PATHOGENESIS OF BACTERIAL INFECTION

PATHOGENICITY
TOXIGENICITY
VIRULENCE

- The pathogenesis of bacterial infection includes the initiation of the infectious process and the mechanisms leading to the development of signs and symptoms of bacterial disease.

- The outcome of the interaction between bacteria and host is determined by characteristics that favour establishment of the bacteria within the host and their ability to damage the host as they are opposed by host defense mechanisms.

- Among the characterics of bacteria are adherence to host cells, invasiveness, toxigenity, and ability to evade the host s immune system.

- If the bacteria or immunological reactions injure the host sufficiently, disease becomes apparent.

Pathogenesis
of bacterial infection

- Humans and animals have abundant normal microflora.

- Most bacteria do not produce disease but achieve a balance with the host that ensures the survival, growth, and propagation of both the bacteria and the host.

- Sometimes bacteria that are clearly pathogens (e.g. *Salmonella typhi*) are present, but infection remains latent or subclinical and the host is a "carrier" of the bacteria.

- It can be difficult to show that a specific bacterial species is the cause of a particular disease.

- In 1884, Robert Koch proposed a series of postulates in his treatise on *Mycobacterium tuberculosis and tuberculosis*.

- These postulates have been applied more broadly to link many specific bacterial species with particular diseases.

Koch s postulates are summarized as follows:

- 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.

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

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

- The microorganism must again be isolated from the lesions of such experimentally produced disease.

Koch s postulates remain a mainstay of microbiology

- However, since the late 19th century, many microorganisms that do not meet the criteria of the postulates have been shown to cause disease.

- For example, *Treponema pallidum* (syphilis) and *Mycobacerium leprae* (leprosy) cannot be grown in vitro, but there are animal models of infection with these agents.

- In another example, *Neisseria gonorrhoeae* (gonorrhea), there is no animal model of infection even though the bacteria can readily be cultivated in vitro.

- The host s immune responses should be considered when an organism is being investigated as the possible cause of a disease.

- Thus, development of a rise in specific antibody during recovery from disease is an important adjunct to Koch s postulates.

Modern-day microbial genetics has opened new frontiers to study pathogenic bacteria and differentiate them from non-pathogens.
The ability to study genes associated with virulence has led to a proposed of Koch´s postulates:

- The phenotype, or property, under investigation should be associated with pathogenic members of a genus or pathogenic strains of a species.

- Specific inactivation of the gene(s) associated with the suspected virulence trait should lead to a measurable loss in pathogenicity or virulence.

- Reversion or allelic replacement of the mutated gene should lead to restoration of pathogenicity.

- Analysis of infection and disease through the application of principles such as Koch s postulates leads to classification of bacteria as pathogenic or non-pathogenic.

- Some bacterial species are always considered to be pathogens, and their presence is abnormal.
  - Examples include *Mycobacterium tuberculosis* (tuberulosis) and *Yersinia pestis* (plague).
  - Other species are commonly part of the normal flora of humans (and animals) but can also frequently cause disease. For example, *Escherichia coli* is part of the gastrointestinal flora of normal humans, but it is also a comon cause of urinary tract infection, traveller s diarrhea, and other diseases.

The infectious process

- Infection indicates multiplication of microorganisms.

- Prior to multiplication, bacteria (in case of bacterial infection) must enter and establish themselves within the host.

- The most frequent portals of entry are the respiratory (mouth and nose), gastrointestinal, and urogenital tracts. Abnormal areas of mucous membranes and skin (e.g. cuts, burns) are also frequent sites of entry.

The infectious process

- Once in the body, bacteria must attach or adhere to host cells, usually epithelial cells.

- After the bacteria have established a primary site of infection, they multiply and spread.

- Infection can spread directly through tissues or via the lymphatic system to bloodstream. Bloodstream infection (bacteremia) can be transient or persistent. Bacteremia allows bacteria to spread widely in the body and permits them to reach tissues particularly suitable for their multiplication.

The infectious process

- As an example of the infectious process, *Streptococcus pneumoniae* can be cultured from the nasopharynx of 5-40% of healthy people.

- Occasionally, *S. pneumoniae* strains from the nasopharynx are aspirated into the lungs. Infection develops in the terminal air space of the lungs in persons who do not have protective antibodies against that type of *S. pneumoniae*. Multiplication of *S. pneumoniae* strains and resultant inflammation lead to pneumonia. The strains then enter the lymphatics of the lung and move to the bloodstream. Between 10% and 20% of persons with *S. pneumoniae* pneumonia have bacteremia at the time the diagnosis of pneumonia is made. Once bacteremia occurs, *S. pneumoniae* strains can spread to their preferred secondary sites of infection (e.g. cerebrospinal fluid, heart valves, joint spaces). The major resulting complications of *S. pneumoniae* pneumonia include meningitis, endocarditis and septic arthritis.

Basic terms frequently used in describing aspects of pathogenesis:

- ***Infection***
  - Multiplication of an infectious agent within the body.
  - Multiplication of the bacteria that are part of normal flora of gastrointestinal tract, skin, etc, is generally not considered an infection.
  - On the other hand, multiplication of pathogenic bacteria (e.g. *Salmonella species*), even if the person is asymptomatic, is deemed an infection.

Basic terms frequently used in describing aspects of pathogenesis:

- ## *Pathogenicity*
  - The ability of an infectious agent to cause disease.

- ## *Virulence*
  - The quantitative ability of an agent to cause disease.
  - Virulent agents cause disease when introduced into the host in small numbers.
  - Virulence involves invasiveness and toxigenicity.

Basic terms frequently used in describing aspects of pathogenesis:

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

- *Invasion*
  - The process whereby bacteria, parasites, fungi and viruses enter the host cells or tissues and spread in the body.

Basic terms frequently used in describing aspects of pathogenesis:

- **_Pathogen_**
  - A microorganism capable of causing disease.

- **_Non-pathogen_**
  - A microorganism that does not cause disease. It may be part of the normal flora.

- **_Opportunistic pathogen_**
  - An agent capable of causing disease only when the host s resistance is impaired (e.g. the patient is immunocompromised).
  - An agent capable of causing disease only when spread from the site with normal bacterial microflora to the sterile tissue or organ.

Bacterial virulence factors

- Many factors determine the virulence of bacteria, or their ability to cause infection and disease.

Toxins

- Toxins produced by bacteria are generally classified into two groups:
  - exotoxins
  - endotoxins

Endotoxins of Gram-negative bacteria

- The endotoxins of Gram-negative bacteria are complex lipopolysaccharides derived from bacterial cell walls and are often liberated when the bacteria lyse.

- The substances are heat-stable and can be extracted (e.g. with phenol-water).

Pathophysiological effects of endotoxins are similar regardless of their bacterial origin:

- fever
- leukopenia
- hypotension
- impaired organ perfusion and acidosis
- activation of C3 and complement cascade
- disseminated intravascular coagulation (DIC)
- shock, death

Exotoxins

- Many Gram-positive and Gram-negative bacteria produce exotoxins of considerable medical importance.

- Some of these toxins have had major role in world history (e.g. toxin of *Clostridium tetani*).

Diphtheria toxin
(toxin of *Corynebacterium diphtheriae*)

- *Corynebacterium diphtheriae* strains that carry a temperate bacteriophage with the structural gene for the toxin are toxigenic and produce diphtheria toxin.

- This native toxin is enzymatically degraded into two fragments: A and B, linked together by a disulfide bound. Both fragments are necessary for toxin activity.

Tetanospasmin (toxin of *Clostridium tetani*)

■ *Clostridium tetani* is an anaerobic Gram-positive rod that is widespread in the environment.

■ *Clostridium tetani* contaminates wounds, and the spores germinate in the anaerobic environment of the devitalized tissue. The vegetative forms of *Clostridium tetani* produce toxin tetanospasmin. The released toxin has two peptides linked by disulfide bounds. Toxin reaches the central nervous system by retrograde transport along axons and through the systemic circulation. The toxin acts by blocking release of an inhibitory mediator in motor neuron synapses. The result is initially localized then generalized, muscle spasms. Extremely small amount of toxin can be lethal for humans.

Botulotoxin (toxin of *Clostridium botulinum*)

- *Clostridium botulinum* is found in soil or water and may grow in foods if the environment is appropriately anaerobic.

- An exceedingly potent toxin (the most potent toxin known) is produced by *Clostridium botulinum* strains. It is heat-labile and is destroyed by sufficient heating. There are eight disctinct serological types of toxin. Types A, B and E are most commonly associated wih human disease. Toxin is absorbed from the gut and carried to motor nerves, where it blocks the release of acetylcholine at synapses and neuromuscular junctions. Muscle contraction does not occur, and paralysis results.

Toxins of *Clostridium perfringens*

- Spores of *Clostridium perfringens* are introduced into the wounds by contamination with soil or faeces. In the presence of necrotic tissue (an anaerobic environment), spores germinate and vegetative cells produce several different toxins.

- Many of these are necrotizing and hemolytic and favour the spread of gangrene:
  - alpha toxin is a lecithinase that damages cell membranes
  - theta toxin also has a necrotizing affect
  - and other

Streptococcal erythrogenic toxin

- Some strains of hemolytic lysogenic streptococci produce a toxin that results in a punctate maculopapular erythematous rash, as in scarlet fewer.

- Production of erythrogenic toxin is under the genetic control of temperate bacteriophage. If the phage is lost, the streptococi cannot produce toxin.

Toxic shock syndrom toxin - 1 (TSST-1)

- Some *Staphylococcus aureus* strains growing on mucous membranes (e.g. on the vagina in association with menstruation), or in wounds, elaborate TSST-1.

- This toxin is associated with toxic shock syndrome.

- The illness is characterized by shock, high fewer, and a diffuse red rash that later desquamates, multiple other organs systems are involved as well.

Exotoxins associated with diarrheal diseases

- *Vibrio cholerae* toxin

- *Staphylococcus aureus* enterotoxin

- Other enterotoxins - enterotoxins are also produced by some strains of:

  - *Yersinia enterocolitica*

  - *Vibrio parahaemolyticus*

  - *Aeromonas species*

Enzymes

- Many species of bacteria produce enzymes that are not intrinsically toxic but play important role in the infectious process.

- *Collagenase*
  - degrades collagen, the major protein of fibrous connective tissue, and promotes spread of infection in tissue.

- *Coagulase*
  - *Staphylococcccus aureus* produce coagulase, which works in conjuction with serum factors to coagulate plasma. Coagulase contributes to the formation of fibrin walls around staphylococcal lesions, which helps them persist in tissues.

Enzymes

- **_Hyaluronidases_**
  - enzymes that hydrolyze hyaluronic acid, a constituent of the ground substance of connective tissue. They are produced by many bacteria (e.g. staphylococci, streptococci and anaerobes) and aid in their spread through tissues.

- **_Streptokinase_**
  - many hemolytic streptococci produce streptokinase (fibrinolysin), substance that activates a proteolytic enzyme of plasma. This enzyme, also called fibrinolysin, is then able to dissolve coagulated plasma and probably aids in the spread of streptococci through tissues. Streptokinase is used in treatment of acute myocardial infarction to dissolve fibrin clots.

Enzymes

- ***Hemolysins and leukocidins***
  - Many bacteria produce substances that are cytolysins - they dissolve red blood cells (hemolysins) or kill tissue cells or leukocytes (leukocidins).
  - Streptolysin O, for example, is produced by group A streptococci and is letal for mice and hemolytic for red blood cells from many animals.

Antiphagocytic factors

- Many bacterial pathogens are rapidly killed once they are ingested by polymorphonuclear cells or macrophages.

- Some pathogens evade phagocytosis or leukocyte microbidical mechanisms by adsorbing normal host componets to their surfaces.

- For example, *Staphylococcus aureus* has surface protein A, which binds to the Fc portion of IgG. Other pathogens have surface factors that impede phagocytosis e.g. *Streptococcus pneumoniae* and many other bacteria have polysaccharide capsules.

Adherence factors

- Once bacteria enter the body of the host, they must adhere to cells of a tissue surface. If they do not adhere, they would be swept away by mucus and other fluids that bathe the tissue surface.

- Adherence (which is only one step in the infectious process) is followed by development of microcolonies and subsequent complex steps in the pathogenesis of infection.

Adherence factors

■ The interactions between bacteria and tissue cell surfaces in the adhesion process are complex.

■ Several factors play important role:
- surface hydrophobicity
- binding molecules on bacteria and host cell receptor interaction
- and other