



Treatment of Coccidioidomycosis

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Disclosures

- No conflict of interest to disclose
- Nearly all medications for coccidioidomycosis discussed will be FDA “off-label”
- The only FDA approved medications with an indication for coccidioidomycosis
 - Ketoconazole
 - Amphotericin B deoxycholate

Objectives

- At the conclusion of this talk, the audience will be able to:
 - Describe the management of chronic pulmonary and disseminated coccidioidomycosis.
 - List the FDA approved antifungal therapies for the management of coccidioidomycosis.
 - Discuss alternative strategies in patients who are intolerant of or not improving with standard antifungal treatment.

Treatment of Coccidioidomycosis

- Begins with a careful history & exam
- Want to define the severity, location and chronicity of infection
- Define the presence of extrapulmonary infection
 - Skin and soft tissues
 - Bone and joints
 - Meningeal infection

No Antifungal Treatment

- Mild-moderate primary pulmonary coccidioidomycosis (healthy host)
- No treatment is common early in 1° infection
 - ie, levofloxacin for presumed bacterial CAP
- Most resolve without sequelae
- VA study
 - Approx 50% pts with 1° pulm cocci given tx on basis of clinical severity
 - Complications only seen in tx group after tx stopped

Therapeutic Agents

- Amphotericin preparations
 - Amphotericin deoxycholate
 - Lipid associated amphotericin
- Azoles
 - Ketoconazole
 - Fluconazole
 - Itraconazole
 - Voriconazole
 - Posaconazole
- Future: Nikkomycin Z, others

Amphotericin B

- First effective med vs. coccidioidomycosis
- IV, IT, intralesionally, intraarticular, not oral
- IV not effective for cocci meningitis
- Perceived to have more rapid onset of action
- Some experts prefer for rapidly progressing infection
- Amphotericin B deoxycholate
 - 0.5 – 1.5 mg/kg IV daily or every other day
 - Infusional toxicity: fever, rigors, hypotension, etc
 - Cumulative toxicity: creatinine ↑, K ↓, Mg ↓

Lipid associated Amphotericin B

- Developed as a safer alternative to AMB
- 3 formulations available in US
 - ABCD: Ampho B Cholestyrl Sulfate Complex
 - ABLC: Ampho B Lipid Complex
 - Liposomal Ampho B
- Acute febrile reactions less frequent, still occur
- All have lower renal toxicity
- Expensive ≈\$400 per day
- ≥ 2-5 mg/kg IV daily
- No data demonstrates improved efficacy vs. coccidioidomycosis

Azoles

- Relative lack of toxicity
- Oral bioavailability
- Tolerable for short or long treatment courses
- Formal studies show azoles are efficacious
- No studies show clear superiority among azoles

Fluconazole

- Good oral bioavailability
- 400-800 mg daily
- Useful to treat many/most coccidioidal infections
- Well tolerated
- Relatively inexpensive
 - Previously ¢, now \$
- Infrequent hepatitis
- Monitor liver enzymes periodically

Itraconazole

- Oral availability
- Requires gastric acid for absorption
- Requires measurement of serum levels
- Black Box warning
 - CHF, Drug interactions
- 200 mg twice or thrice daily
- ≈\$15-20 per day
- Well tolerated
- Has shown superiority vs. flu in skeletal cocci

Voriconazole

- In vitro susceptibility better than itraconazole
- Good tissue & CNS penetration
- Has been used in salvage cases, often, but not invariably, successfully
 - In salvage, 67% improved after 6 months
- 200-300 mg po or IV BID
- ≈\$40-250 per day (vs \$4 flu)
- Phototoxicity
- Transient visual changes

Voriconazole

- Therapeutic drug levels should be performed.
 - Oral bioavailability excellent independent of gastric acid
 - High fat meal ↓ levels
 - Metabolism by CYP219 variable
 - Inhibits CYP 219, 2C8/9, 3A4
(Multiple drug interactions)
 - Inter- intra subject variation
 - Levels may ↓ with time
 - Levels correlate w efficacy in other fungal infections

Posaconazole

Animal studies ?fungicidal activity

- 400 mg BID liquid or 300 QD pill
- Requires fatty meal for absorption
- Saturable absorption
 - In order to ↑ dose delivered, need to ↑ frequency of doses
- Highly protein bound
- Penetration into CNS variable
- ≈\$120 per day (vs fluconazole \$4)

Posaconazole

- 17/20 (85%) satisfactory response in open label, 1^o tx of chronic pulm & nonmeningeal 400/d
Catanzaro 2007 CID
- 11/15 (73%) success in chronic pulm or disseminated patients failing other standard antifungal regimens.
Posa 800 mg/day Stevens 2007 Chest
- 12/16 (75%) pts improved w posaconazole in salvage therapy
Kim CID 2011
- 5 /6 improved with disseminated cocci failing other therapy
Anstead 2005 CID
- Other single cases reported with success

Ketoconazole

- Inexpensive azole option where resources limited.
- 400 mg daily
- Interferes with testosterone production and cortisol responses
 - Male oligospermia, gynecomastia
 - Female menstrual irregularities
- FDA: when other effective antifungal therapy is not available or tolerated and potential benefits are considered to outweigh the potential risks

Nikkomycin Z

- Currently under development
- Inhibitor of chitin synthase, a major component of fungal cell wall
- In vitro studies show potential for cure
- Phase I: No safety concerns
- Phase II: 2015 early pulm cocci
- www.vfce.arizona.edu

Nikkomycin Z

- In vivo studies show promise
 - 7 dogs improved
 - 3 dogs resolved cocci pneumonia

Shubitz et al 2013 Medical Mycology

- www.vfce.arizona.edu

....But what about...?

Newer Azoles

- Ravuconazole
- Isavuconazole

Ecchinocandins

Echinocandins

- No good in vivo studies to suggest efficacy in coccidioidomycosis as a sole agent.
- One animal study suggests efficacy when combined with amphotericin

Gonzalez 2007 J Antimicrob Chemother

- Limited case reports using combination therapy show mixed results

Park 2006 BMC Inf Dis

Antony 2004 CIM

Hsue 2004 J Antimicrob Chemother

- No recommendation for use at present.

Combination Therapy?

- Not uncommonly observed azole + AMB in rapidly progressing illness
- No formal studies addressing the role of combination antifungal therapy for synergy
- Hypothetical risk of antagonism raised concern in other fungal organisms, but antagonism has not been clinically demonstrated.
- Further study is needed

Surgical Debridement

- Occasionally surgery plays important role in control of infection
- Situations where surgery could be considered:
 - Large abscess
 - Progressively enlarging lesions despite medical treatment
 - Destructive lesions
 - Presence of boney sequestration
 - Unstable spine
 - Impingement on critical structure or tissue
 - Recurrent lesion after successful treatment

Treatment Guidelines for Coccidioidomycosis

- Infectious Diseases Society of America
- Revised November 2005
- Revision anticipated 2015
- <http://www.journals.uchicago.edu/doi/pdf/10.1086/496991>
- Cases to illustrate these guidelines

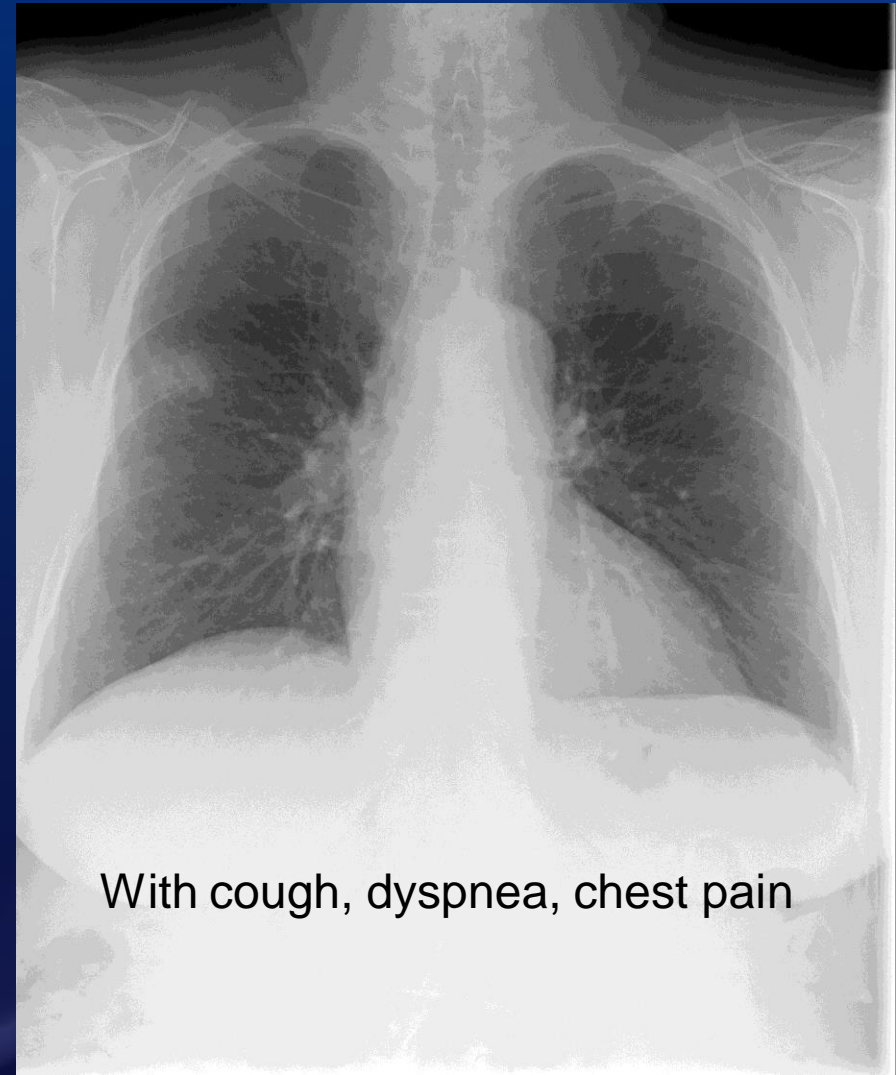
Case 1: Treatment Acute Pulmonary Coccidioidomycosis

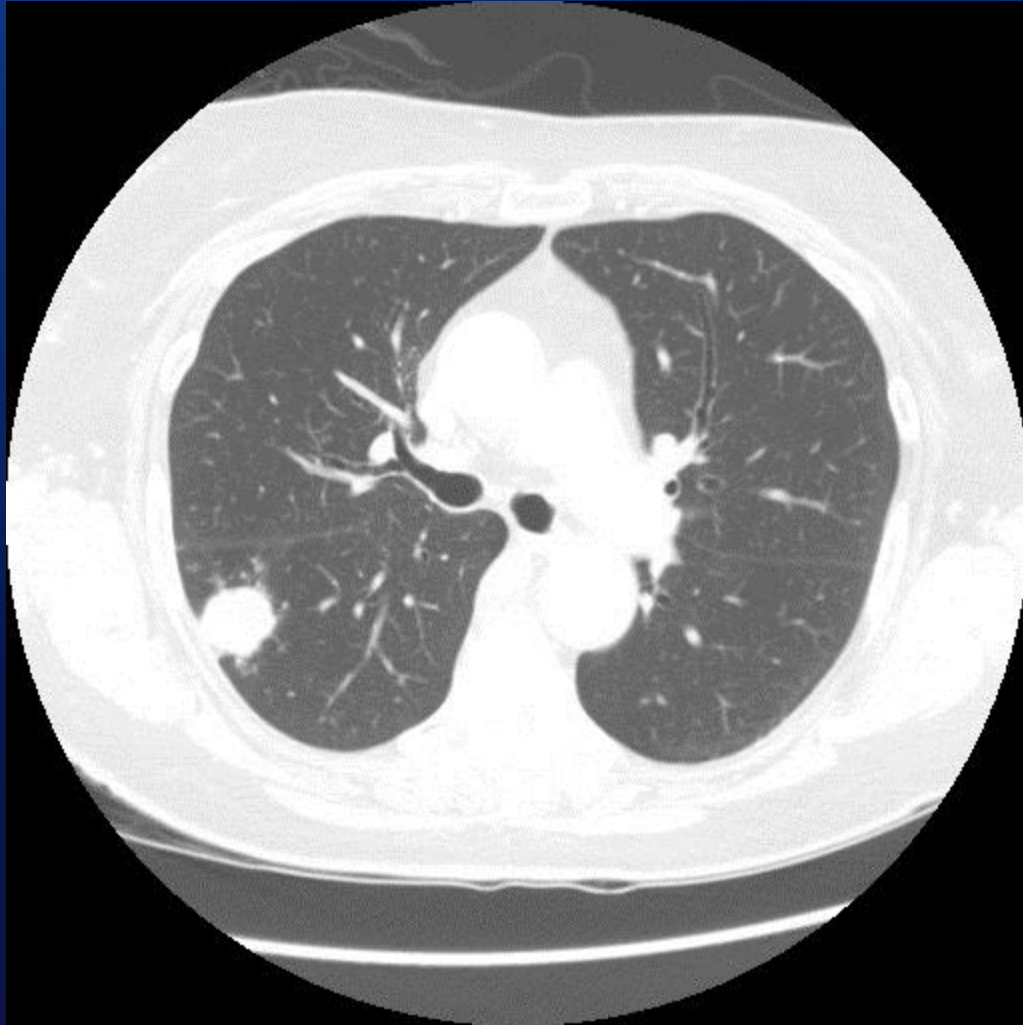
- 74 year old woman
- HTN, hyperlipidemia
- Subacute onset of:
 - HA
 - Cough, green sputum
 - Dyspnea, pleuritic and non pleuritic chest pain
 - Malaise and fatigue
 - Chills and night sweats, no fever

Case 1: Acute Pulmonary Coccidioidomycosis

- WBC 10.2
 - 67% PMNs, 18% Lymphocytes, 8% eosinophils
- ESR 68
- Cocci (EIA) IgG and IgM negative
- CXR performed

Acute Pulmonary Coccidioidomycosis





Case 1: Acute Pulmonary Coccidioidomycosis

- Clinically improves
- Follow up serology
 - EIA IgG+, IgM+
 - CF 1:8
 - ID IgG+
- Diagnosed with acute pulmonary coccidioidomycosis
- Not treated, symptoms slowly resolved
- CT scan nodule followed, stable

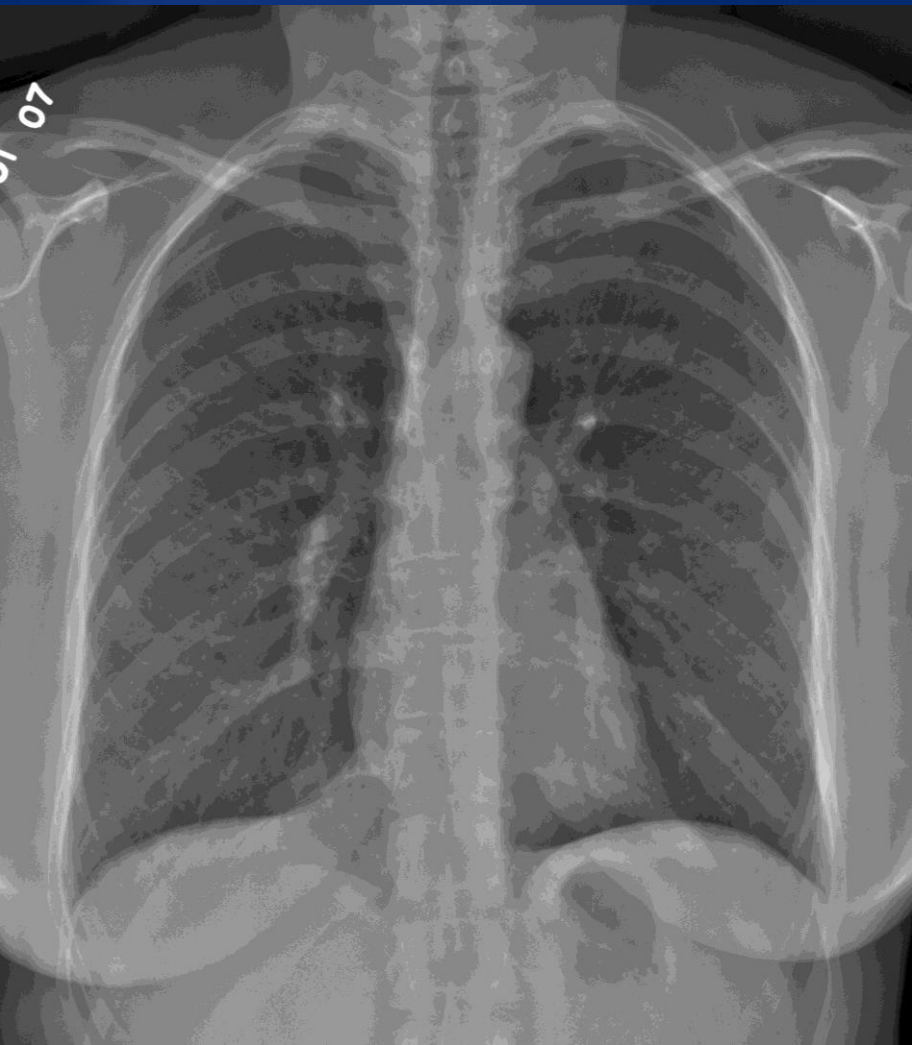
Treatment of Acute Pulmonary Coccidioidomycosis

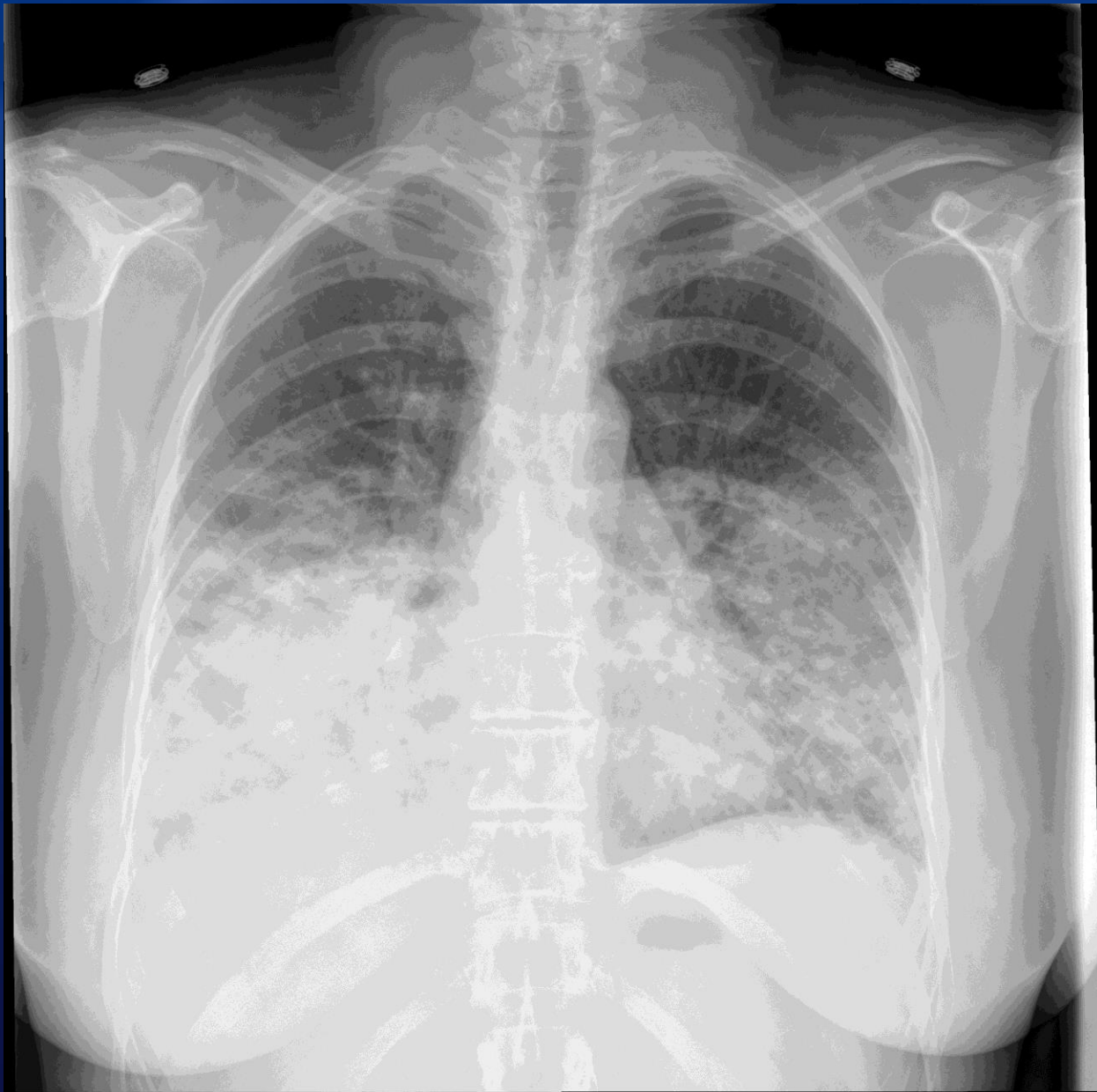
- Mild, absent or resolved symptoms
 - No antifungal therapy
 - Periodic reassessment
- For immunosuppressed patients
 - Treatment may be considered
 - Follow closely

Case 2: Acute Pulmonary Coccidioidomycosis

- 48 year old woman
- Healthy
- Landscaping her AZ winter home
- 1 week later, fever, chills, night sweats, cough, dyspnea, severe headache, fatigue, myalgia
- Hypoxic, septic
- Admitted to the hospital

Case 2: Acute Pulmonary Coccidioidomycosis







Case 2: Acute Pulmonary Coccidioidomycosis

- Required intubation, mechanical ventilation
- Received broad antibiotics
- Sputum culture *Coccidioides*
- Serology (EIA) IgM and IgG positive
- Ambisome 5mg/kg given
- Later changed to fluconazole 400 mg daily

Case 2: Acute Pulmonary Coccidioidomycosis

- Discharged on fluconazole and O₂
- 1 month later, she was recovering, beginning her exercise program, improving daily.
- 3 months later, complete resolution of symptoms

Treatment Guidelines

1° Pulmonary Coccidioidomycosis

- Mild, absent or resolved symptoms
 - No antifungal therapy
 - Periodic reassessment
 - Immunosuppressed: consider treatment, follow closely
- Moderate or severe infection
 - Fluconazole 400 mg/d x 3-6 mo
 - Itraconazole 200 mg BID
 - Liposomal AMB if rapidly progressing

Treatment Guidelines

1° Pulmonary Coccidioidomycosis

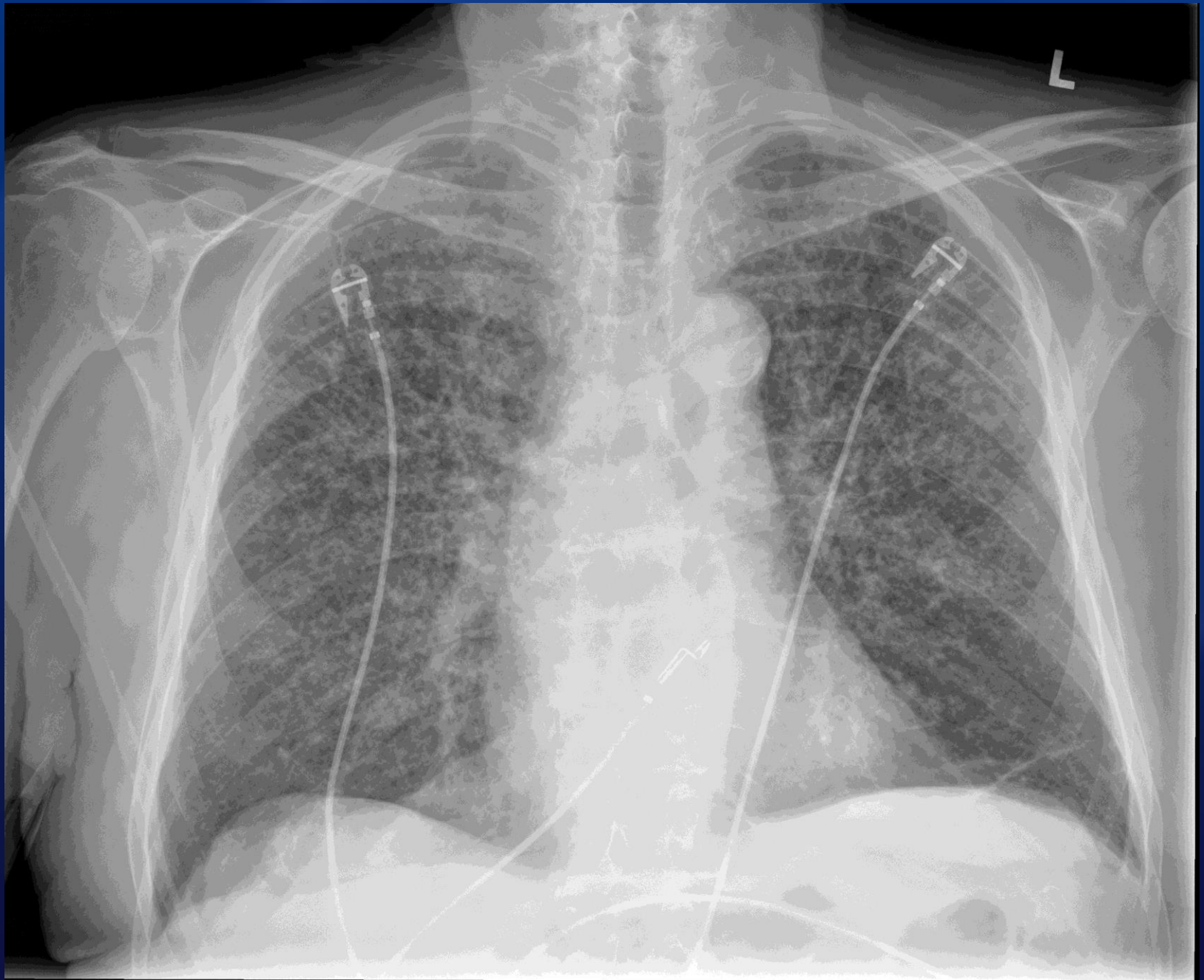
- BUT: what constitutes moderate or severe infection?
 - Symptoms > 2 months
 - Weight loss >10%
 - Night sweats > 3 weeks
 - Pulm infiltrate >50% of lung
 - Inability to work
 - Age > 55
 - CF titer > 1:16
 - Sick enough to hospitalize

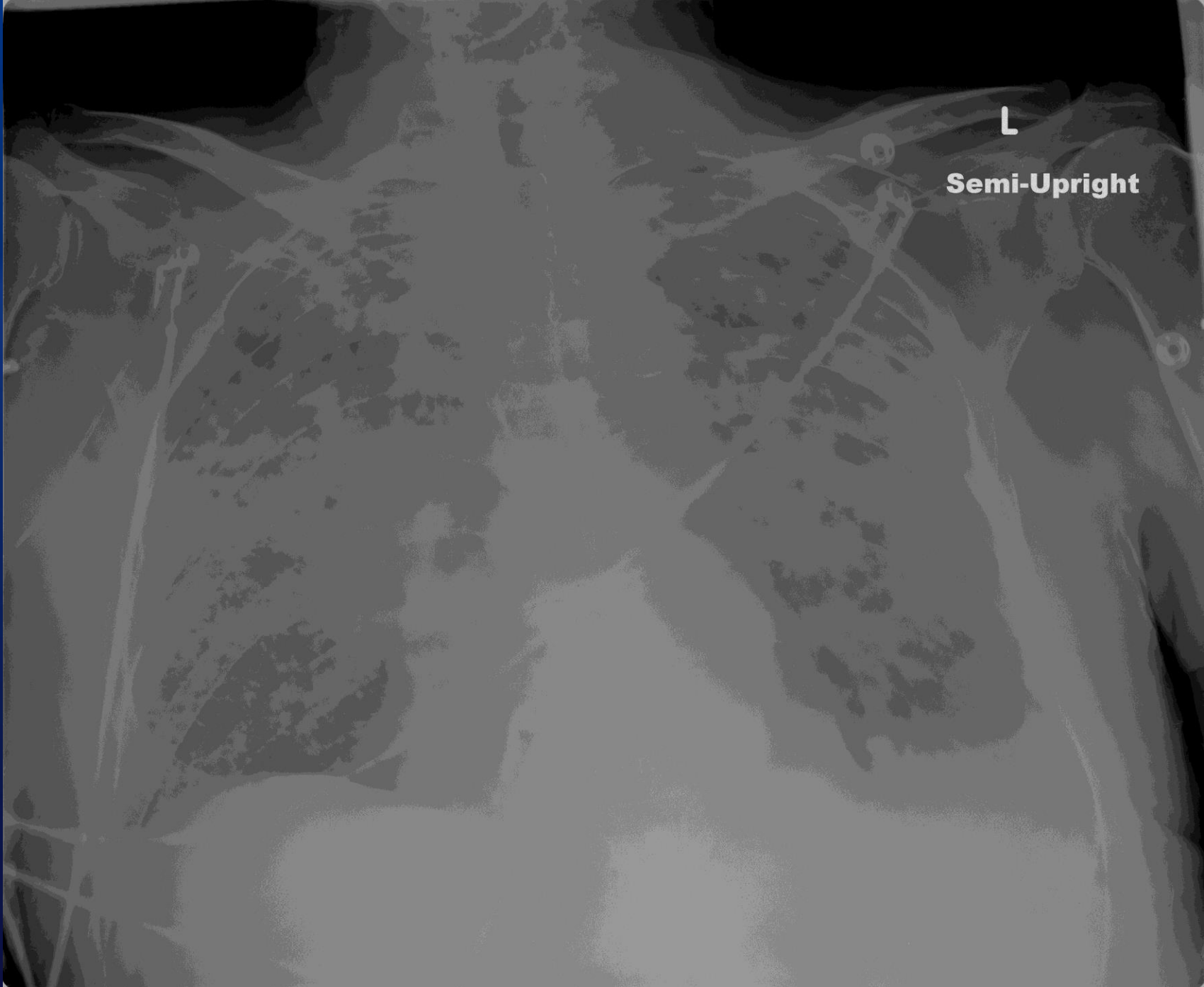
Treatment of 1° Pulmonary Coccidioidomycosis Summary

- Many healthy people do well without treatment.
 - Monitor and follow up
- Treatment of persons with immunosuppression should be considered for treatment
- Moderate-Severe infection
 - Treat with amphotericin if rapid progression, then deescalate to oral azole
 - Treat entire episode oral azole
 - Duration 3-6 months

Case 3 Diffuse Coccidioidal Pneumonia

- 84 year old male
- Hx myasthenia gravis on prednisone and mycophenolate mofetil
- Lives in Hawaii but gets neurological care at Mayo Clinic Arizona
- 2 weeks fever, cough, dyspnea, confusion
- Flew to AZ for evaluation





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Semi-Upright

Case 3 Diffuse Coccidioidal Pneumonia

- Miliary pattern on chest radiograph
- Placed empirically on IV azole, 4-TB medications
(Family refused amphotericin)
- Respiratory failure
 - Bipap (intubation refused)
- Cocci serology
 - EIA igG+, IgM-
 - CF 1:32, ID IgG+, IgM-
 - Cultures of sputum, urine all positive for *Coccidioides*

Case 3 Diffuse Coccidioidal Pneumonia

- After cocci diagnosis was established
- Fluconazole 800-600 mg daily
- Markedly improved after a 3 week hospitalization
- Continued fluconazole

Diffuse Coccidioidal Pneumonia

- Treat at least 12 months
- May treat longer if immunosuppressed
- Mild symptoms
 - Fluconazole 400 mg/d
 - Itraconazole 200 mg twice/d
- Moderate-severe symptoms
 - Consider initiating therapy with AMB or LAMB until clinically stable, then azole

Case 4: Chronic Coccidioidomycosis

- 26 year old healthy Caucasian woman
- 1972 fever, cough, pain in shoulder
 - Dx coccidioidomycosis, no treatment, sx improved
- Felt ok, progressively abnormal CXR
- 1994
 - Cough recurred
 - Sputum culture +, serology +
 - AMB 5.5 months, felt better

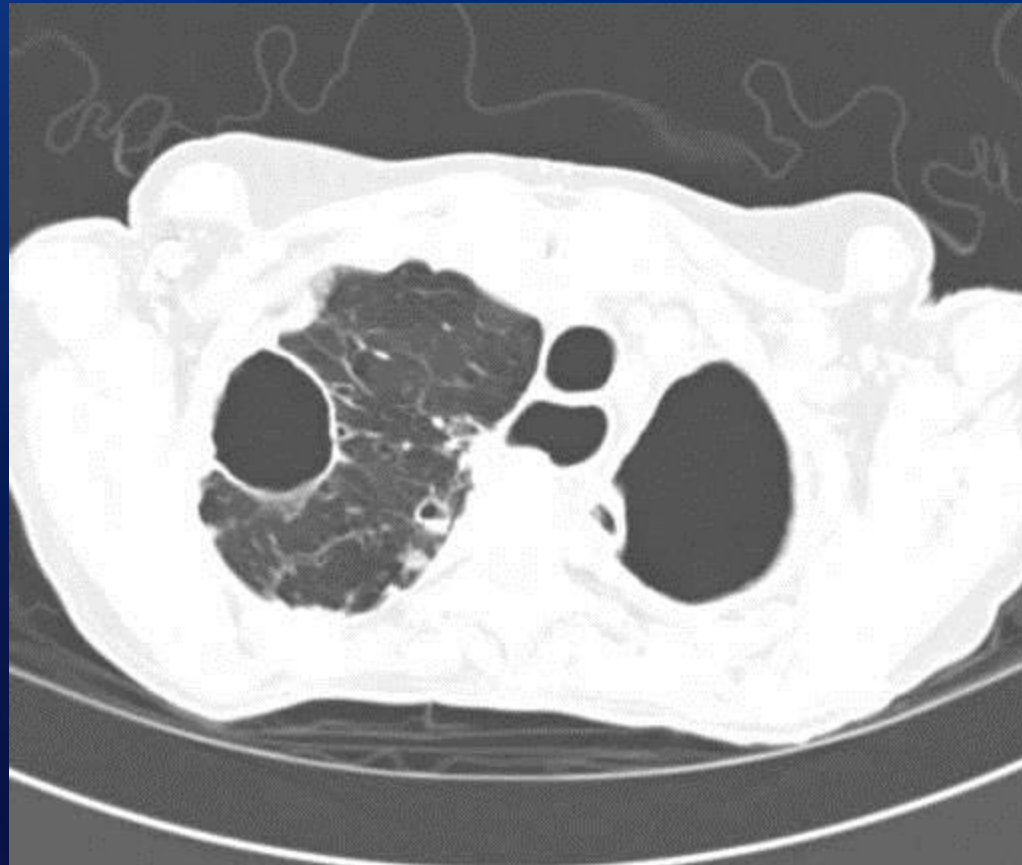
Case 4: Chronic Coccidioidomycosis

- 1995-2000 Cough recurred
- Various trials of fluconazole, no improvement
- 2000
 - Posaconazole trial
 - Symptoms improved
 - Adverse effects of medication, discontinued after 3 years
- 2004 Cough recurred
 - CF 1:128
 - Chronic itraconazole, symptom control is acceptable, but not optimal.

Case 4: Chronic Coccidioidomycosis



Chronic Fibrocavitary Coccidioidal Pneumonia





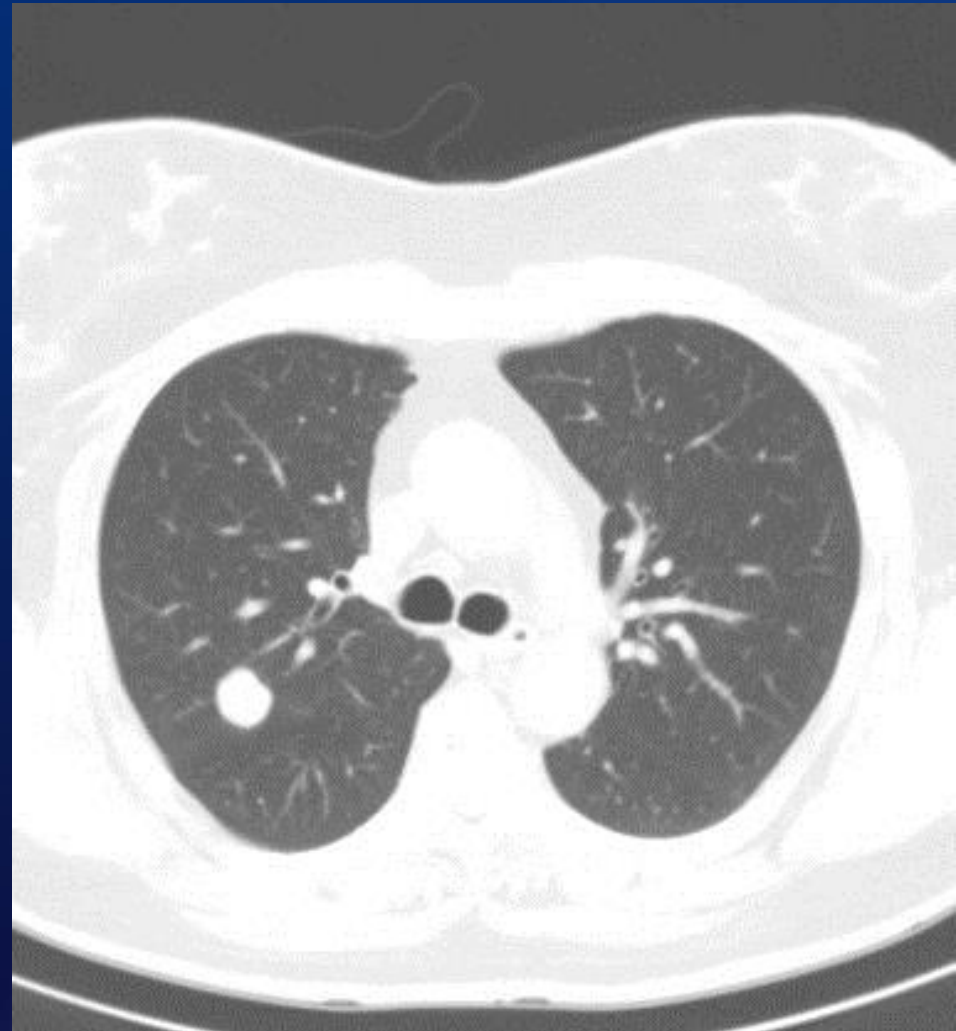


Chronic, Progressive Fibrocavitary Coccidioidomycosis

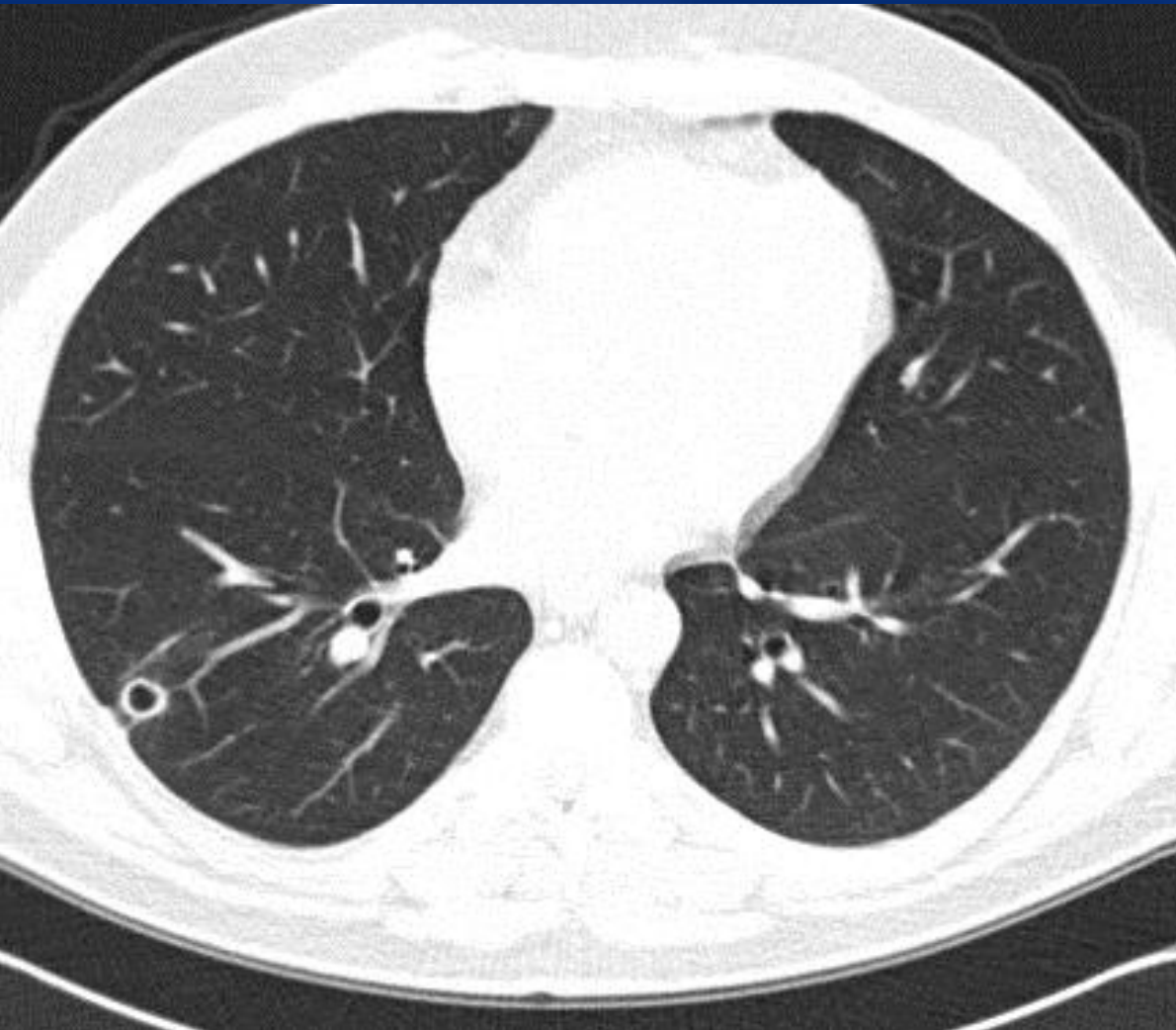
- Treat at least 1 year or longer
- Options
 - Fluconazole 400 mg/d
 - Itraconazole 200 mg twice/d
 - Or AMB or LAMB
 - Or, trial of newer azole or study enrollment

Case 5: Asymptomatic Lung Nodule

- 67 yr woman
- 10 year AZ visitor
- Cardiac chest pain
- Incidental Rt. nodule
- Biopsy +
- Serology negative
- No treatment offered



Case 6: Asymptomatic Cavity



- 35 yr man
- Transient respiratory illness, resolved
- Routine physical
- Cavity noted
- Biopsy +
- CF 1:8
- Not treated
- Followed closely

Asymptomatic lung nodule or cavity

- No treatment needed
- Observe for stability

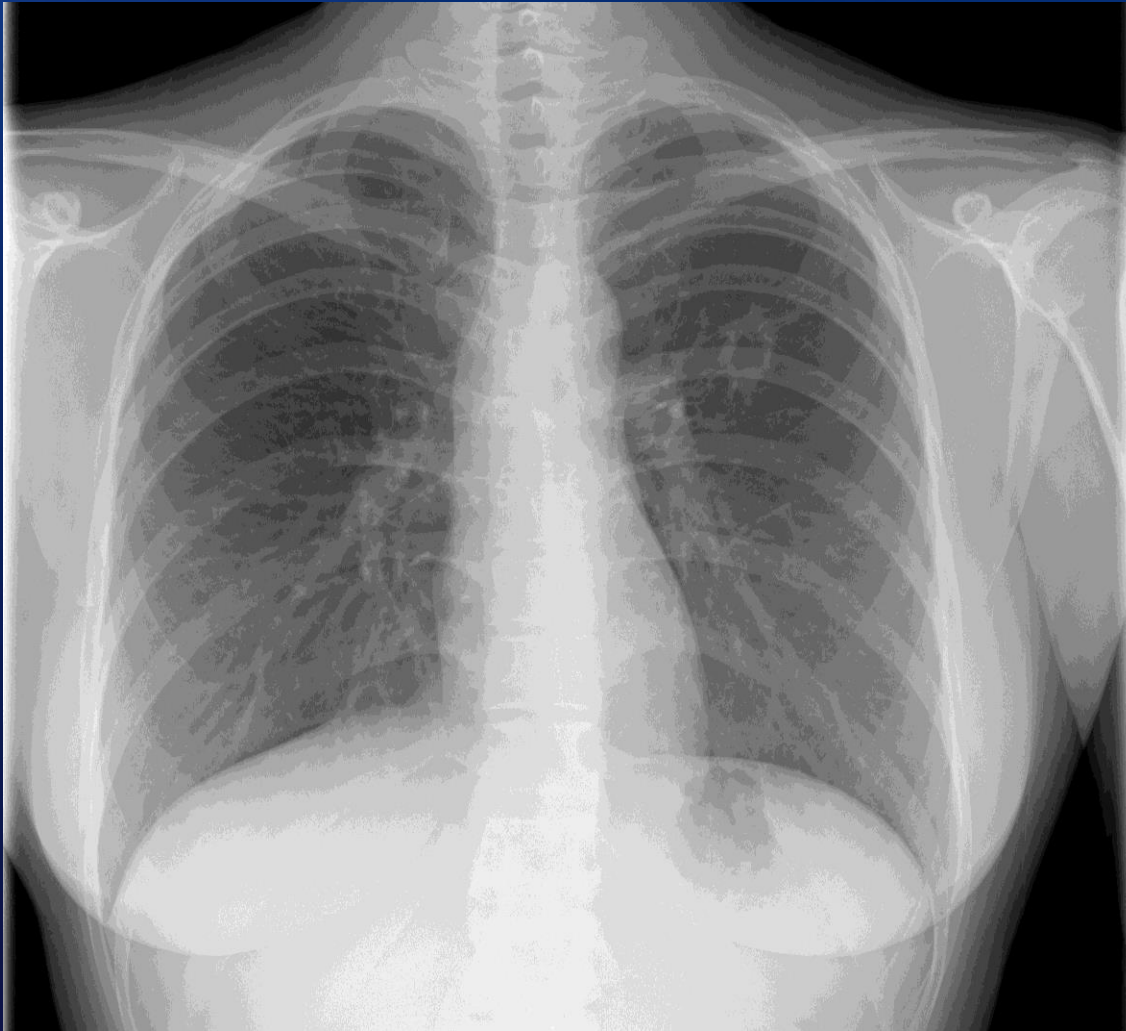
Case 7: Symptomatic Lung Cavity

- 34 year old healthy Chinese woman
- AZ resident x 6 years
- 4 months pregnant
- Hemoptysis
- Hospitalized elsewhere

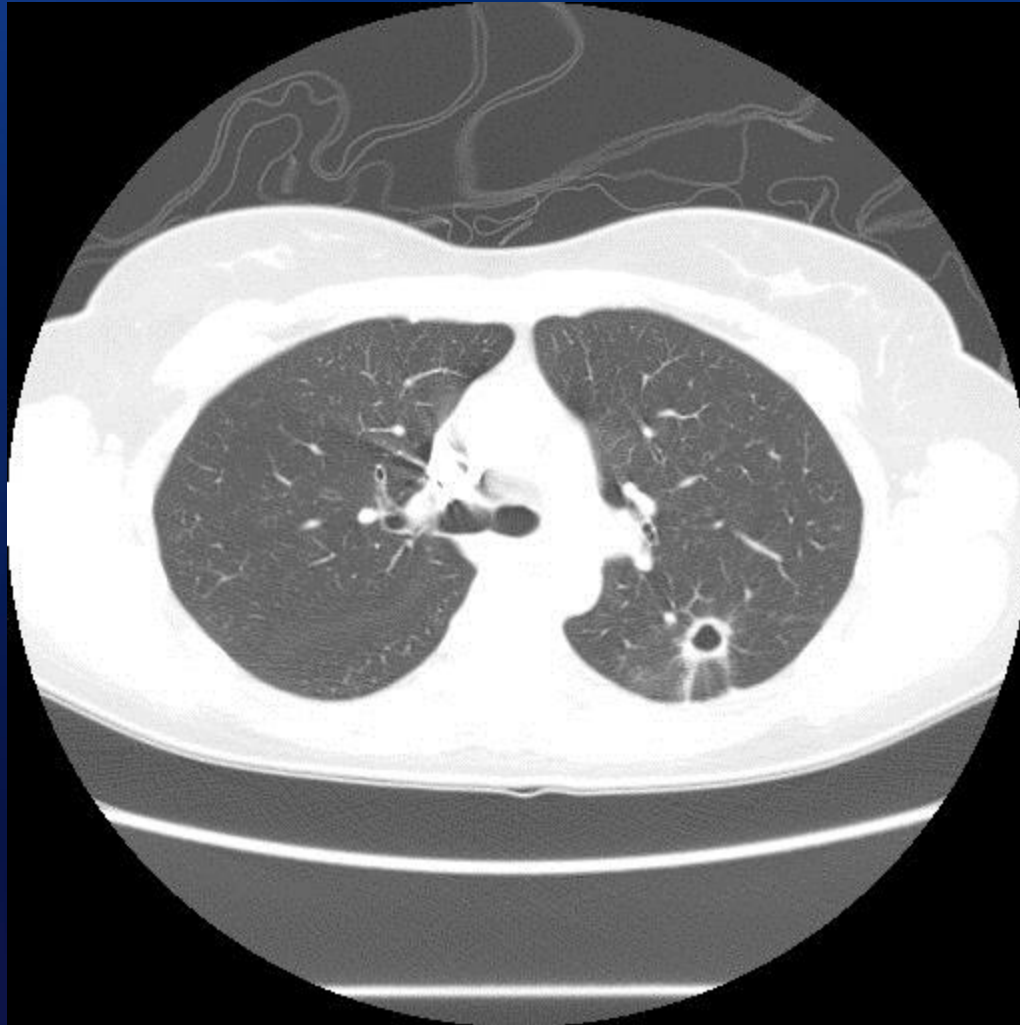
Case 7: Symptomatic Lung Cavity

- Cocci serology positive
- Imaging showed a cavity
- Uncertain other diagnostic workup
- Amphotericin B until shortly prior to delivery.
- Hemoptysis resolved
- Following delivery, she opted for no treatment

Case 7: Symptomatic Lung Cavity



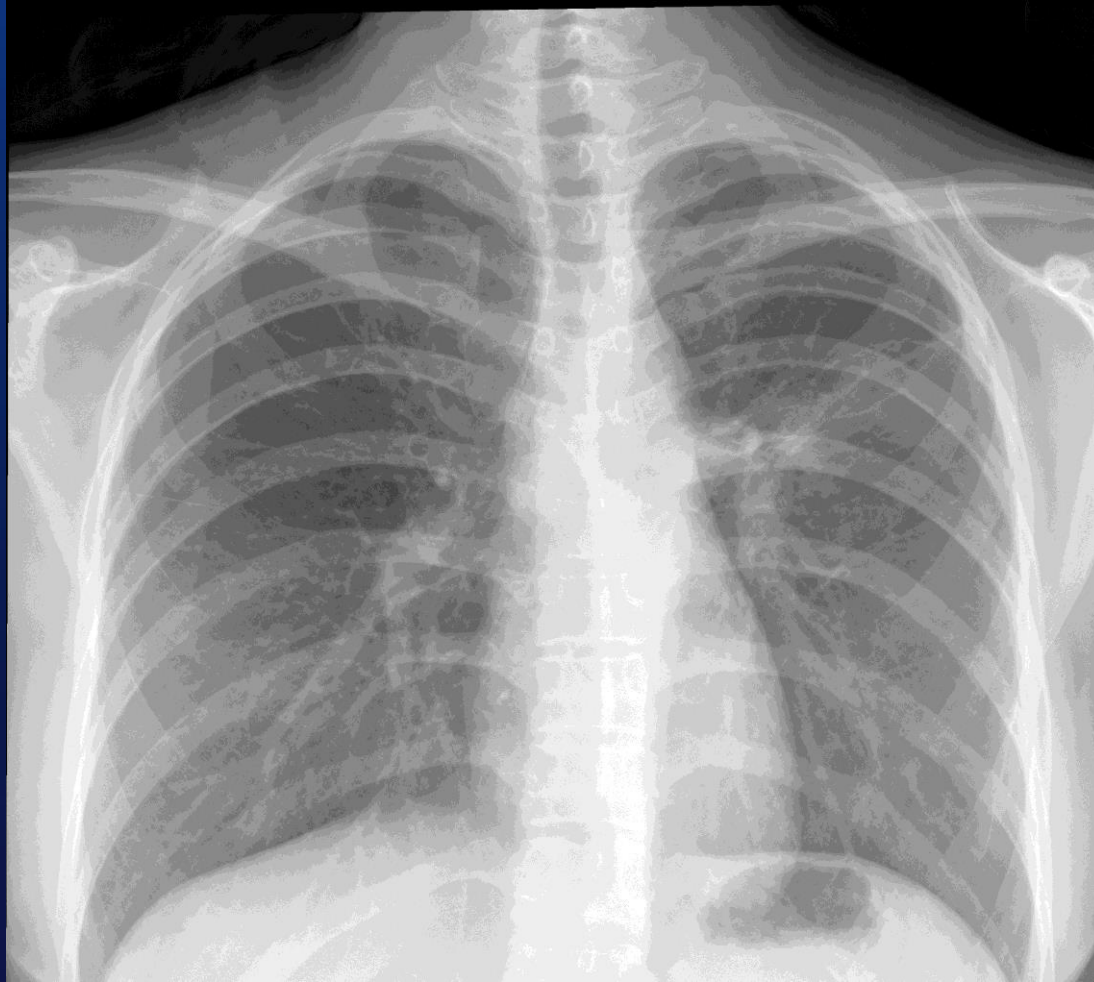
Case 7: Symptomatic Lung Cavity



Case 7: Symptomatic Lung Cavity

- 2 months later, hemoptysis
- Fluconazole various doses (400-800 mg daily)
- Hemoptysis continued
- Later voriconazole begun
- Episodic hemoptysis continued
- Left upper lobe and left middle lobe wedge resections.
- Voriconazole x a few months, then stopped.
- Hemoptysis resolved & never recurred.

Case 7: Symptomatic Lung Cavity, resected



Symptomatic cavity

- Optimal duration of treatment not established
- Options
 - Fluconazole 400 mg/d
 - Itraconazole 200 mg BID
 - Escalate azole, if needed
 - Consider surgical resection

Special Populations

- Pregnancy
 - Avoid azoles; FDA category D
 - (1st trimester is time of highest risk)
 - AMB
- Immunosuppression
 - May need longer treatment
 - May need to decrease or stop immunosuppressant
 - May relapse
- Transplant
 - Lifelong secondary prophylaxis

Skin and Soft tissue infections

Examples.....







Skin/Soft tissue Dissemination

- Duration of treatment: prolonged
 - To resolution of abnormality then longer, follow serology
- Prospective studies: 60-90% efficacy
- Relapses common 20-30%
- Options
 - Fluconazole 400-800 mg/d
 - Itraconazole 200 mg BID-TID
 - AMB or L-AMB
 - May require debridement or resection







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Skeletal Infection

- Prospective trials 60-80% azole efficacy
- Itraconazole superior to fluconazole in one study
- Relapses common
- Debridement recommended for most
- Options
 - Itraconazole 200 mg BID-TID
 - Fluconazole 400-800 mg daily
 - AMB or lipid associated AMB
- Prolonged duration
 - Minimum of radiographic-serological resolution

Case 8: Coccidioidal Meningitis

- 34 year old health man
- Oct. 2007 intermittent cough
- Followed by intermitted sinus headaches
- Dec.2007 progressive headache, N/V
 - CT and MRI head performed
 - CSF exam
 - TNC 670 4%PMN, 61%lymphs, 26%eos
 - TPro 126, Glu 26
 - Cocci serology + in CSF and in serum
- Fluconazole 800 then 1200 mg daily with slow improvement

Treatment Coccidioidal Meningitis

- Fluconazole \geq 800 mg daily
- May decrease to 400-600 mg daily after improvement
- Shunt for hydrocephalus
- Alternatives
 - Intrathecal AMB
 - Newer azole
- Lifelong treatment needed

Summary

- Guidelines for treatment of coccidioidomycosis have been written, to be periodically updated.
- <http://www.journals.uchicago.edu/doi/pdf/10.1086/496991>
- Many infections do not require treatment.
- Every infection needs to be assessed for location, extent and chronicity of symptoms
- Treat according to location and characteristics of infection.
- If treatment needed, most infections can be treated with azoles

Summary, cont.

- Fluconazole and itraconazole most often used
- Voriconazole, posaconazole reserved for salvage situations at this time.
- Nikkomycin Z under development
- Much more study is needed.

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