

## Endemic Fungi: Histoplasmosis, Coccidioidomycosis, Blastomycosis and Sporotrichosis

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### Histoplasmosis

Causative fungus	<i>Histoplasma capsulatum</i> var. <i>capsulatum</i>
Primary geographic distribution	Worldwide; most common in North America and Latin America
Primary route of acquisition	Respiratory (inhalation of spores)
Principal sites of disease	Lungs, lymph nodes, liver, spleen, bone marrow, adrenal glands, GI tract
Opportunistic infection in compromised hosts	Frequent in patients with depressed cellular immunity, especially AIDS patients

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### Other Varieties of *H. capsulatum*

- ▶ *H. capsulatum* var. *dubosii* is found solely in Central Africa. Yeast form is larger (8-15  $\mu$ m), and thick walled. Mainly causes skin and bone disease. Usually indolent and non-life-threatening infection.
- ▶ *H. capsulatum* var. *farciminosum*. A non-human pathogen which causes disease in horses and mules. Mainly lymphangitis and ulcerated skin lesions in equines living in Middle East, Northern Africa, central and southern Europe, Japan, Philippines and southern Asia.

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## ***H. capsulatum*: Epidemiology**

- ▶ Greatest prevalence in tropical and temperate zones, (endemic areas in South Central and North Central United States, esp., along major river basins, also selected areas of eastern US) and most of Latin America. Isolated cases in Southeast Asia and Africa.
- ▶ **Cases worldwide imported from endemic areas.**
- ▶ In highly endemic areas, more than 80% of persons infected by age 20 years.
- ▶ ***H. capsulatum* grows in soil enriched with guano of various avian species or bats. Because of high body temperatures, birds are not infected, whereas bats are.**

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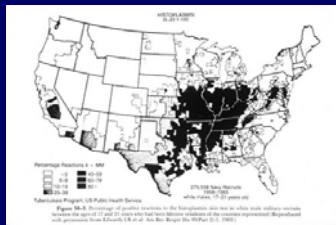
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Histoplasmin skin test positivity in the U.S. (1958-65)

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## **Forms of Histoplasmosis**

- ▶ Acute pulmonary
  - Sporadic or epidemic
  - Symptomatic or asymptomatic
- ▶ Chronic cavitary pulmonary
- ▶ Complications of pulmonary histoplasmosis
  - Histoplasmosis (coin lesion)
  - Mediastinal granuloma
  - Fibrosing mediastinitis
  - Broncholithiasis
  - Pericarditis
- ▶ Disseminated
  - Acute - often rapidly fatal
  - Chronic progressive
- ▶ Focal organ system involvement
  - Central nervous system - Cardiac - POHS
  - Gastrointestinal - Adrenal

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## Disseminated Histoplasmosis (DH)

- ▶ Acute DH occurs primarily in infants and immunosuppressed patients, e.g., HIV infected persons with CD4 count  $<150/\mu\text{L}$ . Severity of symptoms and signs of DH usually mirror the level of immunocompetence of the host.
- ▶ Chronic DH occurs primarily in non-immunosuppressed middle-aged to older adults, esp. males.
- ▶ Both forms of DH characterized by lymphadenopathy, hepatosplenomegaly, and skin and mucous membrane lesions (papules, pustules, ulcers, and nodules). Adrenal insufficiency and hypercalcemia should raise suspicion of DH.

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Skin lesion – recurrent DH

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### Case #1

35 yo man with advanced HIV; CD4=13 cells/mm<sup>3</sup>  
He presents with 2 week h/o progressive diffuse papular rash, fever (40° C), hypotension (90/50 mmHg) and dyspnea (RR= 36). Clinical images and presenting CXR are demonstrated in the following slides:

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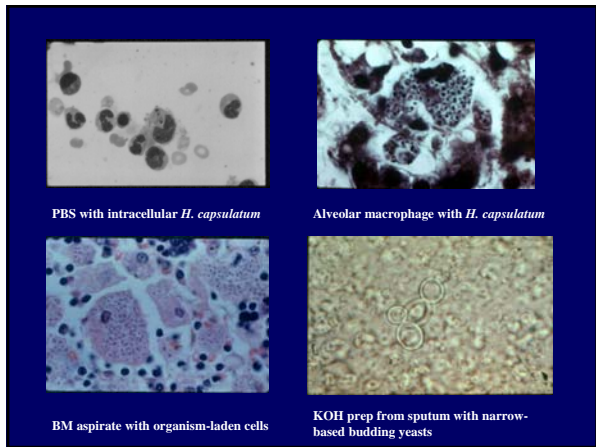
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PBS with intracellular *H. capsulatum*

Alveolar macrophage with *H. capsulatum*

BM aspirate with organism-laden cells

KOH prep from sputum with narrow-based budding yeasts

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## Case #2

An otherwise healthy 69 yo man presents with 3 month h/o low grade fever, 20# weight loss, and worsening headache. No other focal complaints.

Exam reveals no focal findings. Vital signs are WNL. Routine labs reveal elevated alk phos, otherwise nl LFTs, anemia (Hgb 8.3 gms), leukopenia (WBC 2.5K) and thrombocytopenia (65K)

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Abd CT: bilateral adrenal enlargement, hepatosplenomegaly on abdominal CT.

Head MRI: small ring enhancing lesions (9) throughout the cerebrum.

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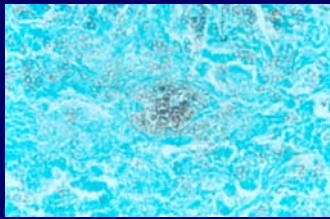
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Adrenal biopsy revealed small budding yeasts c/w *H. capsulatum*

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## Histoplasmosis: Diagnosis

- ▶ **CULTURE** of *H. capsulatum* from blood or body fluids/tissues is definitive. May take as long as 6 weeks to become positive.
- ▶ **ANTIGEN DETECTION.** Circulating *H. capsulatum* polysaccharide in serum and urine, esp. in AIDS patients with DH and large burden of organisms (positive in urine in 90% and serum in 50%).  
**False positives in patients with blastomycosis, paracoccidioidomycosis and penicilliosis.**
- ▶ **SEROLOGICAL TESTS.** Detection of antibodies to *H. capsulatum* by complement fixation (CF) and immunodiffusion (ID) assays. ID more specific than CF.
- ▶ **HISTOPATHOLOGY** of tissue specimens, e.g., lymph nodes, lung, liver and BM.

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## Histoplasmosis: Antifungal Therapy

### Preferred therapy:

Itraconazole 200 – 400 mg qd (mild to mod dz)

LFAMB 3-5 mg/kg qd (acute disseminated, CNS, severe or life-threatening dz)

### Alternative therapy for pts intolerant to or unable to obtain preferred therapy:

Fluconazole

Ketoconazole

Posaconazole

Wheat et al, Clin Infect Dis 2007; 45: 807-25.

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## Histoplasmosis: Other Considerations

### Indications for therapy

- Acute severe pulmonary disease – steroids may be helpful
- Chronic pulmonary disease – AMBd rarely necessary
- Mediastinal granuloma – ITRA may be effective
- Fibrosing mediastinitis – No Rx effective
- Duration of therapy for uncomplicated disease is at least 6 months, but may extend for >12 months

Wheat et al, Clin Infect Dis 2007; 45: 807-25.

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## Coccidioidomycosis

Causative fungus	<i>Coccidioides immitis</i> and <i>C. posadasii</i>
Primary geographic distribution	Lower Sonoran deserts of the Western hemisphere including parts of Arizona, California, New Mexico, west Texas, and parts of Central and South America
Primary route of acquisition	Respiratory (inhalation of arthroconidia)
Principal sites of disease	Lungs most common; skin and soft tissue, bones, joints, and meninges
Opportunistic infection in compromised hosts	Diffuse pneumonia and disseminated infection common in patients with depressed cellular immunity, e.g., HIV infection and chronic corticosteroid therapy

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## Coccidioidomycosis

- ▶ Recent genetic evidence indicates that *Coccidioides* consists of two distinct species:
  - *C. immitis* – found only in California
  - *C. posadasii* – found elsewhere
- ▶ At this time, no clear microbiological or clinical characteristics that distinguish these species.

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## Coccidioidomycosis: Epidemiology

- ▶ Endemic regions of coccidioidomycosis – areas in which the organism inhabits the soil, between latitudes of 40°N and 40°S in Western Hemisphere.
- ▶ In North America, endemic regions associated with lower Sonoran Life Zone (hot summers, mild winters, rare freezes, and alkaline soil). Cases wane in wet winter season.
- ▶ In Central and South America, several geographic endemic pockets (arid or semiarid). Examples are north-central Argentina, Venezuela, and ? NE Brazil.

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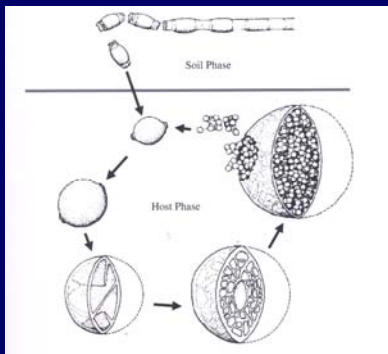
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Life cycle of *C. immitis*

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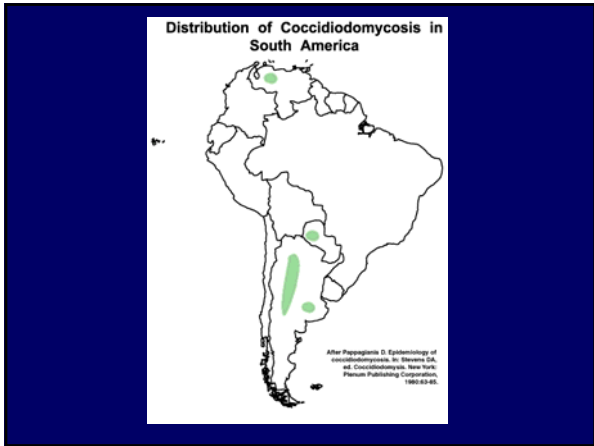
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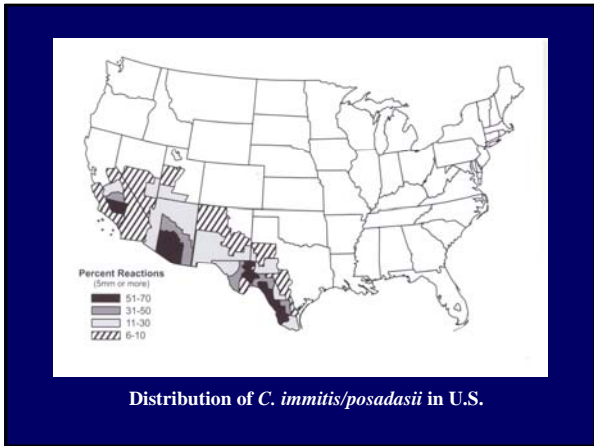
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## Coccidioidomycosis

- ▶ 60% of persons asymptomatic at time of primary infection. Manifest only by positive coccidioidin skin test.
- ▶ 40% have “flu-like” illness, often with profound weakness. Other manifestations that may signal coccoy infection:
  - Skin rash, either diffuse pruritic erythematous rash or erythema multiforme or erythema nodosum
  - Arthralgias, esp. knees and ankles
    - “Desert Rheumatism”
  - Pleural effusion – ipsilateral to pulmonary opacity in 20% of cases; eosinophilia
- ▶ CXR – typically, unilateral patchy infiltrate. Less common, dense lobar or segmental infiltrate with atelectasis. Hilar and/or mediastinal adenopathy often present.

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## Coccidioidomycosis: Special Hosts

- ▶ Persons with depressed cellular immunity are at increased risk for developing severe and disseminated disease.
  - Cancer/lymphoma associated chemotherapy
  - Chronic corticosteroid therapy
  - HIV/AIDS
  - Allogenic transplant recipients (most cases appear to result from reactivation of previously acquired infection)
- ▶ Other risk factors – male sex especially, African American men and Filipino men and age >60 years.
- ▶ Pregnant women in second and third trimesters.

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## Pulmonary Coccidioidomycosis

- ▶ Pulmonary nodule – single or multiple. Must distinguish from neoplasm
- ▶ Cavitation of nodule – usually thin walled cavity. Complications include cough and chest pain, hemoptysis, and pyopneumothorax.
- ▶ Chronic progressive pulmonary disease – often associated with bronchiectasis and fibrosis. CXR resembles reactivation TB and cavitary histo.
- ▶ Diffuse pulmonary pneumonia – rare, high mortality.

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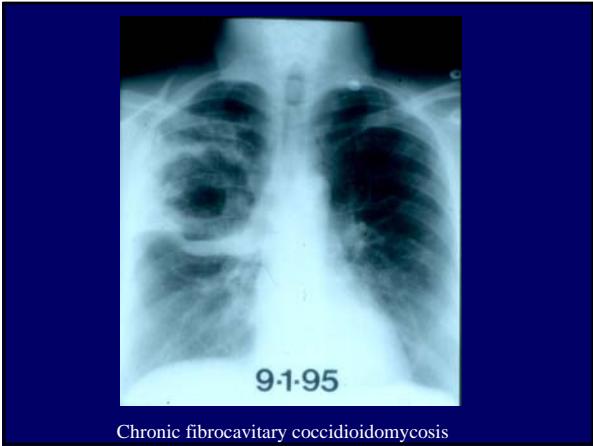
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Chronic fibrocavitary coccidioidomycosis

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CT chest: Chronic fibrocavitary cocci

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### Case #3

18 yo male college student from south Alabama with a 6 months h/o scant sputum production with streaky hemoptysis. He denies any constitutional symptoms. PMH: 2 years ago he was diagnosed with CAP and also had a left upper lobe solitary nodule. He was treated with an antibacterial and recovered without problems. Insulin-dependent DM (age 3), HBA1c 9%. SH: He visited Laredo, TX, and Northern Mexico on a hunting trip approx 2 years ago (2 weeks prior to initial episode of CAP). No tobacco or drugs. He drinks alcohol Occasionally. PE: VSS; no focal findings

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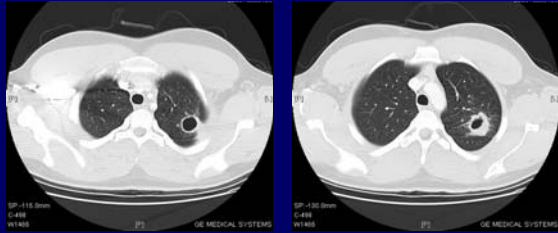
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CT chest reveals LUL cavitary lesion; sputum and BAL grow *Coccidioides spp.* Serum cocci CF positive 1:8

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### Disseminated Coccidioidomycosis (DC)

- ▶ DC occurs in <1% of infected persons. DC portends a poorer prognosis than pulmonary coccy and is associated with less vigorous cellular immune response. DC often occurs in persons with asymptomatic primary infection.
- ▶ Skin most common site of DC. Variety of lesions including papules, plaques, verrucous nodules, draining sinuses, and subcutaneous abscesses.
- ▶ Bones and joints are frequent sites. Vertebrae commonly affected and associated with soft tissue swelling. Knee most common joint → chronic synovitis with swelling and pain.
- ▶ Strong racial predisposition to DC...Blacks, Filipinos, Asians >> Caucasians

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The many faces of coccidioidomycosis

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### Case #4

53 yo black man presents with 3 week h/o progressive mid-back pain and lower extremity weakness. Has a 20# wt loss over 3 mos, no fever or night sweats. No h/o trauma  
PMH: Long standing Type 2 DM, HBP.  
SH: Lives in Birmingham, works as a hotel porter. Tours the US biannually with his gospel group. Spends several weeks every other year in Tucson, AZ.

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Destructive lesion at T5-6 vertebrae; biopsy reveals spherules, and culture positive for *Coccidioides spp.*

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### Case #4 (con't)

Pt responded well to AmB, then itraconazole, then posaconazole. 18 mo later, he developed a painless swelling in the right anterior chest. Chest CT is demonstrated on the next slide.

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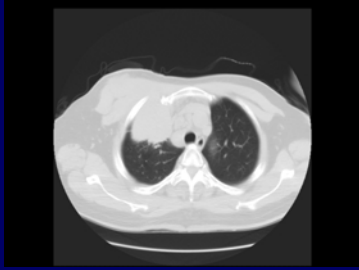
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Pulmonary, osseous and soft tissue coccidioidomycosis: note destruction of the 2<sup>nd</sup> rib and extension of the process into the soft tissue.

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### Coccidioidal Meningitis

- ▶ In 50% of cases, meningitis is the only clinically overt manifestation of disease.
- ▶ Severe and progressive headache with decreasing mental acuity are hallmark clinical features. Common complication is hydrocephalus, either communicating or non-communicating. CNS scan, MRI preferred, is indicated in all patients.
- ▶ CSF formula: lymphocytic pleocytosis (eosinophils may be present), elevated protein, depressed glucose, and elevated OP. Detection of anticoccidioidal antibodies in the CSF is the rule.
- ▶ Important cause of chronic lymphocytic meningitis. Must differentiate from neoplastic, tuberculous, sarcoid and other fungal, esp. crypto, causes.

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### Coccidioidomycosis: Diagnosis

- ▶ **CULTURE.** Organism grows as a mould after 3-7 days of incubation at 35°C on artificial media. Sputum or respiratory secretions more likely to yield positive culture than biopsy specimens. Notify lab that *Coccidioides spp.* is suspected clinically.
- ▶ **HISTOPATHOLOGY.** Identification of spherules by special stains (GMS or PAS preferred over H & E).
- ▶ **SEROLOGY.** Very useful for both diagnosis and management. Goal is detection of IgM or IgG anticoccidioidal antibodies by various serological tests: IDTP, CF and IDCF. IgG titer  $\geq 1:16$  associated with risk of dissemination. IgG Ab in CSF diagnostic of coccidioidal meningitis.

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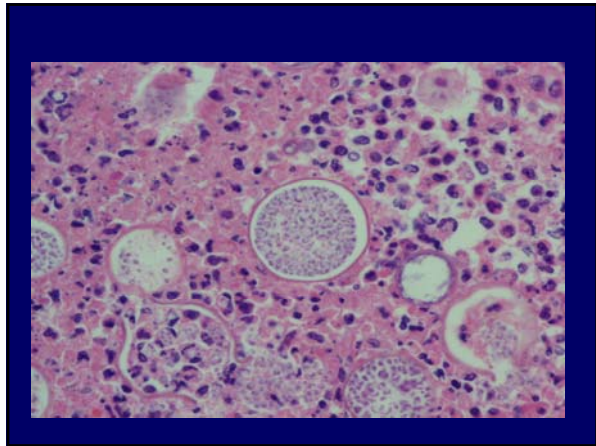
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## Coccidioidomycosis Treatment

### ▶ Therapeutic options:

Itraconazole 200 mg bid

Fluconazole 400 – 800 mg q d

Posaconazole 400 mg bid

AMBd 0.5 – 1.0 mg/kg/d or LFAmB 3-5 mg/kg/d

### ▶ Indications

- Primary pulmonary infection – most patients do not require therapy.
- Severe primary pulmonary and pulmonary sequelae – treat in selected cases with oral azole.

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## Treatment (Cont)

### ▶ Indications

- Diffuse primary pneumonia and chronic pneumonia
  - begin with AMB for diffuse dz. Azole therapy.
- Disseminated non-meningeal dz, depending on severity
  - AMB initially, then azole drug
  - AMB plus azole
  - azole alone
- Coccidioidal meningitis
  - azole alone, FLU more effective than ITRA
  - AMB intrathecal plus azole
  - AMB intrathecal and iv
  - voriconazole

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## Blastomycosis

- Causative organism is *Blastomyces dermatitidis*, a dimorphic fungus found in decaying organic material.
- The disease is reported worldwide, but is mainly seen in North America (Eastern US and Canada)
- Acquisition is primarily through inhalation of aerosolized spores

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## Blastomycosis

- Disease manifestations are pulmonary (60-80%), skin (40-60%), osseous (20-30%), genitourinary (10%), and CNS (<5%)
- Disseminated disease with multiple visceral organ involvement occurs in severely compromised patients
- Clinical manifestations mimic neoplasia, chronic pneumonia, immunologic skin disorders, TB, nocardia, and other deep mycoses

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Classic verrucous and subcutaneous lesions of blastomycosis

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The many faces of blastomycosis

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## Blastomycosis

- Diagnosis is based on finding characteristic broad-based budding yeasts in clinical specimens.
- Culture is sensitive, but time consuming and requires expertise
- Serologic tests (urine assay) is sensitive but non-specific

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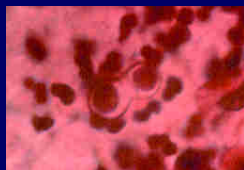
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Classic broad-based budding yeast with doubly refractile cell wall of *B. dermatitidis*

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## Treatment of Blastomycosis

- Itraconazole 200 mg bid: the regimen of choice for most pts
- Fluconazole 400-800 mg/d: reserved for pts unable to tolerate itraconazole; alternative rx for CNS blasto
- Ketoconazole 200-400 mg bid: older regimen, still effective
- Voriconazole 200 mg bid: reserved for pts with CNS blasto.
- AmB 0.5-1.0 mg/kg/d: reserved for pts with life threatening blasto, initial rx for CNS blasto

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## Sporotrichosis

- Causative organism is *Sporothrix schenckii* and other sub-species (*S. mexicana*, *S. globosa*, *S. brasiliensis*)
- Ubiquitous organism in all geographic regions
- Prefers enriched soil, decaying plants
- Some regions are 'hyperendemic' for *Sporothrix spp.* (eg, Peruvian highlands, urban Brazil)

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## Sporotrichosis

- Clinical disease occurs in all age groups; family outbreaks reported
- M>>F
- Skin trauma is prerequisite to most infections
- Domestic cat exposure is important means of transmission in certain regions (e.g. Brazil)

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## Cutaneous Sporotrichosis

- Most clinical disease is cutaneous and/or subcutaneous, most common cause of nodular lymphangitis
- Mostly extremities, but facial involvement is common among children
- Multifocal involvement is less common, but occurs, especially in children

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Classic subcutaneous sporotrichosis

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Solitary chronic ulcerative lesions of sporotrichosis

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## Differential Diagnosis of Cutaneous Sporotrichosis

- Non-tuberculous mycobacteria (esp MAI, *M. chelonae*, *M. marinum*)
- Nocardiosis
- Leishmaniasis
- Other endemic fungi (histo, crypto, blasto)
- Bacteria causing fixed ulcers (eg, *S. aureus*, *F. tularensis*, *B anthracis*)

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*M. chelonae* nodular lymphangitis

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*M. chelonae* – nodular lymphangitis

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## Extracutaneous Sporotrichosis

- Osteoarticular: most commonly seen in alcoholics
- Pulmonary: pre-existing lung disease, COPD, smokers
- CNS: just unlucky, I guess
- Disseminated: almost always associated with readily identifiable immune disorder

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## Cutaneous Sporotrichosis: Treatment

- SSKI: 5 qts tid, increasing to 40-50 qts tid  
Poorly tolerated, causes N/V, lacrimation, distorted taste, rash. Least expensive, but very effective
- Itraconazole 200 mg bid  
Treatment of choice in most settings
- Fluconazole 800 mg qd  
Not as good as itra, but available and well tolerated
- Terbinafine 500 mg bid  
Expensive but effective
- Ketoconazole 400 mg bid  
Least effective, poorly tolerated at these doses

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## Extracutaneous Sporotrichosis

- For osteoarticular disease, itraconazole 200 mg bid is acceptable
- For other forms of disease (esp pulmonary and CNS), AmB 0.5-1.0 mg/kg/d is generally advised for initial therapy
- Chronic suppressive therapy is the rule, as relapsing disease is common

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