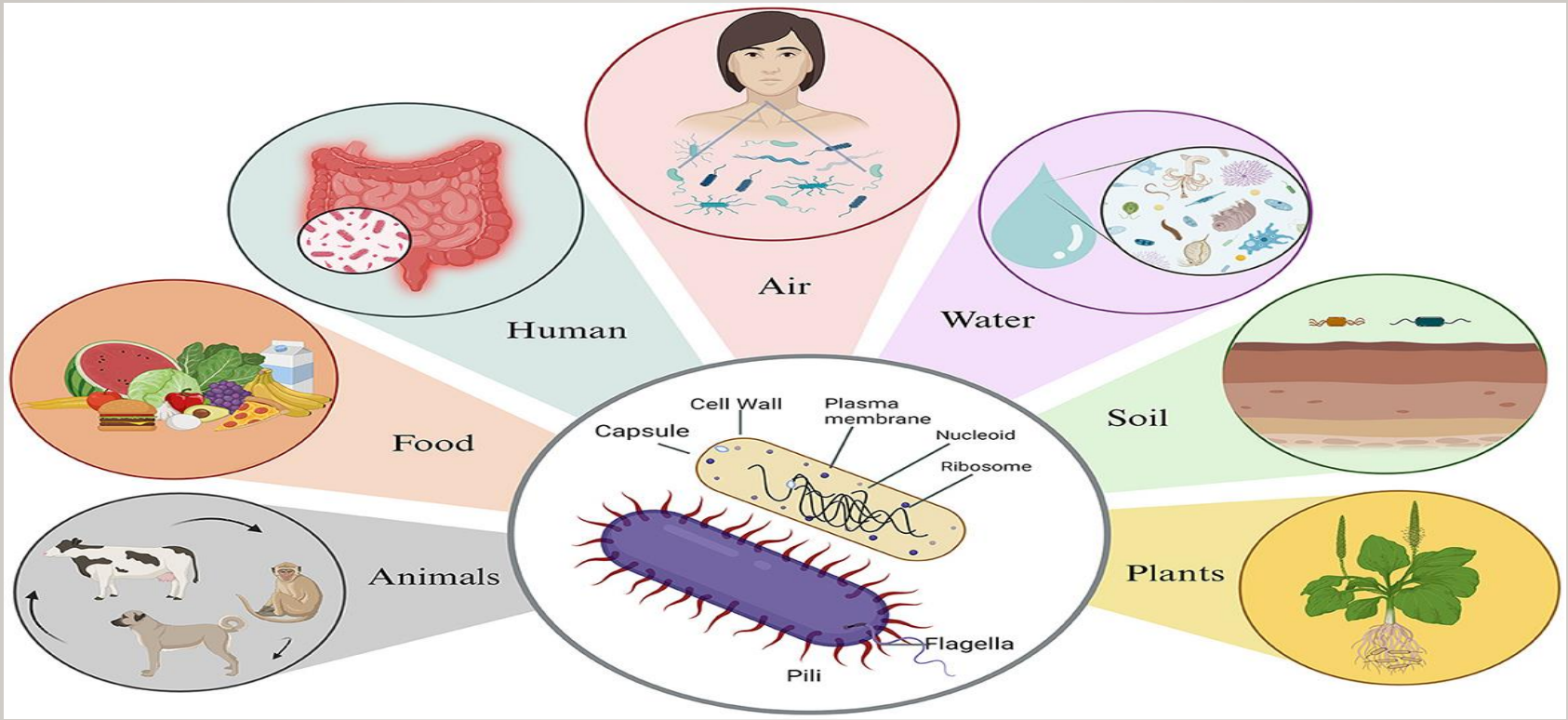

Pathogenesis of bacterial infections

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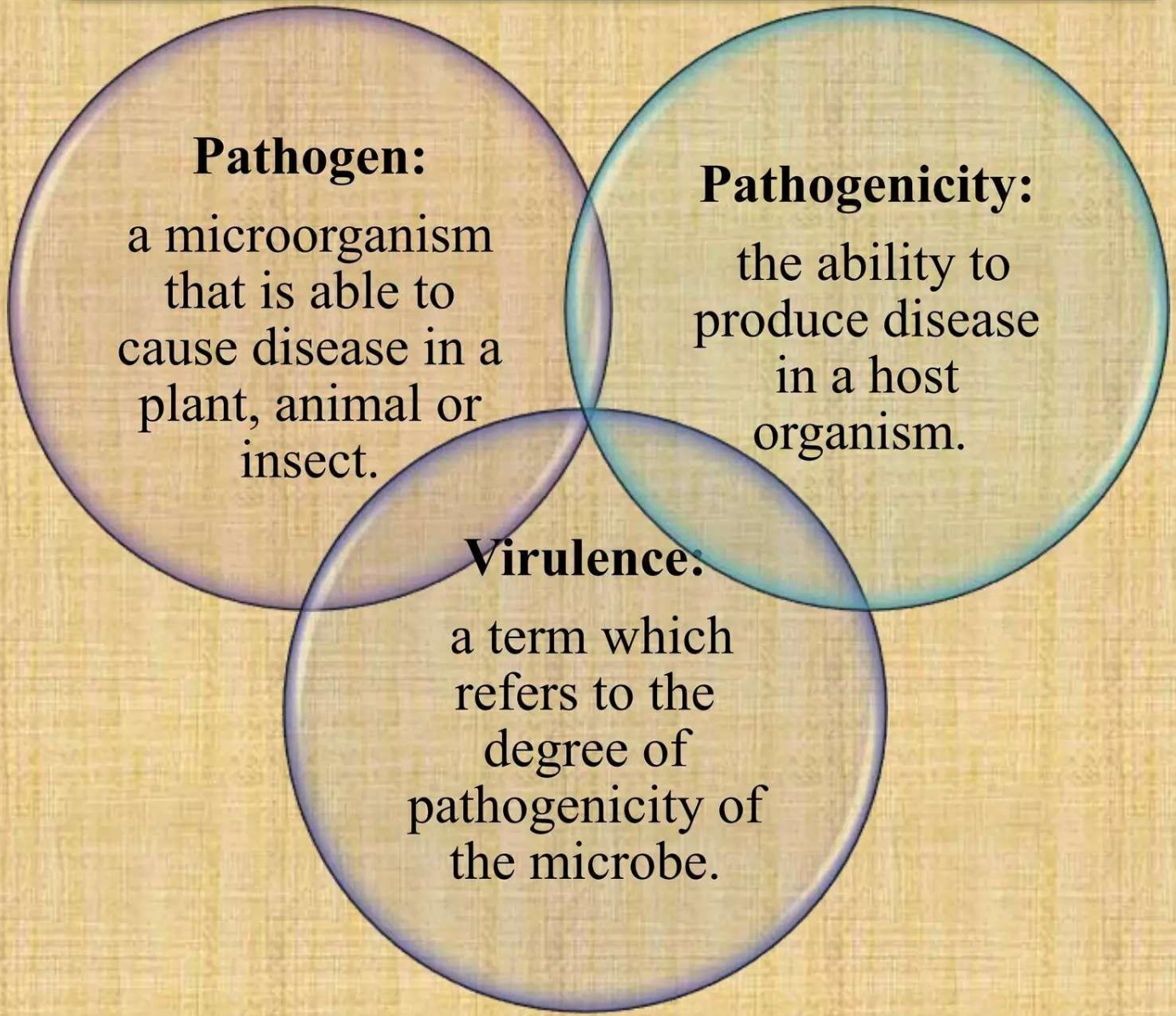
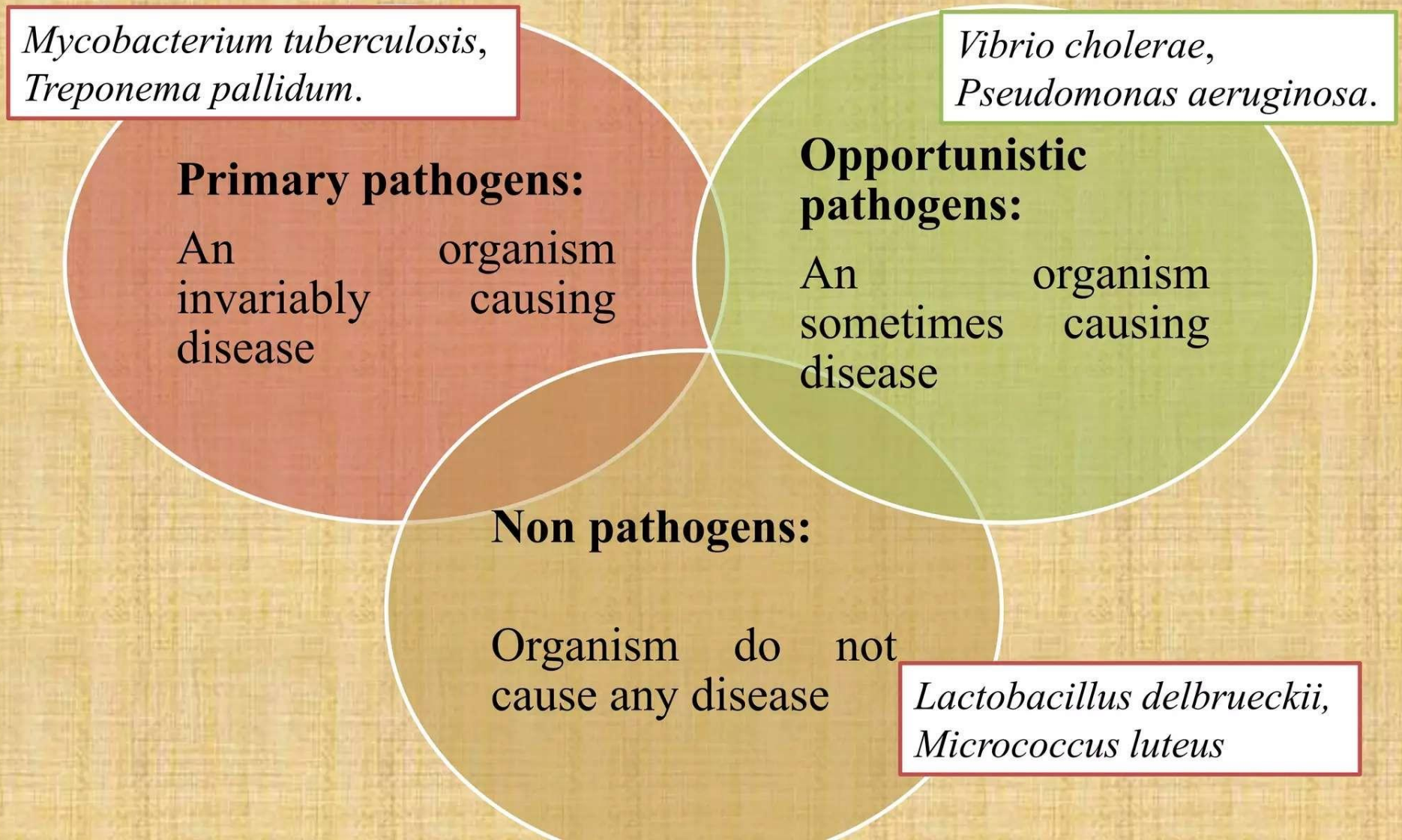
General Objectives:

1. To define the basic concepts in pathology such as Pathogen, Pathogenicity, Virulence, and Opportunistic pathogens.
2. To explain the sequential stages of bacterial infection development, starting from transmission and adherence until the appearance of symptoms.
3. To identify and classify the factors that enable bacteria to cause disease (e.g., pili, capsule, toxins).
4. To analyze the two main mechanisms of causing disease: Toxin production versus Invasion and spread.
5. To compare and contrast Endotoxins and Exotoxins in terms of structure, source, and effect.
6. To recognize the different modes of transmission of pathogenic bacteria (human-to-human, animal-to-human, environmental sources).

INTRODUCTION



Classification of bacteria



PATHOGENESIS OF BACTERIAL INFECTION

The pathogenesis of bacterial infection includes initiation of the infectious process and the mechanisms that lead to the development of signs and symptoms of disease. Characteristics of bacteria that are pathogens include transmissibility, adherence to host cell, invasion of the host cell & tissues, toxigenicity, and ability to evade the host immune response.

Adherence (adhesion, attachment): The process by which bacteria stick to the surface of host cell. It is the major initial step in the infection process.

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

Invasion: The process whereby bacteria, animal parasites, fungi, and viruses enter host cell or tissues & spread in the body.

Pathogenesis of bacterial infection

Infection: Multiplication of an infectious agent within the body. Multiplication of the normal flora in or on the body generally not considered an infection. Multiplication of pathogenic bacteria even if the person is asymptomatic is infection.

Nonpathogenic: A microorganism that does not cause disease (may be part of normal flora).

Opportunistic pathogen: An agent capable of causing disease only when the host resistance is impaired (immunocompromised patients).

Pathogen: A microorganism capable of causing disease.

Pathogenicity: The ability of an infectious agent to cause disease.

Toxigenicity: The ability of microorganism to produce toxin that contribute to the development of disease.

Virulence: The quantitative ability of an agent to cause disease. It involves adherence, invasion, and toxigenicity.

BACTERIAL VIRULENCE FACTORS

Virulence factors: are molecules expressed and secreted by pathogens (bacteria , viruses, fungi and protozoa) that enable them to achieve the **following**:

1. colonization of a niche in the host (this includes adhesion to cells)
2. Immunoevasion, evasion of the host's immune response
3. Immunosuppression, inhibition of the host's immune response
4. entry into and exit out of cells (if the pathogen is an intracellular one)
5. obtain nutrition from the host.

Virulence factors are very often responsible for causing disease in the host as they inhibit certain host functions. Pathogens possess a wide array of virulence factors. Some are intrinsic to the bacteria (e.g. capsules and endotoxin) whereas others are obtained from plasmids (e.g. some toxins).

Bacterial pathogenesis

Some infections results in a latent state, after which reactivation of the growth of the organism and recurrence of symptoms may occur. Certain other infections lead to a chronic carrier state, in which the organisms continue to grow with or without producing symptoms in the host.

Colonization refers to the presence of a new organism that is neither a member of the normal flora nor the cause of symptoms.

The infectious dose of an organism required to cause disease varies greatly among the pathogenic bacteria. For example, Shigella and Salmonella both cause diarrhea by infecting the gastrointestinal tract, but the infectious dose of Shigella is less than 100 organisms, whereas the infectious dose of Salmonella is on the order of 100,000 organisms.

The infectious dose of bacteria **depends** primarily on their virulence factors, for example, whether their pili allow them to adhere well to mucous membranes, whether they produce exotoxins or endotoxins, whether they possess capsule to protect them from phagocytosis, and whether they can survive various nonspecific host defenses such as acid in the stomach.

Bacteria cause disease by two major mechanisms:

(1) toxin production

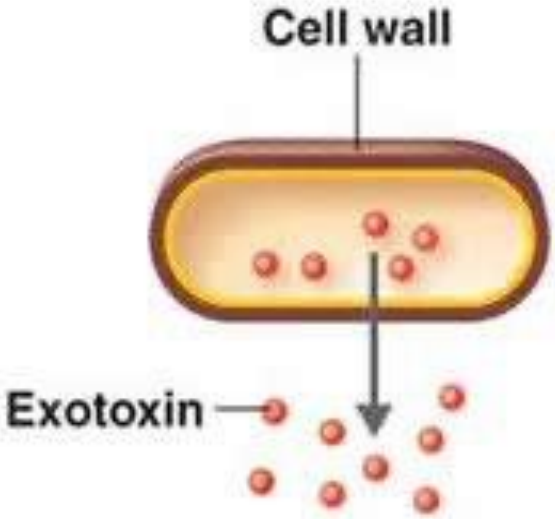
(2) invasion and inflammation.

Toxins fall into two general categories: **Exotoxins** and **endotoxins**.

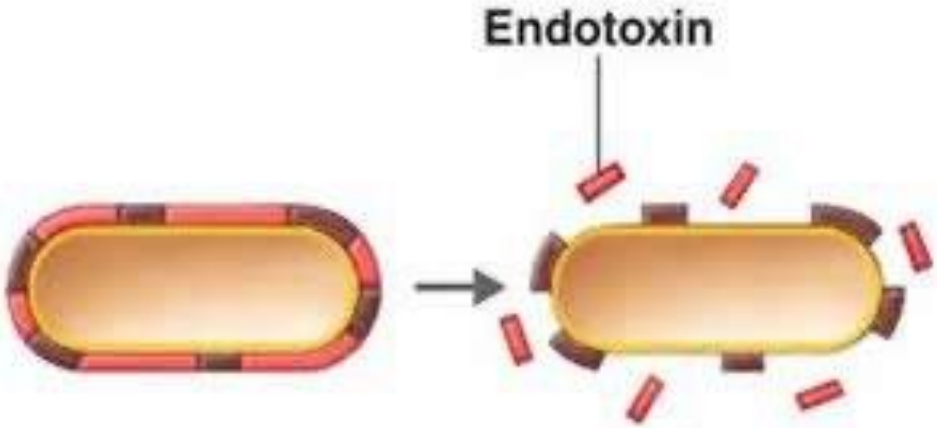
Exotoxins are polypeptides released by the cell, whereas **endotoxins** are lipopolysaccharides (LPS), which form an integral part of the cell wall.

Endotoxins occur only in gram- negative rods and cocci; are not actively released from the cell; and cause fever, shock, and other generalized symptoms. Invasive bacteria, grow to large numbers locally and induce an inflammatory response consisting of erythema, edema, warmth, and pain.

Differences Between Exotoxins and Endotoxins



(a) Exotoxins are proteins produced inside pathogenic bacteria, most commonly gram-positive bacteria, as part of their growth and metabolism. The exotoxins are then secreted or released into the surrounding medium following lysis.



(b) Endotoxins are the lipid portions of lipopolysaccharides (LPSs) that are part of the outer membrane of the cell wall of gram-negative bacteria (lipid A; see Figure 4.13c). The endotoxins are liberated when the bacteria die and the cell wall breaks apart.

STAGES OF BACTERIAL PATHOGENESIS

Some bacterial infections are caused by members of the normal flora and, as such, are not transmitted directly prior to the onset of infection. A generalized sequence of the stages of infection is as **follows**:

1. Transmission from an external source into the portal of entry
2. Evasion of primary host defenses such as skin or stomach acid
3. Adherence to mucous membranes, usually by bacterial pili
4. Colonization by growth of the bacteria at the site of adherence
5. Disease symptoms caused by toxin production or invasion accompanied by inflammation
6. Host responses, both nonspecific and specific (immunity).
7. Progression or resolution of the disease.

TRANSMISSION

An understanding of the mode of transmission of bacteria and other infectious agents is extremely important from a public health perspective, because interrupting the chain of transmission is an excellent way to prevent infectious diseases.

Modes of transmission.

1.Human to human :

A. Direct contact Gonorrhea Intimate contact: e.g., sexual, or passage through birth canal.

B. No direct contact (Dysentery) Fecal–oral: e.g., excreted in human feces, then ingested in food or water.

C. Transplacental :Congenital syphilis Bacteria cross the placenta and infect the fetus.

D. Blood-borne Syphilis Transfused blood or intravenous drug use can transmit.

2. Nonhuman to human

1. Soil source :Tetanus Spores in soil enter wound in skin.

2.Water source :Legionnaire's disease Bacteria in water aerosol are inhaled into lungs.

3. Fomite source : Staphylococcal skin infection; Bacteria on an object, e.g., a towel, are transferred onto skin.

3. Animal source:

A. Directly Cat-scratch fever: Bacteria enter in cat scratch

B. Via insect vector: Lyme disease: Bacteria enter in tick bite

C. Excrete Via animal: hemolytic–uremic syndrome ,*E. coli*; Bacteria in cattle feces are ingested in undercooked hamburger.

➢ Portals of Entry

A. Respiratory tract:

- *Streptococcus pneumonia*(Pneumonia).
- *Neisseria meningitides* (Meningitis).
- *Haemophilus influenza* (Meningitis).
- *Mycobacterium tuberculosis* (Tuberculosis).

B. Gastrointestinal tract:

- *Shigella dysenteriae* (Dysentery).
- *Salmonella typhi* (Typhoid fever).
- *Vibrio cholera* (Cholera).

C. Skin:

- *Clostridium tetani* (Tetanus).
- *Rickettsia rickettsia*(Rocky Mountain spotted fever).

D. Genital tract:

- *Neisseria gonorrhoeae* (Gonorrhea).
- *Treponema pallidum* (Syphilis).
- *Chlamydia trachomatis*(Urethritis)

GRAM-POSITIVE BACTERIA

The exotoxins produced by gram-positive bacteria have several different mechanism of action and produce different clinical effect:

1. **Diphtheria toxin**, produced by *Corynebacterium diphtheriae*, inhibits protein synthesis by ADP-ribosylation of EF-2.
2. **Tetanus toxin**, produced by *Clostridium tetani*, is a neurotoxin that prevents release of the inhibitory neurotransmitter glycine.
3. **Botulinum toxin**, produced by *Clostridium botulinum*, is a neurotoxin that blocks the release of acetylcholine at the synapse, producing a flaccid paralysis.
4. **Two exotoxins** are produced by *Clostridium difficile*, both of which are involved in the pathogenesis of pseudomembranous colitis. **Exotoxin A** is an enterotoxin that causes watery diarrhea. **Exotoxin B** is a cytotoxin that damages the colonic mucosa and causes pseudo membranes to form.

5. **TSST** is a superantigen produced primarily by certain strains of S. aureus but also by certain strains of *S. pyogenes*. TSST binds directly to class II major histocompatibility (MHC) proteins on the surface of antigen-presenting cells (macrophages) without intracellular processing.

6. **Staphylococcal enterotoxin** is also a superantigen but, because it is ingested , acts locally on the lymphoid cells lining the small intestine.

7. **Exfoliatin** is a protease produced by *S. aureus* that causes scalded skin syndrome. Exfoliatin cleaves desmoglein, a protein in the desmosomes of the skin, resulting in the detachment of the superficial layers of the skin. Exfoliatin is also called **epidermolytic toxin.**

GRAM-NEGATIVE BACTERIA

The exotoxins produced by gram-negative bacteria also have several different mechanisms of action and produce different clinical effects :

1. **The heat-labile enterotoxin** produced by ***E. coli*** causes watery, nonbloody diarrhea by stimulating adenylate cyclase activity in cells in the small intestine.

2. **Heat-stable toxin**, which is a polypeptide that is not inactivated by boiling for 30 minutes. It stimulates guanylate cyclase and thus increases the concentration of cyclic GMP, which inhibits the reabsorption of sodium ions and causes diarrhea.

3. **Verotoxin** is an exotoxin produced by strains of ***E. coli*** with the O157:H7 serotype. These enterohemorrhagic strains cause bloody diarrhea. When verotoxin enters the bloodstream, it can cause hemolytic–uremic syndrome (HUS).

4. **The enterotoxins produced by *V. cholerae***, the agent of ***cholera*** and ***Bacillus cereus***, a cause of diarrhea, act in a manner similar to that of the heat-labile toxin of E. coli.

5. **Pertussis toxin**, produced by ***B. pertussis***, the cause of whooping cough, is an exotoxin that catalyzes the transfer of ADP-ribose from NAD to an inhibitory G protein.


Thank You