Pathogenic Fungi
• Diagnosis, management, and prevention of fungal diseases, or mycoses

• Mycoses are among the most difficult human diseases to diagnose and treat
  • Signs of mycoses are often missed or misinterpreted
  • Fungi are often resistant to antifungal agents
Epidemiology of Mycoses

- Fungi and their spores are almost everywhere in the environment (Most people will experience a mycosis)
- Spores are light and spread easily
  - Geographical Disease
- Typically acquired via inhalation, trauma, or ingestion
- Spread from person to person is infrequent
- Most mycoses are not contagious
  - Dermatophytes, fungi found on the skin, are the major exception
Epidemiology of Mycoses

• Epidemics result from mass exposure to some environmental source of fungi
• Mycoses are generally not reportable to CDC
  • No good information on occurrence or spread
• Most are weakly invasive and have no virulence
  • Few true pathogens

Human infective agents are dimorphic
Thermal Dimorphism

What is the normal role of fungi in the environment?
Categories of Fungal Agents

- Only four fungi are usually considered true pathogens
  - Have the ability to actively attack and invade tissues
  - Exhibit dimorphism
    - Based on differences in temperature
      - Environment (<30°C) - mycelia thalli composed of hyphae
      - In the body (>30°C) exist as yeast thalli
    - Yeast forms are invasive
      - Production of enzymes and proteins
  - Endemic to certain regions, primarily in the Americas
Opportunistic fungi account for the remaining diseases in humans

- Usually 2\textdegree\ infections
- Take advantage of a weakness in a host’s defenses
- Distributed throughout the world
- Dermatophytes are considered opportunists
  - often occur in individuals susceptible to opportunistic fungi
- Four factors increase an individual’s risk for acquiring an opportunistic mycoses
Factors that Predispose Individuals to Opportunistic Mycoses

<table>
<thead>
<tr>
<th>Factors</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Medical procedures</td>
<td>Surgery; insertion of medical implants (heart valves, artificial joints); catheterization</td>
</tr>
<tr>
<td>Medical therapies</td>
<td>Immunosuppressive therapies accompanying transplantation; radiation and other cancer therapies; steroid treatments; long-term use of antibacterial agents</td>
</tr>
<tr>
<td>Preexisting conditions</td>
<td>Inherited immune defects; leukemia and lymphomas; AIDS; diabetes and other metabolic disorders; severe burns; preexisting chronic illnesses</td>
</tr>
<tr>
<td>Lifestyle factors</td>
<td>Poor diet; poor hygiene; IV drug abuse</td>
</tr>
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</table>
Clinical Manifestations of Fungal Disease

- Fungal diseases are grouped in three categories of clinical manifestation
  - Fungal infections
    - Most common mycoses
    - Caused by the presence in the body of either true pathogens or opportunists
  - Toxicoses
    - Acquired through ingestion
    - Occurs when poisonous mushrooms are eaten
  - Allergies
    - Most often result from the inhalation of fungal spores
Diagnosis of Fungal Infections

• Patient history is critical for diagnosis of most mycoses
• Definitive diagnosis often requires
  • isolation, laboratory culture, and morphological analysis of the fungus involved (2 weeks to grow)
• What media is best for growing fungi?
  • This medium favors fungal growth over bacterial growth
Immunological tests are not always useful for fungi

Due to the prevalence of fungi in the environment

hard to distinguish between an infection and simple exposure

Opportunistic infections are particularly difficult to diagnose

Fungal types can be confused with one another as well as with other diseases

Fungi can display abnormal morphology in tissues where infection wouldn’t normally occur
Antifungal Therapies

• Mycoses are among the most difficult diseases to heal
  • Fungi can often resist the oxidative damage of T cells during cell-mediated immune responses
  • As eukaryotes, fungi are similar to human cells and antifungal drugs can harm human tissues
• Fungi have ergosterol in their membranes rather than cholesterol and it is often a target for antifungal treatment
  • Side effects can still result, especially with long-term use
Amphoterecin B is the ‘gold standard’ of antifungal agents but also the most toxic.

Other antifungal agents include various azole drugs, fluorocytosine, and griseofulvin.

Opportunistic infections treatment requires two steps:
- High-dose treatment to eliminate or reduce the fungal pathogens
- Long-term maintenance therapy to control and prevent reinfection

Topical Antifungals – imidazoles
- Arrest synthesis of fungal cell walls (What in particular?)
Infections spread throughout the body

Caused by one of the four pathogenic, dimorphic fungi of the division Ascomycota

- *Blastomyces*, *Coccidioides*, *Histoplasma*, and *Paracoccidioides*

Acquired through inhalation

Begin as a generalized pulmonary infection that disseminates to the rest of the body

Individuals working with dimorphic fungi in the laboratory must take multiple precautions to avoid exposure to spores
Blastomycosis

- *Blastomyces dermatitidis* is the causative agent
  - Chicago Disease
- Endemic in the southeastern United States north to Canada
- Fungi found in soils rich in organic matter
- Inhalation of dust can carry fungal spores or hyphal pieces into the lungs
- Pulmonary blastomycosis is the most common manifestation in humans
  - Initial pulmonary lesions are mostly asymptomatic and symptoms, when they develop, are often vague
  - The disease resolves in most people but in others it may be chronic
Blastomycosis

• Chronic Disease
  • Tumor-like growth in the lungs
  • Nodules on the liver, face and hands

• Dissemination of the fungus can occur
  • Results in cutaneous or osteoarticular blastomycosis
  • AIDS patients may develop meningitis

• Treatment is with amphotericin B
Coccidioidomycosis

- *Coccidioides immitis* is the causative agent
  - San Joaquin Fever or Valley Fever
- Almost exclusively in the southwestern United States
- Fungi found in desert soil, rodent burrows, archaeological remains, and mines
- Inhalation of dust can carry the arthrospores (asexual spores) into the lung
  - The spores germinate into spherules that in turn produce more spores that are released into surrounding tissue
Coccidioidomycosis

- Coccidioidomycoses most often result in pulmonary conditions
  - Many patients show no or few symptoms but some may develop severe or chronic pulmonary disease
- Dissemination to other sites occurs mostly in immunocompromised individuals
- Infections in healthy individuals resolve on their and require no treatment
  - And have life-long immunity
- Amphotericin B is the preferred drug for those who require treatment
Histoplasmosis

- *Histoplasma capsulatum* is the causative agent
  - Ohio Valley Fever
- Most common fungal pathogen affecting humans
  - Skin Sensitivity test shows huge distribution of the fungus
  - 500,000 cases/yr US
- Found mostly in the eastern United States but also in Africa and Asia - (exists in soil of most countries except Australia)
- Fungi found in moist soils containing high levels of nitrogen from bat and bird droppings
Inhalation of spores into the lungs is the most common route of infection. *H. capsulatum* first attacks alveolar macrophages and is then dispersed beyond the lungs via the blood and lymph. These infections are usually asymptomatic and resolve without damage. Clinical histoplasmosis can result in one of four diseases: chronic pulmonary histoplasmosis, chronic cutaneous histoplasmosis, systemic histoplasmosis, ocular histoplasmosis. Infections in healthy individuals resolve on their own and require no treatment.
Histoplasmosis

- Diagnosis – sputum culture
  - PCR
  - Fish eye test for macrophages
- Treatment – IV amphotericin B for days or weeks
• *Paracoccidioides brasiliensis* - causative agent
• Found in southern Mexico and regions of S. America
• Relatively rare disease found most in farm workers
• Disease *similar to* blastomycosis & coccidiodomycosis
• Infection begins as a *pulmonary condition*
• Dissemination almost always follows
  • Produces a chronic inflammatory disease of mucous membranes
• Treatment is with amphotericin B or ketoconazole
Paracoccidioides brasiliensis

A) KOH preparation from sputum of patient with paracoccidiomycosis, showing multiple budding yeast

B) X-ray of patient with paracoccidiomycosis
Systemic Mycoses Caused by Opportunistic Fungi

• Opportunistic mycoses don’t typically affect healthy humans

• Limited to people with poorly functioning immune systems
  • Number of immunocompromised individuals is rising

• Difficult to identify
  • Symptoms are often atypical

• The five genera routinely encountered are considered “classical” opportunists
  • Aspergillus, Candida, Cryptococcus, Pneumosystis, and Mucor
Emergence of Fungal Opportunists in Immunosuppressed Individuals

• AIDS patients
  • permanent immune dysfunction
  • Mycoses account for most AIDS deaths
• Candida albicans, Aspergillus fumigatus, and Cryptococcus neoformans are so common in HIV-positive individuals their mycoses partly define end-stage AIDS

• Emergence of new fungal opportunists
  • increase in immunocompromised individuals
  • fungi resistant to antifungal drugs
Dermatophytoses

- Fungal infections of the skin or nails caused by dermatophytes
- Infections were previously called ringworms because they resemble a worm lying below the surface of the skin
- Result from fungi that use keratin as a nutrient source and thus colonize only dead layers of skin, nails, and hair
- No living tissues are infected
Dermatophytoses

- Dermatophytes are classified into three groups
  - Anthropophilic
    - Fungi of humans that are transmitted by human contact or infected objects
  - Zoophilic
    - Fungi of animals that are transmitted by contact with animals or their products
  - Geophilic
    - Soil fungi that are transmitted to humans via exposure to soil or dusty animals
Dermatophytoses

• Signs & Symptoms - variety of clinical manifestations
• Treatment - topical antifungal agents
  • Imidazoles – arrest the synthesis of fungal cell wall (chiton)

• Two most common
  • Trichophyton
  • Microsporum
# Common Dermatophytoses

<table>
<thead>
<tr>
<th>Disease</th>
<th>Agents</th>
<th>Common Signs</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinea pedis (&quot;athlete’s foot&quot;)</td>
<td><em>Trichophyton rubrum</em>; <em>T. mentagrophytes var. interdigitale</em>; <em>Epidermophyton floccosum</em></td>
<td>Red, raised lesions on and around the toes and soles of the feet; webbing between the toes is heavily infected</td>
<td>Human reservoirs in toe-webbing; carpeting holding infected skin cells</td>
</tr>
<tr>
<td>Tinea cruris (&quot;jock itch&quot;)</td>
<td><em>T. rubrum</em>; <em>T. mentagrophytes var. interdigitale</em>; <em>E. floccosum</em></td>
<td>Red, raised lesions on and around the groin and buttocks</td>
<td>Usually spreads from the feet</td>
</tr>
<tr>
<td>Tinea unguium (onychomycosis)</td>
<td><em>T. rubrum</em>; <em>T. mentagrophytes var. interdigitale</em></td>
<td><em>Superficial white onychomycosis</em>: patches or pits on the nail surface; <em>Invasive onychomycosis</em>: yellowing and thickening of the distal nail plate, often leading to loss of the nail</td>
<td>Humans</td>
</tr>
<tr>
<td>Tinea corporis</td>
<td><em>T. rubrum</em>; <em>Microsporum gypseum</em>; <em>M. canis</em></td>
<td>Red, raised, ringlike lesions occurring on various skin surfaces (tinea corporis on the trunk, tinea capitis on the scalp, tinea barbae of the beard)</td>
<td>Can spread from other body sites; can be acquired following contact with contaminated soil or animals</td>
</tr>
<tr>
<td>Tinea capitis</td>
<td><em>M. canis</em>; <em>M. gypseum</em>; <em>T. equinum</em>; <em>T. verrucosum</em>; <em>T. tonsurans</em>; <em>T. violaceum</em>; <em>T. schoenleinii</em></td>
<td><em>Ectothrix invasion</em>: fungus develops arthroconidia on the outside of the hair shafts, destroying the cuticle; <em>Entothrix invasion</em>: fungus develops arthroconidia inside the hair shaft without destruction; <em>Favus</em>: crusts or scutula form on the scalp, with associated hair loss</td>
<td>Humans; can be acquired following contact with contaminated soil or animals</td>
</tr>
</tbody>
</table>

Table 22.3
Fungal Intoxications and Allergies

- Some fungi cause allergies or produce toxins that cause toxicosis
- 2 types of toxicosis
  - Mycotoxicosis
    - Eating foods contaminated with fungal toxins
  - Mycetismus
    - Mushroom poisoning from eating a fungus
- Fungal allergens can elicit a hypersensitivity response in sensitive individuals
  - Result from inhalation, ingestion, or other contact
Mycotoxicoses

- **Mycotoxins** (some use to make drugs)
  - produced by fungi during normal metabolic activities
  - poisonous to animals and humans
- Consumed in contaminated food crops
- Long term ingestion of mycotoxins
  - cause liver and kidney damage, gastrointestinal or gynecological disturbances, or cancers
- Aflatoxins are the most well-known mycotoxins
  - Fatal to many vertebrates and carcinogenic at low levels when consumed continually
  - Prevalent in the tropics
Mycetismus

- Most mushrooms are not toxic
- Mushrooms that produce poisons
  - cause neurological dysfunction or hallucinations
  - organ damage, or even death
- Poisoning typically occurs when untrained individuals pick and eat wild mushrooms
- The deadliest mushroom toxin is produced by the “death cap” mushroom
Allergies to Fungi

• Fungal allergens are common both indoors and out
• Determining the specific cause can be difficult because of their presence in the environment
• Fungal allergens usually cause type I hypersensitivity reactions that can result in asthma, eczema, and hay fever
• Type II and III hypersensitivity reactions can occur but much less frequently