MEDICAL MICROBIOLOGY (MCB 408)

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INTRODUCTION

- Medical microbiology is a subdiscipline of microbiology dealing with the study of microorganisms (parasites, fungi, bacteria, viruses, and prions) capable of infecting and causing diseases in humans.

- Medical microbiology involves the identification of microorganisms for the diagnosis of infectious diseases and the assessment of likely response to specific therapeutic interventions.

Microbial pathogens of plants

- Microbial pathogens of plants and animals encompass a diverse array of microorganisms that cause diseases and infections in their respective hosts. These pathogens are bacteria, viruses, fungi, protozoa, nematodes, and other microorganisms
- Microbial Pathogens of Plants:
- Bacteria: *Xanthomonas* spp., *Pseudomonas syringae*, *Ralstonia solanacearum*
- Viruses: Tobacco mosaic virus (TMV), Potato virus Y (PVY), Tomato spotted wilt virus (TSWV).
- Fungi: *Fusarium* spp., *Phytophthora* spp., *Botrytis cinerea*
- Oomycetes: *Phytophthora infestans*.
- Nematodes: Root-knot nematodes (*Meloidogyne* spp.), Cyst nematodes (*Heterodera* spp.).

Microbial pathogens of animals

- Microbial Pathogens of Animals:
- Bacteria: *Escherichia coli*, *Salmonella* spp., *Mycobacterium tuberculosis*.
- Viruses: Rabies virus, Foot-and-mouth disease virus (FMDV), Avian influenza virus.
- Fungi: *Candida albicans*, *Aspergillus fumigatus*, *Microsporum canis*
- Protozoa: *Trypanosoma* spp., *Toxoplasma gondii*.
- Helminths (Worms): *Ascaris lumbricoides*, *Taenia solium*, *Fasciola hepatica*.

Characteristics of Microbial Pathogens:

- They are organisms that cause disease in an individual.
- They are transmissible and can be transferred from one organism to the other.
- They have the ability to adhere to host cells.
- They can cause invasion of the host cells and tissues.
- They can cause evasion of the host's immune system.
- Host Specificity
- Pathogens infect plants, animals, and humans.
- Pathogenic microorganisms may be bacteria, protists, algae, fungi, viruses, etc.

Geographical distribution of human pathogens in Nigeria

- The geographical distribution of human pathogens in Nigeria varies based on factors such as population density, environmental conditions, healthcare infrastructure, socio-economic status, and cultural practices.
- Here's an overview of some key human pathogens and their distribution across different regions of Nigeria:
- Malaria: Pathogen: *Plasmodium* spp. (predominantly Plasmodium falciparum).
- Geographical Distribution: Malaria is endemic throughout Nigeria, with transmission occurring year-round in most parts of the country. The prevalence of malaria varies across regions, with higher transmission intensity in the humid and forested areas of southern Nigeria compared to the drier and savannah regions in the north.
- Human Immunodeficiency Virus (HIV): Pathogen: Human Immunodeficiency Virus (HIV).
- Geographical Distribution: HIV/AIDS is prevalent across Nigeria, higher prevalence rates are generally reported in urban areas, commercial hubs, and regions with high population density, such as the Niger Delta region and major cities like Lagos and Kano.
- Viral Hepatitis: Pathogen: Hepatitis B virus (HBV), Hepatitis C virus (HCV).
- Geographical Distribution: Viral hepatitis is widespread in Nigeria, with high endemicity rates reported across the country. Hepatitis B and C infections are prevalent in both urban and rural areas, with transmission occurring through contaminated blood, unsafe injections, and vertical transmission from mother to child.

Geographical distribution of human pathogens in Nigeria

- Lassa Fever: Pathogen: Lassa fever virus (Lassa mammarenavirus).
- Geographical Distribution: Lassa fever is endemic in Nigeria, particularly in the southern and middle belt regions of the country. States such as Edo, Ondo, Ebonyi, and Plateau have reported recurrent outbreaks of Lassa fever, with sporadic cases occurring in other parts of the country.
- Yellow Fever: Pathogen: Yellow fever virus (Yellow fever flavivirus).
- Geographical Distribution: Yellow fever is endemic in Nigeria, with outbreaks reported periodically in various states, particularly in the forested and savannah regions. States in the southwest and southeast regions, such as Ogun, Delta, and Enugu, have reported significant yellow fever activity.
- Tuberculosis (TB): Pathogen: *Mycobacterium tuberculosis*.
- Geographical Distribution: Tuberculosis is prevalent throughout Nigeria, with varying TB burden across different regions. Higher TB incidence rates are generally observed in urban areas, densely populated states, and regions with poor healthcare access and socio-economic disparities.
- Meningitis: Pathogen: *Neisseria meningitidis* (bacterial meningitis), *Streptococcus pneumoniae* (pneumococcal meningitis).
- Geographical Distribution: Meningitis outbreaks occur sporadically in Nigeria, particularly during the dry season (December to June). The meningitis belt, which includes states in the northwest and northeast regions, is prone to recurrent outbreaks of bacterial meningitis.
- Cholera: Pathogen: *Vibrio cholerae*.
- Geographical Distribution: Cholera outbreaks occur intermittently in Nigeria, particularly during the rainy season (May to October). States with inadequate water and sanitation infrastructure, such as Lagos, Kano, and Borno, are susceptible to cholera epidemics.

Isolation and Identification Techniques for Microbial Pathogens

- Isolation and identification of microbial pathogens are essential steps in diagnosing infectious diseases and understanding their epidemiology. Here's an overview of common techniques used for these purposes:
- **1. Culture-Based Techniques:**
- **Sample Collection**:
  - Clinical specimens (e.g., blood, urine, sputum, swabs) or environmental samples (e.g., water, soil) are collected aseptically from suspected sources of infection.
- **Inoculation**:
  - Samples are inoculated onto appropriate culture media selective for the suspected pathogens. Examples include blood agar, MacConkey agar for bacteria, Sabouraud agar for fungi, and Thayer-Martin agar for Neisseria species.
- **Incubation**:
  - Inoculated plates or broth cultures are incubated at optimal conditions (temperature, humidity, oxygen levels) to promote the growth of target pathogens.
- **Colonial Morphology**:
  - After incubation, colonies with distinctive morphological features (color, size, shape, texture) are observed macroscopically. This can provide initial clues about the identity of the pathogen.
- **Biochemical Tests**:
  - Selected colonies are subjected to biochemical tests to identify specific metabolic characteristics. These tests include catalase, oxidase, coagulase tests for bacteria, and urease, carbohydrate fermentation tests for fungi.

Isolation and Identification Techniques for Microbial Pathogens.

- **2. Molecular Techniques: Polymerase Chain Reaction (PCR), DNA Sequencing, Gene Probes**:
- **3. Immunological Techniques: Enzyme-Linked Immunosorbent Assay (ELISA), Immunofluorescence Assay (IFA), Western Blotting**.
- **4. Mass Spectrometry: Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS), e.t.c.**

Morphology and life cycles of pathogenic microorganisms

- The morphology and life cycles of pathogenic microorganisms vary widely depending on their taxonomic classification and specific characteristics. Here's an overview of the morphology and life cycles of some common pathogenic microorganisms:
- **1. Bacteria:**
- **Morphology**:
  - Bacteria can have various shapes, including cocci (spherical), bacilli (rod-shaped), and spirilla (spiral-shaped).
  - Some bacteria may form chains, clusters, or pairs depending on their arrangement.
  - Cell walls of bacteria can be Gram-positive (retain crystal violet stain) or Gram-negative (lose crystal violet stain).
- **Life Cycle**:
  - Bacteria reproduce primarily by binary fission, where one bacterial cell divides into two identical daughter cells.
  - Some bacteria can also exchange genetic material through processes like conjugation, transformation, and transduction.
  - Certain bacterial species may form endospores under adverse conditions, allowing them to survive harsh environments and re-enter a vegetative state when conditions improve.

Morphology and life cycles of pathogenic microorganisms

- **2. Viruses:**
- **Morphology**:
  - Viruses are non-cellular entities composed of genetic material (DNA or RNA) surrounded by a protein coat called a capsid.
  - Some viruses have an additional lipid envelope derived from the host cell membrane.
  - Viruses vary in shape and size, ranging from simple helical or icosahedral structures to more complex shapes.
- **Life Cycle**:
  - Viruses require host cells to replicate and multiply. The viral life cycle typically involves attachment, penetration, replication, assembly, and release.
  - Attachment: Viruses bind to specific receptors on host cell surfaces.
  - Penetration: Viral genetic material enters the host cell either by direct fusion with the cell membrane or endocytosis.
  - Replication: Viral nucleic acid is replicated and transcribed using host cell machinery.
  - Assembly: New viral particles are assembled from replicated components.
  - Release: Newly formed viruses exit the host cell, either by budding (enveloped viruses) or cell lysis (non-enveloped viruses).

Morphology and life cycles of pathogenic microorganisms

- **3. Fungi:**
- **Morphology**:
  - Fungi can exist as single-celled yeasts or multicellular molds and mushrooms.
  - Yeasts are round or oval-shaped cells that reproduce by budding.
  - Molds form branching filaments called hyphae, which collectively make up the fungal mycelium.
- **Life Cycle**:
  - Fungi reproduce sexually or asexually depending on the species.
  - Asexual reproduction involves the formation of spores (conidia) through processes like budding, fragmentation, or sporulation.
  - Sexual reproduction involves the fusion of specialized reproductive structures (gametangia) and the formation of spores with genetic variation.
- **4. Protozoa:**
- **Morphology**:
  - Protozoa are unicellular eukaryotic organisms with diverse shapes and structures.
  - They may be amoeboid (shape-changing), flagellated (with whip-like flagella), ciliated (covered in hair-like cilia), or sporozoan (lacking locomotory structures).
- **Life Cycle**:
  - Protozoa have complex life cycles involving various stages, such as trophozoites (actively feeding), cysts (dormant, resistant stage), and sometimes intermediate hosts.
  - Reproduction can occur through binary fission, multiple fission, budding, or sexual processes like conjugation.

Morphology and life cycles of pathogenic microorganisms

- **5. Helminths (Parasitic Worms):**
- **Morphology**:
  - Helminths are multicellular organisms with elongated, cylindrical bodies.
  - They may be classified as flatworms (platyhelminths) or roundworms (nematodes).
  - Flatworms are often flattened dorsoventrally and may have complex internal structures like suckers or hooks.
- **Life Cycle**:
  - Helminths have complex life cycles that often involve multiple hosts (definitive and intermediate hosts).
  - Eggs or larvae are released into the environment through feces or other routes and can infect new hosts through ingestion, penetration, or direct contact.

Sources of Pathogenic infections

- **Humans**
- **Animals**
- **Environment**
- **Food and Water**
- **Vectors**
- **Fomites**
- **Medical Settings**
- **Community Settings**
- **Travel and Migration**
- **Environmental Contamination**

Host-pathogen interactions

- Host-pathogen interactions play a critical role in determining the outcome of infectious diseases and the manifestation of symptoms in the host.
- These interactions involve complex molecular and cellular processes that influence the virulence of the pathogen and the immune response of the host. Here's an overview of host-pathogen interactions and how they contribute to disease manifestations:
- **1. Adhesion and Colonization:**
- **Adhesion**: Pathogens adhere to host cells or tissues through specific molecular interactions between pathogen-associated adhesins and host cell receptors. Adhesion facilitates the colonization of host tissues and the establishment of infection.
- **Colonization**: Pathogens multiply and form colonies within host tissues, leading to local tissue damage and inflammation. The extent of colonization depends on the virulence factors of the pathogen and the host's immune response.
- **2. Invasion and Tissue Damage:**
- **Invasion**: Some pathogens have mechanisms to invade host cells or breach physical barriers (e.g., epithelial barriers, mucosal surfaces) to access deeper tissues or organs. Invasion can result in direct cellular damage, dissemination of the pathogen, and systemic infection.
- **Tissue Damage**: Pathogens can induce tissue damage through various mechanisms, including the production of toxins, enzymes, and inflammatory mediators. Tissue damage contributes to the development of clinical symptoms such as fever, pain, swelling, and organ dysfunction.
- **3. Immune Evasion and Evasion Strategies:**
- **Immune Evasion**: Pathogens employ various strategies to evade or subvert the host immune response, allowing them to persist and establish chronic infections. These strategies include antigenic variation, inhibition of phagocytosis, interference with complement activation, and modulation of cytokine signaling pathways.
- **Host Response**: The host immune system responds to the presence of pathogens by activating innate and adaptive immune mechanisms. Innate immune cells (e.g., macrophages, neutrophils) recognize and eliminate pathogens through phagocytosis, inflammation, and cytokine production. Adaptive immune cells (e.g., T cells, B cells) mount specific immune responses against pathogens through antibody production, cytotoxicity, and memory formation.

Host-pathogen interactions

- **4. Disease Manifestations:**
- **Acute Infections**: Acute infections are characterized by rapid onset of symptoms, often accompanied by fever, inflammation, tissue damage, and systemic manifestations. Examples include respiratory infections (e.g., influenza), gastrointestinal infections (e.g., norovirus), and skin infections (e.g., cellulitis).
- **Chronic Infections**: Chronic infections result from persistent or recurrent interactions between the host and the pathogen. Chronic infections may have insidious onset, prolonged duration, and variable clinical manifestations. Examples include chronic viral infections (e.g., HIV, hepatitis B), bacterial infections (e.g., tuberculosis), and parasitic infections (e.g., malaria).
- **5. Host Factors:**
- **Host Susceptibility**: Host factors such as age, genetic background, underlying health conditions, immunocompetence, and nutritional status influence susceptibility to infection and disease severity.
- **Host Response**: The host immune response plays a dual role in combating pathogens and contributing to tissue damage. Dysregulated immune responses can lead to immunopathology, autoimmune reactions, or cytokine storms, exacerbating disease severity.
- **6. Outcome:**
- **Resolution vs. Persistence**: The outcome of host-pathogen interactions depends on the balance between pathogen clearance and host tolerance. Successful clearance of the pathogen leads to resolution of infection and recovery, whereas failure to eliminate the pathogen results in chronic infection, sequelae, or death.

Ecology of Microbial Pathogens and Their Environmental Reservoirs

- The ecology of microbial pathogens encompasses their interactions with the environment, including their distribution, survival, and transmission dynamics.
- **1. Environmental Reservoirs: Soil, Water, Air, Plants, Animals**
- **2. Transmission Dynamics: Direct Contact, Indirect Contact, Vector-Borne Transmission, Foodborne and Waterborne Transmission, Airborne Transmission**
- **3. Environmental Factors: Temperature, Moisture, pH and Chemical Composition, Ecological Niches**
- **4. Anthropogenic Influences: Urbanization, Agricultural Practices, Climate Change, Globalization and Travel.**

VIRAL INFECTIONS

- 1. Respiratory Viral Infections: Influenza Virus, Respiratory Syncytial Virus (RSV), Coronaviruses (including SARS-CoV-2),
- 2. Gastrointestinal Viral Infections: Norovirus, Rotavirus
- 3. Dermatological Viral Infections: Herpes Simplex Virus (HSV), Varicella-Zoster Virus (VZV),
- 4. Neurological Viral Infections: Enteroviruses (e.g., Poliovirus, Enterovirus D68), Arboviruses (e.g., West Nile Virus, Zika Virus).
- 5. Hepatotropic Viral Infections: Hepatitis Viruses (e.g., Hepatitis A, B, C).
- 6. Hemorrhagic Fever Viruses: Ebola Virus, Marburg Virus, Dengue Virus, Yellow Fever Virus
- 7. Other Viral Infections: Human Immunodeficiency Virus (HIV)

FUNGAL INFECTIONS

- Medical mycoses can be divided into four categories: (1) **cutaneous,** (2) **subcutaneous,** (3) **systemic,** and (4) **opportunistic**
- **1. CUTANEOUS MYCOSES**
- **Dermatophytoses**
- **Tinea Infections** (Dermatophytoses): The most important dermatophytes are classified in to three genera: *Trichophyton*, *Epidermophyton*, and *Microsporum*. They are spread from infected persons by direct contact.
- *Microsporum* is also spread from animals such as dogs and cats. This indicates that to prevent reinfection, the animal must be treated also.
- infect only superficial keratinized structures (skin, hair, and nails), not deeper tissues.
- The disease is typically named for the affected body part (i.e., tinea capitis [head], tinea corporis [body], tinea cruris [groin], and tinea pedis [foot]) . Tinea unguium, also called onychomycosis, is a disease of the nails, especially toe nails. The nails become thickened, broken, and discolored.
- *Trichophyton tonsurans* is the most common cause of outbreaks of **tinea capitis** in children and is the main cause of endothrix (inside the hair) infections.
- *Trichophyton rubrum* is also a very common cause of tinea capitis.
- *Trichophyton schoenleinii* is the cause of **favus,** a form of tinea capitis in which crusts are seen on the scalp.
- *Trichophyton* species also cause an inflammatory pustular lesion on the scalp called a **kerion**. The marked inflammation is caused by an intense T-cell–mediated reaction to the presence of the fungus.

FUNGAL INFECTIONS

- **2. Cutaneous and Subcutaneous Fungal Infections: Dermatophytosis: Onychomycosis, Tinea Barbae, Sporotrichosis**
- **3. Deep-Seated Systemic Fungal Infections: Candidiasis, Aspergillosis, Cryptococcosis, Histoplasmosis**
- **4. Opportunistic Fungal Infections: Pneumocystis Pneumonia, Mucormycosis, Rhino-Orbito-Cerebral Mucormycosis, Candida Auris Infection.**
- **5. Disseminated Fungal Infections: Disseminated Candidiasis, Aspergillosis, Cryptococcosis.**

FUNGAL INFECTIONS

- In some infected persons, hypersensitivity causes **dermatophytid ("id")** reactions (e.g., vesicles on the fingers).
- Scrapings of skin or nail placed in 10% potassium hydroxide (KOH) on a glass slide show septate hyphae under microscopy.
- Cultures on Sabouraud's agar at room temperature develop typical hyphae and conidia.
- Tinea capitis lesions caused by *Microsporum* species can be detected by seeing fluorescence when the lesions are exposed to ultraviolet light from a Wood's lamp.
- **Candidiasis**: **Oral Candidiasis (Thrush)** , **Vulvovaginal Candidiasis, Intertrigo.**
- **Pityriasis Versicolor**

FUNGAL INFECTIONS

- **SUBCUTANEOUS MYCOSES :** These are caused by fungi that grow in soil and on vegetation and are introduced into subcutaneous tissue through **trauma**.
- **Sporotrichosis caused by** *Sporothrix schenckii* is a **dimorphic** fungus.
- In the clinical laboratory, round or cigar-shaped budding yeasts are seen in tissue specimens.
- In culture at room temperature, hyphae occur bearing oval conidia in clusters at the tip of slender conidiophores (resembling a daisy).
- The drug of choice for skin lesions is itraconazole (Sporanox).
- It can be prevented by protecting skin when touching plants, moss, and wood.
- **Chromomycosis** caused by *Fonsecaea, Phialophora, Cladosporium*, etc. when introduced into the skin through trauma. These fungi are collectively called **dematiaceous** fungi, so named because their conidia or hyphae are dark-colored, either gray or black.
- The disease occurs mainly in the tropics and is found on bare feet and legs. In the clinical laboratory, dark brown, round fungal cells are seen in leukocytes or giant cells. The disease is treated with oral flucytosine or thiabendazole, plus local surgery.
- **Mycetoma :** Soil fungi (*Petriellidium, Madurella*) enter through wounds on the feet, hands, or back and cause abscesses, with pus discharged through sinuses.
- Sulfonamides may help the actinomycotic form. There is no effective drug against the fungal form; surgical excision is recommended.

FUNGAL INFECTIONS

Systemic Mycoses: These infections result from **inhalation** of the spores of **dimorphic** fungi

- ***COCCIDIOIDES :*** *Coccidioides immitis* and *C. posadasi* cause coccidioidomycosis. The clinical manifestations of disease caused by these two species are the same, but the geographical distribution differs.
- *C. immitis* and *C. posadasi* are distinguished by genotyping but not by routine diagnostic tests in the clinical laboratory.
- **Transmission & Epidemiology :** Arthrospores are very light and are carried by the wind. They can be **inhaled** and infect the lungs.
- **Pathogenesis :**
- In the lungs, arthrospores form **spherules** that are large, have a thick, doubly refractive wall, and are filled with **endospores**.
- Upon rupture of the wall, endospores are released and differentiate to form new spherules.
- The organism can spread within a person by direct extension or via the bloodstream.
- Granulomatous lesions can occur in virtually any organ but are found primarily in bones and the central nervous system (meningitis).
- **Dissemination** from the lungs to other organs occurs in people who have a defect in cell-mediated immunity.

FUNGAL INFECTIONS

- **Laboratory Diagnosis**
- In tissue specimens, spherules are seen microscopically. The presence of spherules is pathognomonic for *Coccidioides* infection.
- Cultures on Sabouraud's agar incubated at 25°C show septate hyphae with arthrospores
- Serologic testing
- Polymerase chain reaction (PCR) assay

- **Treatment & Prevention**
- No treatment is needed in asymptomatic or mild primary infection.
- Fluconazole or itraconazole is used for persisting lung lesions or mild disseminated disease.
- Severe disseminated disease including bone lesions should be treated with amphotericin B.
- There is no vaccine.
- Prevention involves avoiding travel to endemic areas.
- Patients with *Coccidioides* infection who are significantly immunocompromised (e.g., organ transplant patients) should receive fluconazole.
- Patients who have recovered from coccidioidal meningitis should receive long-term suppressive therapy with fluconazole.

FUNGAL INFECTIONS

- ***HISTOPLASMOSIS:*** *Histoplasma capsulatum* causes histoplasmosis.
- **Properties:** *Histoplasma capsulatum* is a **dimorphic** fungus that exists as a **mold** in soil and as a **yeast** in tissue.
- **Transmission:** This fungus occurs in many parts of the world. It grows in soil, particularly if the soil is heavily contaminated with **bird droppings**, especially from starlings.
- In several tropical African countries, histoplasmosis is caused by *Histoplasma duboisii*.
- **Pathogenesis & Clinical Findings**
- **Inhaled spores** are engulfed by **macrophages** and develop into yeast forms. In tissues, *H. capsulatum* occurs as an **oval budding yeast inside macrophages**. The yeasts survive within the phagolysosome of the macrophage by producing alkaline substances, such as bicarbonate and ammonia, which raise the pH and thereby inactivate the degradative enzymes of the phagolysosome.
- The organisms spread widely throughout the body, especially to the liver and spleen, but most infections remain asymptomatic.
- **Laboratory Diagnosis**
- In tissue biopsy specimens or bone marrow aspirates, oval **yeast cells within macrophages** are seen microscopically
- Cultures on Sabouraud's agar show hyphae with tuberculate macroconidia when grown at low temperature (e.g., 25°C) and yeasts when grown at 37°C.
- Enzyme-linked immunosorbent assay (ELISA) and DNA probes are also useful.
- Serology tests: complement fixation (CF) and immunodiffusion (ID).
- **Treatment & Prevention**
- Oral itraconazole, parenteral itraconazole (or amphotericin B) is the treatment of choice.

FUNGAL INFECTIONS

- **Opportunistic Mycoses:** Opportunistic fungi fail to induce disease in most immunocompetent persons but can do so in those with **impaired host defenses**.
- There are five genera of medically important fungi: *Candida*, *Cryptococcus*, *Aspergillus*, *Mucor*, and *Rhizopus*.
- ***CANDIDA :***
- *Candida albicans* causes thrush, vaginitis, esophagitis, diaper rash, and chronic mucocutaneous candidiasis. It also causes disseminated infections such as right-sided endocarditis (especially in intravenous drug users), bloodstream infections (candidemia), and endophthalmitis. Infections related to indwelling intravenous and urinary catheters are also important.
- *Candida glabrata* is the second most common cause of disseminated candidal infections and is more drug resistant than *C. albicans*.
- *Candida auris* causes serious bloodstream infections and is highly antibiotic resistant.
- **Properties**
- *Candida albicans* is an **oval yeast with a single bud.** It is part of the **normal flora** of mucous membranes of the upper respiratory, gastrointestinal, and female genital tracts.
- Carbohydrate fermentation reactions can be used to differentiate it from other species (e.g., *Candida tropicalis, Candida parapsilosis, Candida krusei,* and *C. glabrata*) that cause human infections.
- *Candida dubliniensis* is closely related to *C. albicans*. It also causes opportunistic infections in immunocompromised patients, especially AIDS patients. Both species form chlamydospores, but *C. albicans* grows at 42°C, whereas *C. dubliniensis* does not.
- **Transmission**
- Thrush in the newborn is the result of passage through a birth canal heavily colonized by the organism.
- The presence of *C. albicans* on the skin predisposes to infections involving instruments that penetrate the skin, such as needles (intravenous drug use) and indwelling catheters. It is often found in the urine of patients with indwelling urinary (Foley) catheters.

FUNGAL INFECTIONS

- **Pathogenesis**
- The first line of defense against *Candida* infections is **intact skin and mucous membranes**.
- The second line is cell-mediated immunity,
- **Neutrophils** are also important as evidenced by the finding that neutropenia predisposes to disseminated *Candida* infections.
- Overgrowth of *C. albicans* in the mouth produces white patches called **thrush .**
- Vaginitis with itching and discharge is favored by high pH, diabetes, or **use of antibiotics**.
- Antibiotics suppress the normal flora *Lactobacillus*, which keep the pH low. As a result, the pH rises, which favors the growth of *Candida*.

FUNGAL INFECTIONS

- **Laboratory Diagnosis**
- In exudates or tissues, budding yeasts and pseudohyphae appear gram-positive and can be visualized by using calcofluor-white staining.
- In culture, typical yeast colonies are formed that resemble large staphylococcal colonies. *Candida albicans* forms **germ tubes** in serum at 37°C, whereas most other species of pathogenic *Candida* species do not
- Polymerase chain reaction (PCR)-based assays and (2) mass spectrometry (matrix-assisted laser desorption ionization-time of flight [MALDI-TOF]).
- **Treatment & Prevention**
- The drug of choice for most candidal infections is fluconazole, including oropharyngeal or esophageal thrush. Itraconazole and voriconazole are also effective. An echinocandin, such as caspofungin or micafungin, can also be used for esophageal candidiasis.

FUNGAL INFECTIONS

- ***CRYPTOCOCCUS***
- **Disease**
- *Cryptococcus neoformans* causes cryptococcosis and cryptococcal meningitis. Cryptococcosis is the most common, life-threatening, invasive fungal disease worldwide. It is especially important in AIDS patients. Another species, *Cryptococcus gattii* causes human disease less frequently than *C. neoformans*.
- **Properties**
- *Cryptococcus neoformans* is an **oval, budding yeast** surrounded by a **wide polysaccharide capsule**
- **Transmission**
- *Cryptococcus neoformans* occurs widely in nature and grows abundantly in **soil containing bird (especially pigeon) droppings**.
- **Pathogenesis & Clinical Findings**
- Lung infection is often asymptomatic or may produce pneumonia.
- Disease caused by *C. neoformans* occurs mainly in patients with reduced cell-mediated immunity, especially AIDS patients, in whom the organism disseminates to the central nervous system (meningitis) and other organs.

FUNGAL INFECTIONS

- **Laboratory Diagnosis**
- In spinal fluid mixed with **India ink**, the yeast cell is seen microscopically surrounded by a wide, unstained capsule.
- The colonies are highly mucoid—a reflection of the large amount of capsular polysaccharide produced by the organism.
- Serologic tests and PCR-based assays that detect the ribosomal DNA of *Cryptococcus* are also useful.
- Distinguishing between *C. neoformans* and *C. gattii* in the laboratory requires specialized media not generally available, so many *C. gattii* infections may go undiagnosed.
- **Treatment & Prevention**
- Combined treatment with amphotericin B and flucytosine is used in meningitis and other disseminated disease. Liposomal amphotericin B should be used in patients with preexisting kidney damage.

FUNGAL INFECTIONS

- ***ASPERGILLUS***
- *Aspergillus fumigatus,* cause infections of the skin, eyes, ears, and other organs; "fungus ball" in the lungs; and allergic bronchopulmonary aspergillosis.
- *Aspergillus* species exist **only as molds;** they are not dimorphic.
- **Transmission** is by **airborne conidia**.
- **Pathogenesis**
- *Aspergillus fumigatus* can colonize and later invade abraded skin, wounds, burns, the cornea, the external ear, or paranasal sinuses.
- In immunocompromised persons, especially those with neutropenia, it can invade the lungs, producing hemoptysis, and the brain, causing an abscess.
- **Laboratory Diagnosis**
- Biopsy specimens show **septate, branching hyphae** invading tissue.
- Cultures show colonies with characteristic radiating chains of conidia .
- However, positive cultures do not prove disease because colonization is common.
- **Treatment & Prevention**
- Voriconazole is the drug of choice for invasive aspergillosis. Liposomal amphotericin B, posaconazole, caspofungin, and isavuconazonium are alternative drugs.

FUNGAL INFECTIONS

- ***MUCOR & RHIZOPUS***
- Mucormycosis (zygomycosis, phycomycosis) is a disease caused by saprophytic **molds** (e.g., *Mucor, Rhizopus,* and *Absidia*) found widely in the environment.
- Transmitted by airborne asexual spores and invade tissues of patients with reduced host defenses.
- Patients with **diabetic ketoacidosis**, burns, bone marrow transplants, or leukemia are particularly susceptible.
- In biopsy specimens, organisms are seen microscopically as **nonseptate hyphae** with broad, irregular walls and branches that form more or less at right angles.
- Cultures show colonies with spores contained within a sporangium.
- If diagnosis is made early, treatment of the underlying disorder, plus administration of amphotericin B and surgical removal of necrotic infected tissue,

- ***PNEUMOCYSTIS***
- *Pneumocystis jiroveci* is classified as a yeast on the basis of molecular analysis, but it has many characteristics of a protozoan. Some regard it as an "unclassified" organism.
- *Pneumocystis* is acquired by inhalation of airborne organisms into the lungs.
- The clinical findings of *Pneumocystis* pneumonia include fever, nonproductive cough, and dyspnea
- The diagnosis is typically made by finding the cysts of *Pneumocystis* in bronchial lavage specimens.
- Fluorescent antibody stains or tissue stains, such as methenamine silver or Giemsa, are used to identify the organism. PCR-based tests are also used. Serologic tests are not useful.
- The drug of choice for *Pneumocystis* pneumonia is trimethoprim-sulfamethoxazole. Trimethoprim-sulfamethoxazole or aerosolized pentamidine can be used for prophylaxis in patients with CD_4 counts below 200.

BACTERIAL INFECTIONS

- **Central Nervous System Infections**
- **MENINGITIS :** Meningitis is an infection of the meninges, the membranes that line the brain and spinal cord.. Acute meningitis is caused by either pyogenic bacteria, such as *Streptococcus pneumoniae* and *N. meningitidis*, or viruses, such as Coxsackie virus and herpes simplex virus type 2.
- Viral meningitis is often called aseptic meningitis because routine cultures for bacterial pathogens are negative.
- Subacute meningitis is caused by *Mycobacterium tuberculosis* and fungi, such as *Cryptococcus*. The causative organisms are often found in the spinal fluid located in the subarachnoid space.
- **Pathophysiology**
- Hematogenous spread (i.e., bacteremia or viremia) is the most common route by which organisms reach the meninges.
- Direct spread occurs less frequently.
- Acute bacterial meningitis begins with nasopharygeal colonization followed by local invasion, entry into the bloodstream, and invasion of the meninges . This is followed by an inflammatory response that causes many of the clinical manifestations, especially the edema resulting in increased intracranial pressure leading to headache. Cerebral vasculitis and infarction can also occur.
- **Clinical Manifestations**
- Early symptoms include the **classic triad of fever, headache, and stiff neck** (nuchal rigidity). Altered mental status also commonly occurs. If untreated, meningitis may progress to vomiting, seizures, photophobia, and focal neurologic deficits

Meningitis

- **Diagnosis**
- Gram stain and
- Culture of Cerebrospinal Fluid.
- PCR-based tests

- **Prevention**
- Prevention strategies include both immunization and chemoprophylaxis.

ENCEPHALITIS

- Encephalitis is an infection of the brain parenchyma predominantly caused by viruses. Sometimes both the brain and the meninges are involved, a condition called meningoencephalitis.
- **Pathophysiology**
- HSV-2, Arboviruses,Varicella Zooster Virus, Cytomegalovirus (CMV) can cause encephalitis
- Postinfection encephalitis typically follows an infection or an immunization by several weeks. It is a demyelinating disease caused by an immune attack on neurons, primarily those of the white matter.
- Note that the lesions in encephalitis are inflammatory (contain WBCs, especially lymphocytes), whereas the lesions of an encephalopathy show degenerating neurons but no inflammation and do not contain WBCs.

ENCEPHALITIS

- **Clinical Manifestations**
- fever, headache, and altered mental status, as well as seizures and focal neurologic deficits.
- **Diagnosis**
- A mild elevation in CSF lymphocytes can be seen along with an elevation of protein and a normal glucose.
- A normal CSF pattern can also be seen in encephalitis.
- PCR-based testing of CSF
- Direct fluorescent antibody staining of a biopsy of skin from the nape of the neck.
- **Treatment**
- Intravenous acyclovir is the treatment of choice for HSV-1, HSV-2, and VZV encephalitis. There is no antiviral therapy for arboviral or rabies encephalitis.
- **Prevention**
- Prevention of rabies includes both preexposure (before the bite) and postexposure (after the bite) prophylaxis.

ENTERIC FEVER SUCH AS TYPHOID FEVER

- Enteric fever caused by *Salmonella typhi*. *S. typhi* is also known as *Salmonella enterica* serotype Typhi. Typhoid fever is a significant global health problem.
- **Pathophysiology**
- Following the consumption of contaminated food, *Salmonella* bacteria enter through the intestinal mucosal epithelium by transcytosis. The microbes then replicate in the macrophages of Peyer patches, mesenteric lymph nodes, and spleen. Bacteremia then occurs with dissemination to lungs, gallbladder, kidneys, or central nervous system.
- Humans are the only reservoir for *S. typhi*, so contamination of food or water by human feces should be suspected.
- **Clinical Manifestations**
- Malaise, together with abdominal pain, constipation, and headache.
- Fever increases over the next several days.
- During the second week of disease, a typical transient rash of pink maculopapular lesions (**rose spots**) may be seen.
- Diarrhea is uncommon.

ENTERIC FEVER (TYPHOID FEVER)

- **Pathogens**
- *Salmonella typhi* and other *Salmonella* species, such as *Salmonella paratyphi* A and *S. paratyphi* B, cause typhoid fever.
- **Diagnosis**
- Blood cultures are typically positive and stool cultures are often negative.
- Later in the disease and in the carrier state, stool cultures are positive and blood cultures are negative.
- Stool cultures are positive at this stage because bile from an infected gallbladder carries organisms into the stool.
- **Treatment**
- Oral or intravenous ciprofloxacin is often used. Intravenous ceftriaxone is another effective treatment modality
- **Prevention**
- Hygienic measures to protect the food and water supply from human fecal contamination are an important public health intervention. Immunization may not always be effective but can be considered in epidemic outbreaks, for travelers to endemic countries, and for household contacts of typhoid carriers.

Pelvic Infections
GENITAL ULCER DISEASE

- Genital ulcer disease manifests as a breach in the skin or mucosa of the genitalia, usually caused by a sexually transmitted infection.
- Caused by herpes simplex virus type 2 (HSV-2) ,causing genital herpes, *T. pallidum* (causing primary syphilis), and *H. ducreyi* (causing chancroid).
- **Clinical Manifestations**
- Lesions
- Ulcer on the shaft of the penis
- **Diagnosis**
- Direct fluorescent antibody (DFA) test for HSV antigens,
- viral culture for HSV, or nucleic acid amplification methods for HSV DNA using a specimen taken from the base of the ulcer
- syphilis serologic testing (e.g., rapid plasmin reagin, RPR) using a serum sample.
- **Treatment**
- Genital herpes (acyclovir or famciclovir or valacyclovir).
- Syphillis: penicillin, benzathine penicillin G.
- Chancroid is azithromycin, whereas for lymphogranuloma venereum, it is doxycycline
- **Prevention**
- Consistent use of condoms
- Prophylaxis with drugs
- Partner notification and treatment

VAGINITIS

- Vaginitis is inflammation of the vagina that can result in discharge, itching, and pain.
- These symptoms occur primarily in three diseases: candidiasis, trichomoniasis, and bacterial vaginosis. *Candida albicans* is the most common cause of vaginal candidiasis. *Trichomonas vaginalis* is the cause of trichomoniasis.
- Overgrowth of bacteria such as *Gardnerella vaginalis* is implicated in bacterial vaginosis, but anaerobes such as *Mobiluncus* and *Prevotella* and nonanaerobes such as *Mycoplasma hominis* and *Ureaplasma* are also involved.
- Noninfectious causes include lichen planus and certain medications (e.g., oral contraceptives)
- Note that a vaginal discharge can occur in both vaginitis and cervicitis.
- **Pathophysiology**
- The use of antibiotics that inhibit the normal flora of the vagina, especially lactobacilli, predisposes to *Candida* vaginitis.
- *Candida* is a member of the normal flora of many women. The pathogenesis of bacterial vaginosis is uncertain, but it does not appear to be a sexually transmitted disease. Trichomoniasis, on the other hand, is a sexually transmitted disease.
- **Clinical Manifestations**
- Abnormal vaginal discharge.
- Pruritus,
- pain (including dyspareunia
- **Diagnosis**
- Microscopic examination
- Nucleic acid amplification test (NAAT) are performed to increase sensitivity.
- Culture based tests
- **Treatment**
- Metronidazole is the drug of choice for both bacterial vaginosis and trichomoniasis. For candidiasis, either oral fluconazole or vaginally administered miconazole or butoconazole is the

PELVIC INFLAMMATORY DISEASE

- Pelvic inflammatory disease (PID) is a polymicrobial infection of upper genital tract structures, namely, the uterus, fallopian tubes, and ovaries.
- **Pathophysiology**
- When the endocervical canal barrier is compromised, vaginal bacteria can ascend into the normally sterile space of the upper genital tract (uterus, fallopian tubes, and ovaries). A sexually transmitted infection affecting the cervix (e.g., *N. gonorrhoeae* and *C. trachomatis*) can initiate the process, permitting the anaerobic bacteria of the vagina to ascend.
- Having multiple sex partners increases the risk of PID. Multiple episodes of PID lead to scarring of the fallopian tubes and an increased risk of ectopic pregnancy and sterility. PID is especially common in adolescent and young adult women.
- **Clinical Manifestations**
- Patients can present with a range of symptoms, from lower back pain to fever, chills, lower abdominal pain, and cervical and adnexal tenderness. The abrupt onset of abdominal pain associated with menses is a common finding in PID. On physical exam, tenderness on motion of the cervix and an abnormal vaginal discharge are important diagnostic signs.
- **Pathogens**
- PID is primarily caused by *N. gonorrhoeae* and *C. trachomatis*, together with *Mycoplasma genitalium*, enteric gram-negative rods, and anaerobes.
- **Diagnosis**
- Because it is often difficult to diagnose PID precisely (given the nonspecific findings) and because the consequences of not treating PID can be grave, many opt to treat with minimum diagnostic criteria such as uterine, adnexal, or cervical motion tenderness.
- Fever, the presence of leukocytes on cervical or vaginal discharge, elevated C-reactive protein, and laboratory evidence of cervical infection with *N. gonorrhoeae* or *C. trachomatis*, such as NAATs for these organisms, can increase the specificity of the diagnosis.
- **Treatment**
- Cefoxitin or ceftriaxone (one dose) plus doxycycline (14 days).
- Metronidazole.
- **Prevention**
- There is no vaccine against any of the organisms that cause PID.

Upper Respiratory Tract Infections

- **OTITIS MEDIA**
- Otitis media is an infection of the middle ear caused by either viruses or bacteria. Among bacteria, *Streptococcus pneumoniae* is the most common cause.
- Nontypeable strains of *Haemophilus influenzae* and *Moraxella catarrhalis* are also common causes. Among viruses, respiratory syncytial virus, coronaviruses, and rhinoviruses are commonly involved.
- **Pathophysiology**
- Any process that leads to eustachian tube obstruction can result in fluid retention and concomitant infection of the middle ear. The most common predisposing factors are upper respiratory tract infections and seasonal allergic rhinitis.
- **Clinical Manifestations**
- Patients present with ear pain (otalgia) and pressure, often accompanied by an upper respiratory tract infection
- **Diagnosis**
- Gram stain and culture.
- **Treatment**
- Amoxicillin orally is usually the drug of choice together with nasal decongestants to open the eustachian tube. In cases of bacterial resistance, amoxicillin-clavulanate (Augmentin) may be used.
- **Prevention**
- Recurrent episodes of otitis media can be suppressed by prophylactic antibiotics such as amoxicillin or sulfisoxazole. Ventilating tubes may be inserted as a strategy to prevent recurrent infections.
- The conjugate pneumococcal vaccine is effective in preventing invasive pneumococcal disease but is less effective in preventing otitis media.

COMMON COLD

- The common cold is a viral infection of the upper respiratory tract, including some or all of the following structures: the nose, throat, sinuses, eustachian tubes, trachea, and larynx.
- **Pathophysiology**
- The viruses that cause the common cold are transmitted primarily by aerosols generated by sneezing, or by direct contact.
- **Clinical Manifestations**
- Clinical manifestations include nasal congestion, decreased sense of smell, rhinorrhea (watery nasal discharge without purulence), and sneezing. Patients also complain of general malaise and sore throat. In some cases, headache may also be reported.
- **Pathogens**
- Rhinoviruses (more than 100 serotypes) are the most common etiology (up to 50%). Coronaviruses, adenoviruses, and enteroviruses such as Coxsackie viruses are other causes. Viruses such as parainfluenza virus and respiratory syncytial virus are also possible causes of the common cold, although they primarily cause other diseases (croup and bronchiolitis, respectively).
- **Treatment**
- Generally, only symptomatic therapy is offered. It is controversial whether zinc salts may be helpful. Zinc acetate in doses greater than 75 mg/d may reduce the duration of symptoms. Other strategies include oral decongestants and buffered hypertonic saline nasal irrigation. If used for more than a few days, nasal sprays may be associated with rebound congestion after stopping.
- There are no antiviral drugs useful against the common cold. Antibacterial drugs should *not* be prescribed for patients with the common cold.
- **Prevention**
- Vitamin C taken prophylactically may be helpful in a population of cold weather athletes. However, when vitamin C was tested in the general population (rather than athletes), its ability to prevent colds was marginal.
- Handwashing may prevent the transmission of respiratory viruses.
- There is no vaccine against any virus that causes the common cold.

Lower Respiratory Tract Infections

- **BRONCHITIS**
- Bronchitis is a self-limited inflammation of the bronchi.
- **Pathophysiology**
- The coughing so characteristic of bronchitis is an attempt to clear the mucus produced by the inflammatory response to viral infection
- Bronchitis occurs more often in the winter months than in the summer.
- Smoking predisposes to bronchitis (and pneumonia) by damaging the cilia in the bronchi, leading to an inability to clear mucus from the respiratory tract.
- **Clinical Manifestations**
- Cough is the most prominent symptom of bronchitis.
- **Pathogens**
- Respiratory viruses are the most common pathogens (influenza A and B, parainfluenza virus, coronavirus, rhinovirus, respiratory syncytial virus [RSV], and human metapneumovirus). Bacterial pathogens do not play a significant role in acute bronchitis.
- **Treatment**
- Nonsteroidal anti-inflammatory drugs and/or a bronchodilator such as ipratropium.
- If influenza is diagnosed, oseltamivir (Tamiflu) may reduce the length and severity of symptoms.
- Antibiotics should be used *only* in those for whom a bacterial etiology has been clearly demonstrated.
- **Prevention**
- Handwashing is recommended to reduce the carriage of respiratory viruses.

PNEUMONIA

- Pneumonia is an inflammation of the lung affecting the alveoli caused by gram-negative rods such as *Escherichia coli*, *Pseudomonas*, and *Acinetobacter*.
- **Pathophysiology**
- The alveoli of the lungs are continually exposed to microbes from the environment via the upper respiratory tract. Our host defenses usually keep these potential pathogens in check. However, disease can occur when there is a particularly virulent organism, when there is a large burden of organisms inhaled from the environment or aspirated from the oropharynx, or when there is a defect in host immunity.
- Predisposing factors to pneumonia include ;
- i. the extremes of age (the very young and very old),
- ii. chronic obstructive pulmonary disease (COPD) and chronic bronchitis,
- iii. diabetes mellitus,
- iv. cystic fibrosis, and
- v. congestive heart failure.

PNEUMONIA

- **Clinical Manifestations**
- Cough that may be productive of sputum, fever, chills, chest pain, and shortness of breath. “
- Patients who are intubated and who acquire a nosocomial pneumonia may only have fever as a presenting sign, which may be accompanied by increased respiratory secretions or increased oxygen requirements.
- Pneumonia may be complicated by an infected pleural effusion or a pleural empyema. A pleural empyema is a walled-off collection of pus in the pleural space.
- **Diagnosis**
- Sputum analysis for Gram stain
- Culture and blood cultures
- **Treatment**
- Macrolide such as azithromycin, a tetracycline such as doxycycline, or a respiratory quinolone such as levofloxacin. Amoxicillin-clavulanate with or without a macrolide can also be used.
- **Prevention**
- The influenza vaccine is effective in decreasing the likelihood of pneumonia.

Skin & Soft Tissue Infections

- **IMPETIGO :** an infection of the epidermal layer of skin.
- **Pathophysiology**
- Bacteria invade into the epidermal layer and cause local damage. Bullous impetigo occurs when strains of *S. aureus* secrete exfoliative toxin, a protease that degrades desmoglein, resulting in loss of adhesion of the superficial epidermis. This is the same toxin that causes staphylococcal scalded skin syndrome.
- **Clinical Manifestations**
- There are three clinical variants of impetigo: (1) classic impetigo, (2) bullous impetigo, and (3) ecthyma.
- **Pathogens**
- *Staphylococcus aureus* and *S. pyogenes* are the two main pathogens that cause impetigo.
- **Diagnosis**
- Culture of bullous fluid or pus can be considered when patients do not respond to standard treatment.
- **Treatment**
- Antibacterial therapy should be directed against both *S. aureus* and *S. pyogenes*.
- Topical therapy with mupirocin or retapamulin is preferred when only a few lesions are present.
- In patients with widespread disease, a systemic antimicrobial is preferred. If concern for methicillin-resistant *S. aureus* (MRSA) exists, clindamycin is recommended; otherwise, cephalexin or dicloxacillin would be appropriate.

SKIN ABSCESS (FURUNCLE & CARBUNCLE)

- A skin abscess is an infection of the dermis and deeper layers of skin that contains purulent material caused by *Staphylococcus aureus,* Beta-hemolytic streptococci, *Mycobacterium tuberculosis*, nontuberculous mycobacteria, and fungi such as *Coccidioides, Candida*, and *Cryptococcus* can cause abscesses.
- **Pathophysiology**
- Abscesses occur when pathogens enter a break in the skin following trauma or when they spread from infected hair follicles (Figure 77–8). When a single follicle is infected and tracks down into the dermis, it is termed a furuncle ("boil"), and when multiple infected hair follicles coalesce, it is termed a carbuncle. Occasionally an abscess may develop following hematogenous dissemination of an infection.
- **Clinical Manifestations**
- A furuncle consists of a central pustule usually surrounded by an area of erythema, warmth, and tenderness with underlying fluctuance
- A carbuncle is a larger, more serious lesion than a furuncle. It is composed of several adjacent furuncles that have coalesced into an inflamed, indurated lesion that typically extends deep into subcutaneous tissue. Carbuncles are often found on the nape of the neck, where a shirt collar rubs in people with poor hygiene
- **Diagnosis**
- Gram stain and culture of purulent material obtained from the abscess allow for diagnosis.
- **Treatment :**The primary treatment for abscesses is incision and drainage. Oral antibiotic regimens that is active on MRSA
- **Prevention**
- Handwashing and covering draining lesions should be used to prevent the spread of bacteria.

Urinary tract infections

- Urinary tract infections are a group of common diseases that occur predominantly by ascension of normal enteric flora through the urethra into the bladder.
- These infections more frequently affect women due to anatomic differences including a shorter urethra.
- Diagnosis is made by identifying related clinical symptoms in combination with an abnormal urinalysis and growth on urine culture.
- Antibiotics are often effective therapy, although antibiotic resistance is increasing.

Sepsis/Bacteremia

- **Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.**
- Evidence of organ dysfunction includes clinical and laboratory abnormalities of the respiratory system, coagulation, liver, cardiovascular system, nervous system, and kidneys.
- A subset of patients with sepsis can develop **septic shock**, which is defined by profound cellular abnormalities and inadequate organ perfusion.
- **Bacteremia** is an associated term, defined as the presence of bacteria in the bloodstream. Approximately 25% of patients with sepsis have detectable bacteremia. The remaining 75% without bacteremia have organ system infections, most often in the respiratory tract, urinary tract, gallbladder, or intestine, caused by viruses, fungi, and protozoa.

Sepsis/Bacteremia

- **PATHOPHYSIOLOGY**
- Sepsis results from the interaction of the infectious agent, usually bacteria, with the host's immune, cardiovascular, neuronal, metabolic, and coagulation systems.
- Sepsis caused by **gram-negative bacteria** is mediated primarily by **endotoxin**, also known as **lipopolysaccharide (LPS)**.
- The main effects of LPS are caused by its lipid A component. Lipid A in conjunction with LPS-binding protein binds to Toll-like receptor (TLR)-4 on the surface of the macrophage. This stimulates the production of interleukin (IL)-1, tumor necrosis factor (TNF), and IL-6.
- These cytokines cause fever, alter the endothelial cells to cause vascular leak, and recruit and activate inflammatory white blood cells.
- Nitric oxide is also released, causing vasodilation and hypotension, contributing to hypotension.
- Endotoxin also activates the coagulation cascade causing **disseminated intravascular coagulation (DIC)**.
- Sepsis caused by gram-positive bacteria is *not* mediated by endotoxin because these bacteria do not contain LPS. Rather, there are surface components such as **peptidoglycan** and **teichoic acid** that stimulate the macrophage to produce the same cytokines as does endotoxin.
- Similarly, some fungi, viruses, and protozoa have elements that can trigger macrophages to generate the same effect.
- **Neonatal sepsis** is the result of the infant's immature immune system coupled with carriage of the bacteria in the female genital tract that are transmitted during the passage through the birth canal. The most common causes are group B streptococci (*Streptococcus agalactiae*), *Escherichia coli*, and *Listeria monocytogenes*.

Sepsis/Bacteremia

- **CLINICAL MANIFESTATIONS**
- **Fever** and **elevated neutrophils** along with signs of **organ system dysfunction.**
- **PATHOGENS**
- Gram-negative rods, such as Enterobacteriaceae (e.g., *E. coli*, *Enterobacter*, *Klebsiella*, *Serratia*, and *Proteus*) and *Pseudomonas*, are common causes of endotoxin-mediated sepsis.
- *Neisseria meningitidis* causes meningococcemia, a common cause of septic shock in young adults.
- Gram-positive bacteria , such as *Staphylococcus aureus* and *Enterococcus faecalis*, are also important causes of sepsis. *Streptococcus spp*Group B streptococci (*S. agalactiae*) are the most common cause of neonatal sepsis.
- The gram-negative rod, *E. coli,* and the gram-positive rod, *Listeria*, are also important causes of neonatal sepsis.
- Uncommon bacteria that cause sepsis include *Rickettsia rickettsiae* (Rocky Mountain spotted fever), *Salmonella typhi* (typhoid fever), *Francisella tularensis* (tularemia), *Bacillus anthracis* (anthrax), and *Vibrio vulnificus*.
- *Yersinia pestis* causes plague that can progress to life-threatening septic shock.

Sepsis/Bacteremia

- **DIAGNOSIS**
- To identify the microbiologic cause of sepsis, **blood cultures** are the mainstay of diagnosis of bloodstream infections.
- Urinalysis and urine cultures should also be done.
- **TREATMENT**
- Broad-spectrum bactericidal antibiotics
- **PREVENTION**
- There are vaccines against *N. meningitidis*, *S. pneumoniae*, *S. typhi*, influenza virus, and yellow fever virus.
- There is no vaccine against the enteric gram-negative rods, *Pseudomonas*, *S. aureus*, or *E. faecalis*.