Pulmonary Coccidioidomycosis

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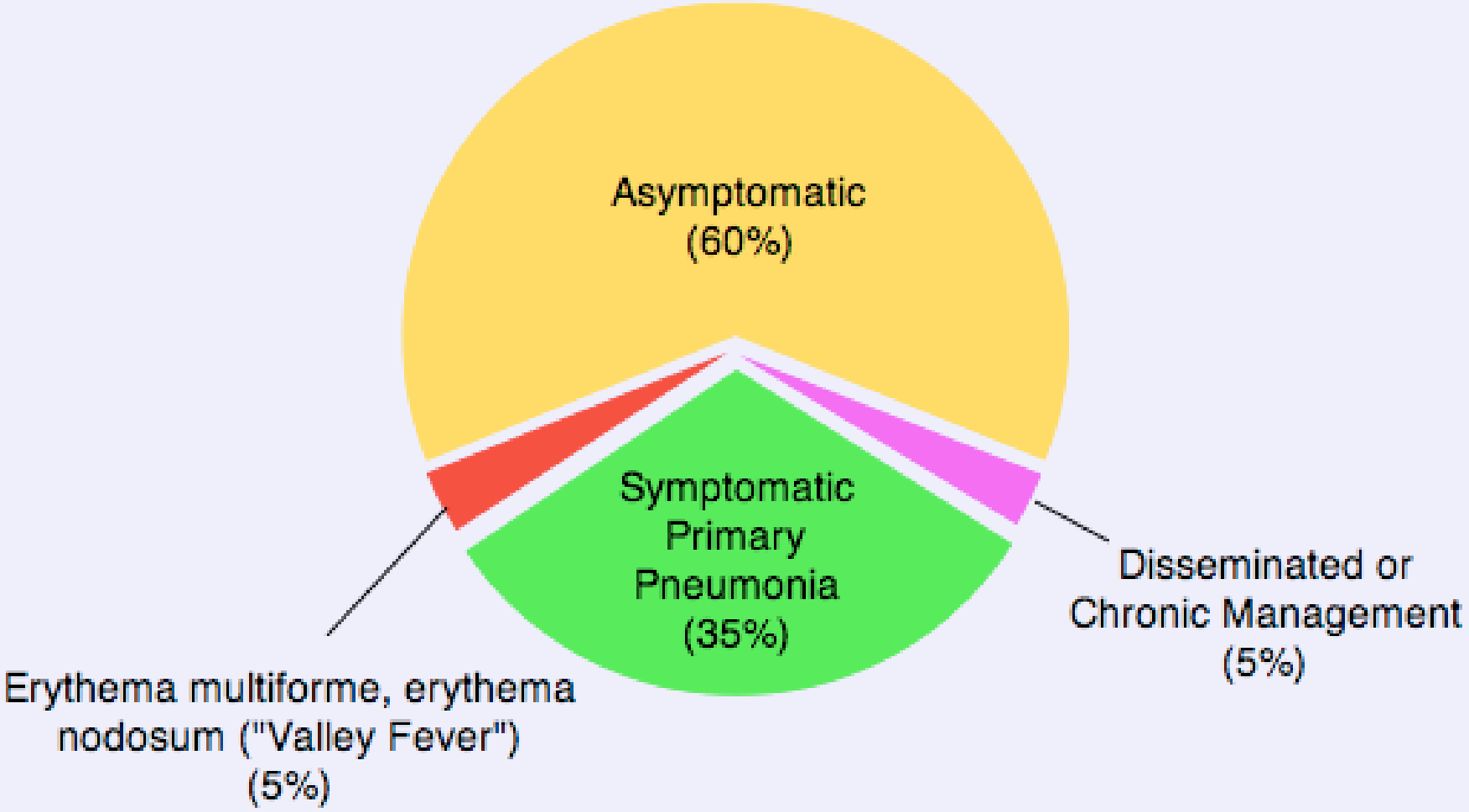
November 8, 2014

Clinical Manifestations of Coccidioidomycosis



adapted from Kirkland and Fierer, Emerging Infect Dis, 1996

Common presenting symptoms of pulmonary coccidioidomycosis

- Cough
- Pleuritic chest pain
- Fever
- Usually acute (over days)
- May be difficult to distinguish from community-acquired pneumonia (“CAP”) that is due to bacterial etiology

Primary coccidioidal pneumonia is a common cause of community-acquired pneumonia or “CAP” in Arizona

- 54 patients in a primary care and urgent care clinic in Tucson, AZ diagnosed with CAP during 2 time periods:
  - December 2003 through February 2004
  - May 2004 through August 2004
- 16 (30%) were seropositive for coccidioidomycosis (CI 16 - 45%)

Valdivia et al, Emerg Infect Dis, 2006; 12:958

Coccidioidal pneumonia, Phoenix, Arizona USA, 2000–2004

- Evaluated patients with acute pneumonia at Mayo Clinic, Scottsdale
- 59 subjects accrued
  - 35 completed paired serology
- 6 (17%) seroconverted
  - 95% confidence interval (7-34%)
  - rash more common (p = 0.002)
  - no other factors associated with coccidioidomycosis

Kim et al, Emerg Infect Dis, 2009;15:397

Symptoms suggestive of pulmonary coccidioidomycosis

- Night sweats
- Fatigue
- Rash
- Headache
- Weight loss
- Symptoms persisting for weeks

Rashes and pulmonary coccidioidomycosis

- Toxic erythroderma
  - diffuse, red, scaly
- Erythema nodosum
  - over lower extremities
  - violaceous
  - painful
  - usually in women
- Erythema multiforme
  - target lesions
  - often in a “necklace” distribution

Rashes associated with primary pulmonary coccidioidomycosis

Toxic erythema

(from D. Pappagianis)

Erythema multiforme

Erythema nodosum

“Desert Rheumatism”

- Arthralgias and arthritis associated with primary pulmonary coccidioidomycosis
- Usually occurs in association with erythema nodosum in women
- Ankle, wrist, knee, most common
- Usually symmetric

Coccidioidomycosis as a cause of chronic fatigue

- 48 subjects with symptomatic coccidioidomycosis were studied
- 65% had significant fatigue as measured by a validated scale
- Associated with a low body mass index (BMI)
- Over 4 months, fatigue significantly improved

Bowers et al, Med Mycol 2006; 44:585

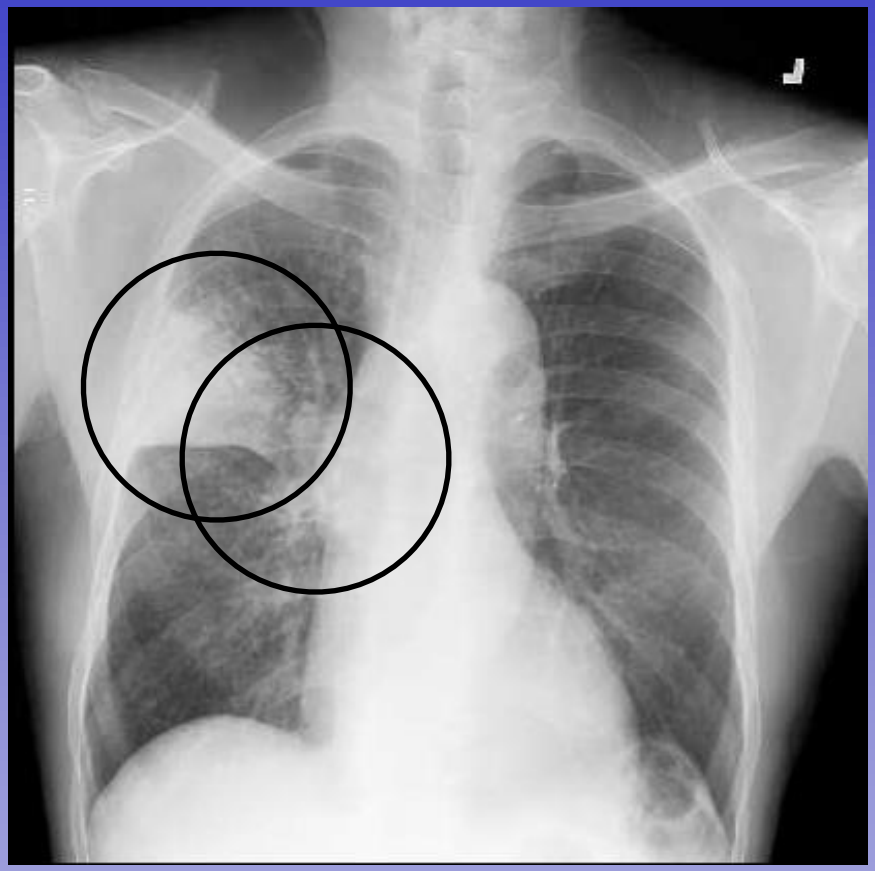
The chest radiograph in pulmonary coccidioidomycosis

- Usually focal
- May be upper or lower lobe

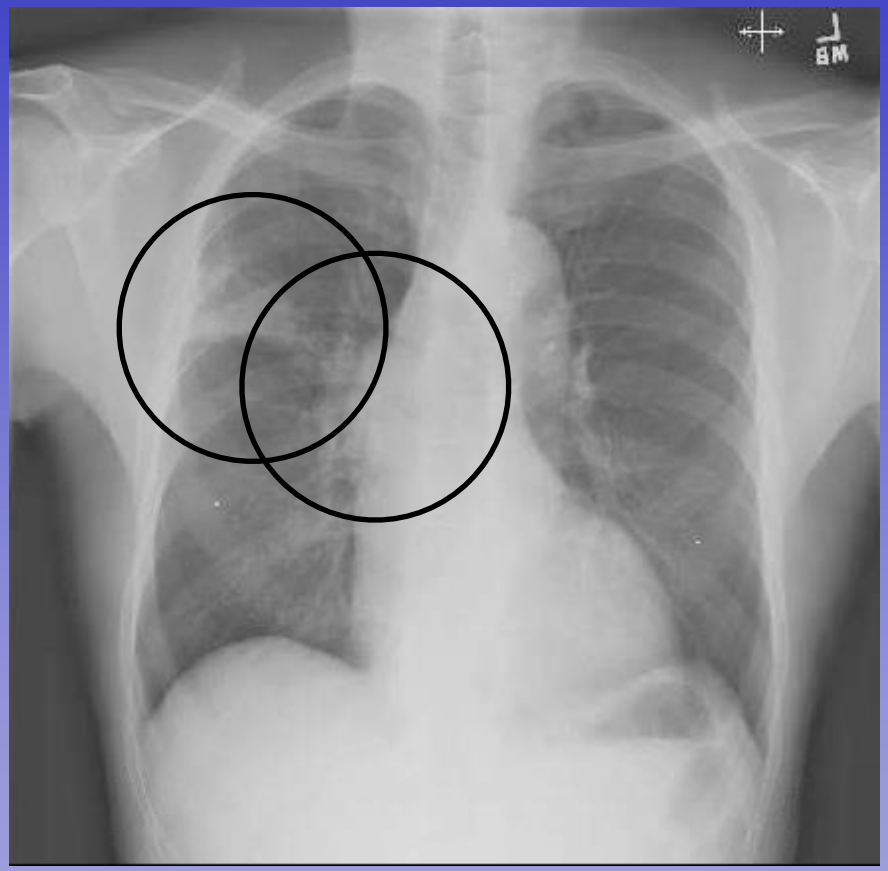
Distinctive radiographic features

- Dense infiltrate
- Upper lobe
- Associated hilar or mediastinal adenopathy

Characteristic X-ray

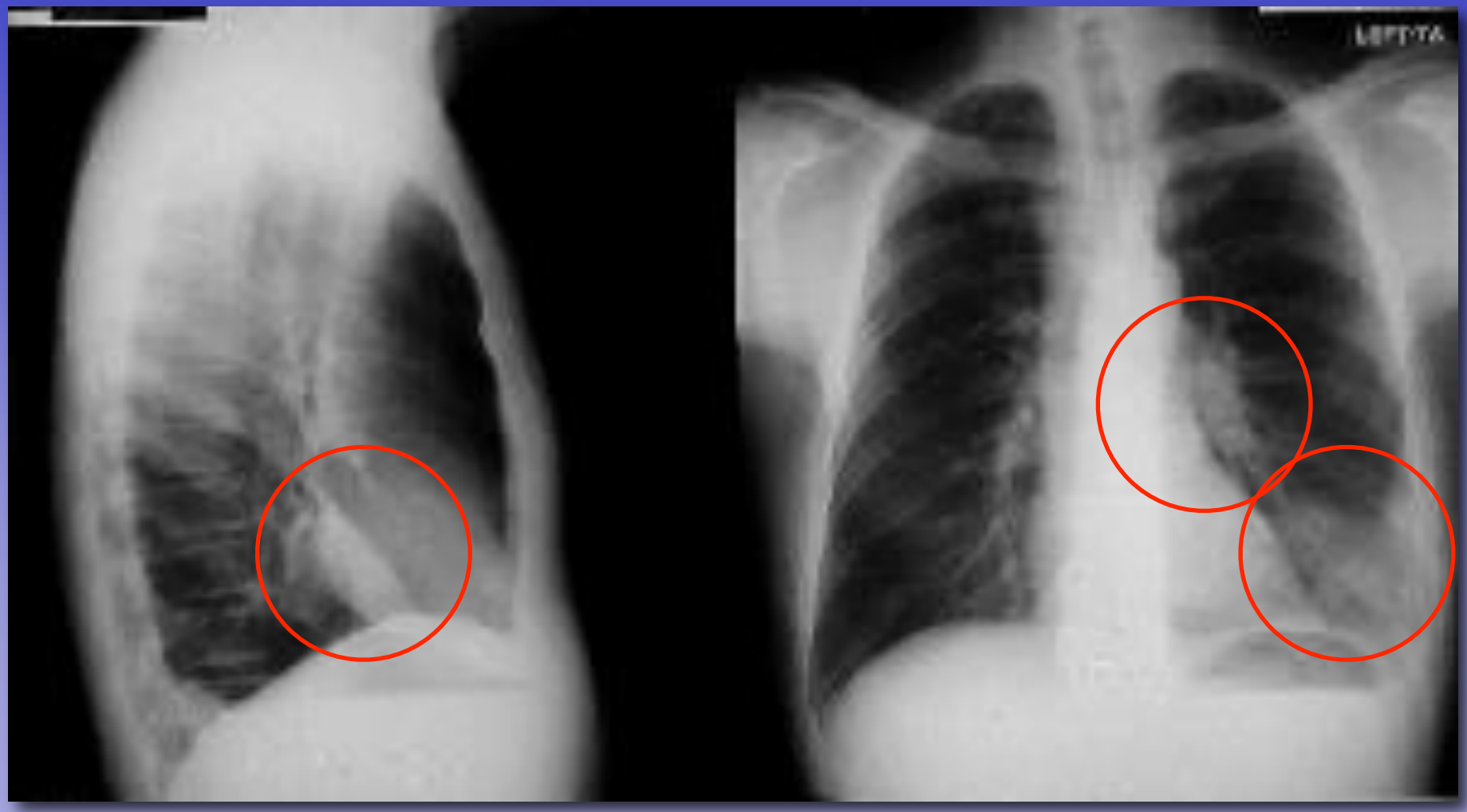


January 12, 2008



March 13, 2008

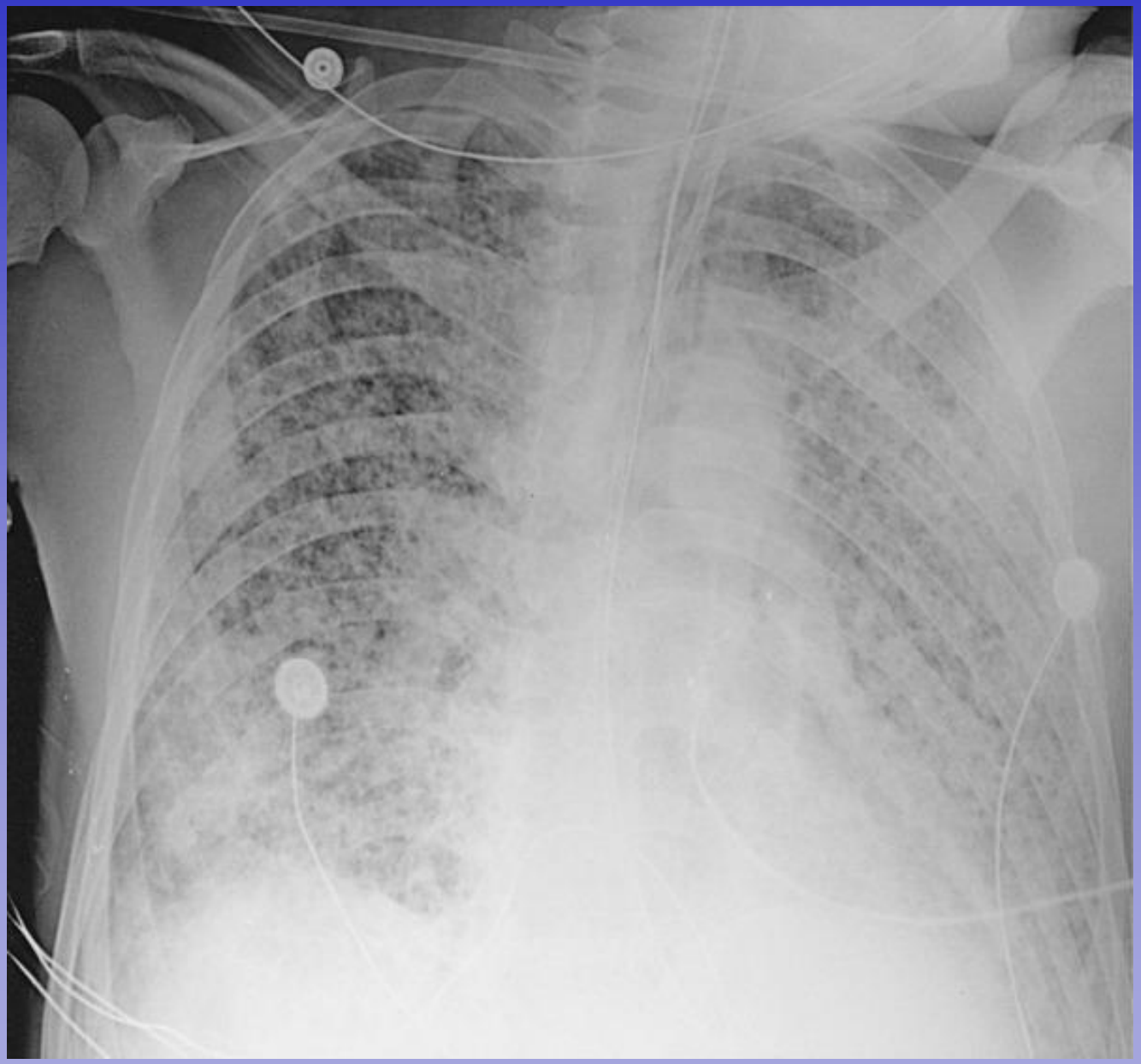
Another example



Diffuse or “miliary” pulmonary coccidioidomycosis

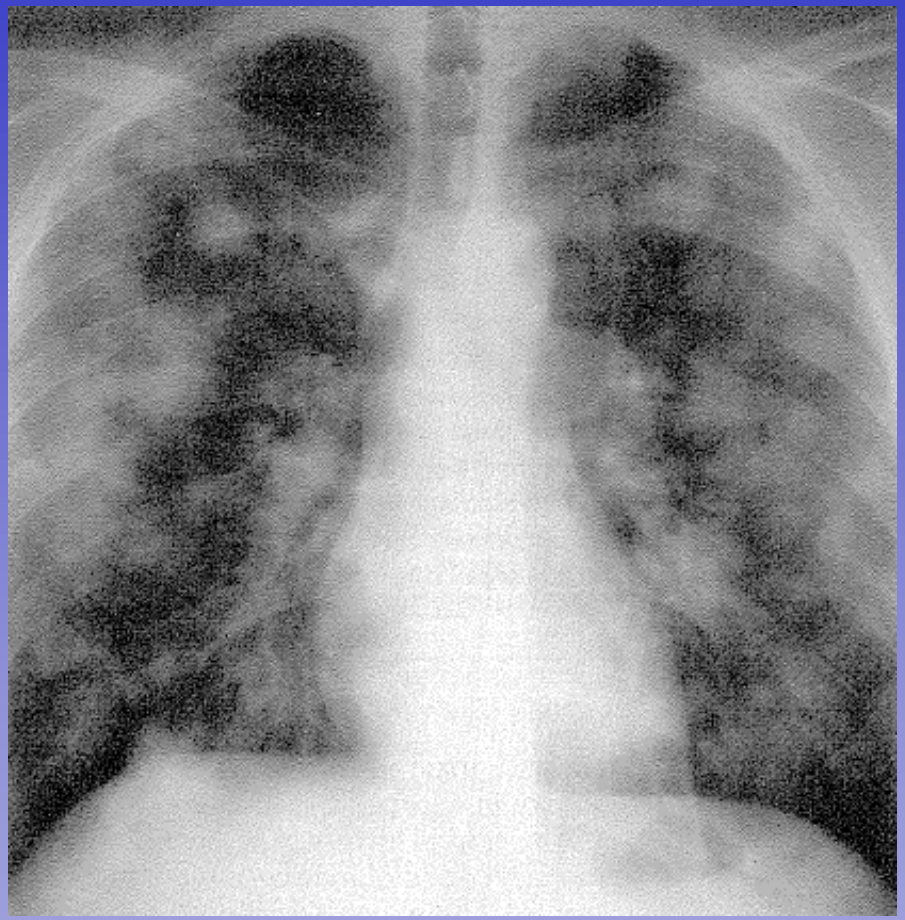
- Occurs in highly immunocompromised patients
  - presentation of AIDS in coccidioidal endemic region
  - manifestation of fungemia
- May also occur from high inoculum exposure
  - archeology

Diffuse pulmonary coccidioidomycosis in an AIDS patient

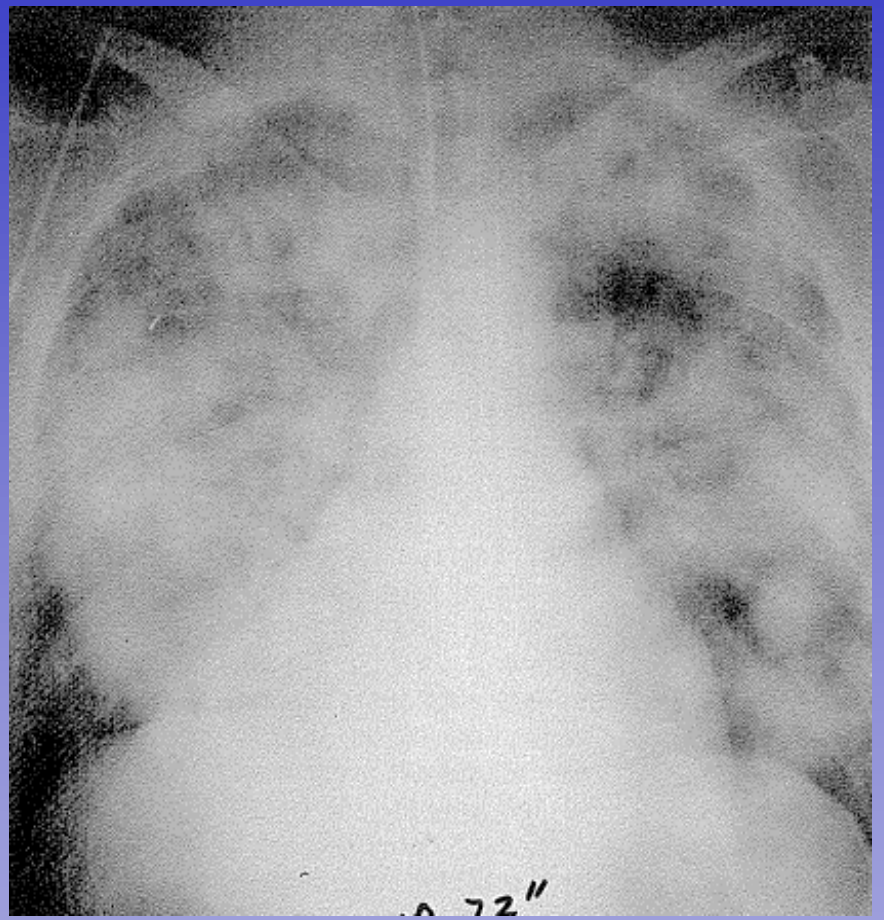


from JN Galgiani, PPID 2009

High-inoculum exposure



Day 1



Day 4

Larsen et al, Am Rev Respir Dis 1985; 131:797

When to suspect coccidioidal pneumonia

- Fatigue
- Headache
- Night sweats
- Weight loss

- Upper lobe infiltrate
- Dense pulmonary infiltrate
- Hilar or mediastinal adenopathy

- Failure to improve with antibiotics
- Peripheral blood eosinophilia

Complications of primary pulmonary coccidioidomycosis

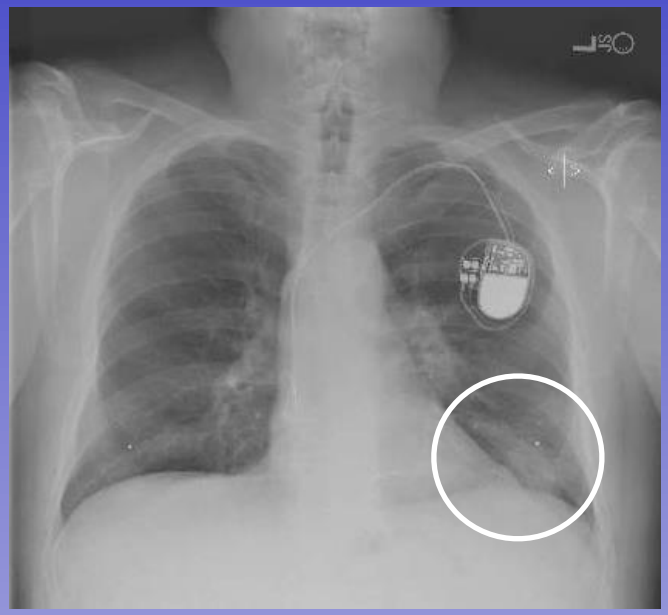
Pulmonary residua

- Nodules
- Cavities
- Pyopneumothorax
- Chronic pulmonary coccidioidomycosis

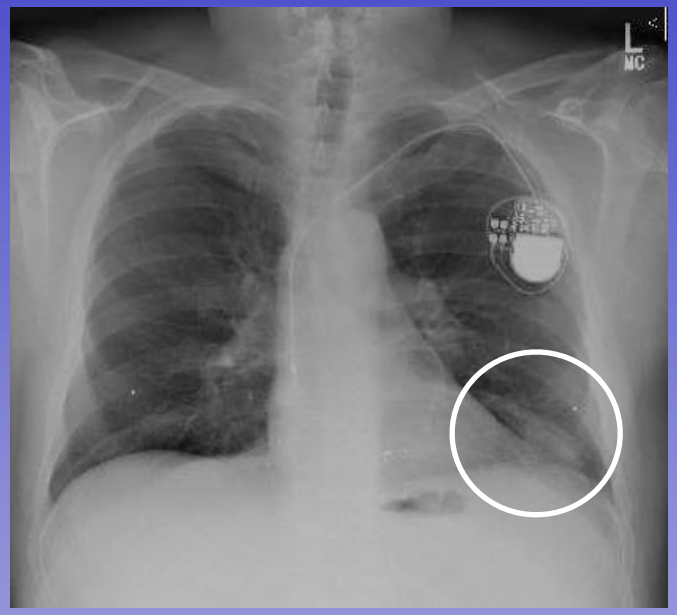
Nodules

- Resolution of initial pulmonary infiltrate
- Usually benign course
  - may cavitate
  - generally resolve over 1-5 years
- Unless evolution from infiltrate observed, difficult to distinguish from pulmonary malignancy

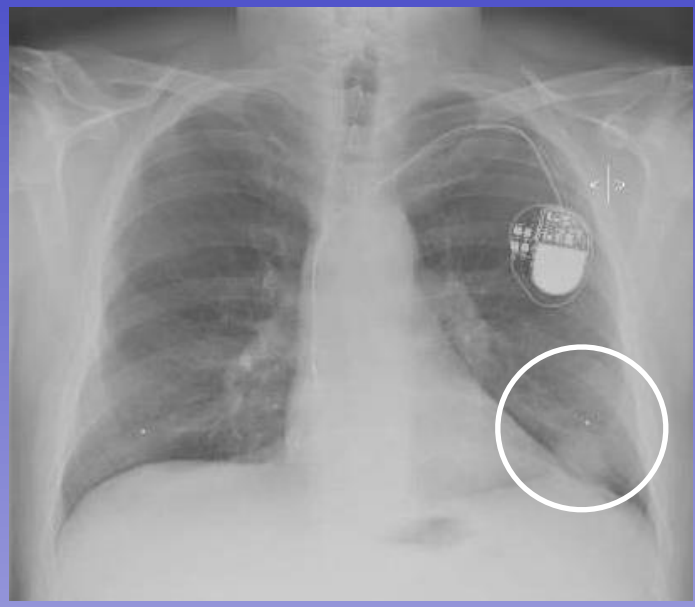
Example: infiltrate into nodule



Oct 1, 2008



Oct 10, 2008



Oct 31, 2008

Solitary coccidioidal pulmonary nodule

Diagnostic approach to nodules

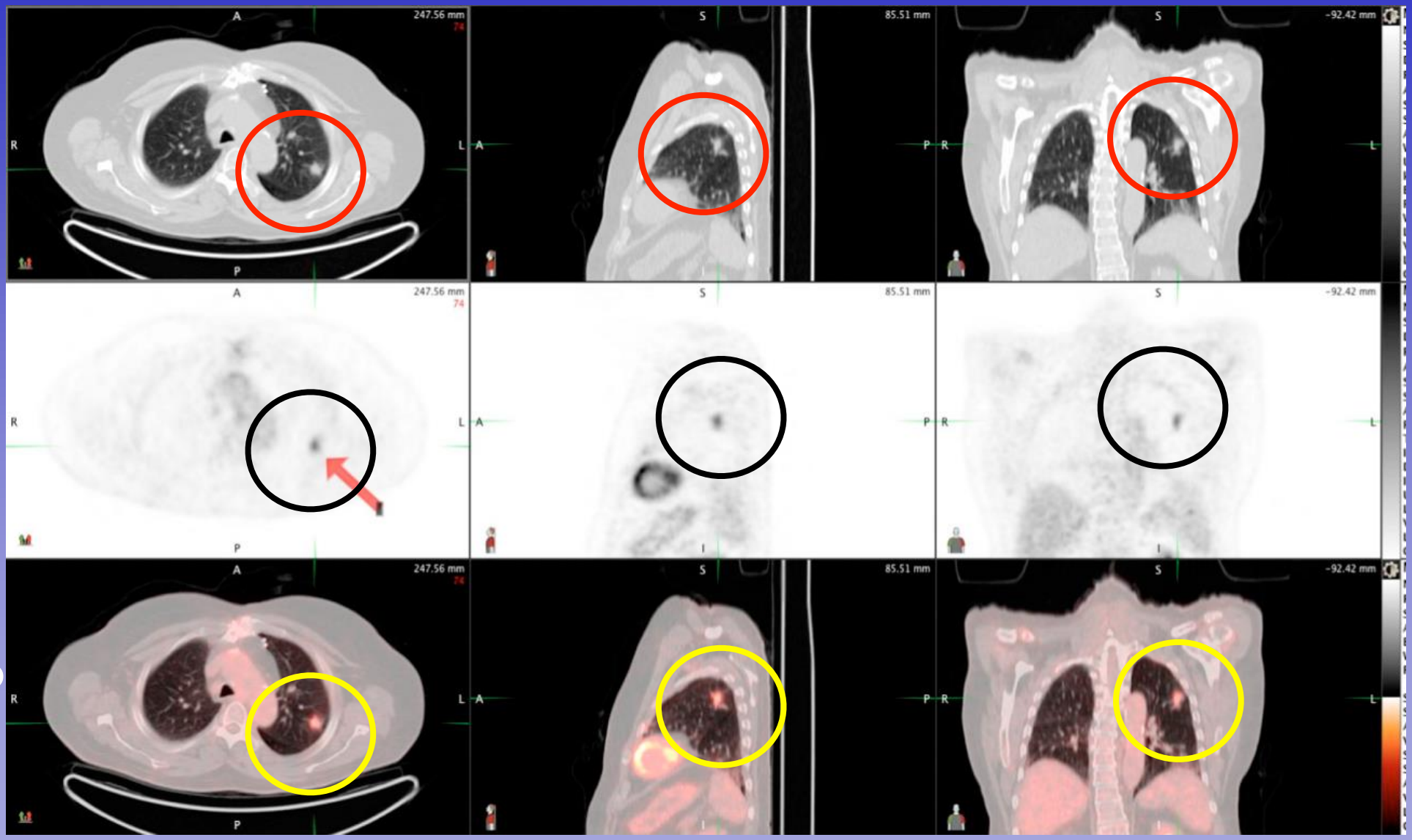
- Observation
  - non-smoker
  - positive serum coccidioidal serology positive
  - obtain plain chest radiograph every 3 months
- PET scans are frequently positive
  - see Reyes et al, Lung 2014; 192:589
- Biopsy
  - smoker
  - negative coccidioidal serology

PET scan in pulmonary coccidioidomycosis

CT

PET

CT/PET



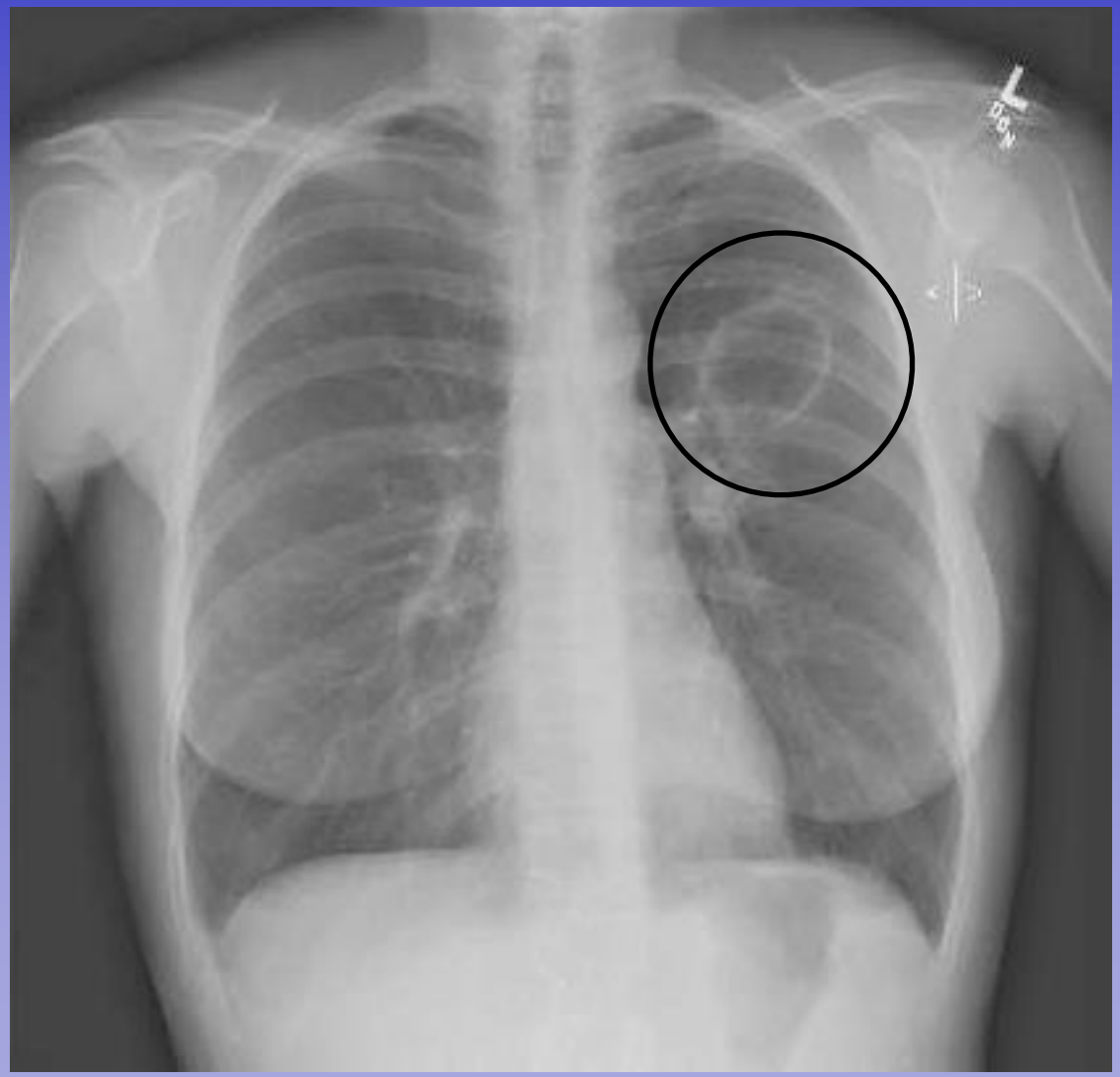
Modalities available for biopsy of pulmonary nodules

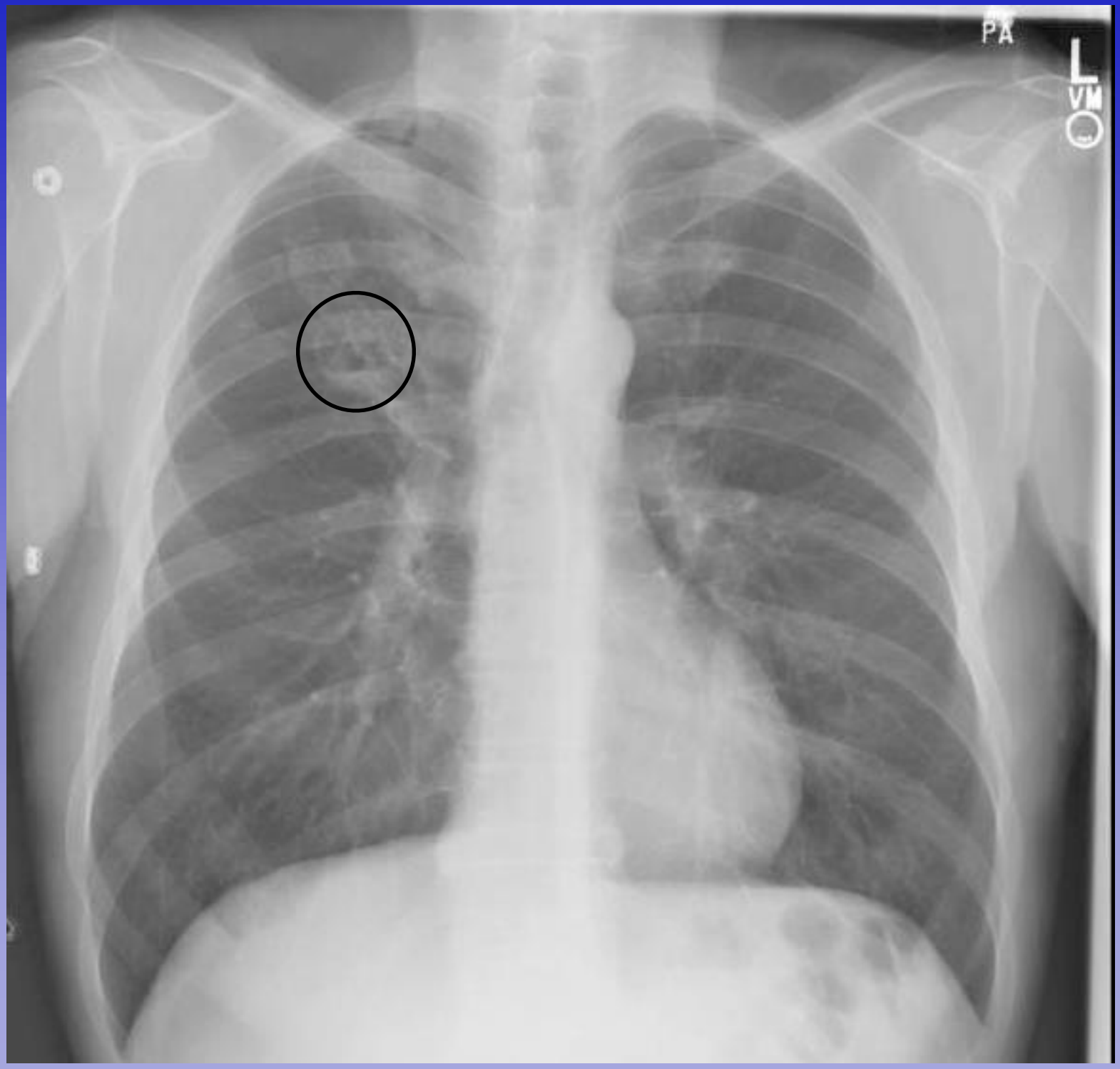
- Bronchoscopy with transthoracic biopsy
- Percutaneous fine-needle aspirate
  - false negative result in ~25-50%
- Video-assisted thoracotomy biopsy
- Open thoracotomy

Cavities

- Cavitations of previous nodules
- May be asymptomatic or symptomatic
  - Cough
  - Hemoptysis
  - Pleuritic chest pain
  - Positive sputum culture
- Less likely to close if >4 cm or present >1-2 years
- May become secondarily infected

Chest radiographs of coccidioidal cavities

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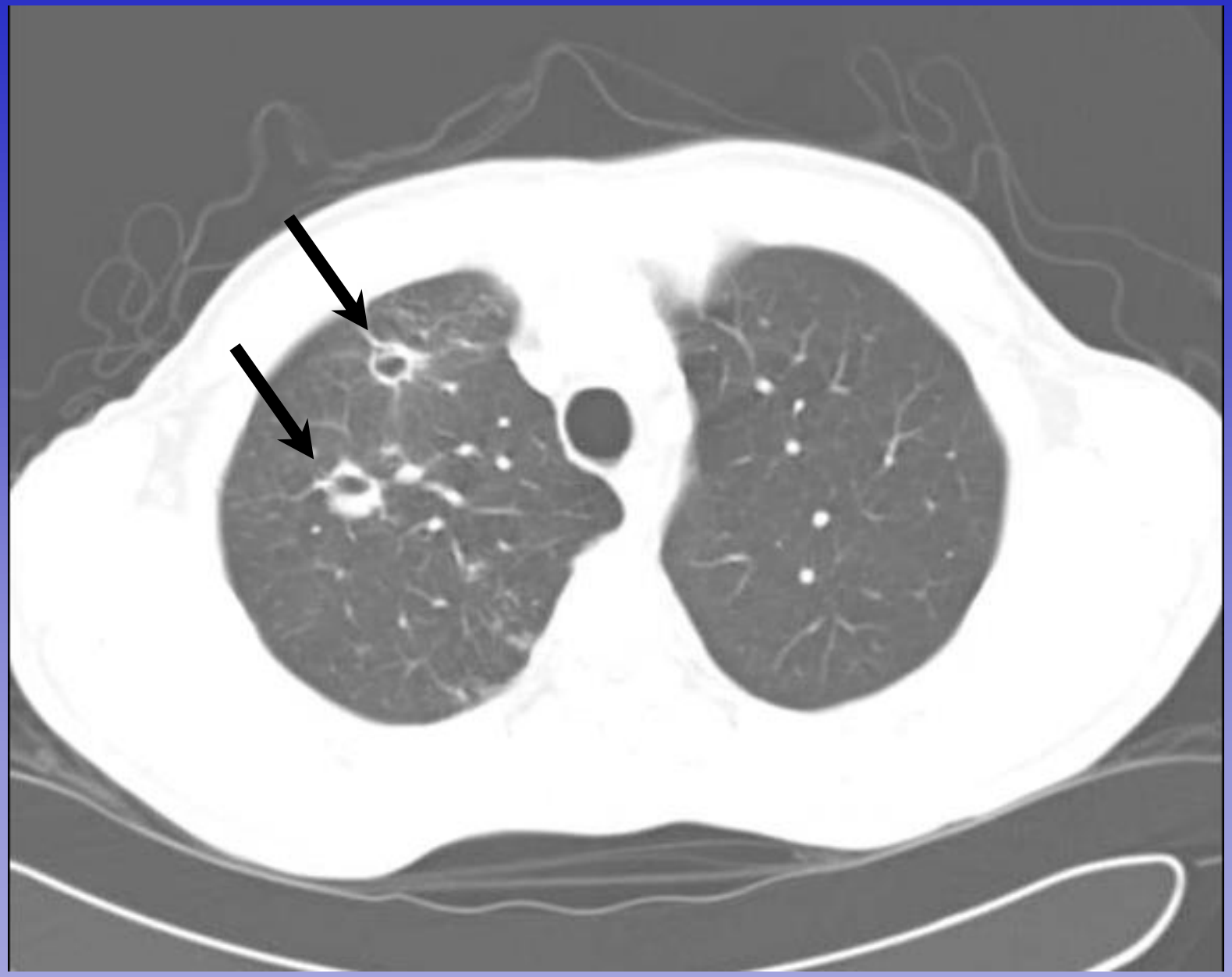
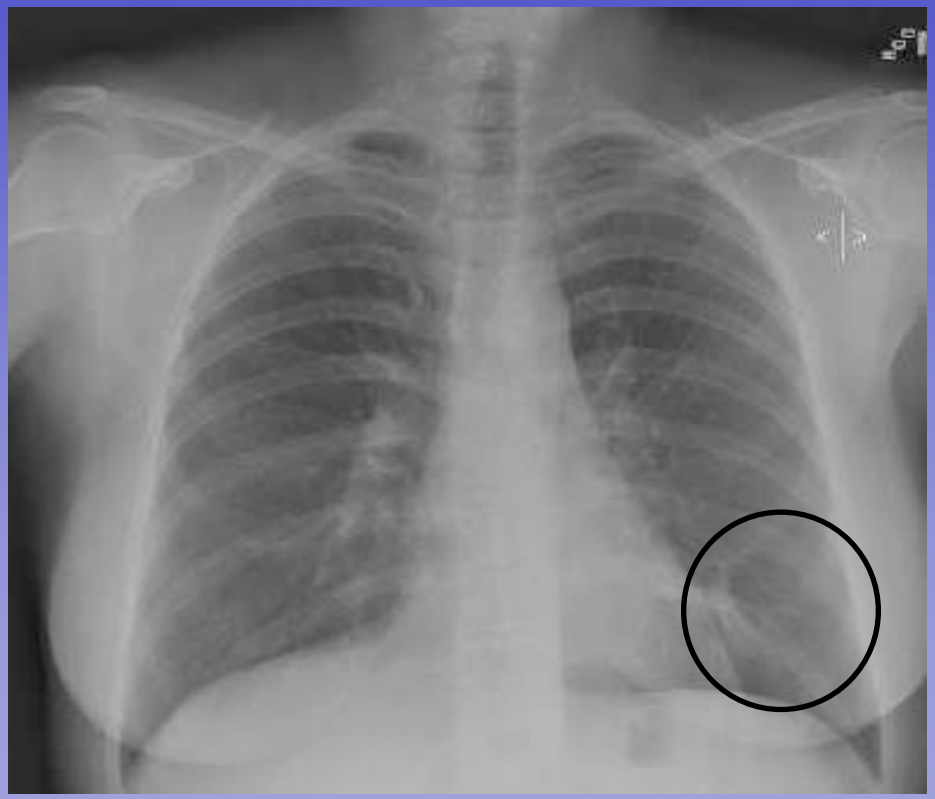
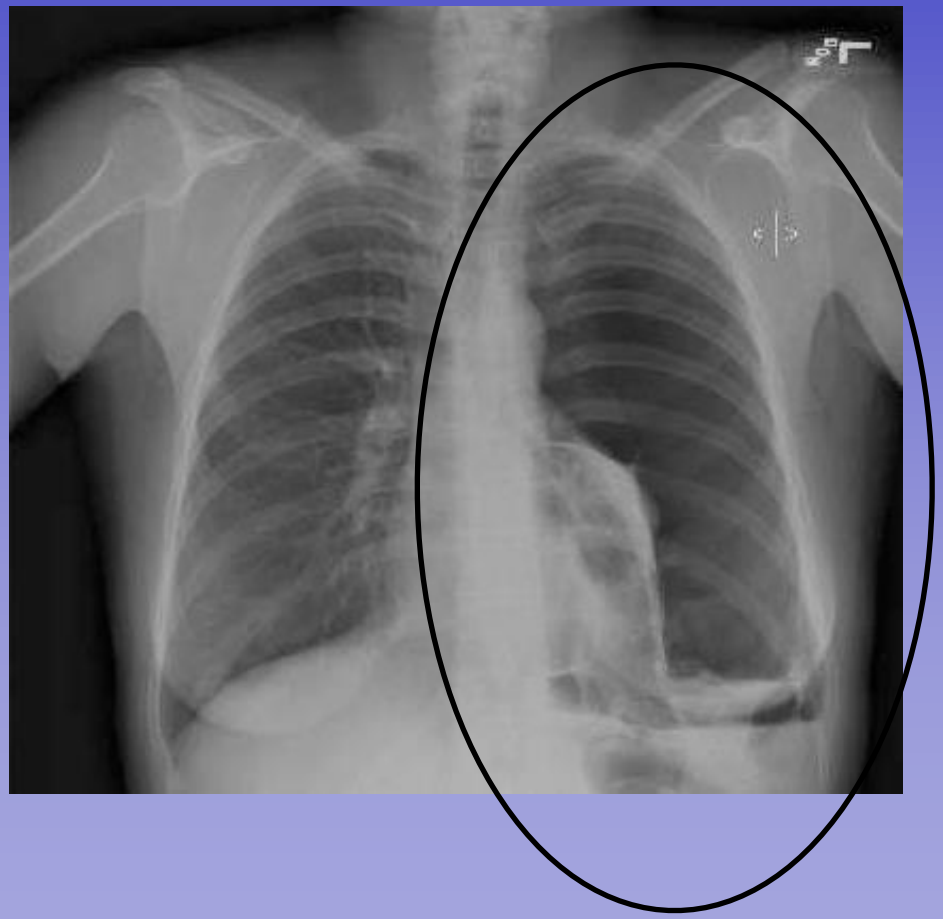


Pyopneumothorax

- Occurs when a subpleural cavity ruptures into the pleural space
- Results in lung collapse with pleural fluid collection
- Sudden dyspnea and pleuritic chest pain most common presentaton

Radiographic appearances of coccidioidal pyopneumothorax





CT scan of cavity associated with pyopneumothorax

Chronic pulmonary coccidioidomycosis

- Uncommon
- Occurs in patients with chronic lung disease
- Monitor course with sputum culture and serology

Chronic pulmonary coccidioidomycosis

Diagnosis

Issues of diagnosis

- Most cases are diagnosed based on positive serology
  - some patients, particularly with primary pneumonia, are never positive
- Sputum culture is may be positive if obtained
  - KOH is insensitive
- There is a need for more organism-based diagnostic tests
  - antigenic, genomic

Approach to the patient with suspected primary pulmonary coccidioidomycosis

- Obtain chest radiograph
- Obtain serology
- Obtain sputum for fungal culture
  - first morning specimen
  - obtain even if production is scant!
  - Alert the laboratory!
    - *Coccidioides* is a major laboratory hazard
- Follow and repeat testing

Treatment

Treatment of primary pulmonary coccidioidomycosis

- Most patients with primary pulmonary coccidioidomycosis will not require therapy
- Consider therapy if:
  - symptoms are on-going and not improving after 8 weeks
  - intense night sweats for 3 weeks
  - there has been a >10% loss of weight
  - infiltrate >1/2 lung or both lungs
  - prominent or persistent hilar adenopathy
  - IgG titer ≥1:16
  - inability to work
  - age > 55 years

Galgiani et al., Clin Infect Dis 2005; 41:1217

Treatment vs non-treatment of primary pulmonary coccidioidomycosis

- We performed a prospective, observational study of 105 patients with primary pulmonary coccidioidomycosis
- 54 were prescribed antifungals
- 51 were not
- Patients prescribed therapy had higher clinical severity scores
  - based on symptoms, coccidioidal IgG titer and culture

Ampel et al., Clin Infect Dis 2009; 48:172

Results

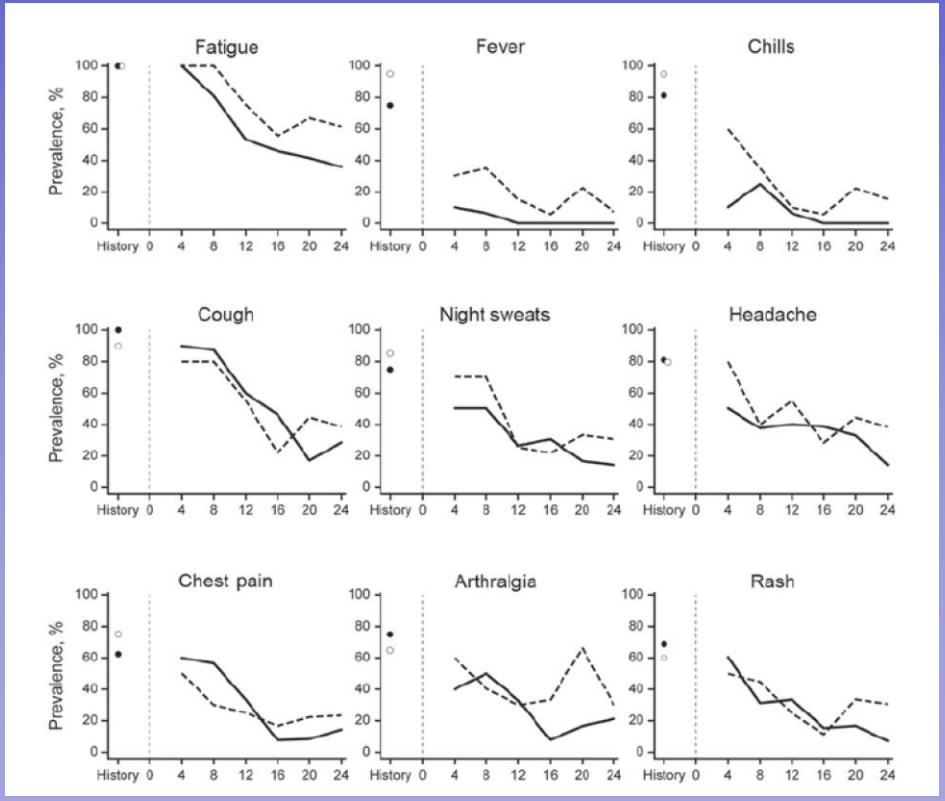
- There was no difference in rate of improvement between those treated and those not treated
- None of the untreated patients had any complications
- Two of the treated patients developed disseminated infection after prolonged courses of azole therapy

Characteristics of Patients with Mild to Moderate Primary Pulmonary Coccidioidomycosis

Janis E. Blair, Yu-Hui H. Chang, Meng-Ru Cheng, Laszlo T. Vaszar, Holenarasipur R. Vikram, Robert Orenstein, Shimon Kusne, Stanford Ho, Maria T. Seville, and James M. Parish

Emerg Infect Dis 2014; 20:983

- 36 patients with primary pulmonary coccidioidomycosis followed for 24 weeks. Twenty received antifungal therapy.



Conclusions

- If a patient with primary pulmonary coccidioidomycosis is already improving when seen, no antifungal therapy is indicated
- Therapy is indicated in those with persistent signs and symptoms of active pulmonary infection
  - should be continued at least 6 months
  - patients should be followed for at least 1 year after therapy is discontinued
- Antifungal therapy has not been shown to prevent subsequent dissemination and is not recommended

Primary pulmonary coccidioidomycosis in special hosts

- Patients with suppressed cellular immunity are at ↑ risk for severe or disseminated disease
  - HIV infection
  - 2nd & 3rd trimester of pregnancy
  - Patients on corticosteroids
  - Patients with allogeneic transplants
  - Patients on TNF-α inhibitors
- Most clinicians would treat

Sex, age, and race

- Males > females for symptomatic coccidioidomycosis
- Risk for symptomatic coccidioidomycosis increases as age > 60 years
- Black men are at increased risk for disseminated disease
  - Filipino men appear to also be at increased risk
  - There is no obligation to start therapy but close follow-up is advised
    - every 6 - 12 weeks for the 1st year

Flynn, et al. N Engl J Med 1979 301:358-61.
Rosenstein, et al. Clin Infect Dis 2001; 32:708-15.
Crum, et al. Medicine (Baltimore) 2004; 83:149-75.

Nodules and cavities

- Nodules are generally benign sequellae of primary pulmonary infection
  - do not require therapy
  - they do not enlarge over time
    - if they do, work-up for malignancy
- Cavities are more problematic
  - consider therapy if
    - persistent cough
    - hemoptysis
    - pleuritic chest pain
  - be aware of secondary infection
    - air-fluid level
  - consider surgical extirpation if
    - non-closure after 1-2 years
    - >4 cm

Which antifungal?

- Oral azoles have supplanted amphotericin B in all but the most severe cases
- Fluconazole or itraconazole?
  - fluconazole well tolerated, well absorbed, fewer adverse reactions
  - but itraconazole may be more active
    - Galgiani et al, Ann Intern Med 2000; 133:676
- Newer azoles
  - Posaconazole and voriconazole reserved for non-responsive cases