Unit One
Pathogenesis of Bacterial Infection

Pathogenesis of bacterial infection includes
• the mechanisms that lead to the development of signs and symptoms of disease.

Characteristics of bacteria that are pathogens include
• initiation of the infectious process
• transmissibility
• Adherence to host cells
• Persistence
• invasion of host cells and tissues
• toxigenicity
• ability to evade or survive the host’s immune system
• Resistance to antimicrobials and disinfectants
• Disease occurs if the bacteria or immunologic reactions to their presence cause sufficient harm to the person.

GLOSSARY

• **Adherence (adhesion, attachment):** The process by which bacteria stick to the surfaces of host cells.

• **Carrier:** A person or animal with asymptomatic infection that can be transmitted to another susceptible person or animal.

• **Infection:** Multiplication of an infectious agent within the body. Multiplication of the bacteria that are part of the normal flora is not considered an infection
**Invasion:** The process whereby bacteria, animal parasites, fungi, and viruses enter host cells or tissues and spread in the body.

**Microbiota:** Microbial flora harbored by normal, healthy individuals.

**Nonpathogen:** A microorganism that does not cause disease; may be part of the normal microbiota.

**Opportunistic pathogen:** An agent capable of causing disease only when the host’s resistance is impaired.

**Pathogen:** A microorganism capable of causing disease.

**Pathogenicity:** The ability of an infectious agent to cause disease. (See also virulence.)

**Superantigens:** Protein toxins that activate the immune system by binding to major histocompatibility complex (MHC) molecules and T-cell receptors (TCR) and stimulate large numbers of T cells to produce massive quantities of cytokines.

**Toxigenicity:** The ability of a microorganism to produce a toxin that contributes to the development of disease.

**Virulence:** The quantitative ability of an agent to cause disease.
IDENTIFYING BACTERIA THAT CAUSE DISEASE

Koch’s Postulates

1. The microorganism should be found in all cases of the disease in question, and its distribution in the body should be in accordance with the lesions observed.

2. The microorganism should be grown in pure culture in vitro (or outside the body of the host) for several generations.

3. When such a pure culture is inoculated into susceptible animal species, the typical disease must result.

4. The microorganism must again be isolated from the lesions of such experimentally produced disease.
TRANSMISSION OF INFECTION

Bacteria (and other microorganisms) can adapt to a variety of environments that include external sources such as soil, water and organic matter or internal milieu as found within insect vectors, animals and humans, where they normally reside and subsist.

The most frequent **portals of entry of pathogenic bacteria** into the body are the sites where mucous membranes meet with the skin, which are:

1. the **respiratory** (upper and lower airways)
2. **gastrointestinal** (primarily mouth)
3. **genital**, and **urinary tracts**.
4. Abnormal areas of **mucous membranes and skin** (e.g., cuts, burns, and other injuries) are also frequent sites of entry. Normal skin and mucous membranes provide the primary defense against infection.
• **THE INFECTIOUS PROCESS**
  • most bacteria that cause disease do so first by attaching or adhering to host cells, usually epithelial cells.
  • After that, they multiply and spread directly through tissues or via the lymphatic system to the bloodstream.
  • This infection (bacteremia) can be transient or persistent.
  • e.g. *Pneumococcal pneumonia* is an example of the infectious process. *S pneumoniae* can be cultured from the nasopharynx of 5–40% of healthy people.
  • Occasionally, pneumococci from the nasopharynx are aspirated into the lungs; aspiration occurs most commonly in debilitated people and in settings such as coma when normal cough reflexes are diminished.
  • Infection develops in the terminal air spaces of the lungs in persons who do not have protective antibodies. Multiplication of the pneumococci and resultant inflammation lead to pneumonia.
  • The pneumococci enter the lymphatics of the lung and move to the bloodstream. When bacteremia occurs, the pneumococci can spread to secondary sites of infection (eg, cerebrospinal fluid, heart valves, and joint spaces).
The Clonal Nature of Bacterial Pathogens

- important result of the conservation of chromosomal genes in bacteria is that the organisms are clonal.
- For most pathogens, there are only one or a few clonal types that are spread in the world during a period of time.
- Epidemic serogroup A meningococcal meningitis occurs in Asia, the Middle East, and Africa and occasionally spreads into Northern Europe and the Americas. Only a single clonal type of serogroup A Neisseria meningitidis have been observed to appear in one geographic area and subsequently spread to others with resultant epidemic disease.
Pathogenicity Islands

- Large groups of genes that are associated with pathogenicity and are located on the bacterial chromosome are termed **pathogenicity islands (PAIs)**. They are
  - large organized groups of genes, usually 10–200 kb in size.
  - they have one or more virulence genes
  - they are present in the genome of pathogenic members but absent in the nonpathogenic members
  - they typically have a different guanine plus cytosine (G + C) content than the rest of the bacterial genome;
  - they are often found with parts of the genome associated with mobile genetic elements
  - they often have genetic instability
REGULATION OF BACTERIAL VIRULENCE FACTORS

- Pathogenic bacteria (and other pathogens) have adapted both to saprophytic or free-living states.
- They have evolved complex signal transduction systems to regulate the genes important for virulence.
- Environmental signals often control the expression of the virulence genes. Common signals include
  - temperature
  - Iron availability
  - Osmolality
  - growth phase
  - PH
  - specific ions (Ca2+)
  - nutrient factors.
**BACTERIAL VIRULENCE FACTORS**

Many factors determine bacterial virulence or the ability to cause infection and disease.

Adherence Factors: When bacteria enter the body of the host, they must adhere to cells of a tissue surface.

- The interactions between bacteria and tissue cell surfaces in the adhesion process are complex. Several factors play important roles, including:
  - surface hydrophobicity
  - net surface charge (Bacteria and host cells commonly have net negative surface charges and therefore repulsive electrostatic forces).
  - binding molecules on bacteria (ligands)
  - host cell receptor interactions.

- Many bacteria have pili, thick rod-like appendages or fimbriae, shorter “hairlike” structures that extend from the bacterial cell surface and help mediate adherence of the bacteria to host cell surfaces. *E. coli* strains have type 1 pili, which adhere to epithelial cell receptors, also *Streptococcus pyogenes* have hair-like appendages, termed fimbriae, that extend from the cell surface and contain Lipoteichoic acid, protein F, and M protein are found on the fimbriae. The lipoteichoic acid and protein F cause adherence of the streptococci to buccal epithelial cells; this adherence is mediated by fibronectin, which acts as the host cell receptor molecule. **M protein acts as an antiphagocytic molecule and is a major virulence factor.**
• **Invasion of Host Cells and Tissues**
  • invasion of the host’s epithelium is central to the infectious process.
  • When inside the host cell, bacteria may remain enclosed in a vacuole composed of the host cell membrane, or the vacuole membrane may be dissolved and bacteria may be dispersed in the cytoplasm.
  • In many infections, the bacteria produce virulence factors that influence the host cells, causing them to engulf (ingest) the bacteria.

• **Note: Toxin production and other virulence properties are generally independent of the ability of bacteria to invade cells and tissues.**

**Toxins**
Toxins produced by bacteria are generally classified into two groups: **exotoxins** and **endotoxins**.
<table>
<thead>
<tr>
<th>Property</th>
<th>Exotoxin</th>
<th>Endotoxin</th>
</tr>
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<tbody>
<tr>
<td>Bacterial Source</td>
<td>Mostly from gram-positive bacteria</td>
<td>Gram-negative bacteria</td>
</tr>
<tr>
<td>Relation to Microorganism</td>
<td>Metabolic product of growing cell</td>
<td>Present in LPS of outer membrane of cell wall and released with destruction of cell or during cell division</td>
</tr>
<tr>
<td>Chemistry</td>
<td>Proteins, usually with two parts (A-B)</td>
<td>Lipid portion (lipid A) of LPS of outer membrane (lipopolysaccharide).</td>
</tr>
<tr>
<td>Pharmacology (Effect on Body)</td>
<td>Specific for a particular cell structure or function in the host (mainly affects cell functions, nerves, and gastrointestinal tract)</td>
<td>General, such as fever, weaknesses, aches, and shock; all produce the same effects</td>
</tr>
<tr>
<td>Heat Stability</td>
<td>Unstable; can usually be destroyed at 60–80°C (except staphylococcal enterotoxin)</td>
<td>Stable; can withstand autoclaving (121°C for 1 hour)</td>
</tr>
<tr>
<td>Toxicity (Ability to Cause Disease)</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Fever-Producing</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Immunology (Relation to Antibodies)</td>
<td>Can be converted to toxoids to immunize against toxin; neutralized by antitoxin</td>
<td>Not easily neutralized by antitoxin; therefore, effective toxoids cannot be made to immunize against toxin</td>
</tr>
<tr>
<td>Lethal Dose</td>
<td>Small</td>
<td>Considerably larger</td>
</tr>
<tr>
<td>Representative Diseases</td>
<td>Gas gangrene, tetanus, botulism, diphtheria, scarlet fever</td>
<td>Typhoid fever, urinary tract infections, and meningococcal meningitis</td>
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Lipopolysaccharides of Gram-Negative Bacteria
- The LPS (endotoxin) of gram-negative bacteria are bacterial cell wall components
- The pathophysiologic effects of LPS are similar regardless of their bacterial origin except for those of Bacteroides species
- LPS in the bloodstream is initially bound to circulating proteins, which then interact with receptors on macrophages neutrophils and other cells of the RES.
- Proinflammatory cytokines such as IL-1, IL-6, IL-8, TNF-á are released
- Complement and coagulation cascades are activated.

Clinically: fever, leukopenia, and hypoglycemia; hypotension and shock resulting in impaired perfusion of essential organs (eg, brain, heart, kidney); intravascular coagulation; and death from massive organ dysfunction.

Peptidoglycan of Gram-Positive Bacteria
- The peptidoglycan of gram-positive bacteria is made up of cross-linked macromolecules that surround the bacterial cells.
- Caused vascular changes leading to shock
- PG is much less potent than LPS.
Enzymes: Many species of bacteria produce enzymes that are not intrinsically toxic but do play important roles in the infectious process.

A. Tissue-Degrading Enzymes

- **Lecithinase** (lecithin degrading substances)
- **Collagenase**, which degrades collagen, the major protein of fibrous connective tissue, and promotes spread of infection in tissue.
- **Coagulase**, which works in conjunction with blood factors to coagulate plasma. It contributes to the formation of fibrin walls around staphylococcal lesions, which helps them persist in tissues and may help protect them from phagocytosis or from destruction within phagocytic cells.
- **Hyaluronidases** are enzymes that hydrolyze hyaluronic acid, a constituent of the ground substance of connective tissue.
- **Streptokinase** (**fibrinolysin**), a substance that activates a proteolytic enzyme of plasma. This enzyme is then able to dissolve coagulated plasma and probably aids in the rapid spread of streptococci through tissues.
- Many bacteria produce substances that are **cytolysins**—that is, they dissolve red blood cells (**hemolysins**) or kill leukocytes (**leukocidins**).
- **Streptolysin O**, for example, is produced by group A streptococci. It caused hemolysis for red blood cells from many animals. It is oxygen labile, antigenic. The same streptococci also produce oxygen-stable, serum-inducible **streptolysin S**, which is not antigenic.
B. IgA1 Proteases

- Immunoglobulin A is the secretory antibody on mucosal surfaces. It has two primary forms, IgA1 and IgA2, that differ near the center, or hinge region of the heavy chains of the molecules.
- Some bacteria that cause disease produce enzymes, IgA1 proteases, that split IgA1 at specific proline–threonine or proline–serine bonds in the hinge region and inactivate its antibody activity.
- IgA1 protease is an important virulence factor of the pathogens *N. gonorrhoeae*, *N. meningitidis*, *H. influenzae*, and *S. pneumoniae*.

**Antiphagocytic Factors:** Many bacterial pathogens are rapidly killed after they are ingested by polymorphonuclear cells or macrophages. Some pathogens evade phagocytosis or leukocyte by

1. Adsorbing normal host components to their surfaces. E.g. *S aureus* has surface protein A.
2. Other pathogens have surface factors that impede phagocytosis (*S. pneumoniae*, *N. meningitidis*) e.g. polysaccharide capsules.
3. *S. pyogenes* (group A streptococci) has M protein.
4. *N. gonorrhoeae* (gonococci) has pili.
5. A few bacteria (eg, *Capnocytophaga* and *Bordetella* species) produce soluble factors or toxins that inhibit chemotaxis by leukocytes and thus evade phagocytosis.
Intracellular Pathogenicity

Some bacteria (eg, *M tuberculosis*, *Listeria monocytogenes*, *Brucella* species, and *Legionella* species) live and grow within polymorphonuclear cells, macrophages, or monocytes. The bacteria accomplish this by several mechanisms:

- they may avoid entry into phagolysosomes and live within the cytosol of the phagocyte
- they may prevent phagosome–lysosome fusion and live within the phagosome
- they may be resistant to lysosomal enzymes and survive within the phagolysosome.
Antigenic Heterogeneity

The surface structures of many microorganisms have considerable antigenic heterogeneity. Often these antigens are used as part of a serologic classification system for the bacteria.

• The classification of the 2000 or so different salmonellae is based principally on the types of the O (LPS side chain) and H (flagellar) antigens.
• There are more than 150 E coli O types and more than 100 E coli K (capsule) types.
• V cholerae O antigen type 1 and O antigen type 139 typically produce cholera toxin.
• N meningitides capsular polysaccharide types A and C are associated with epidemic meningitis.

Some bacteria and other microorganisms have the ability to make frequent shifts in the antigenic form of their surface structures. e.g. Borrelia recurrentis, which causes relapsing fever and N gonorrhoeae which has three surface-exposed antigens that switch from one to another at a very high rate.
Importance of Bacterial Biofilms

- A biofilm is an aggregate of interactive bacteria attached to a solid surface or to each other by exopolysaccharide matrix.
- A single species of bacteria may be involved or more than one species may coaggregate to form a biofilm. Fungi, including yeasts, are occasionally involved.
- After a biofilm is formed, quorum-sensing molecules (e.g. Homoserine Lactone) produced by the bacteria in the biofilm accumulate, resulting in a modification of the metabolic activity of the bacteria.
- The bacteria in the exopolysaccharide matrix may be protected from the host’s immune mechanisms.
- Some of the bacteria within the biofilm show marked resistance to antimicrobials compared with the same strain of bacteria grown free living in broth.
- Biofilms are important in human infections that are persistent and difficult to treat.