

Coccidioidomycosis...

“Valley Fever” Update—2023

Diagnosis and Therapy

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“At risk” Coxy activities



Fomite-transmitted coccidioidomycosis in an immunocompromised child.

- 3 yr old child undergoing Rx for bilateral Wilm's tumor developed disseminated coccidioidomycosis
- No travel outside Washington DC
- Grandfather recently arrived from Arizona..construction on property
- Brought “dusty” suitcase and “dirty” sneakers



Stagliano D, et al. *Pediatr Infect Dis J.* 2007 May;26(5):454-6.

Coccidioidomycosis Outbreak among United States Navy SEALs -- Coalinga, California

- **6- week training period in endemic area**
 - Extensive exposure to soil
- **10/22 (45%) developed + serology**
 - All pts were symptomatic
 - 50% had abnormal CXR
 - No *E. nodosum*, rash or dissemination
- **5 pts treated with fluconazole...all recovered**



Coccidioidomycosis in pts with Diabetes

- **329 pts with Coxy in Arizona
(44 diabetes; 285 non-diabetic)**
- **Diabetic pts...**
 - **More likely to have relapsing or cavitory disease**
 - **Trend (p = .09) towards higher dissemination,
especially in pts with poor glucose control**

In general, diabetic pts have more complicated coxy with higher cavity rate and decreased likelihood of resolution.



Coxy and Pneumonia (CAP)

How common?

- **One yr surveillance in Tucson, Arizona**
- **55 pts with pneumonia in 3 medical offices**
- **16 (29%) had Coxy by serology (ELISA)**
- **At risk: Newer (< 10 yrs) residents**
- **Few distinguishing clinical features**
 - **Myalgias, prolonged fatigue, hilar adenopathy, eosinophilia**

Valdivia L, et al. Coccidioidomycosis as a Common Cause of Community-Acquired Pneumonia. Emerg Infect Dis 2006;12 958-62.



Coccidioidomycosis (Natural history)

100 Primary Pulmonary

60 Asymptomatic
(+ skin test)

40 Symptomatic

**Most recover with
full immunity**

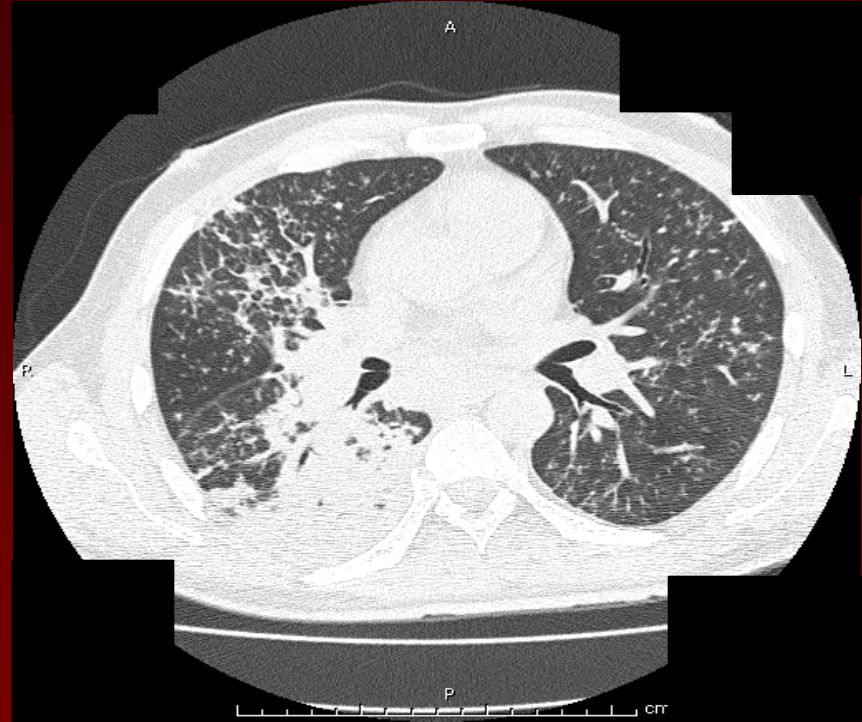
3 - 4

**Pulmonary residua
(cavity,nodule)**

1 - 10

**Disseminated
Skin
Bone/joint
Meninges**

40-year-old male with DM and 2-week hx of fever and cough



WBC 14K 45% eosinophilia

Serology: + ELISA (IgG;IgM) CF 1:16

Coccidioidomycosis

(Clinical presentation)

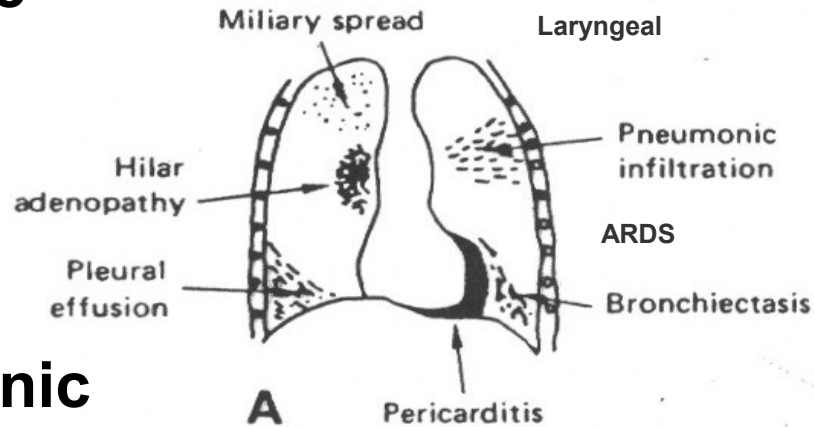
Table 1: Clinical Manifestations of 1° Coxy

Clinical symptoms	% Cases
Fever	76
Cough	73
Chest pain	44
Shortness of breath	32
Fatigue	39
Chills	29
Erythema nodosum	26
Peripheral eosinophilia	47

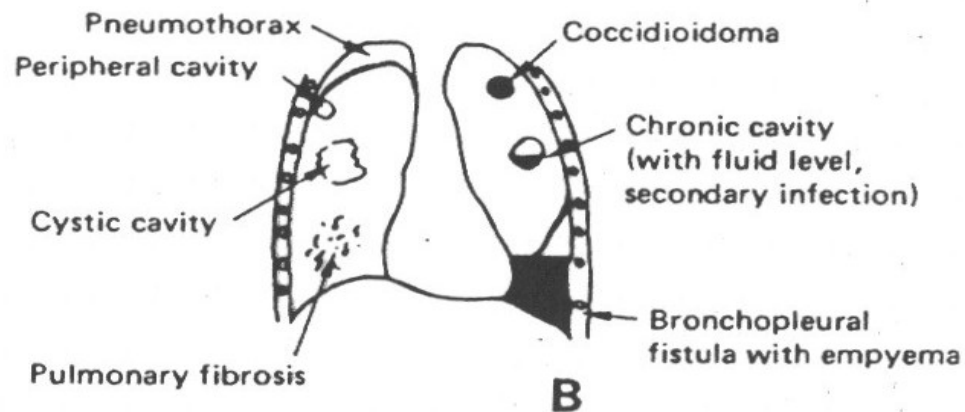
* 538 patients with new onset infection Johnson RH et al. (eds.) in Coccidioidomycosis. Fifth International Conference. NFID. Bethesda MD. 1998.

Pulmonary Coccidioidomycosis

Acute



Chronic

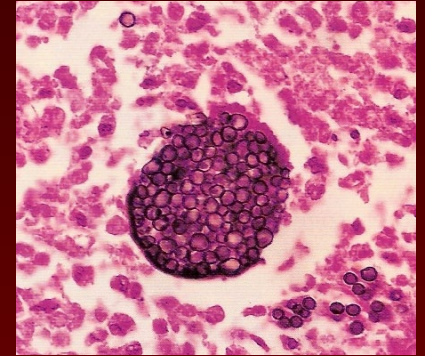


- Infiltrate 68 %
- Effusion 10 %
- Nodule 2 %
- Cavity 2 %

Hilar adenopathy, Cavity
Clinical clues to Coxy

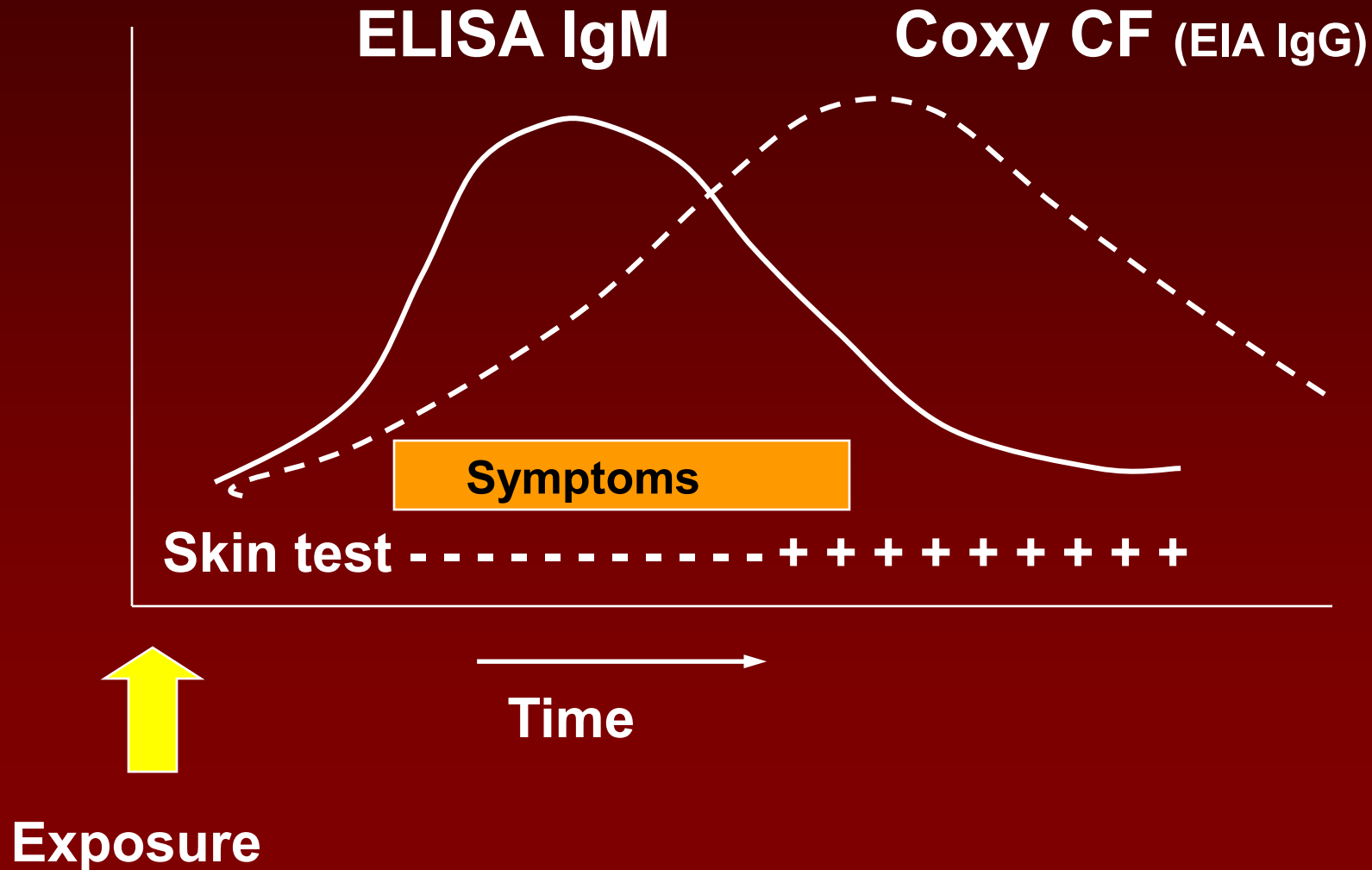


Coccidioidomycosis (Diagnosis)

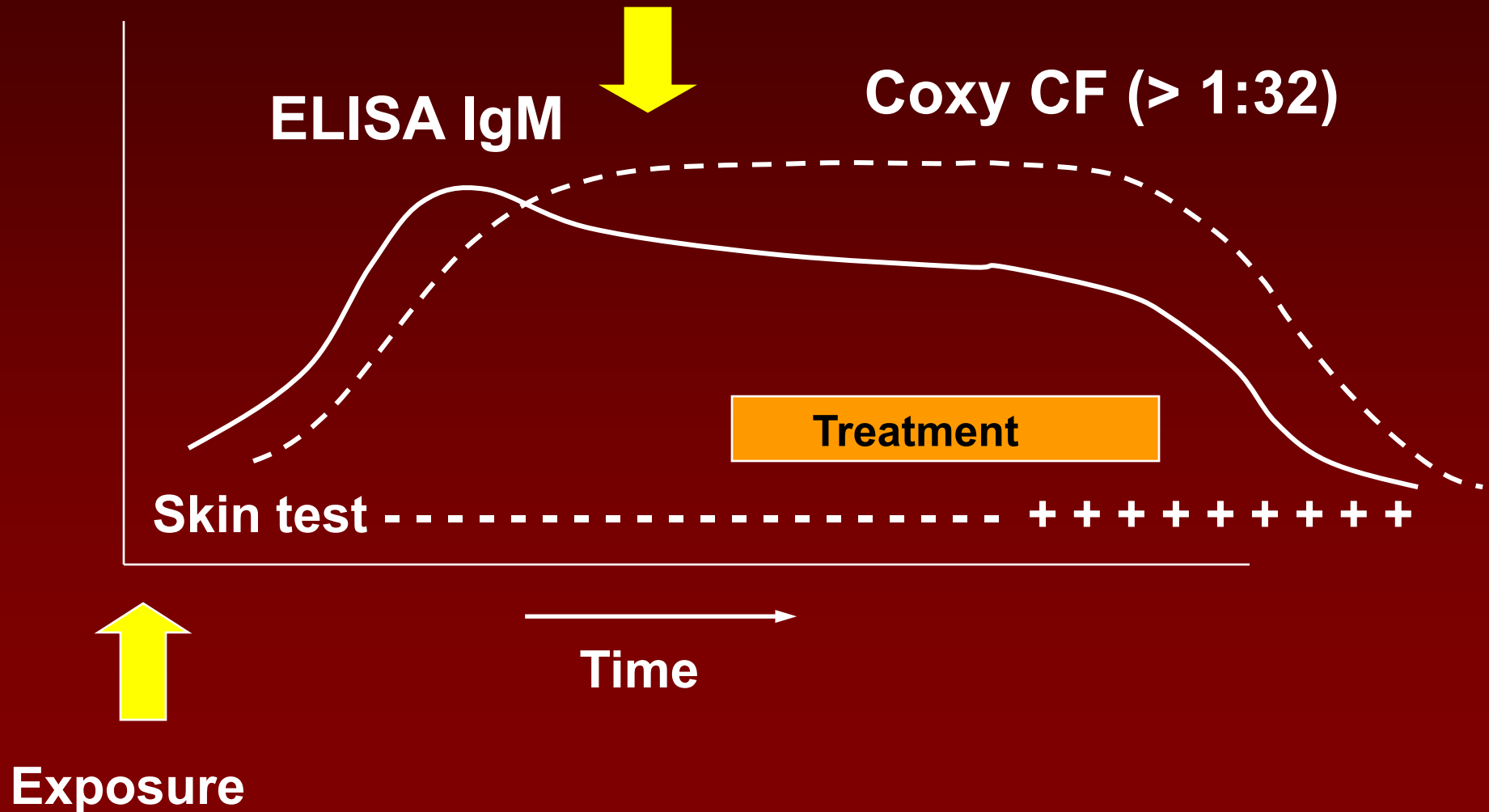


- **Pathology**
 - KOH prep; GMS; cytology
- **Culture** (Lab calls with “mold”)
- **PCR: Sputum; CSF (U Wash)**
- **Serology**
 - EIA (ELISA): IgG; IgM)
 - IDTP (Immunodiffusion tube precipitins)
 - Complement fixation (CF)

Coccidioidomycosis serology (Normal host response)



Coccidioidomycosis serology (Disseminated Infection)





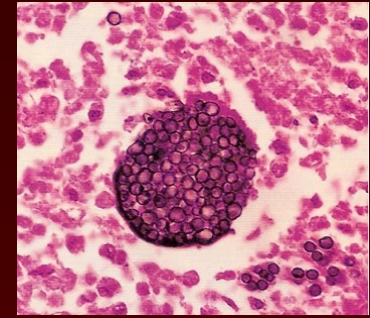
Primary Pulmonary Coxy

Who should be treated?

- **? Treat all symptomatic pts**
 - No controlled data to support
 - Pt improving? ...*Probably no Rx needed*
- **Special populations**
 - Immunocompromised pts (AIDS, transplant, steroids)
 - Diabetes; cardiopulmonary disease; pregnancy
 - Pts of Filipino or African descent
 - Severe primary pulmonary disease

Severe Primary Pulmonary Coxy

Indications for Rx



- Weight loss > 10%
- Intense night sweats > 3 weeks
- Infiltrates > 50% of one lung or bilat pulm
- Persistent hilar adenopathy
- CF > 1:16
- Inability to work; age > 55; Sx > 2 months

Rx: Azole x 3-6 months with reevaluation

Pulmonary Uncomplicated Coxy

(Management--IDSA guidelines)

- **Oral azole antifungals at dosages of 200-400mg per day x 3-6 months**
- **F/U: 1-3 month intervals for ≥ 1 year**
 - **Resolution of pulmonary infiltrates,**
 - **Identify patients with disseminated infection**
- **? Poor response:**
 - **Check fluconazole levels and alter dose**
 - **? Switch to voriconazole or posaconazole**
 - **Liposomal Amphotericin B**

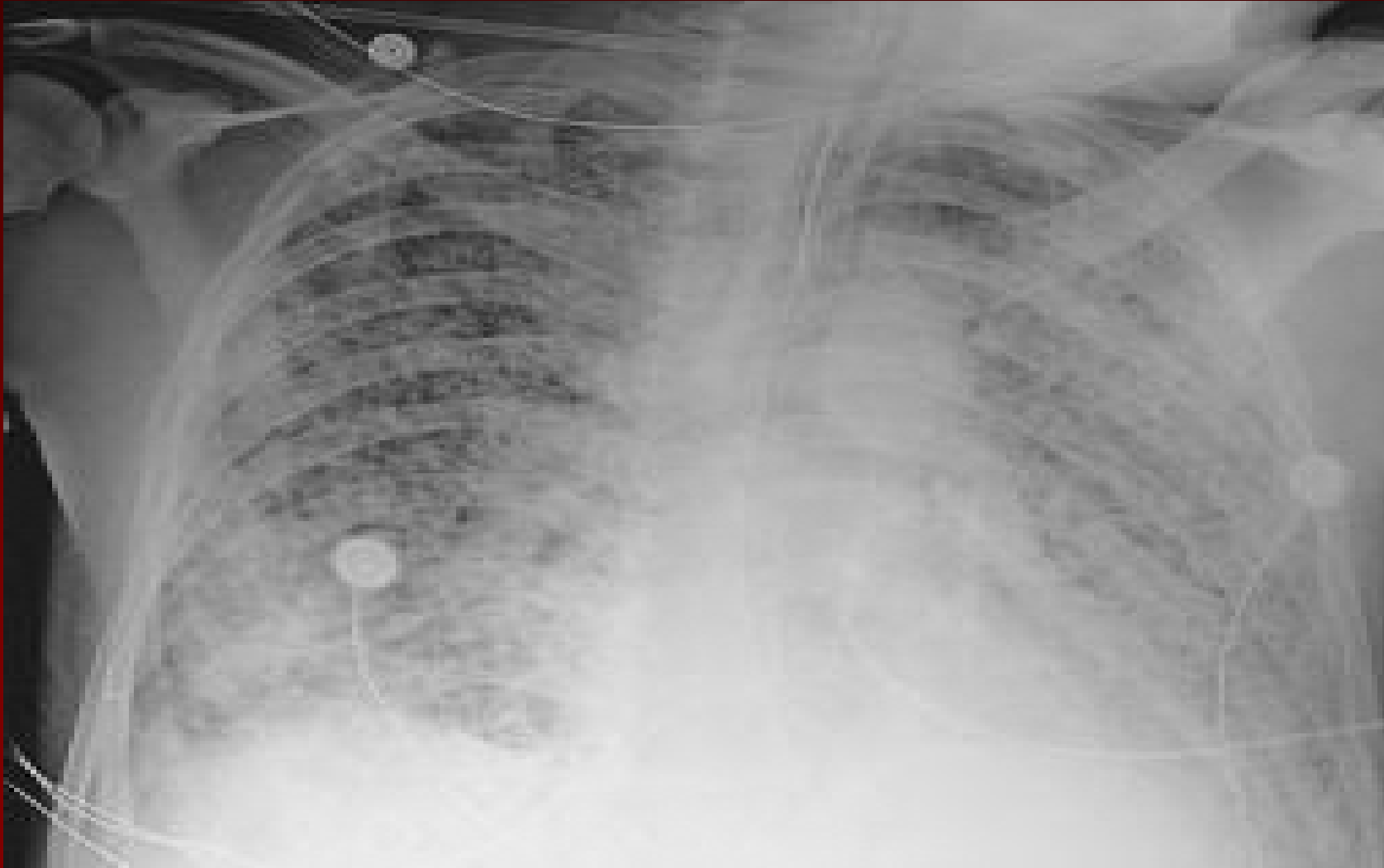
40 yo male with Pneumonia

(case continued)

- Dx: Pulmonary coccidioidomycosis
- Rx with Hi Dose Fluconazole
- Discharged on Fluconazole 400 mg qDay
- 2 months later...still severe fatigue

*Prolonged fatigue is common with Coxy
Pts usually improve c physical therapy*

Diffuse reticulonodular infiltrates due to *Coccidioides immitis* in a patient with HIV.



Diffuse Coxy Pneumonia/Septic shock

(Management--IDSA guidelines)

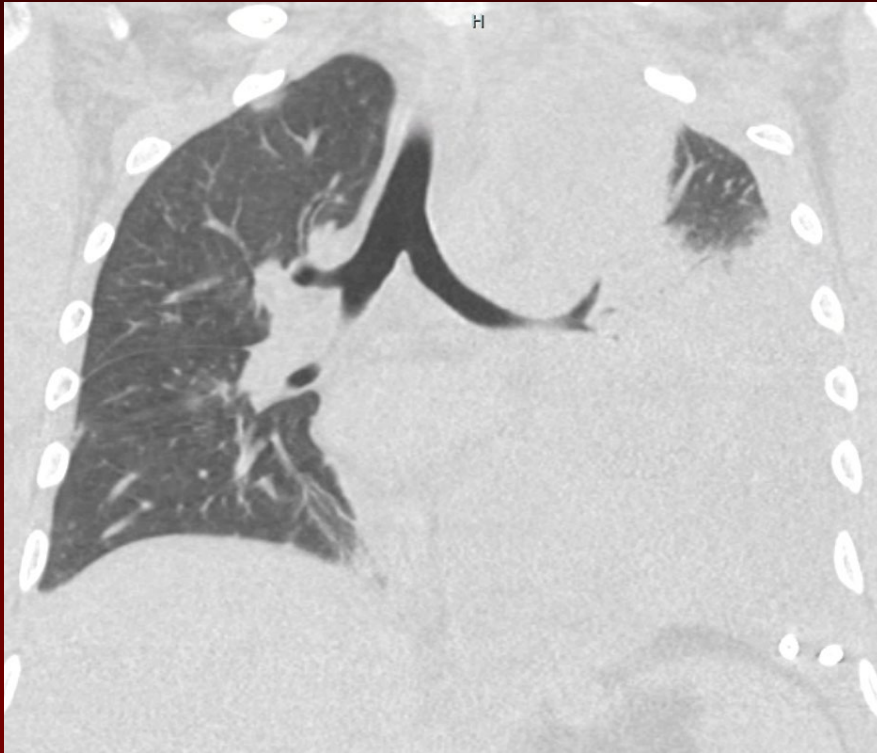
- **Rx: Amphotericin B or hi-dose fluconazole**
 - AmB if significant hypoxia or rapid deterioration
 - AmB → stable → oral azole antifungal therapy
 - Immunosuppressed: Indefinite fluconazole
- **Evaluate for disseminated disease**
 - Meningitis, skin, bone/joint
- **? Corticosteroids**

Pulmonary Coccidioidomycosis

Complications

- **Asymptomatic nodule 2° to coxy (Bx)**
 - Observe with repeat CXR
 - ? Possibility of lung cancer
- **Pulmonary cavity: 50% resolve w/i 2 yrs**
 - Resect if > 2 yrs, progressive enlargement or immediately adjacent to pleura
 - ? Role of azole therapy
- **Ruptured cavity**
 - If patient can tolerate, perform lobectomy with decortication and surgical closure
 - Supportive antifungal therapy

19 yr old c fever, chest pain and L pleural effusion...



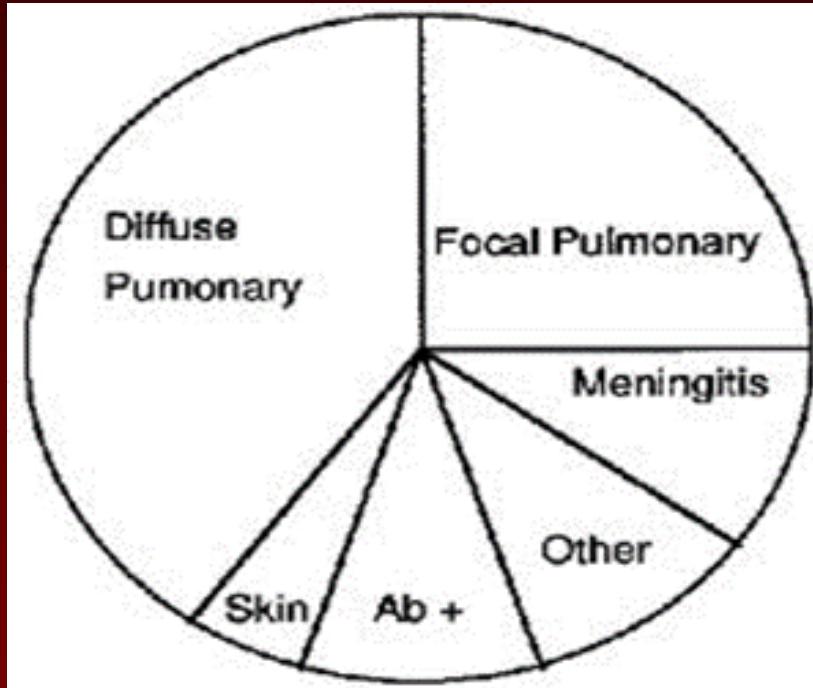
- Works in construction
- Lab: WBC: 17K c 800 eosinophils
- Serology: Coxy IgM+ Coxy IgG “negative”
Coxy Immunodiffusion- Negative

19 yr old pt c empyema continued...

- **Exudative loculated pleural effusion**
 - Negative Pleural fluid Coxy PCR and antigen
 - Tube thoracostomy → DNAase
 - VATS c Decortication
- **Plasma cell free DNA (Karius test):**
 - Low levels *C. immitis*
- **Path: + Spherules on Bx c + culture for Coxy**
- **Rx: IV amphotericin B → Fluconazole**

***Dx: Pulmonary coccidioidomycosis c
empyema***

Disseminated Coccidioidomycosis



- Diffuse pulmonary
- Bone/Joint
- Skin
- GU: Prostate
- GYN: Endometritis
- Meningitis

- *“Target” organs in coxy (Lung, bone, skin, meninges)*
- *Most pts have + serology*
- *Sometimes “surprise” Dx on Pathology*

Coccidioidomycosis (Bone/joint)

- 32 yo male c pneumonia and back pain
- Lab: + Coxy CF 1:32
+ Culture *C. immitis*
- Initial Rx: Ampho + flucon
- Surgical drainage
- Continued Rx
 - Liposomal Amphotericin
 - Caspofungin
 - Posaconazole



Coccidioidomycosis (Skin manifestations)



Erythema nodosum
("Desert bumps")



Erythema multiforme



Nodules



Pustules Ulcers



Plaques

Association Between Facial Cutaneous Coccidioidomycosis and Meningitis



38 yr old male with fever,
pneumonitis and facial lesion 11/09

Arsura et al. Western J Med 1998; 169: 13-16

Coccidioidomycosis (Meningitis)

- 48 yr old female with one week of fever/headache
- Recent travel to Vietnam
Hx of pneumonia 5 wk PTA
Coxy serology (ELISA): Negative
- Pex: T 38.9 °C mild confusion
Non-focal exam
- LP: OP 380 WBC 580 (65 L, 10 N, 5 M)
Glu 37 TP 261
- ? TB ? Lymphoma

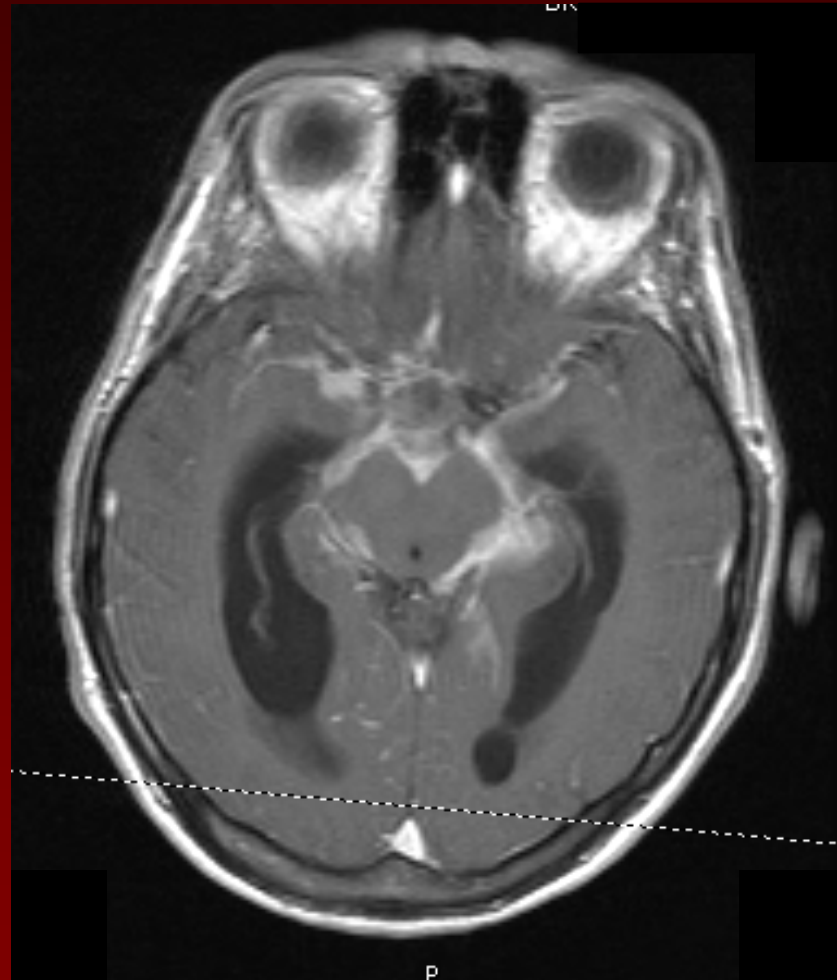
**CSF culture (12 wks later) + *Coccidioides immitis*
+ serum/CSF Coxy CF test**



Coccidioidomycosis (Meningitis)

- **Subacute/chronic onset**
- **PEX: Early...Non-focal
Late...CN findings
Stroke**
- **LP: Low glucose (Mimics TB)
Mononuclear pleocytosis**
- **CSF Culture + < 50%
+ serum/CSF ELISA/CF (~ 80%)
CSF β -glucan (? > 90%)**

HIV patient with Coxy Meningitis



T1 weighted scan c contrast

Coxy Meningitis—Clinical Sx

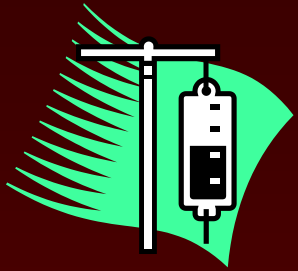
(2008 vs 1980—LA study: Medicine (Balt) 9/2010)

	2008 %	1980 %
Headache	77	79
Fever (on admx)	66	77
Mental status changes	73	45
Focal Neuro signs/Sx	23	16
Meningeal irritation	39	32
Lumbar arachnoiditis	10	35
Hydrocephalus	10/29 (33%)	5/6 (83%)
Mortality	30% (12 pt)	31% (12 pt)

Azole

IT Ampho





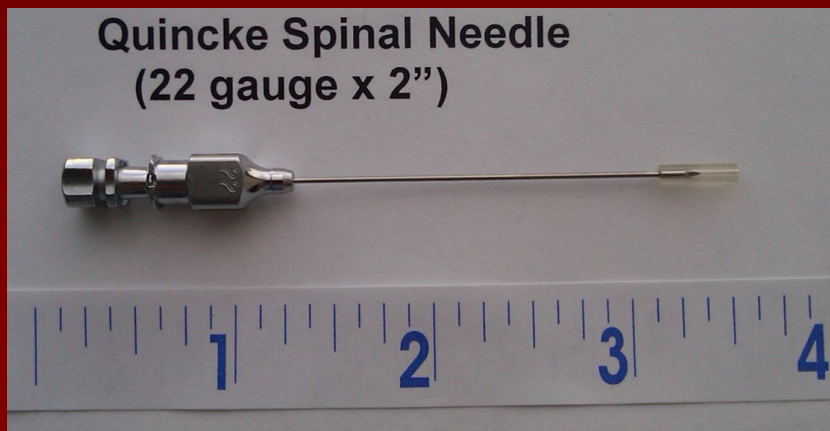
Coccidioidal Meningitis

(Therapy)

- **Fluconazole:**
 - Hi-dose 800-1200 mg IV/day
 - Check levels
- **Fluconazole “failure” → voriconazole**
- **Intrathecal amphotericin B**
- **Corticosteroids**
- **VP shunt for hydrocephalus**
- **High dose Liposomal Amphotericin B**

Intrathecal Amphotericin B

- **Amphotericin B**
Don't use liposomal drug
- **Route**
 - Lumbar
 - Cisternal
 - Omayo reservoir
- **Complications**





Coccidioidomycosis and Pregnancy

- **Coxy acquired during pregnancy → major risk factor for severe or disseminated disease**
 - High mortality...especially during 3rd trimester
 - ? Previous Coxy...recurrence uncommon
- **Azole toxicity during 1st trimester**
 - Antley-Bixler syndrome: Craniosynostosis; fetal malformations
- **Treatment during pregnancy**
 - 1st Trimester: Observe (Mild disease) or Amphotericin
 - 2nd/3rd Trimester: Azoles (Mild) or Amphotericin B (severe)
 - Coxy meningitis: Avoid azoles (1st Trimester)...
consider IT Amphotericin B

Coxy and pregnancy

32 y.o. female c coxy meningitis and 6 wk IUP

- **Dxed in 2000**
- **Initial rx c hi-dose fluconazole**
- **Fluconazole “failure” → voriconazole**
- **2011: Hydrocephalus → VP shunt**
- **2016: Skin cancer/pigmentation
→ switch to posaconazole**
- **10/18: 6 weeks pregnant**
 - **Stopped azole (? Risk of Antley Bixler syndrome)**
 - **IV Ampho B (Mon; Thur)....restart azole 2nd trimester**

Avoid high-dose azoles during 1st Trimester



Coccidioidomycosis

Antifungal therapy



Amphotericin B

AmB deoxycholate
Liposomal AmB

**Severe
Disease**

Azoles

Fluconazole
Itraconazole
Voriconazole
Posaconazole

**Mainstay of
therapy**

Echinocandins

Caspofungin
Micafungin
Anidulafungin

**Little
Activity**



Coccidioidomycosis Therapy (Amphotericin B)

- **Amphotericin B desoxycholate**
 - “Standard” ampho B
 - High incidence of nephrotoxicity
 - Used for intra-theatal therapy (Coxy meningitis)
- **Liposomal amphotericin B**
 - Used for “severe” or disseminated disease
 - Less nephrotoxicity (but still tubular abnormalities)
 - Overall, better tolerated (Less infusion related rxn)

Use amphotericin B for severe, disseminated infection

Coccidioidomycosis (Therapy)



- “Standard” Azoles
 - Fluconazole: mainstay of Rx for most patients
 - Good oral absorption and CSF penetration
 - Adverse effects: Hepatitis; Dry skin; Cheilitis; Arthralgias
 - Itraconazole
 - Absorption variable; check levels
 - May be better for bone/joint disease
 - Adverse effects: CHF; edema; hypertension; \uparrow K^+

Azoles metabolized via CYP450 enzyme—watch out for drug interactions



Coccidioidomycosis ("Newer" Azoles)

- **Voriconazole**
 - Good absorption and CSF penetration
 - Coxy meningitis: "Rescue" drug for flucon "failures"
 - Adverse rxn: Photosensitivity (skin cancer)
Visual disturbances/hallucinations
- **Posaconazole**
 - Oral liquid and tablets
 - Excellent in vitro activity against Coxy
 - Good "rescue" drug but poor CNS penetration

Isavuconazole in the Treatment of Coccidioidal Meningitis

Arash Heidari, Miriam Quinlan, David J. Benjamin, Brett Laurence, Anandit Mu, Tiffany Ngai, Wes J. Hoffman, Stuart H. Cohen, Ian McHardy, Royce Johnson, George R. Thompson III

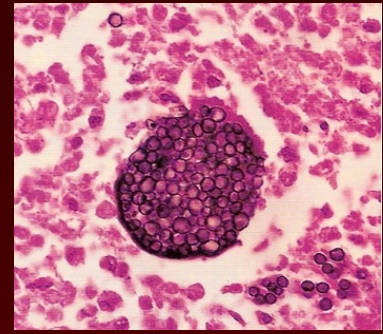
DOI: 10.1128/AAC.02232-18



- **Isavuconazole demonstrated efficacy in animal and human CNS fungal infection**
 - Good brain penetration; fair-poor CSF penetration
- **9 patients**
 - 3 pts fluconazole or voriconazole “failure”
 - 6 pts voriconazole adverse rxn
 - Photodermatitis; photopsia; SCC; hepatitis
 - Successful Rx in 3 pts
- **Outcome**
 - Improvement in 3 pts; Stable disease in 6 pts

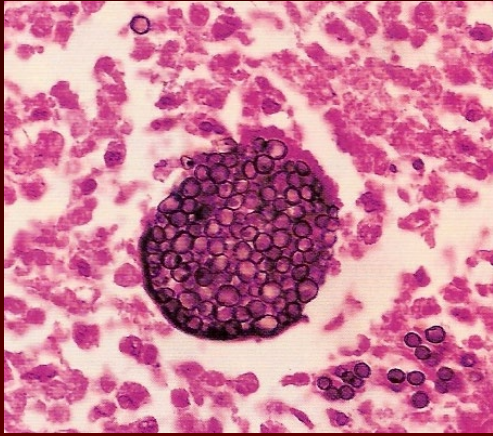


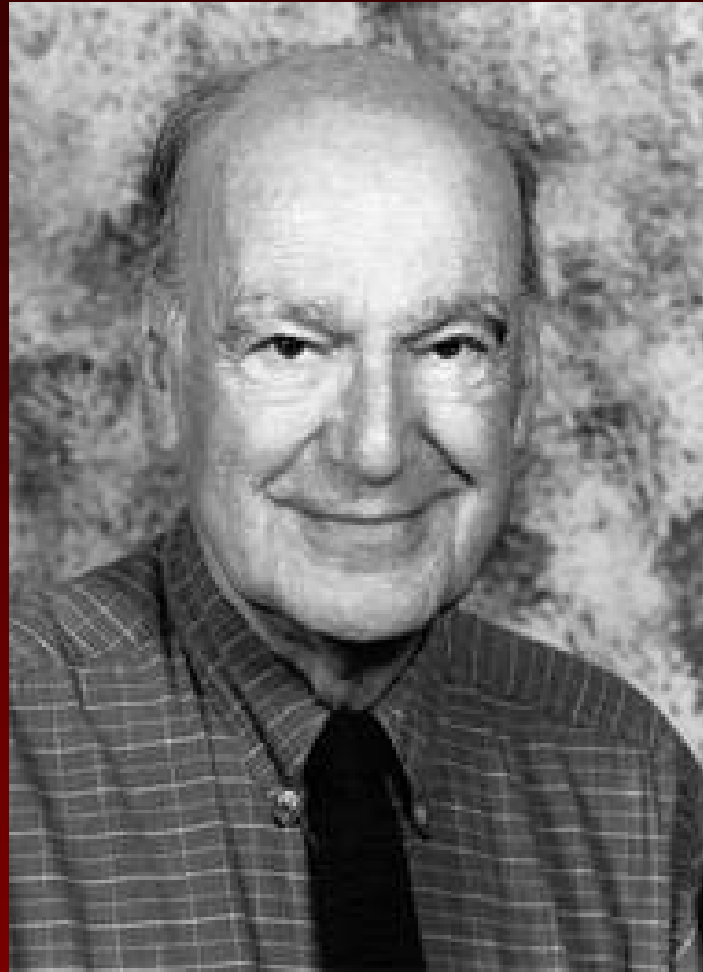
Coccidioidomycosis Dx/Rx Summary



- ? Pneumonia → think “Coxy”
- Look for eosinophilia...check EIA serology
- Rx: Fluconazole for 3-6 months
- Severe Coxy? → Amphotericin B
- ? Disseminated Coxy: Meningitis; skin; B/J
- Most “normal” hosts have + serology c elevated CF titer







Hans Albert Einstein (1923-2012)
“Coxy” pioneer