Microbiology Lectures of the Respiratory Diseases
Prepared by: Rizalinda Sjahril
Microbiology Department
Faculty of Medicine
Hasanuddin University
2016

OVERVIEW OF CLINICAL MYCOLOGY

- Among 150,000 fungi species only 100-150 are human pathogens → 25 spp most common pathogens
- Majority are saprophytic
- Transmission
  - Person to person (rare)
  - SPORE INHALATION OR ENTERS THE TISSUE FROM TRAUMA
  - Animal to person (rare) – usually in dermatophytosis
OVERVIEW OF CLINICAL MYCOLOGY

- Human is usually resistant to infection, unless:
  - Immunoscompromised (HIV, DM)
  - Serious underlying disease
  - Corticosteroid/antimetabolite treatment

- Predisposing factors:
  - Long term intravenous cannulation
  - Complex surgical procedures
  - Prolonged/excessive antibacterial therapy

- Several fungi can cause a variety of infections: clinical manifestation and severity varies.
  - **True pathogens** -- have the ability to cause infection in otherwise healthy individuals
Opportunistic/deep mycoses which affect the respiratory system are:

- Cryptococcosis
- Aspergillosis
- Zygomycosis

True pathogens are:

- Blastomycosis
- Coccidioidomycosis
- Histoplasmosis
- Paracoccidioidomycosis

Seldom severe
Treatment not required unless extensive tissue destruction compromising respiratory status Or extrapulmonary fungal dissemination

COMMON PATHOGENS OBTAINED FROM SPECIMENS OF PATIENTS WITH RESPIRATORY DISEASE

<table>
<thead>
<tr>
<th>Fungi (Note: <em>dimorphic</em>)</th>
<th>Common site of infection</th>
<th>Mode of transmission</th>
<th>Infectious form</th>
<th>Clinical form</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLASTOMYCES DERMATITIDIS*</td>
<td>Lungs, skin, long bones</td>
<td>(Usually) INHALATION</td>
<td>(probably) Conidia</td>
<td>YEAST</td>
</tr>
<tr>
<td>COCCIDIOIDES IMMITIS*</td>
<td>Lungs, skin, meninges</td>
<td>INHALATION</td>
<td>Arthro conidia</td>
<td>SPHERULES, ENDOSPORES</td>
</tr>
<tr>
<td>HISTOPLASMA*</td>
<td>Lungs, bone marrow, blood</td>
<td>INHALATION</td>
<td>Conidia</td>
<td>YEAST</td>
</tr>
<tr>
<td>PARACOCIDIOIDES BRAZILIENSIS*</td>
<td>Lungs, skin, mucous membrane</td>
<td>INHALATION /TRAUMA</td>
<td>Conidia</td>
<td>YEAST</td>
</tr>
<tr>
<td>SPOROTHRIX SCHENKII*</td>
<td>Skin and lymphatics, lungs, meninges</td>
<td>TRAUMA, rarely inhalation</td>
<td>Conidia/hyphae</td>
<td>YEAST</td>
</tr>
<tr>
<td>CRYPTOCOCCUS NEOFORMANS</td>
<td>Lungs, skin, meninges</td>
<td>INHALATION</td>
<td>Yeast x</td>
<td>YEAST</td>
</tr>
<tr>
<td>ASPERGILLUS</td>
<td>Lung, eye, skin, nail</td>
<td>INHALATION</td>
<td>Conidia</td>
<td>Hyphae</td>
</tr>
</tbody>
</table>

*conidia of telemorphic stage
CRYPTOCOCCUS

Cryptococciosis

- Etiology: *Cryptococcus neoformans*.
- Replicate by budding new yeast cells 4-6 µm, has large characteristic complex polysacharide capsule (>25 µm) -- Able to evade phagocytosis
- Culture appearance in Saboraud Dextrose agar containing no cycloheximide*: smooth, creamy, mucoid white colony in 2-3 days
- Phenoloxidase → produces melanine
- Produces urease in culture
C. neoformans 
A-B-D-E

A. niger 
C-F
- Capsule of Cryptococci:
  - protection against some stress conditions (dehydration)
  - strong immunomodulatory properties -- promotes immune evasion
  - capsular components are key virulence determinants
- Composed primarily of two polysaccharides:
  - glucuronoxylomannan (GXM) 90-95%
  - galactoxylomannan (GalXM) 5-8%
  - mannoproteins (MP) <1%
- acapsular strains (mutants) can be pathogenic for severely immunocompromised hosts

Host reaction to encapsulated cryptococci
- During the first hours of infection, a significant proportion of the yeast cells injected in the lungs are found inside phagocytic cells → this will overcome the antiphagocytic effect of the capsule.
- Mechanisms that allows phagocytosis:
  1) the presence of opsonins (antibodies and proteins from the complement system)
  2) direct interaction of the polysaccharide fibers with phagocytic receptors that occur after capsule structure rearrangements.

Ref: Feldmesser et al, 2000
Cryptococcosis - pathogenesis

- Major risk factors: HIV/AIDS, lymphoma, corticosteroid therapy, and idiopathic CD4, T lymphocytopenia (T cell disfunction)
- Predisposing conditions: lymphoma, sarcoidosis or treatment of corticosteroid
- Aerosolized spores in soil reach the lung → in the tissue, spores start to produce capsule that enables to evade immune response.
- GXM binds to complement C3 and interfere with antigen presentation.
- Lung lesions: intense granulomatous inflammation

Cryptococcosis – Clinical Manifestation

- Causes chronic meningitis and pneumonia.
- Silent hematogenous spread to the brain → clusters of cryptococci in the perivasc areas of the gray matter
- Symptoms:
  - Headache, nausea, staggering gait, dementia, irritability, confusion, blurred vision
  - Fever, nuchal rigidity often mild
- **Cryptococcal pneumonia** is mostly **asymptomatic**.
  - Chest pain (40%), cough (20%)
Cryptococcosis - diagnosis

- Cryptococcal meningitis: CSF $\rightarrow$ increased pressure, pleocytosis, glucose depression
- Isolation of fungi in CSF requires large volume specimen
- *C. neoformans* is thickly encapsulated when observed in mammalian tissues. However, upon culture in artificial media, capsule thickness is variable and strain dependent
  - Capsule in CSF can be stained by China Ink

- The capsule is not visible by regular microscopy because it is highly hydrophilic and due to its high water content it has the same refraction index as the medium.
- However, it can be easily made visible by several techniques
  - Ink $\rightarrow$ halo effect
  - scanning electron microscopy
  - Fluorescence microscope
Cryptococcus neoformans

Different micrographs and compositions showing the polysaccharide capsule of C. neoformans: A) Suspension of the cells in India ink; B) Scanning electron microscopy; C-H) Immunofluorescence using specific mAbs to the capsule (green and red fluorescence) showing also the cell wall localization (blue fluorescence). D) 3D image composition of a C. neoformans cell labeled with two different mAbs to the capsule. In blue, the cell wall. E) Side view of a section of cell shown in D. F-H) Sections showing the 3 dimension of the capsule, visualized after staining with mAbs (green and red). Pictures by Oscar Zaragoza, and from (Macon et al, 2007b).

Opportunistic fungal infections

Cryptococcosis

Appearance of Cryptococcus neoformans on Niger seed agar.
Infection with the encapsulated yeast Cryptococcus neoformans.

Most infections occur in immunocompromised patients especially those with AIDS.

Meningitis is the most common clinical presentation.

(a) Section showing the presence of intracellular and extracellular organisms, H and E, ×40.

(b) PAS stained section showing the presence of capsulated organisms with morphology of Cryptococcus. ×40.

(c) India ink preparation showing capsulated yeast; there is mother yeast cell with the attached daughter cell that is budding off, ×40

Ref: Tarai B., et al, 2010
**C. neoformans**

Wide nonstaining capsule

Budding of cell

(modified Wright’s stain; bar = 40 μm)

Opportunistic

**ASPERGILLUS**
Aspergillus

- Aspergillus spp. are molds with branching septate hyphae and characteristic conidia arrangement on the conidiophore.
- Fluffy colonies 1-2 days – 5 days full pigmented growth covering plate
- Most frequent spp:
  - *Aspergillus fumigatus*
  - *Aspergillus flavus*
  - *Aspergillus niger*

Aspergillus (KOH)

Growth on SAB Agar (grows in 48 hr)
Aspergillosis

Forms of disease caused by Aspergillus

- Pulmonary aspergillosis
- Invasive aspergillosis
- Allergic bronchopulmonary aspergillosis

Aspergillosis

- Occurs in immunocompromised individuals, rapid progression to death.
- The only sign and symptom may be fever and dry cough.
- Conidia is small enough to enter the lung
- Adherence with fibrinogen and laminin.
- Extracellular elastase, proteinase, phospholipase \(\rightarrow\) more virulent
Histologic microphotograph of Aspergillus spp in HE

Dichotomous Branching septate hyphae

Bar = 30 um

Invasive aspergillosis

- Occurs in the presence of preexisting pulmonary disease (bronchiectasis, bronchitis, asthma, TB) or immunosuppression.
- Aspergillus invade tissues by forming branching septate hyphae → 'fungus ball' = aspergilloma within preexisting cavity.
- Invasion into blood vessels → hemoptysis
- Erosion to other organs → fistula
Aspergillus - Diagnosis

- Isolation and identification
- Rapid growth, frequently as contamination
- Specimen: lung aspiration, biopsy and bronchoalveolar lavage

Grocott stain colours the hyphae of Aspergillus in lung tissue black

Aspergillus fumigatus bar represents 10 µm

Ref: Barton et al, 2013
## Laboratory Diagnosis for Invasive aspergillosis

### Table 2: Main approaches to laboratory diagnosis.

<table>
<thead>
<tr>
<th>Test</th>
<th>Specimens</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct microscopy</td>
<td>Respiratory</td>
<td>Low cost</td>
<td>Inensitive, labour intensive</td>
</tr>
<tr>
<td>Culture</td>
<td>Respiratory, tissue</td>
<td>Low cost, enables further analysis</td>
<td>Insensitive</td>
</tr>
<tr>
<td>Histopathology</td>
<td>Tissue</td>
<td>Enables proven diagnosis</td>
<td>Requires biopsy tissue</td>
</tr>
<tr>
<td>Galactomannan (GM)</td>
<td>Serum, BAL</td>
<td>Sensitive, specimens easy to obtain</td>
<td>Lacks sensitivity in patients on antifungals</td>
</tr>
<tr>
<td>β-D-glucan (BDG)</td>
<td>Serum</td>
<td>Sensitive, specimens easy to obtain</td>
<td>Lacks specificity</td>
</tr>
<tr>
<td>PCR (DNA detection)</td>
<td>Any</td>
<td>Sensitive, can be applied to any specimen</td>
<td>Labour intensive, expensive</td>
</tr>
</tbody>
</table>

Note: GM is carbohydrate molecule with mannose backbone and side chain galactofuranosil

Ref: Richard Barton, 2013

---

## Characteristic microscopy and Available serologic tests

<table>
<thead>
<tr>
<th>Fungi</th>
<th>Cytologic morphology</th>
<th>Serologic test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptococcus neoformans</td>
<td>Round, thin walled yeast like cell (5-10 um), and large heteropolysaccharide capsule (1-30 um)</td>
<td>Caspular Ag ELISA (Ag) Latex agglutination (Ag)</td>
</tr>
<tr>
<td></td>
<td>Capsule best stained in mucocarmine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Narrow based budding</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No endospores</td>
<td></td>
</tr>
<tr>
<td>Coccioidiodes immitis</td>
<td>Relatively large spherules (20-80 um; up to 200 mm with double contoured cell wall)</td>
<td>Agar gel immunodiffusion (Ab) for TgM and IgG</td>
</tr>
<tr>
<td></td>
<td>The mature spherules are called sporangiospores (2-5 um)</td>
<td>CF (Ab) may have some false positive results</td>
</tr>
<tr>
<td>Aspergillus spp</td>
<td>Broad (2-4 um) septate hyphae with parallel sides and acute, right angle branching</td>
<td>Aspergillus galactomannan EIA (sandwich immunoassay Ag test; some reactivity with penicillium, Alternaria and paecilomyces spp</td>
</tr>
</tbody>
</table>
Zygomycosis

- Zygomycosis (mucormycosis) is caused by any of zygomycetes (Absidia, Rhizopus, Mucor).
- Saprophyts
- Immunocompromised hosts with diabetes are infected
- Pulmonary disease is similar to other fungi
- Pathologic finding in tissue: ribbonlike non septate hyphae.

Histoplasma

TRUE PATHOGEN
Histoplasma capsulatum (1)

- It is found worldwide, in soil and in bat’s feces
- Endemic to the temperate zones: Americas, Asia, Africa
- Multiply by budding (blastoconidia)
- **Dimorphic**: yeast form 2-4 µm at 37°C and Mold phase at 22-25°C
- Grows in culture in weeks time
- Mycelial phase produces microconidia and macroconidia
- Able to survive in macrophage by modulating pH inside fagosome thus stops fusion with lysosome – virulence fc of Histoplasma
- Diagnostic structure: *tuberculate macroconidium*

Histoplasma Clinical Manifestation

- Most cases are asymptomatic
- Clinical symptoms of acute or epidemic histoplasmosis: high fever, non productive cough, asthenia and retrosternal pain, enlargement of the cervical lymph nodes, hepatosplenomegaly, erythema nodosum, erythema multiforme.
- X-ray: mediastinal lymphadenopathy, infiltrates
- Histoplasmin skin test positive in 3 weeks.
- Residual nodule may continue to enlarge over a year and mimic pulmonary neoplasma.
- Progressive pulmonary disease resembles pulmonary tuberculosis
Histoplasma - Pathogenesis

- Reticuloendothelial system is the focus of infection.
- Inhaled microconidia/spores → changes to yeast form in the host body
- When phagocytosed (by macrophage and PMNs) it may grow inside macrophages by controlling lysosomal pH (increased to neutral) → remains able to multiply inside macrophage → to mediastinal lymph nodes → hematogenous spread
- Further lymphatic spread and development of primary lesion is similar to Mycobacteria

- 10-14 days in Macrophage—necrosis—caseation, fibrous encapsulation, calcium deposition, calcified granulomas
- → persist for years, dormant
- → reactivate if immunity decreases
Histoplasmosis

Definition
A mild and transient pulmonary infection in normal individuals caused by the dimorphic fungus *Histoplasma capsulatum*. Can proceed to a chronic infection of the lungs or more widespread infection in predisposed patients.
Numerous tuberculate macroconidia of Histoplasma capsulatum on culture on SDA. ×400. LPCB mount.

FIG. 7. Yeast forms of H. capsulatum found in a neutrophil in a peripheral blood smear.

Ref: Kauffman, 2007
Yeast forms of *H. capsulatum* observed on BHIA. ×400. LPCB mount

**Histoplasma diagnosis**

- **Culture** → GOLD STANDARD : Grows up to 4 weeks
  - INFECTIOUS → Work in Biosafety cabinet !!
- **Histopathology** → rapid but less sensitive than culture or antigen detection
  - Disseminated histoplasmosis → use blood and bone marrow, Wright or Hematoxylin Eosin staining shows intracellular histoplasma, tuberculate macroconidium and dimorphism
Histoplasmosis diagnosis

- **Antigen Detection** ➔ EIA (immunodiffusion)
- **PCR Assays** ➔ Real Time PCR
- **Antibody Tests** ➔ false neg in the initial phase of disease and in immunocompromised patients
- **Skin Tests** ➔ high background positivity in endemic area ➔ rarely useful

Histoplasmosis - treatment

- Mild cases: symptomatic
- Severe/prolonged acute pulmonary infection and disseminated disease: antifungal therapy
  - Amphotericin B ➔ agent of choice
  - Itraconazole
Blastomyces dermatitidis

- Caused by the dimorphic fungus that changes to mycelial at 250C. Produces microconidia, but no macroconidia
- Blastomyces is similar to histoplasma, but larger yeast cells (8-15 µm), has broad base buds and thick wall.
Blastomyces – clinical manifestation

- Most clinical features are similar to histoplasmosis (asymptomatic or cough or mild fever).
- Infection typically presents as an acute or self-limited pneumonia, but chronic pulmonary, cutaneous, and disseminated forms of blastomycosis.
- Disseminated infection: skin lesions.

Blastomyces – pathogenesis

- Has surface glucan and glycoprotein adhesin (BAD₁) for binding to host cells.
- Yeast are large cells, thick double walls, extracellular.
Blastomyces – Clinical manifestation

- Pulmonary infection: cough, sputum production, chest pain, fever.
- Hilar lymphadenopathy, nodular pulmonary infiltrates with alveolar consolidation \(\rightarrow\) resembles pulmonary tumor, tuberculosis, other mycosis.
- Skin lesions: occur on exposed skin

Blastomyces – Diagnosis

- The presence of large yeast cells with broad-based buds (blastoconidia) in KOH preparation
- Biopsy \(\rightarrow\) H & E staining
- Culture: grow in weeks, but conidia not distinctive
- Immunodiffusion test
- Serologic tests mostly negative
TRUE PATHOGEN: COCCIDIOIDES

Coccidioides

- History
- Clinical symptoms
- Fungal Morphology
- Diagnosis and Treatment
Coccidioides – History

- Named after a medical student: Alejandro Posadas
- Skin lesion $\rightarrow$ cultured $\rightarrow$ observed microscopical hyphae and spherule in the culture

Coccidioides – disease

- The disease Coccidioidomycosis is also known as
  - = Posadas-Wernicke disease
  - = Desert rheumatism
  - = San Joaquin Valley Fever
  - = Coccidioidal Granuloma
- **Endemic** in the southwestern US and Central America (Mexico); but recently has been reported in India, Turkey, Japan, (and possibly will be in other countries) as a disease obtained after travelling in the endemic areas.

Ref: De Deus Filho, 2009
Coccidioides – Clinical Form

1. Primary Pulmonary ➔ THIS FORM IS THE MOST FOUND
2. Progressive pulmonary
3. Disseminated diseases: skin, bone, endocarditis, meningitis, bowel, genito-urinary infection

Coccidiodes - infection of the lungs

- After inhalation of spores flowing in the dust 1-15 days
  - 60% benign and resolves spontaneously
  - 40% progressive disease with pulmonary and other organs symptoms
- Symptoms: malaise, cough, chest pain, fever, dyspnea, hemoptysis, fever, arthralgia 2-6 weeks (Valley Fever), diverse skin reactions: maculopapular rash, erythema multiforme, erythema nodosum (common in women)
- Chronic: pulmonary cavity
Coccidioides immitis

- Disseminated disease is more common in men, and related with racial orientation and immune status
- Differential Diagnosis:
  - nonspecific pneumoniae
  - Tuberculosis
  - Pneumoconiosis
  - Silicosis

Coccidioides immitis

- Symptomatic infection typically presents as **pneumonitis** with hilar adenopathy and cutaneous rashes → subacute and self limiting: Valley Fever
- Hematogenous spread: extensive granulomatous reactions and tissue damage in the skin, bones and joints, meninges, and genitourinary tract.
Coccidioidomycosis – Diagnosis

- X ray: Cavity and fungus ball formation
- Fibre optic bronchoscopy
- Laboratory:
  - Serology
  - **Culture on Saboraud Agar**
  - Microscopy on Histology preparations
  - **Nucleic Acid Amplification Techniques (NAAT)**

Coccidioides – culture

- Grow at most media, at room temperature
- Day 3-4: White cotton-like colonies
  - Micr: hyalin hyphae, septate, ramified, Ø 2-4 µm
- Day 5: forms (multinucleated) arthroconidia
  - Arthroconidia in lab culture is **highly infectious**
  - Arthroconidia detaches: barrel shape Ø 2-4 µm, containing endospores
  - Arthroconidia if inhaled from the air ➔ in the lungs ➔ converts into spherules and progeny endospores
Coccidioides immitis

- **Culture:**
  - Grows on most media
  - Grows in 5 days
  - Colonial structure of the mycelial phase is not diagnostic \(\rightarrow\) MYCELIAL PHASE IS HIGHLY INFECTIOUS \(\rightarrow\) perform lab work in biological containment cabinet !!

Coccidioides - Microscopy

- **Tissue biopsy**
  - KOH
  - Hematoxylin eosin
  - Periacid Schif (PAS)
  - Grocott-Gomori Methenamin Silver Stain

- **Microscopy of tissue:** spherules containing endospores
Case Report:
Fungus Ball detected in a Japanese man’s lung after a short stay in an endemic area

Histological examination of the fungus ball showed numerous septate hyphae with terminal expansion (Grocott stain ×400).

Osaki T et al, 2005

Chest radiograph on admission showing a thin-wall cavity in the right lower lung field.

Macroscopic view of the resected lung demonstrates a cavity of 1.5×1.0 cm diameter encapsulated by a thick and fibrous wall.

The cavity contains a gray fungus ball and indents the pleura.

Ref: Osaki T et al, 2005
Case report:
Fungus Ball in the lung of a 20 y.o. women 15 years living in an endemic area

Chest X ray showing cavity at the right lower lung

Enlargement of the radiography

Ref: Winn et al, 1994

Systemic mycoses

Erythema multiforma in a patient with primary pulmonary coccidioidomycosis.
Coccidioides – Etiology

- *Coccidioides immitis*
- *Coccidioides posadasii*

Dimorphic life cycle

- Arthroconidia (2-3 x 4-6 µm) if inhaled, enters the bronchioles and convert into invasive-spherules.
- The spherules enlarge (20 to 100 mm) and segment internally into hundreds of endospores.
- Endospore is capable to become another spherule
- Spherules are coated with an extracellular matrix which restricts PMN access.
- Arthroconidia has antiphagocytic action due to the outer portion of the cell wall
Coccidioides Dimorphic life cycle

Ref: Nguyen et al, 2013

Coccidioides tests

- Skin Test (coccidioidin or spherulin) will show delayed hypersensitivity – proof of past infection
- Serology:
  - IgM – Acute disease
  - IgG antibody -- a decrease indicates effective R/ but an increase indicates non effective R/ → intensify R/ or change R/
  - If negative result -- does not rule out an infection
Coccidioidomycosis Treatment

- Localized acute pulmonary infection and no risk factors for complications → assess the self-limiting process and R/azole antifungals
- Extensive spread or immunosuppression → R/azole or polyenes antifungals and/or surgical debridement.
  - 1st class = polyenes (amphotericin B desoxycholate)
  - 2nd class = fluconazole, itraconazole, voriconazole, posaconazole

PARACOCIDIDIODOMYCOSIS

True Pathogens
Paracoccidioidomycosis

- A soil saprophyte
- Inhalation of propagules → lung → disseminate mucous membrane, lymph node, skin, adrenal gland, oral, nasal, GI mucous membranes.
- Subacute infection (in children) becomes chronic systemic mycoses (in adults)
- Among rural men workers restricted to Latin America
- Is the most frequent endemic systemic mycosis in many countries of South America.

Paracoccidioidomycosis - etiology

- *P. brasiliensis*
- *P. lutzii*
Paracoccidioides brasiliensis

- Paracoccidioidomycosis = South American Blastomycosis
- Occurs mainly in men → estrogen receptors block the change of hyphae to an invasive yeast form
- Causes primary pulmonary infection even in immunocompetent person
- Dimorphic fungi: slow growing (20-30 days)
- Thermomorphemic: growth is induced by temperature

Paracoccidioidomycosis - Differential Diagnosis

1. Pulmonary tuberculosis and atypical mycobacterioses
2. Sarcoidosis
3. Histoplasmosis
4. Idiopathic diffuse interstitial pneumonitis
5. Chronic silicosis
6. Coccidioidomycosis
7. Chromoblastomycosis
8. Cutaneous and visceral leishmaniasis
9. Leprosy
10. Cutaneous and laryngeal neoplasia

Ref: Hahn et al, 2014
Paracoccidioides brasiliensis

- **Diagnosis:**
  - Culture → Saboraud Agar
  - Direct microscopy on tracheal aspirate: multiple budding on a large yeast cell (20-60 um) → pilot’s or steering wheels or Mickey mouse appearance
  - Serology: Antifungal antibody
    - Immunodiffusion (ID)
    - Counter immunoelectrophoresis (CIE)
    - ELISA

Culture of a conidia at 36oC converts it into multiple budding yeast cell (as viewed under the microscope)

Ref: Brummer et al, 1993
# Thermo-dimorphism of *Paracoccidioides lutzii*

Hyohae at 25°C on Potato Dextrose Agar  
Yeast at 37°C on Fava –Netto Medium

<table>
<thead>
<tr>
<th>Organism</th>
<th>Growth</th>
<th>Tissue</th>
<th>Source</th>
<th>Primary Disease</th>
<th>Disseminated Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. neoformans</em></td>
<td>Encaps. Yeast</td>
<td>Encaps. Yeast</td>
<td>Environm, worldwide</td>
<td>Pnie</td>
<td>Chronic meningitis</td>
</tr>
<tr>
<td><em>H. capsulatum</em></td>
<td>Mold, Tuberculate</td>
<td>Small yeast</td>
<td>Environm, US midwest</td>
<td>Pnie, hilar adenopath</td>
<td>RES enlargement</td>
</tr>
<tr>
<td><em>B. dermatitidis</em></td>
<td>Mold</td>
<td>Yeast</td>
<td>Environm, US midwest</td>
<td>Pnie</td>
<td>Skin and bone lesion</td>
</tr>
<tr>
<td><em>C. immitis</em></td>
<td>Mold, arthrocon.</td>
<td>Spherules</td>
<td>Environm, Sonoran desert</td>
<td>Pnie</td>
<td>Pnie, meningitis, skin, bone</td>
</tr>
<tr>
<td><em>P. brasiliensis</em></td>
<td>Mold, multiple blastokon</td>
<td></td>
<td>Environm, Latin America</td>
<td>Pnie</td>
<td>Mukokutan, RES</td>
</tr>
</tbody>
</table>