**LESSON 12.
Microbiology diagnosis of mycosis**

**LESSON PLAN:**

1. Classification of fungi pathogenic to humans.

2. Classification of mycoses: superficial mycoses (keratomycoses), skin mycoses (dermatomycoses), subcutaneous mycoses (subcutaneous) mycoses, systemic or visceral mycoses and opportunistic mycoses.

3. Morpho-biological characteristics of causative agents of superficial mycoses (scaly scabies, black scabies, black and white piedra), pathogenesis, microbiological diagnosis of the diseases caused by them.

4. Morpho-biological characteristics of causative agents of skin mycoses (trichophytia, epdermophytia, microsporia, favus), pathogenesis of the diseases caused by them, microbiological diagnosis.

5. Morpho-biological characteristics of causative agents of subcutaneous (subcutaneous) mycoses (sporotrichosis, chromomycosis, mycetoma), pathogenesis and microbiological diagnosis of diseases caused by them.

6. Morpho-biological characteristics of agents of systemic (deep) mycoses (coccidioidoiosis, histoplasmosis, blastomycosis, paracoccidioidoiosis), pathogenesis and microbiological diagnosis of the diseases they cause.

7. Morpho-biological characteristics of agents of opportunistic (conditional-pathogenic) mycoses (candidosis, cryptococcosis, aspergillosis, mucoromycosis, pneumocystosis), pathogenesis and microbiological diagnosis of the diseases they cause.

8. Understanding of mycotoxicoses

**Characteristics of Primary and Opportunistic Fungal Pathogens**

**Antifungal spectrum:** This is the range of activity of an antifungal agent against fungi. A broad-spectrum antifungal agent inhibits a wide variety of fungi, including both yeastlike fungi and molds, whereas a narrow-spectrum agent is active only against a limited number of fungi.

**Fungistatic activity:** This is the level of antifungal activity that **inhibits** the growth of an organism. This is determined in vitro by testing a standardized concentration of organisms against a series of antifungal dilutions. The lowest concentration of the drug that inhibits the growth of the organism is referred to as the **MIC.**

**Fungicidal activity:** This is the ability of an antifungal agent to **kill** an organism in vitro or in vivo. The lowest concentration of the drug that kills 99.9% of the test population is called the **MFC.**

**Antifungal combinations:** These combinations of antifungal agents may be used (1) to enhance efficacy in the treatment of a refractory fungal infection, (2) to broaden the spectrum of empiric antifungal therapy, (3) to prevent the emergence of resistant organisms, and (4) to achieve a synergistic killing effect.

**Antifungal synergism:** These are combinations of antifungal agents that have enhanced antifungal activity when used together compared with the activity of each agent alone.

**Antifungal antagonism:** This is a combination of antifungal agents in which the activity of one of the agents interferes with the activity of the other agent.

**Efflux pumps:** These are families of drug transporters that serve to actively pump antifungal agents out of the fungal cells, decreasing the amount of intracellular drug available to bind to its target.

*MFC-*Minimum fungicidal concentration; *MIC-*minimum inhibitory concentration.

**DERMATOPHYTES**

**Trigger Words** Tinea, KOH preparation, ringworm, azoles, terbinafine, circular, scaling lesion with central clearing and hair loss

**Biology, Virulence, and Disease**

• Include filamentous fungi in the genera *Trichophyton, Epidermophyton,* and

*Microsporum*

• Keratinophilic and keratinolytic; able to invade and break down skin, hair, and nails

• In infections of skin, hair, and nails, only outermost keratinized layers invaded

• Various forms of dermatophytosis (tineas or “ringworm”) classified according to anatomic site or structure involved

• Clinical signs and symptoms vary

**Epidemiology**

• Classified into three categories based on natural habitat: geophilic, zoophilic, and anthropophilic

• Geophilic: live in soil, occasional pathogens of both animals and humans

• Zoophilic: parasitize hair and skin of animals but can be transmitted to humans

• Anthropophilic: infect humans, may be transmitted directly or indirectly from person to person

• Occur worldwide, especially in tropical and subtropical regions

**Treatment, Prevention, and Control**

• Localized infections that do not involve hair or nails may be treated effectively with topical antifungal agents (azoles, terbinafine, haloprogin)

• All others require oral therapy (griseofulvin, itraconazole, fluconazole, terbinafine)

***Subcutaneous Mycoses***

**SPOROTRICHOSIS *(Sporothrix schenckii)***

**Trigger Words**

Thorn prick, rose handler’s disease, sphagnum moss, lymphocutaneous nodules

**Biology, Virulence, and Disease**

ᑏᑏ Thermally dimorphic fungus; grows as a mold at room temperature (e.g., 25° C) and as a pleomorphic yeast at 37° C and in tissue

ᑏᑏ Infection is chronic; nodular and ulcerative lesions develop along lymphatics that drain primary site of inoculation

**Epidemiology**

ᑏᑏ Sporadic, most common in warmer climates: Japan, North and South America

ᑏᑏ Outbreaks related to forest work, mining, gardening

ᑏᑏ Classic infection associated with traumatic inoculation of soil, vegetable, or organic matter contaminated with fungus

ᑏᑏ Zoonotic transmission reported in armadillo hunters and in association with infected cats

**Diagnosis**

ᑏᑏ Subcutaneous infection with lymphangitic spread

ᑏᑏDefinitive diagnosis requires culture of infected pus or tissue

ᑏᑏ In tissue, organism appears as a pleomorphic budding yeast

**Treatment, Prevention, and Control**

ᑏᑏ Classic treatment: oral potassium iodide in saturated solution

ᑏᑏ Itraconazole: safe, highly effective, treatment of choice

ᑏᑏ Alternatives: terbinafine, fluconazole, posaconazole

ᑏᑏ Local application of heat shown to be effective

**EUMYCOTIC MYCETOMA**

***(Phaeoacremonium, Curvularia, Fusarium, Madurella, Mediacopsis, Nigrograna, Trematosphaeria, Exophiala, Falciformispora, AND Scedosporium species)***

**Trigger Words**

Grains, sinus tract, dematiaceous, subcutaneous, mycetoma

**Biology, Virulence, and Disease**

ᑏᑏ Caused by a wide array of true fungi (as opposed to actinomycotic mycetomas, which are caused by bacteria)

ᑏᑏ Localized chronic granulomatous infectious process involving cutaneous and subcutaneous tissues

ᑏᑏ Painless subcutaneous nodule; increases slowly but progressively in size

ᑏᑏ Local spread may breach tissue planes, destroying muscle, fascia, and bone

ᑏᑏ Hematogenous or lymphatic spread rare

**Epidemiology**

ᑏᑏ Primarily in tropical areas with low rainfall; most common in Africa and India

ᑏᑏ Traumatic implantation into exposed body parts; foot and hand most common; back, shoulders, chest wall may also be involved

ᑏᑏ Men more often affected than women

ᑏᑏ Etiologic agent varies from country to country

ᑏᑏ Mycetomas not contagious

**Diagnosis**

ᑏᑏDemonstration of grains or granules grossly visible in draining sinus tracts; may also be seen on tissue biopsy

ᑏᑏMicroscopic examination of granules

ᑏᑏCulture usually needed for identification of organism

**Treatment, Prevention, and Control**

ᑏᑏ Usually unsuccessful; poor response to most antifungal agents

ᑏᑏ Specific antifungal therapy may slow progression: terbinafine, voriconazole, posaconazole

ᑏᑏ Local excision usually ineffective; amputation is the only definitive treatment

***SYSTEMIC MYCOSES CAUSED BY DIMORPHIC FUNGI***

**BLASTOMYCOSIS (*BLASTOMYCES DERMATITIDIS* AND *B. GILCHRISTII*)**

**Trigger Words**

Mississippi River Valley, broad-based budding yeast, healthy and immunocompromised, granuloma

**Biology, Virulence, and Disease**

ᑏᑏ Thermally dimorphic fungus: large nonencapsulated budding yeast cells in tissue and in culture at 37° C; mold colonies form in culture at 25°C

ᑏᑏUsual route of infection is inhalation of conidia

ᑏᑏ Severity of symptoms and course of disease depends on extent of exposure and immune status of exposed individual; most are asymptomatic

ᑏᑏClassic form of blastomycosis: chronic cutaneous involvement

**Epidemiology**

ᑏᑏ Ecologic niche: decaying organic matter

ᑏᑏ Area of endemicity: southeastern and southcentral states, especially bordering Ohio and Mississippi river basins; Midwest states and Canadian provinces bordering Great Lakes; and an area in New York and Canada along the St. Lawrence River

ᑏᑏ Outbreaks of infection have been associated with occupational or recreational contact with soil

**Diagnosis**

ᑏᑏMicroscopic detection of fungus in tissue or other clinical material, with confirmation by culture

ᑏᑏAntigen detection and PCR

**Treatment, Prevention, and Control**

ᑏᑏ Pulmonary blastomycosis in immunocompromised patients and those with progressive pulmonary disease should be treated

ᑏᑏ All patients with evidence of hematogenous dissemination require antifungal therapy

ᑏᑏ Lipid formulation of amphotericin B: treatment of choice for meningeal disease and other life-threatening presentations

ᑏᑏ Mild or moderate disease: itraconazole; fluconazole, posaconazole, or voriconazole may be substituted for itraconazole

**COCCIDIOIDOMYCOSIS (*COCCIDIOIDES IMMITIS* AND *C. POSADASII*)**

**Trigger Words**

Valley fever, coccidioidal granuloma, arthroconidia, spherule, skin test, precipitin test

**Biology, Virulence, and Disease**

ᑏᑏ Coccidioidomycosis caused by two indistinguishable species: *C. immitis* and *C. posadasii*

ᑏᑏ *C. immitis* is localized to California; *C.posadasii* causes most infections outside California

ᑏᑏ Disease caused by inhalation of infectious arthroconidia

ᑏᑏ Asymptomatic or subclinical, self-limited flulike illness, acute and chronic pulmonary disease, single or multisystem dissemination

ᑏᑏ Dimorphic fungi; endosporulating spherule in tissue, mold in culture at 25° C and in nature

**Epidemiology**

ᑏᑏ Endemic to U.S. southwestern desert, northern Mexico, scattered areas of Central and South America

ᑏᑏ Organism found in soil; growth in environment enhanced by bat and rodent droppings; cycles of drought/rain enhance organism dispersion

ᑏᑏ Persons ≥65 years and those with HIV infection disproportionately affected

ᑏᑏ Risk of disseminated disease highest in certain ethnic groups (Filipino, African American, Native American, Hispanic), males (9:1), women in third trimester of pregnancy, individuals with cellular immune deficiency, persons at extremes of age

**Diagnosis**

ᑏᑏHistopathologic examination of tissue or other clinical material, isolation of fungus in culture, serology

ᑏᑏHistopathologic examination that reveals endosporulating spherules in sputum, exudates, or tissue is sufficient to establish the diagnosis

ᑏᑏCulture at 25° C takes days and poses risk to laboratory workers; all work with molds should be performed in suitable biosafety cabinet

ᑏᑏ Serology (antigen and antibody) may be useful for initial screening, confirmation, or prognostic evaluation

**Treatment, Prevention, and Control**

ᑏᑏ Most individuals with primary infection do not require therapy

ᑏᑏ For those with concurrent risk factors or a more severe presentation: lipid formulation of amphotericin B followed by an oral azole as maintenance therapy (severe disease)

ᑏᑏ Chronic cavitary pulmonary disease: azole for at least 1 year

ᑏᑏ Nonmeningeal extrapulmonary disseminated infections: oral azole

ᑏᑏ Meningeal coccidioidomycosis: fluconazole; itraconazole, posaconazole or voriconazole are secondary choices

**HISTOPLASMOSIS (*HISTOPLASMA CAPSULATUM*)**

**Trigger Words**

Intracellular yeasts, bird and bat droppings, chicken coop, caves, guano, granulomas

**Biology, Virulence, and Disease**

ᑏᑏ Histoplasmosis caused by two varieties of *H. capsulatum*

ᑏᑏ *H. capsulatum* var. *capsulatum:* causes pulmonary and disseminated infections

ᑏᑏ *H. capsulatum* var. *duboisii:* causes predominantly skin and bone lesions

ᑏᑏ Disease caused by inhalation of infectiousmicroconidia

ᑏᑏ Severity of symptoms and course of disease depend on extent of exposure and immune status of infected individual; most are asymptomatic, self-limited; flulike illness also occurs

ᑏᑏ Thermally dimorphic fungus: hyaline mold in nature and in culture at 25° C, budding yeast in tissue (intracellular) and in culture at 37° C

**Epidemiology**

ᑏᑏ *H. capsulatum* var. *capsulatum:* localized to Ohio and Mississippi river valleys; occurs throughout Mexico and Central and South America

ᑏᑏ *H. capsulatum* var. *duboisii:* confined to tropical Africa (e.g., Gabon, Uganda, Kenya)

ᑏᑏ Found in soil with high nitrogen content (e.g., areas contaminated with bird or bat droppings)

ᑏᑏ Outbreaks of disease have been associated with exposure to bird roosts, caves, and decaying buildings or urban renewal projects involving excavation and demolition

ᑏᑏ Immunocompromised individuals and children most prone to develop symptomatic disease

ᑏᑏ Reactivation of disease and dissemination common among immunosuppressed individuals, especially those with AIDS

**Diagnosis**

ᑏᑏDirect microscopy, culture of clinical material, serology (antigen and antibody), β-D-glucan, and PCR have been useful

ᑏᑏ Yeast phase of organism can be detected in sputum, bronchoalveolar lavage fluid, peripheral blood films, bone marrow, and tissue stained with Giemsa, GMS, or PAS stains

ᑏᑏCultures should be handled in a biosafety cabinet

ᑏᑏ Serologic diagnosis includes tests for antibody and antigen

**Treatment, Prevention, and Control**

ᑏᑏ Severe acute infections: lipid formulation of amphotericin B followed by oral itraconazole

ᑏᑏ Chronic pulmonary histoplasmosis: lipid formulation of amphotericin B followed by itraconazole

ᑏᑏ Disseminated infection: lipid formulation of amphotericin B followed by itraconazole

**PARACOCCIDIOIDOMYCOSIS (*PARACOCCIDIOIDES BRASILIENSIS* AND *P. LUTZII*)**

**Trigger Words**

Pilot’s wheel, South American blastomycosis, ulcer, multiple buds

**Biology, Virulence, and Disease**

* Thermally dimorphic fungus: slowly growing mold phase in nature and at 25° C, yeast phase (variable sized with single or multiple buds) in tissue and in culture at 37° C
* Usual route of infection is inhalation or possible traumatic inoculation of conidia or hyphal fragments
* Paracoccidioidomycosis may be subclinical or progressive with acute or chronic pulmonary forms or acute, subacute, or chronic disseminated forms

**Epidemiology**

* Endemic throughout Latin America, areas of high humidity, rich vegetation, moderate temperatures, acid soil
* Ecologic niche not well established
* Overt disease uncommon among children and adolescents; in adults, disease more common in men aged 30 to 50 years
* Most patients with clinically apparent disease live in rural areas and have close contact with soil
* No reports of epidemics or person-toperson transmission

**Diagnosis**

ᑏᑏDemonstration of characteristic yeastforms on microscopic examination of clinical material: oval to round with double refractile walls and single or multiple buds; “pilot-wheel” morphology

ᑏᑏMay be isolated in culture and should be handled in a biosafety cabinet

ᑏᑏ Serology testing may help in suggesting diagnosis, evaluating response to therapy

**Treatment, Prevention, and Control**

* Itraconazole: treatment of choice for most forms of disease
* More severe or refractory forms: lipid formulation of amphotericin B followed by either itraconazole or sulfonamide therapy

***OPPORTUNISTIC MYCOSES***

**CANDIDIASIS**

**Trigger Words**

*Candida,* pseudohyphae, endogenous,

exogenous, yeast, immunocompromised,

vaginal thrush, oropharyngeal

**Biology, Virulence, and Disease**

ᑏᑏ Opportunistic yeasts causing infections ranging from superficial mucosal and cutaneous disease to hematogenously disseminated, often fatal, infections

ᑏᑏ Vast majority of infections are caused by five major species: *Candida albicans, C. glabrata, C. parapsilosis, C. tropicalis,* and *C. krusei*

ᑏᑏ Morphology ranges from budding yeasts to pseudohyphae and true hyphae

ᑏᑏ Reproduction is by formation of blastoconidia (buds)

ᑏᑏ Most important group of opportunistic fungal pathogens

ᑏᑏ May be community acquired (mucosal infections) or hospital associated (invasive disease)

**Epidemiology**

ᑏᑏ *Candida* spp. are known colonizers of humans and other warm-blooded animals

ᑏᑏ Primary site of colonization is the GI tract; commensals in the vagina, urethra, skin, and nails

ᑏᑏ Most infections are endogenous, involving normally commensal host flora

ᑏᑏ Exogenous transmission in hospitals also occurs

ᑏᑏ *C. albicans* predominates in most types of infection

ᑏᑏ Consequences of *Candida* BSIs are severe; risk factors include hematologic malignancies and neutropenia, abdominal surgery, prematurity in infants, and age >70 years

**Diagnosis**

ᑏᑏClinical appearance, direct microscopic examination, and culture

ᑏᑏHematogenously disseminated infections and candidemia difficult to diagnose on clinical grounds alone

ᑏᑏ Laboratory diagnosis involves procurement of appropriate clinical material, followed by direct microscopic examination; culture; and (increasingly) application of molecular, antigenic, and proteomic analysis

**Treatment, Prevention, and Control**

ᑏᑏ Mucosal and cutaneous infection: topical and systemically active antifungal agents include azoles (itraconazole, fluconazole, miconazole, and many others), polyenes (amphotericin B and nystatin)

ᑏᑏ Invasive candidiasis and candidemia: oral or intravenous administration depending on antifungal agent and severity of disease and/or immunosuppression; azoles (fluconazole, voriconazole, posaconazole, isavuconazole), echinocandins (anidulafungin, caspofungin, micafungin), amphotericin B formulations (deoxycholate and lipid formulations), flucytosine

**CRYPTOCOCCOSIS**

**Trigger Words**

Capsule, budding yeast, CNS, neurotropic, India ink, antigen, AIDS

**Biology, Virulence, and Disease**

ᑏᑏ Systemic mycosis caused by the fungi *Cryptococcus neoformans* and *C. gattii*

ᑏᑏ *C. neoformans* includes capsular serotypes A, D, and AD; var. *grubii* (serotype A) and var. neoformans (serotype D)

ᑏᑏ *C. gattii* includes serotypes B and C

ᑏᑏ Spherical to oval, encapsulated, yeastlike organisms that replicate by budding

ᑏᑏ Both species may cause pulmonary, hematogenously disseminated, and CNS disease

**Epidemiology**

ᑏᑏ Usually acquired by inhaling aerosolized cells of *C. neoformans* and *C. gattii*

ᑏᑏ Both species pathogenic for immunocompetent individuals

ᑏᑏ *C. neoformans*: most often encountered as opportunistic pathogen; found worldwide in soil contaminated with avian excreta

ᑏᑏ *C. gattii*: found in tropical and subtropical climates in association with eucalyptus trees; the focus in the Pacific Northwest has been associated with Douglas fir trees

ᑏᑏ Disease is similar, although *C. gattii* infection tends to occur in immunocompetent individuals and has a lower associated mortality

ᑏᑏ Incidence has progressively declined since early 1990s because of widespread use of fluconazole and successful treatment of HIV infection with antiviral drugs

**Diagnosis**

ᑏᑏMay present as pneumonic process or (more commonly) as CNS infection

ᑏᑏDiagnosis may be made by culture of blood, CSF, or other clinical material

ᑏᑏMicroscopic examination of CSF may reveal characteristic encapsulated budding yeast cells

ᑏᑏCryptococcal meningitis: diagnosis by detection of polysaccharide antigen in serum or CSF

**Treatment, Prevention, and Control**

ᑏᑏ Cryptococcal meningitis and other disseminated forms universally fatal if left untreated

ᑏᑏ Antifungal therapy: amphotericin B (deoxycholate or lipid formulation) plus flucytosine followed by maintenance/consolidation therapy with fluconazole (preferred) or itraconazole

ᑏᑏ Effective management of CNS pressure and IRIS crucial to successful management of cryptococcal meningitis

**ASPERGILLOSIS**

**Trigger Words**

Septate branching hyphae, hypersensitivity pneumonitis, angioinvasive, aspergilloma, conidia

**Biology, Virulence, and Disease**

ᑏᑏ Broad spectrum of diseases caused by filamentous fungi (molds) of genus *Aspergillus*

ᑏᑏ Exposure to spores in environment may cause allergic reactions in hypersensitized hosts or destructive, invasive, pulmonary, and disseminated disease in highly immunocompromised hosts

ᑏᑏ Vast majority of infections caused by *A.fumigatus* (most common), *A. flavus, A.niger*, and *A. terreus*

ᑏᑏ Hyaline molds that produce vast amounts of spores (conidia) that serve as infectious propagules on inhalation by host

ᑏᑏ Invasive aspergillosis marked by angioinvasion and tissue destruction caused by infarction

ᑏᑏ Hematogenous dissemination of infection to extrapulmonary sites (most commonly brain, heart, kidneys, GI tract, liver, spleen)

common because of angioinvasive nature of fungus

**Epidemiology**

ᑏᑏ *Aspergillus* spp. common worldwide; conidia ubiquitous in air, soil, decaying matter

ᑏᑏ Within hospital environment, *Aspergillus* spp. may be found in air, showerheads, water storage tanks, potted plants

ᑏᑏ Conidia (spores) constantly being inhaled; respiratory tract most frequent and important portal of entry

ᑏᑏ Host reaction, associated pathologic findings, and outcome of infection depend more on host factors than virulence or pathogenesis of individual species

**Diagnosis**

ᑏᑏ Serologic, culture, histopathologic, molecular, biochemical, and antigenic methods supplemented by imaging studies

**Treatment, Prevention, and Control**

ᑏᑏ Treatment usually involves administration of corticosteroids coupled with pulmonary toilet

ᑏᑏ Treatment of chronic pulmonary aspergillosis may involve steroids and long-term antifungal therapy, usually with an azole antifungal agent

ᑏᑏ Prophylaxis of high-risk (neutropenic) patients usually accomplished by administration of a mold-active azole (itraconazole, posaconazole, voriconazole)

ᑏᑏ Specific antifungal therapy of invasive aspergillosis usually involves administration of voriconazole or a lipid formulation of amphotericin B; isavuconazole has recently been cleared by the U.S. Food and Drug Administration for treatment of invasive aspergillosis

ᑏᑏ Efforts to decrease immunosuppression and/or reconstitute host immune defenses important, as is surgical resection of infected tissue if possible

ᑏᑏ Resection of aspergillomas only considered in instances of severe hemoptysis

*BSI,* Bloodstream infections; *CNS,* central nervous system; *CSF,* cerebrospinal fluid; *GI,* gastrointestinal; *IRIS,* immune reconstitution inflammatory syndrome.

**Agents of Opportunistic Mycoses**

***Candida* spp.**

*C. albicans*

*C. glabrata*

*C. parapsilosis*

*C. tropicalis*

*C. krusei*

*C. lusitaniae*

*C. guilliermondii*

*C. dubliniensis*

*C. rugosa*

*C. auris*

***Cryptococcus Neoformans* and Other Opportunistic Yeastlike Fungi**

*C. neoformans/gattii*

*Malassezia* spp.

*Trichosporon* spp.

*Rhodotorula* spp.

Saprochaete capitata

**Microsporidia Aspergillus *spp.***

*A. fumigatus*

*A. flavus*

*A. niger*

*A. versicolor*

*A. terreus*

**Mucormycetes**

*Rhizopus* spp.

*Mucor* spp.

*Rhizomucor* spp.

*Lichtheimia corymbifera*

*Cunninghamella* spp.

**Other Hyaline Molds**

*Fusarium* spp.

*Sarocladium* spp.

*Paecilomyces* spp.

*Purpureocillium lilacinum*

*Trichoderma* spp.

*Scopulariopsis* spp.

**Dematiaceous Molds**

*Alternaria* spp.

*Bipolaris* spp.

*Cladophialophora* spp.

*Curvularia* spp.

*Exophiala* spp.

*Exserohilum* spp.

*Lomentospora prolificans*

*Scedosporium* spp.

*Wangiella* spp.

***Pneumocystis jirovecii***

**SPECTRUM OF DISEASES CAUSED BY ASPERGILLUS SPECIES**

**Allergic Reactions**

Nasal cavity

Paranasal sinuses

Lower respiratory tract

**Colonization**

Obstructed paranasal sinuses

Bronchi

Preformed pulmonary cavities

**Superficial Cutaneous Infections**

Wounds

Catheter sites

**Limited Invasive Infections**

Bronchi

Pulmonary parenchyma

Mildly immunodeficient patients

**Frankly Invasive Pulmonary Infection**

Severely immunodeficient patients

Systemic dissemination

Death