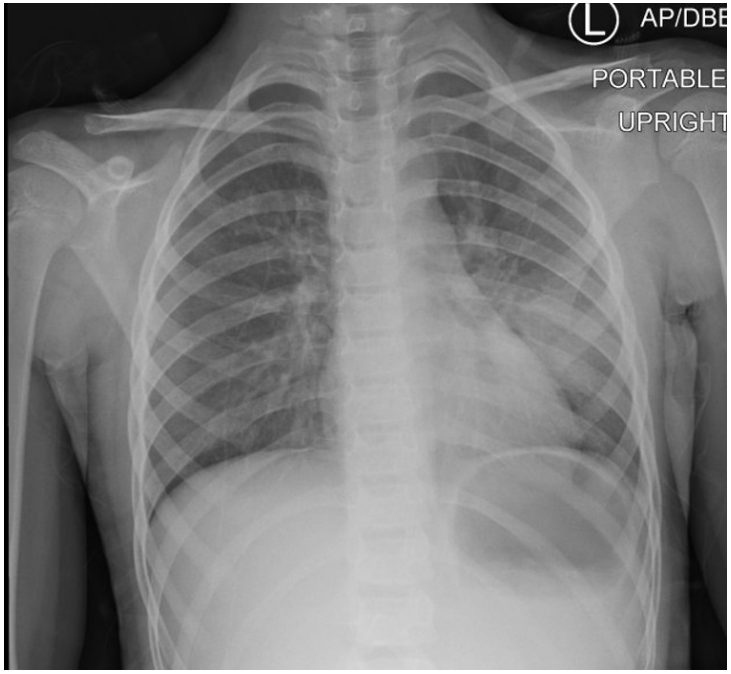
- Disseminated/extrapulmonary disease can be life threatening and usually requires treatment
  - Usually responds to treatment
    - Relapse/progression may occur on therapy
  - CNS disease requires lifelong therapy
    - High rate of relapse and death if azoles stopped
  - Severe immune suppression may require prolonged/lifelong therapy

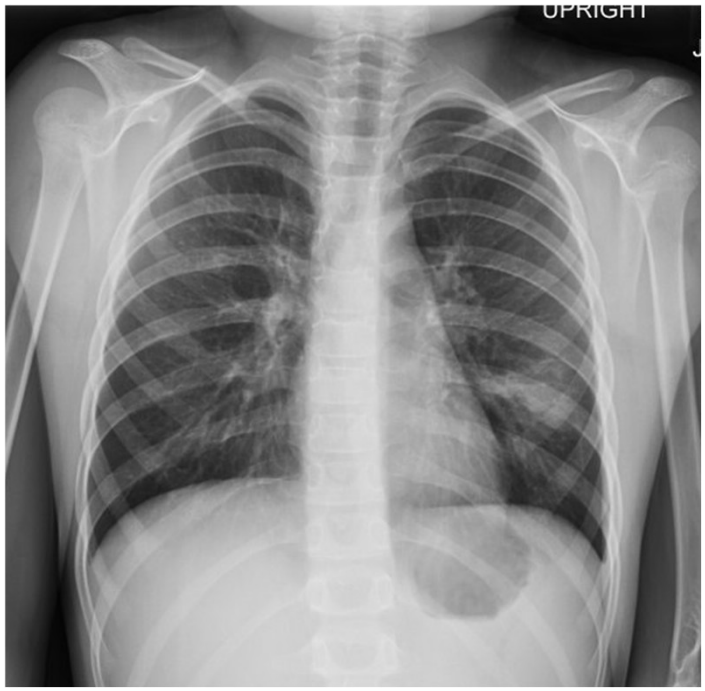
Treatment

- Treatment options
  - Fluconazole
  - Other azoles
  - Amphotericin
  - New agents?
- Treatment principles
  - Monitor symptom progression
  - Follow CF titer?
  - Monitor for treatment related toxicity
- Prophylaxis?
  - Post transplant in endemic area

Our 6y/o girl with EM rash and pneumonia

- Rash and other symptoms resolved within weeks





6m later

4 y/o with chin lesion

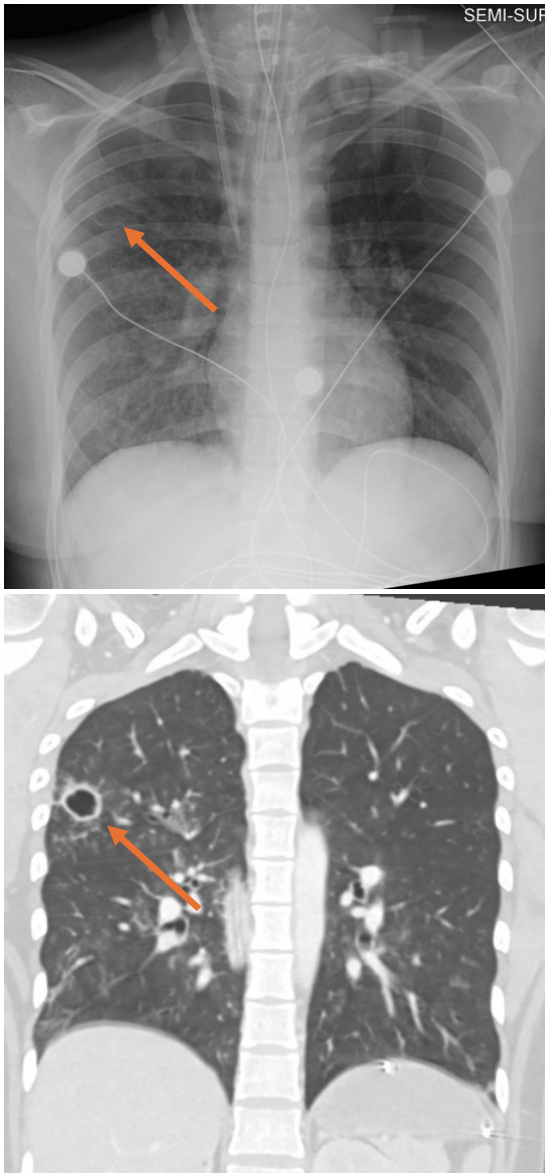
- Cough that lingered for a month
- Chin lesion starts a month after the cough, progresses in size and doesn't respond to antibiotics
- Cocci EIA IgM and IgG positive, IMDF IgM negative IgG positive, CF titer 1:32
- CBC 1340 eos
- I&D culture grew Coccidioides spp
- CXR negative

4 y/o with chin lesion

- Extrapulmonary infection
  - No findings concerning for other sites of infection
  - Treated with fluconazole for 10 months
    - I kept it going for a while because I wasn't sure if just scar tissue vs ongoing skin involvement
    - CF titer <1:2 by 2 months
    - Did fine and no relapse after stopping therapy

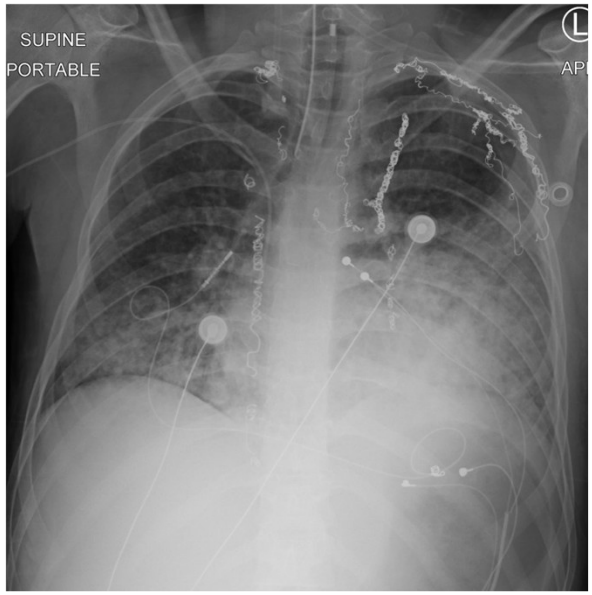
19 y/o girl passed out after a party

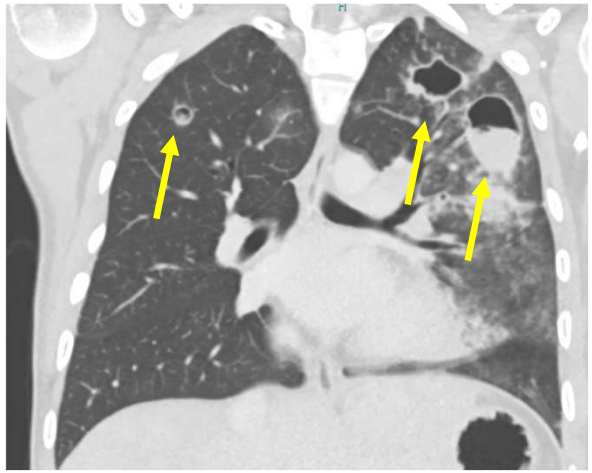
- Had some URI symptoms, COVID positive
- CT scan cavitary lesion and hilar adenopathy
- Cocci EIA IgM+ IgG-, IMDF IgM- IgG+, CF 1:2
- COVID related URI symptoms resolved within days
- Did fine, no treatment given for cocci



18 y/o with hemoptysis

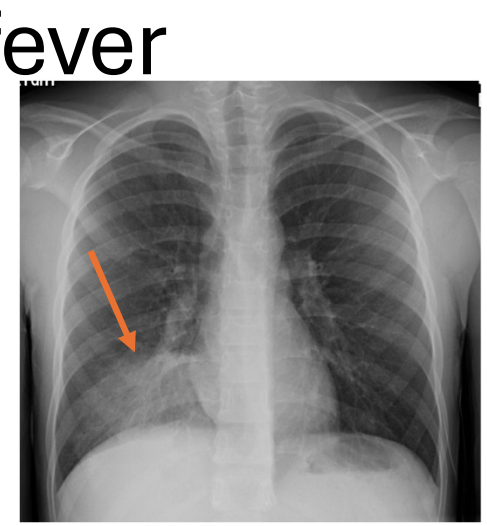
- History of pulmonary atresia, fontan, elevated pulm pressures, recurrent hemoptysis, multiple coils
- Cystic lesions on imaging
- EIA IgM- IgG+, IMDF-, IgG+, CF 1:16
- Not a candidate for resection
- No major change with ambisome and fluconazole
- Later had catastrophic pulmonary hemorrhage and died

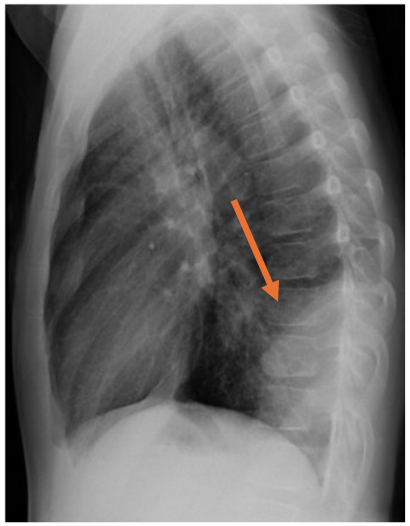


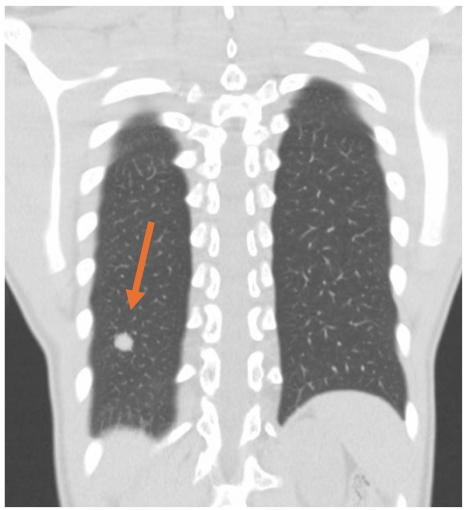


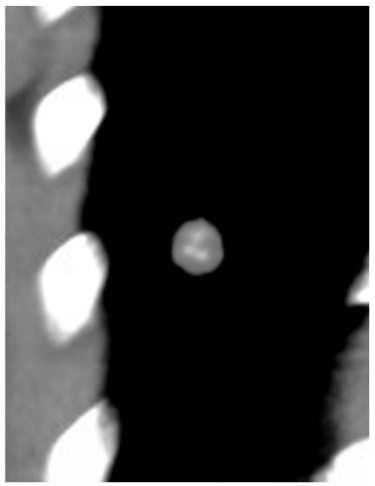
11 y/o girl with cough and fever

- Lobar infiltrate on CXR
  - Didn't respond to antibiotics
- EIA and IMDF IgM and IgG+
  - CF titer **1:64**
  - No risk factors for severe disease
- Lingering symptoms, w/u for disseminated infection neg
  - Fluconazole for a few months, CF titer improved
- Nodule on CT scan done for MVA
  - Stable and calcified 2y later
  - Asymptomatic



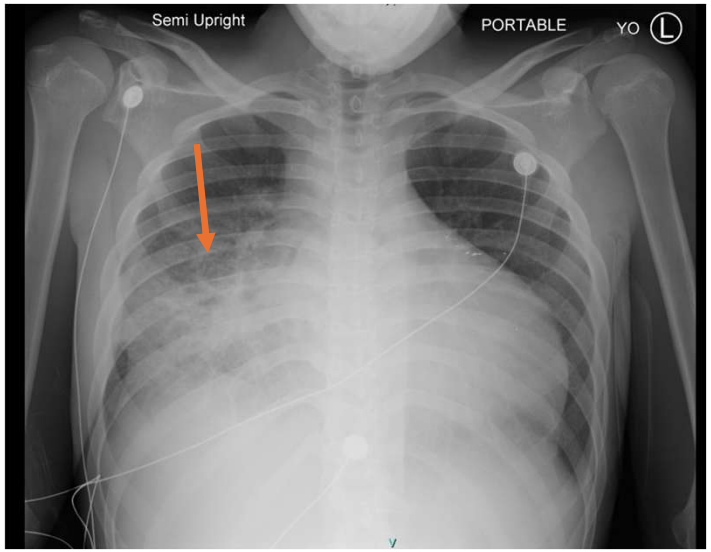


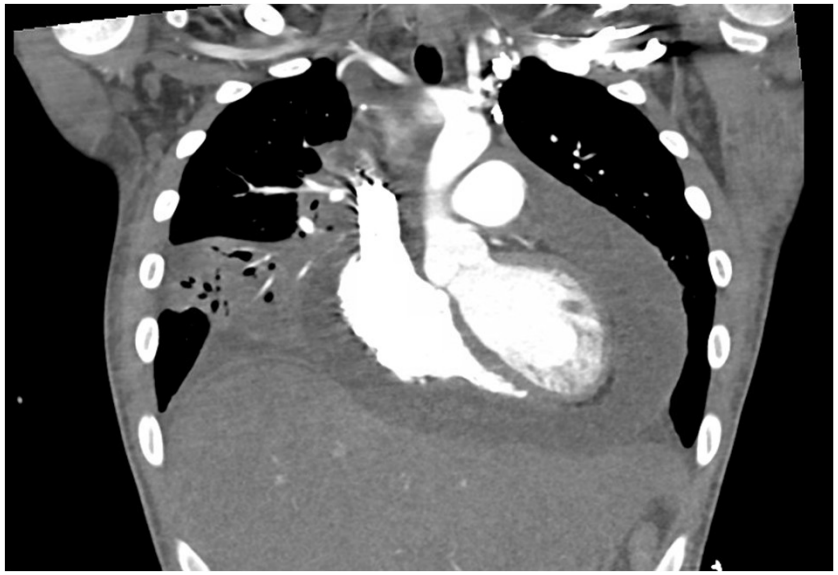




It goes all wrong

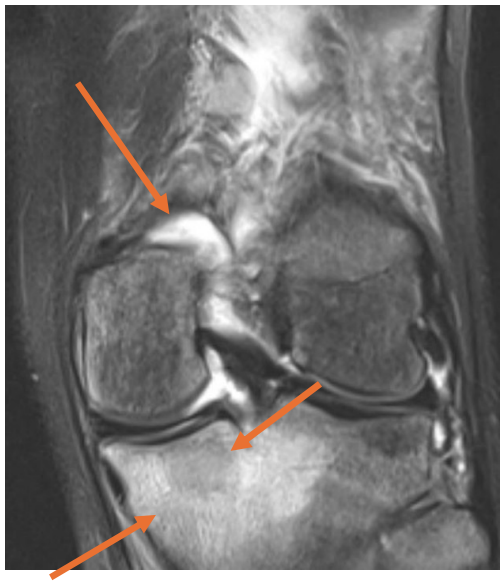
- 16 y/o 70lb wt loss over 7 months
  - Afebrile
- 4 days of acute dyspnea, chest pain
- Imaging pneumonia with pericardial effusion
- Drain the effusion
- CF titer **>1:256**, all ab positive
- Start liposomal ampho, transition to fluconazole
- Clinically improves
  - Doesn't take his meds well





16 months post effusion

- New knee pain/swelling without fever
  - MRI shows arthritis and osteo
  - Gets I&D'd
- Recommits to fluconazole and improves
  - Doesn't take his meds well

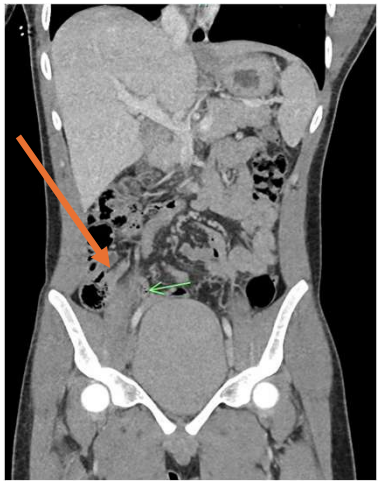


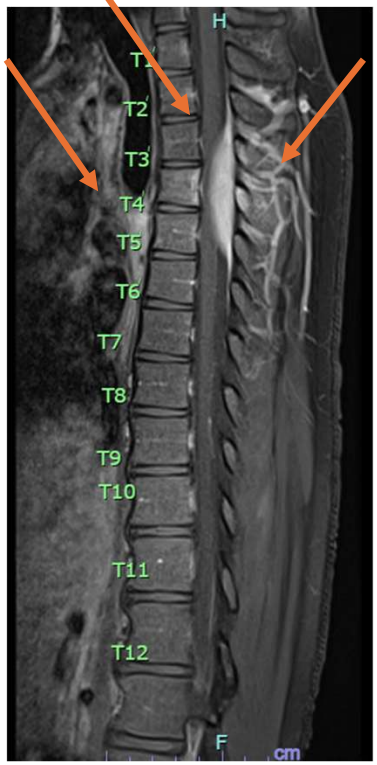
2 years post effusion

- Skin/MSK lesions

2 years post effusion

- Imaging shows soft tissue infection and osteo in multiple areas
- Paraspinous mass, osteo and spinal compression
  - Laminotomy and hardware placement
- Recommits to fluconazole and improves
  - Doesn't take his meds well



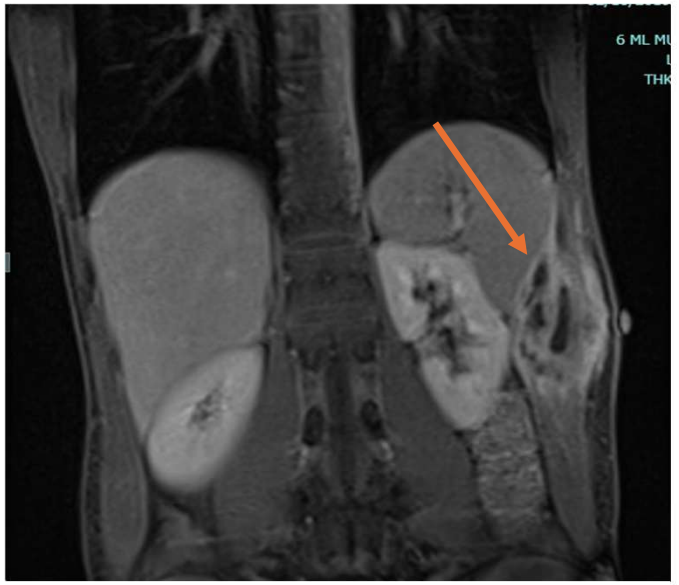


4 years post effusion

- Back swelling and draining wound
  - Soft tissue and bone involvement
- I&D'd, improved, did well at follow up, but hasn't been back for a year....

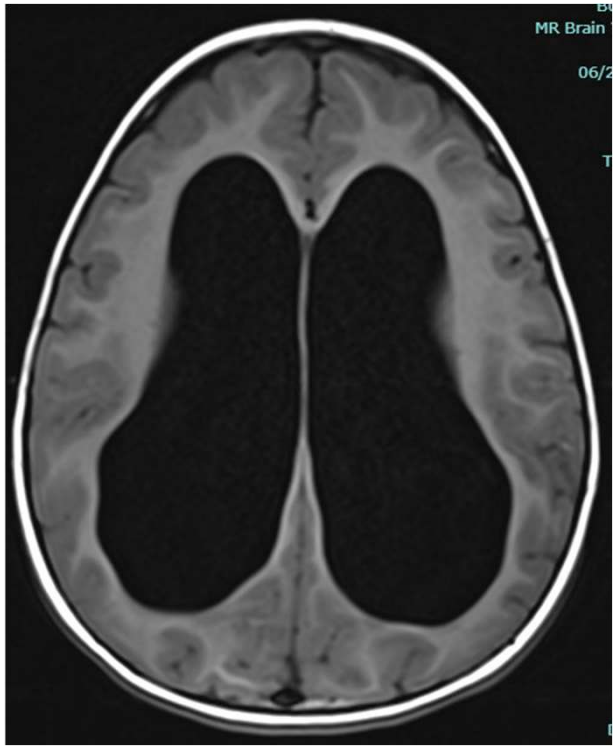
16 y/o boy with left flank swelling

- Born in Africa
- 1 week of painful flank swelling, 1d of low grade fever
- 11th rib osteo on imaging
- Cocci EIA IgM- IgG+, IMDF IgM+ IgG+, CF 1:64
- Lesion I&D'd, culture grew cocci
- No additional lesions found
- Treated with fluconazole, lost to follow up



2 y/o girl macrocephaly, developmental delay

- Born term, initially normal growth and development
  - Stopped progressing sometime before 18m
    - Noted macrocephaly around that time (HC 98%)
- Can’t remember any history of cough or fevers
- Rather fussy, some intermittent emesis
- MRI hydrocephalus and leptomeningeal enhancement concerning for basilar meningitis
- EIA IgM- IgG+, IMDF IgM+ IgG-, CF 1:128
- Urine ag neg
- CSF 79 WBC (94%L), CF 1:8, ag neg

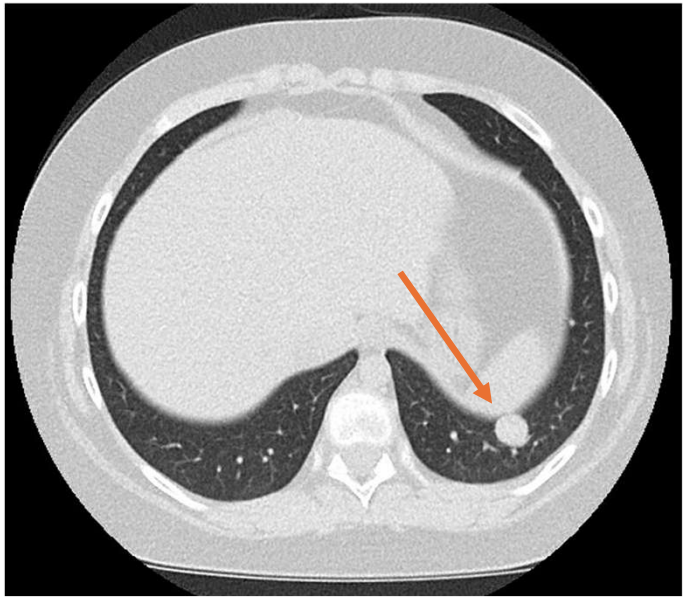


2y/o girl with Cocci meningitis, developmental delay

- VP shunt placed
- Started fluconazole
- CF titers >1:256, now trending downward years later (1:16)
- Doing rather well with some residual developmental delay, but rather smart
- Plan for lifelong therapy

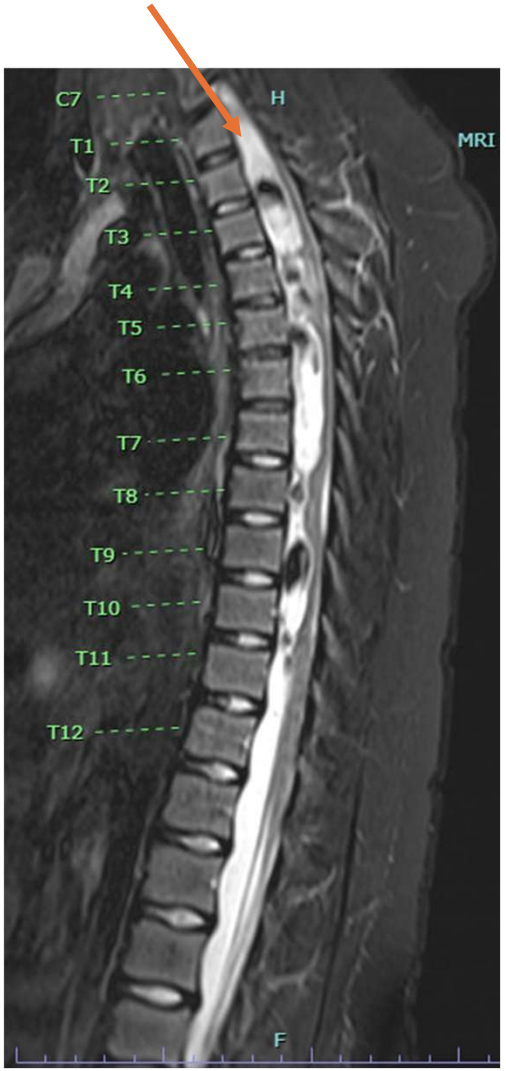
12y/o girl with pulmonary nodule

- Pulmonary nodule seen on imaging done for abdominal pain
  - No significant prior pulmonary symptoms
- No symptoms now, normal PFTs
- Cocci serology ordered but not done



12y/o girl with pulmonary nodule

- 6 months later developed back pain and leg weakness that progressed over 2 weeks
  - Afebrile
- Imaging shows large intraspinal lesion, also has hydrocephalus
- EIA IgM- IgG+, IMDF IgM+, IgG+, CF>1:256
- CSF 345 WBC (77%L, 1% Eos), prot 290, gluc 21, CF >1:128, ag neg
- Urine ag neg
- Got steroids, pain and weakness resolved
- Started ambisome (got AKI, hypocalcemic tetany)
- Doing well on fluconazole, plan lifelong rx
  - Most recent CF titer 1:64



Conclusion

- Coccidioidomycosis is a common cause of CAP in AZ
- Often missed
  - Usually not a problem but we are likely giving antibiotics unnecessarily
- Pulmonary infection doesn’t usually require antifungal therapy
- Serology is helpful, but can have infection with negative testing
- Think Cocci with chronic meningitis, chronic MSK symptoms, verrucous skin lesions in the right setting

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