Infectious diseases

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	4/5th Semester Classes on Infectious Diseases, 8-9AM, Tuesdays (LT-1)
	Topics
1	Approach to Infectious Diseases and their prevention
2	Antibiotic stewardship practices
3	Community-Acquired Infections
4	Health Care–Associated Infections
5	Gram-Positive Bacteria (part-1)
6	Gram-Positive Bacteria (part-2)
7	Gram-Negative Bacteria (part-1)
8	Gram-Negative Bacteria (part-2)
9	Spirochetal Diseases
10	Diseases Caused by Atypical/Miscellaneous Bacterial Infections
11	**Revision-cum-exam on bacteria (Must to know type)**
12	Infections Due to DNA Viruses
13	Infections Due to RNA Viruses (part 1)
14	Infections Due to RNA Viruses (part 2)
15	HIV/AIDS – part 1
16	HIV/AIDS – part 2
17	Fungal Infections
18	Parasitic Infections (part 1)
19	Parasitic Infections (part 2)
20	**Revision-cum-exam on Virus, Fungal, and Parasite (Must to know type)**

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Fungi as Infectious Agents

- Fungi are the most common plant pathogens
- Of the 100,000 fungal species, only 300 have been linked to disease in animals
- Most striking adaptation to survival and growth in the human host is the ability to switch from hyphal cells to yeast cells (**Thermal dimorphism** – grow as molds at 30°C and as yeasts at 37°C)
- True fungal pathogens are distributed in a predictable geographical pattern - climate, soil
- The growth of the fungi generally involves two phases; **vegetative** (mold/yeast) and **reproductive** (asexual (spore) /sex)

Hyphal colonies
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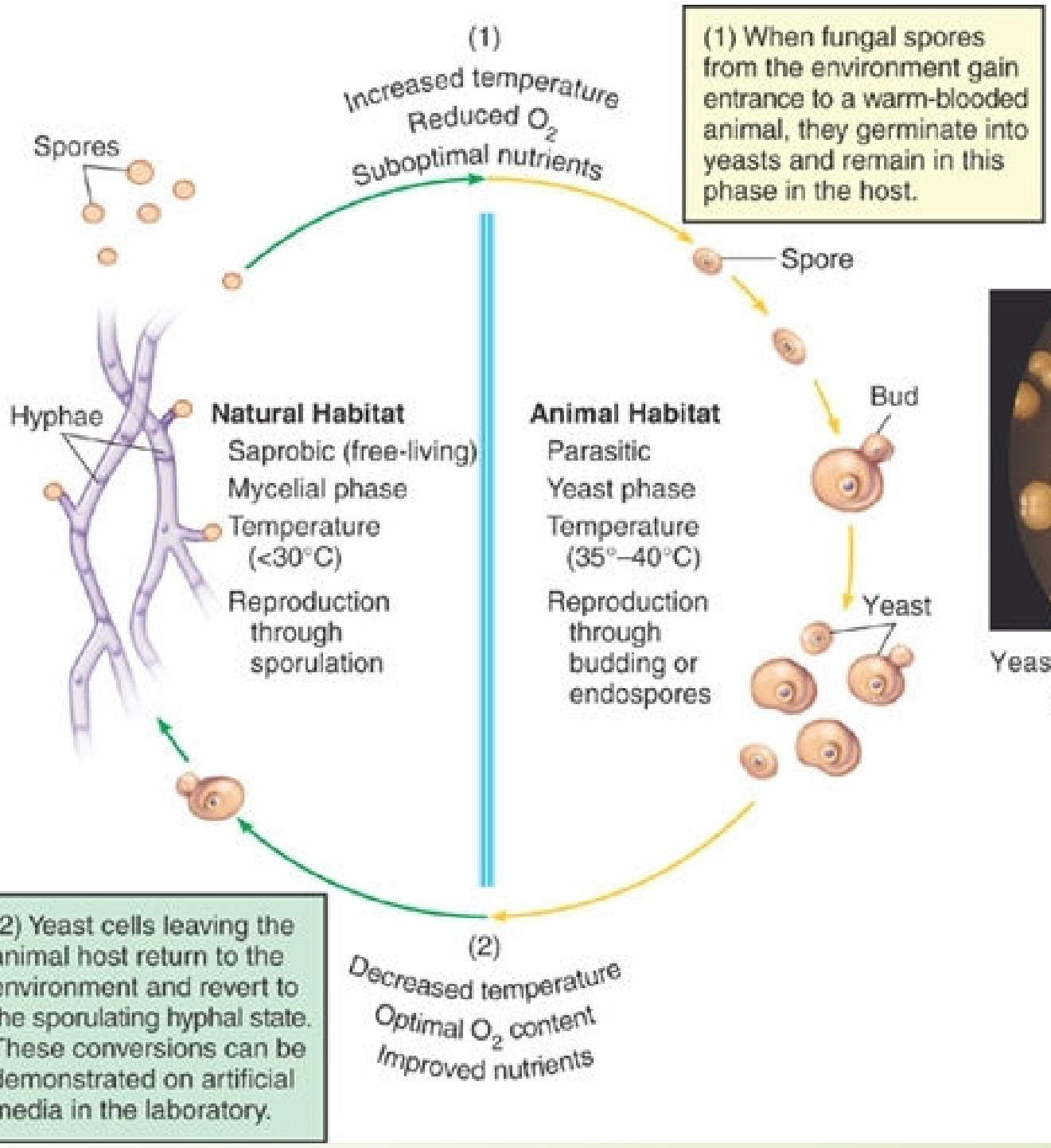

Yeast colonies
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Classification - by both anatomic location and epidemiology

- **Superficial infections** and **Cutaneous infections** (Dermatophycoses)
- **Subcutaneous infections** involve the dermis, subcutaneous tissues and muscle
- **Systemic infections**

Endemic Mycoses[a]	Opportunistic Mycoses
Coccidioidomycosis	Candidiasis
Histoplasmosis	Aspergillosis
Blastomycosis	Cryptococcosis
Phaeohyphomycosis	Mucormycosis (zygomycosis)
Penicilliosis	Scedosporiosis
Sporotrichosis	Trichosporonosis
Paracoccidioidomycosis	Fusariosis
	Pneumocystosis

[a]The endemic mycoses can also occur as opportunistic infections.

Representative Fungal Pathogens, Degree of Pathogenicity, and Habitat

Microbe	Disease/Infection*	Primary Habitat and Distribution
I. Primary True Pathogens		
Histoplasma capsulatum	Histoplasmosis	Soils high in bird guano; Ohio and Mississippi valleys of U.S.; Central and South America; Africa
Blastomyces dermatitidis	Blastomycosis	Presumably soils, but isolation has been difficult; southern Canada; Midwest, Southeast, Appalachia in U.S.; along drainage of major rivers
Coccidioides immitis	Coccidioidomycosis	Highly restricted to alkaline desert soils in southwestern U.S. (California, Arizona, Texas, and New Mexico)
Paracoccidioides brasiliensis	Paracoccidioidomycosis	Soils of rain forests in South America (Brazil, Colombia, Venezuela)
II. Pathogens with Intermediate Virulence		
Sporothrix schenckii	Sporotrichosis	In soil and decaying plant matter; widely distributed
Genera of dermatophytes (*Microsporum, Trichophyton, Epidermophyton*)	Dermatophytosis (various ringworms or tineas)	Human skin, animal hair, soil throughout the world
III. Secondary Opportunistic Pathogens		
Candida albicans	Candidiasis	Normal flora of human mouth, throat, intestine, vagina; also normal in other mammals, birds; ubiquitous
Aspergillus spp.	Aspergillosis	Soil, decaying vegetation, grains; common airborne contaminants; extremely pervasive in environment
Cryptococcus neoformans	Cryptococcosis	Pigeon roosts and other nesting sites (buildings, barns, trees); worldwide distribution
*Pneumocystis (carinii) jirovecii***	*Pneumocystis* pneumonia (PCP)	Upper respiratory tract of humans, animals
Genera in Mucorales (*Rhizopus, Absidia, Mucor*)	Mucormycosis	Soil, dust; very widespread in human habitation

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Common Opportunistic Fungi and Conditions That Predispose Patients to Them

Pathogen	Associated with
Candida	Antibiotic therapy, catheters, diabetes, corticosteroids,* immunosuppression**
Aspergillus	Leukemia, corticosteroids, tuberculosis, immunosuppression, IV drug abuse
Cryptococcus	Diabetes, tuberculosis, cancer, cortico-steroids, immunosuppression
Zygomycota Species	Diabetes, cancer, corticosteroids, IV therapy, third-degree burns

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Pathogenesis

- Mycotic disease is often a consequence of **predisposing factors**
- Only the dermatophytes and *Candida* are communicable from human to human
- The other agents are acquired from the environment
- Portal of entry
  - primary mycoses – respiratory portal; inhaled spores
  - subcutaneous - inoculated skin; trauma
  - cutaneous and superficial – contamination of skin surface
- Virulence factors – thermal dimorphism, toxin production, capsules and adhesion factors, hydrolytic enzymes, inflammatory stimulants
- The role of **humoral defenses** is somewhat controversial, but cell mediated one has predominant role
- Three distinct **tissue responses**;
  - **Chronic inflammation** (scarring, accumulation of lymphocytes)
  - **Granulomatous inflammation**
  - **Acute suppurative inflammation**

Diagnosis

- **Definitive Diagnosis –** histopathologic identification of the fungus invading tissue and accompanying evidence of an inflammatory response
- Laboratory identification require
  - Microscopic examination of stained specimens (KOH mount & PAS/Silver staining) - Most laboratories now use calcofluor white staining coupled with fluorescent microscopy
  - Culturing in selective and enriched media (Sabouraud's dextrose agar)
  - Specific biochemical (GM/B-glucan) and serological tests

Control/treatment

- **Sanitary**: Control by sanitary means is difficult, but the incidence of communicable disease can be reduced by good hygiene
- **Immunological**: No vaccines are currently available
- **Chemotherapeutic**
  - Many antifungals are available but some are very toxic to the host and must be used with caution
  - Topical powders and creams often contain tolnaftate or azole derivatives (miconazole, clotrimazole, econazole)
  - and are useful against superficial dermatophytes.
  - Sporotrichosis may be treated using potassium iodide or AMB
  - Systemic infections are generally treated by AMB , 5- FC, Fluconazole, Voriconazole, Itraconazole, Candins, etc

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Histoplasmosis: Ohio Valley Fever

- Distributed worldwide, most prevalent in eastern and central regions of US
- Most prevalent endemic mycosis
- Grows in moist soil high in nitrogen content (Bird dropings)
- The clinical spectrum ranges from asymptomatic infection to life-threatening illness
- The attack rate and severity of the disease depend on
  - The intensity of exposure,
  - The immune status of the exposed individual,
  - The underlying lung architecture of the host

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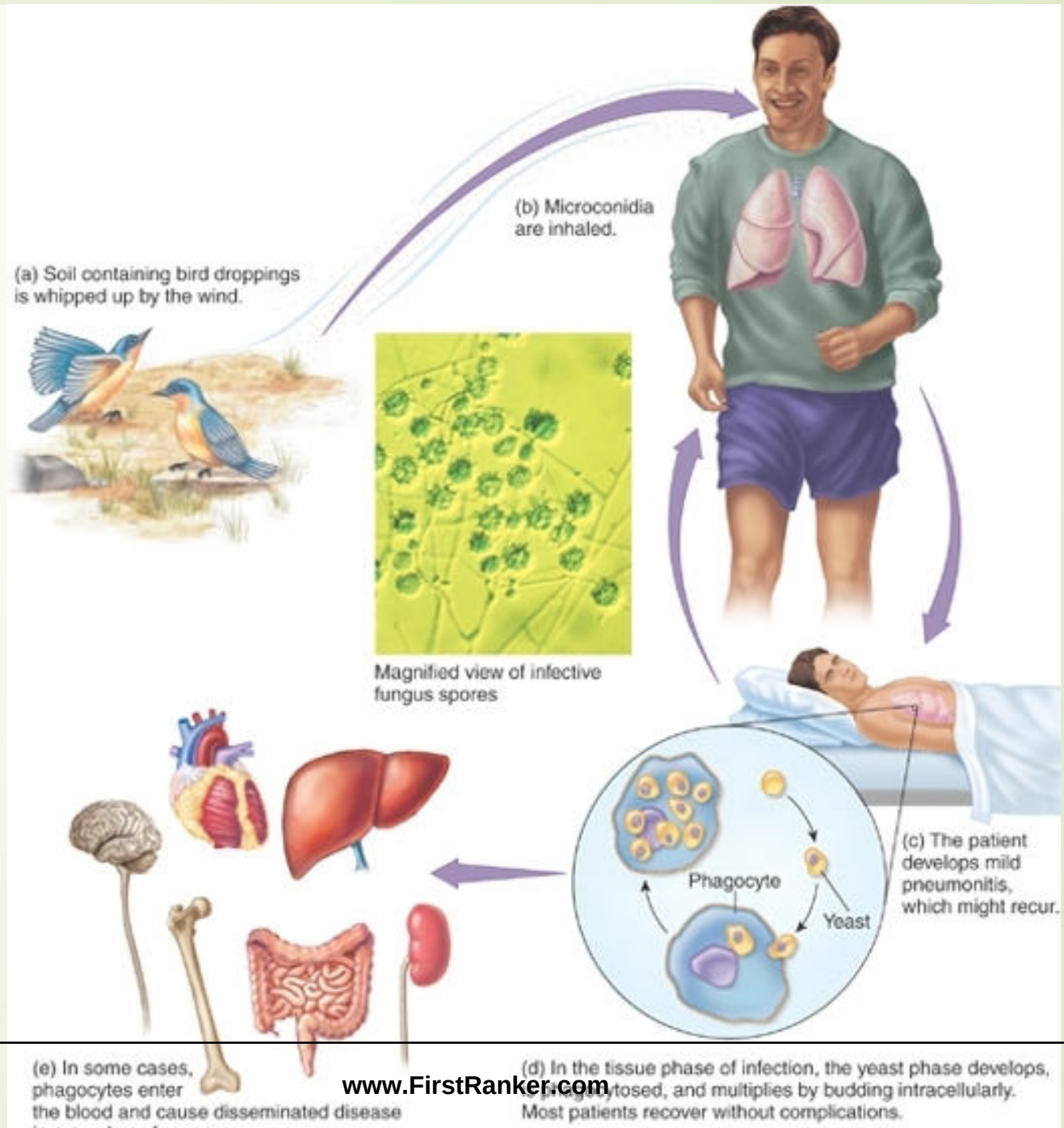
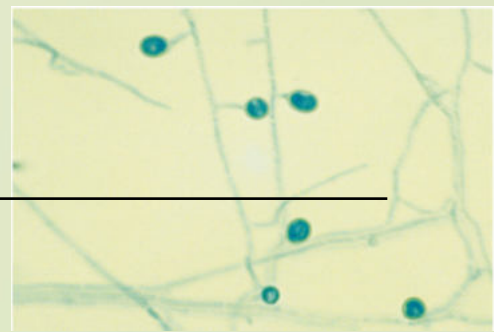


Type of Histoplasmosis	Treatment Recommendations	Comments
Acute pulmonary, moderate to severe illness with diffuse infiltrates and/or hypoxemia	Lipid AmB (3–5 mg/kg per day) ± glucocorticoids for 1–2 weeks; then itraconazole (200 mg bid) for 12 weeks. Monitor renal and hepatic function.	Patients with mild cases usually recover without therapy, but itraconazole should be considered if the patient's condition has not improved after 1 month.
Chronic/cavitary pulmonary	Itraconazole (200 mg qd or bid) for at least 12 months. Monitor hepatic function.	Continue treatment until radiographic findings show no further improvement. Monitor for relapse after treatment is stopped.
Progressive disseminated	Lipid AmB (3–5 mg/kg per day) for 1–2 weeks; then itraconazole (200 mg bid) for at least 12 months. Monitor renal and hepatic function.	Liposomal AmB is preferred, but the AmB lipid complex may be used because of cost. Chronic maintenance therapy may be necessary if the degree of immunosuppression cannot be reduced.
Central nervous system	Liposomal AmB (5 mg/kg per day) for 4–6 weeks; then itraconazole (200 mg bid or tid) for at least 12 months. Monitor renal and hepatic function.	A longer course of lipid AmB is recommended because of the high risk of relapse. Itraconazole should be continued until cerebrospinal fluid or CT abnormalities clear.

Blastomyces dermatitidis: Blastomycosis

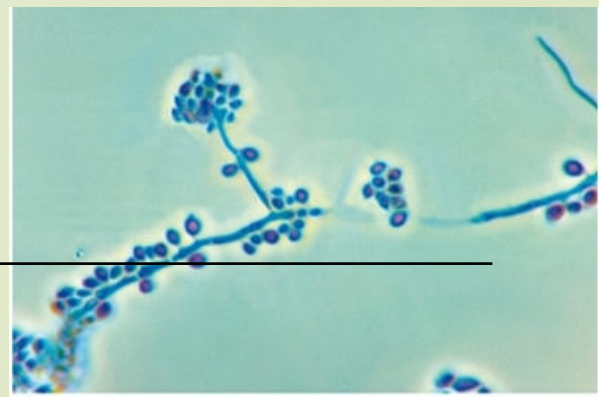
- Dimorphic like Histoplasma but causes systemic pyogranulomatous infection
- Inhaled 10-100 conidia convert to yeasts and multiply in lungs
- Most commonly presents as acute or chronic pneumonia that has been refractory to therapy with antibacterial drugs
- Hematogenous dissemination to skin, bones, and the genitourinary system is common



Disease	Primary Therapy	Alternative Therapy
Immunocompetent Patient/Life-Threatening Disease		
Pulmonary	Lipid AmB, 3–5 mg/kg qd, *or* AmB deoxycholate, 0.7–1.0 mg/kg qd (total dose: 1.5–2.5 g)	Itraconazole, 200–400 mg/d (once patient's condition has stabilized)
Disseminated		
CNS	Lipid AmB, 3–5 mg/kg qd, *or* AmB deoxycholate, 0.7–1.0 mg/kg qd (total dose: at least 2 g)	Fluconazole, 800 mg/d (if patient is intolerant to full course of AmB)
Non-CNS	Lipid AmB, 3–5 mg/kg qd, *or* AmB deoxycholate, 0.7–1.0 mg/kg qd (total dose: 1.5–2.5 g)	Itraconazole, 200–400 mg/d (once patient's condition has stabilized)

Sporothrix schenckii - Sporotrichosis (rose -gardener's disease)

- Very common saprobic fungus that decomposes plant matter in soil
- Infects appendages and lungs
- Lymphocutaneous variety occurs when contaminated plant matter penetrates the skin and the pathogen forms a nodule, then spreads to nearby lymph nodes



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Chromoblastomycosis

- A progressive subcutaneous mycosis characterized by highly visible verrucous lesions
- Etiologic agents are soil saprobes with dark-pigmented mycelia and spores
- *Fonsecaea pedrosoi, Phialophora verrucosa, Cladosporium carrionii*

Mycetoma

- When soil microbes are accidentally implanted into the skin
- Progressive, tumorlike disease of the hand or foot due to chronic fungal infection; may lead to loss of body part
- Caused by *Pseudallescheria or Madurella*

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Cutaneous Mycoses - Infections strictly confined to keratinized epidermis (skin, hair, nails) are called **dermatophytoses**- ringworm and tinea

The Dermatophyte Genera and Diseases

Genus	Name of Disease	Principal Targets	How Transmitted
Trichophyton	Ringworm of the scalp, body, beard, and nails Athlete's foot	Hair, skin, nails	Human to human, animal to human
Microsporum	Ringworm of scalp Ringworm of skin	Scalp hair Skin; not nails	Animal to human, soil to human, human to human
Epidermophyton	Ringworm of the groin and nails	Skin, nails; not hair	Strictly human to human

- Ringworm of scalp (tinea capitis)
- Ringworm of beard (tinea barbae)
- Ringworm of body (tinea corporis)
- Ringworm of groin (tinea cruris)
- Ringworm of foot and hand (tinea pedis and tinea manuum)
- Ringworm of nails (tinea unguium)
- Tinea versicolor – caused by *Malassezia furfur*
- White piedra – caused by *Trichosporon beigelii*; whitish or colored masses develop scalp, pubic, or axillary hair
- Black piedra – caused by *Piedraia* hortae; dark-brown to black gritty nodules, mainly on scalp hairs

TABLE 243-2 SUGGESTED ORAL TREATMENT FOR EXTENSIVE TINEA INFECTIONS AND ONYCHOMYCOSIS

Antifungal Agent	Suggested Dosage	Comments
Extensive Tinea Skin Infection		
Terbinafine	250 mg/d for 1–2 weeks	Adverse reactions minimal with short treatment period
Itraconazole[a]	200 mg/d for 1–2 weeks	Adverse reactions minimal with short treatment period except for drug interactions
Onychomycosis		
Terbinafine	250 mg/d for 3 months	Slightly superior to itraconazole; monitor for hepatotoxicity
Itraconazole[a]	200 mg/d for 3 months *or* 200 mg bid for 1 week each month for 3 months	Drug interactions frequent; monitor for hepatotoxicity; rarely causes hypokalemia, hypertension, edema; use with caution in patients with congestive heart failure

Candidiasis

- Budding cells may form both elongate pseudohyphae and true hyphae
- Forms off-white, pasty colony with a yeasty odor
- Normal flora of oral cavity, genitalia, large intestine or skin of 20% of humans
- Account for 80% of nosocomial fungal infections
- Account for 30% of deaths from nosocomial infections

TABLE 240-1 WELL-RECOGNIZED FACTORS AND CONDITIONS PREDISPOSING TO HEMATOGENOUSLY DISSEMINATED CANDIDIASIS

Antibacterial agents	Abdominal and thoracic surgery
Indwelling intravenous catheters	Cytotoxic chemotherapy
Hyperalimentation fluids	Immunosuppressive agents for organ transplantation
Indwelling urinary catheters	Respirators
Parenteral glucocorticoids	Neutropenia
Severe burns	Low birth weight (neonates)
HIV-associated low CD4+ T cell counts	Diabetes

TABLE 240-2 TREATMENT OF MUCOCUTANEOUS CANDIDAL INFECTIONS

Disease	Preferred Treatment	Alternatives
Cutaneous	Topical azole	Topical nystatin
Vulvovaginal	Oral fluconazole (150 mg) or azole cream or suppository	Nystatin suppository
Thrush	Clotrimazole troches	Nystatin, fluconazole
Esophageal	Fluconazole tablets (100–200 mg/d) or itraconazole solution (200 mg/d)	Caspofungin, micafungin, or amphotericin B

TABLE 240-3 AGENTS FOR THE TREATMENT OF DISSEMINATED CANDIDIASIS

Agent	Route of Administration	Dose[a]	Comment
Amphotericin B deoxycholate	IV only	0.5–1.0 mg/kg daily	Being replaced by lipid formulations
Amphotericin B lipid formulations			Not FDA approved as primary therapy, but used commonly because less toxic than amphotericin B deoxycholate
Liposomal (AmBiSome, Abelcet)	IV only	3.0–5.0 mg/kg daily	
Lipid complex (ABLC)	IV only	3.0–5.0 mg/kg daily	
Colloidal dispersion (ABCD)	IV only	3.0–5.0 mg/kg daily	Associated with frequent infusion reactions
Azoles[b]			
Fluconazole	IV and oral	400 mg/d	Most commonly used
Voriconazole	IV and oral	400 mg/d	Multiple drug interactions Approved for candidemia in nonneutropenic patients
Echinocandins			Broad spectrum against *Candida* species; approved for disseminated candidiasis
Caspofungin	IV only	50 mg/d	
Anidulafungin	IV only	100 mg/d	
Micafungin	IV only	100 mg/d	

Cryptococcosis - *Cryptococcus neoformans*

- A widespread encapsulated budding yeast that inhabits soil around pigeon roosts
- Infection of lungs leads to cough, fever, and lung nodules
- Cryptococcosis should be included in the differential diagnosis when any patient presents with findings suggestive of chronic meningitis

Pneumocystis (carinii) jiroveci

- A small, unicellular fungus that causes pneumonia (PCP)
- The organism was discovered in rodents in 1906 and was initially believed to be a protozoan
- Because Pneumocystis cannot be cultured, our understanding of its biology has been limited
- Presents as acute or subacute pneumonia that may initially be characterized by a vague sense of dyspnea alone but that subsequently manifests as fever and nonproductive cough with progressive shortness of breath ultimately resulting in respiratory failure and death
- Extrapulmonary manifestations of PCP are rare but can include involvement of almost any organ, most notably lymph nodes, spleen, and liver

TABLE 244-1 TREATMENT OF PNEUMOCYSTOSIS (14–21 DAYS)

Drug(s)	Dose, Route	Adverse Effects
First-Choice Agent		
TMP-SMX	TMP (5 mg/kg) plus SMX (25 mg/kg) q6–8h PO or IV (2 double-strength tablets tid or qid)	Fever, rash, cytopenias, hepatitis, hyperkalemia
Alternative Agents		
TMP	5 mg/kg q6–8h PO	Hemolysis (G6PD deficiency), methemoglobinemia, rash, fever, gastrointestinal disturbances
plus		
Dapsone	100 mg qd PO	
Atovaquone	750 mg bid PO	Rash, fever, hepatitis
Clindamycin	300–450 mg q6h PO or 600 mg q6–8h IV	Hemolysis (G6PD deficiency), methemoglobinemia, neutropenia, rash
plus		
Primaquine	15–30 mg qd PO	
Pentamidine	3–4 mg/kg qd IV	Hypotension, azotemia, cardiac arrhythmias (torsades des pointes), pancreatitis, dysglycemias, hypocalcemia, neutropenia, hepatitis
Adjunctive Agent		
Prednisone or methylprednisolone	40 mg bid × 5 d, 40 mg qd × 5 d, 20 mg qd × 11 d; PO or IV	Peptic ulcer disease, hyperglycemia, mood alteration, hypertension

Aspergillosis

- 600 species, 8 involved in human disease; *A. fumigatus* most commonly
- Infection usually occurs in lungs – spores germinate in lungs and form fungal balls; can colonize sinuses, ear canals, eyelids, and conjunctiva
- Invasive aspergillosis can produce necrotic pneumonia, and infection of brain, heart, and other organs
- The primary risk factors for invasive aspergillosis are profound neutropenia and glucocorticoid use

TABLE 241-2 MAJOR MANIFESTATIONS OF ASPERGILLOSIS

	Type of Disease			
Organ	Invasive (Acute and Subacute)	Chronic	Saprophytic	Allergic
Lung	Angioinvasive (in neutropenia), non-angioinvasive, granulomatous	Chronic cavitary, chronic fibrosing	Aspergilloma (single), airway colonization	Allergic bronchopulmonary, severe asthma with fungal sensitization, extrinsic allergic alveolitis
Sinus	Acute invasive	Chronic invasive, chronic granulomatous	Maxillary fungal ball	Allergic fungal sinusitis, eosinophilic fungal rhinosinusitis
Brain	Abscess, hemorrhagic infarction, meningitis	Granulomatous, meningitis	None	None
Skin	Acute disseminated, locally invasive (trauma, burns, IV access)	External otitis, onychomycosis	None	None
Heart	Endocarditis (native or prosthetic), pericarditis	None	None	None
Eye	Keratitis, endophthalmitis	None	None	None described

TABLE 241-3 TREATMENT OF ASPERGILLOSIS[a]

Indication	Primary Treatment	Evidence Level[b]	Precautions	Secondary Treatment	Comments
Invasive[c]	Voriconazole	AI	Drug interactions (especially with rifampin), renal failure (IV only)	AmB, caspofungin, posaconazole, micafungin	As primary therapy, voriconazole carries 20% more responses than AmB. Consider initial combination therapy with an echinocandin in non-neutropenic patients.
Prophylaxis	Posaconazole, itraconazole solution	AI	Diarrhea and vomiting with itraconazole, vincristine interaction	Micafungin, aerosolized AmB	Some centers monitor plasma levels of itraconazole and posaconazole.
Single aspergilloma	Surgery	BII	Multicavity disease: poor outcome of surgery, medical therapy preferable	Itraconazole, voriconazole, intracavity AmB	Single large cavities with an aspergilloma are best resected.
Chronic pulmonary[c]	Itraconazole, voriconazole	BII	Poor absorption of itraconazole capsules with proton pump inhibitors or H_2 blockers	Posaconazole, IV AmB, IV micafungin	Resistance may emerge during treatment, especially if plasma drug levels are subtherapeutic.
ABPA/SAFS	Itraconazole	AI	Some glucocorticoid interactions, including with inhaled formulations	Voriconazole, posaconazole	Long-term therapy is helpful in most cases. No evidence indicates whether therapy modifies progression to bronchiectasis/fibrosis.

Mucormycosis (Previously Zygomycosis)

- Genera most often involved are *Rhizopus, Absidia, and Mucor, Cunninghamella*
- *Rhizopus oryzae is by far the most common cause of infection (not mucor)*
- Usually harmless air contaminants invade the membranes of the nose, eyes, heart, and brain of people with diabetes and malnutrition, with severe consequences

- Infection primarily in patients with diabetes or defects in phagocytic function (e.g., those associated with neutropenia or glucocorticoid treatment) or Patients with elevated levels of free iron
- Divided into at least six clinical categories:
  - Rhino-orbital-cerebral,
  - Pulmonary,
  - Cutaneous,
  - Gastrointestinal,
  - Disseminated,
  - Miscellaneous

- The successful treatment of mucormycosis requires four steps:

(1) early diagnosis;

(2) reversal of underlying predisposing risk factors, if possible;

(3) surgical debridement;

(4) prompt antifungal therapy

Primary Antifungal Therapy			
AmB deoxycholate	1.0–1.5 mg/kg qd	• >5 decades of clinical experience • Inexpensive • Only licensed agent for treatment of mucormycosis	• Highly toxic • Poor CNS penetration
LAmB	5–10 mg/kg qd	• Less nephrotoxic than AmB deoxycholate • Better CNS penetration than AmB deoxycholate or ABLC • Better outcomes than with AmB deoxycholate in murine models and a retrospective clinical review	• Expensive
ABLC	5 mg/kg qd	• Less nephrotoxic than AmB deoxycholate • Murine and retrospective clinical data suggest benefit of combination therapy with echinocandins	• Expensive • Possibly less efficacious than LAmB for CNS infection

Fungal Allergies and Intoxications

Fungal spores are common sources of atopic allergies

- Seasonal allergies and asthma
  - farmer's lung, teapicker's lung, bark stripper's disease
- Fungal toxins lead to **mycotoxicoses** usually caused by eating poisonous or hallucinogenic mushrooms.
  - **aflatoxin** toxic and carcinogenic; grains, corn peanuts; lethal to poultry and livestock
- *Stachybotrys chartarum* – sick building syndrome; severe hematologic and neurological damage

Thank you