Chapter four

Pathogenesis

- **Pathogen** is a microorganism capable of causing disease
- **Opportunistic pathogens** are those that rarely if ever cause disease in healthy people, but can cause serious infections in immunocompromised patients. These are mainly members of the normal flora
- **Virulence** is the degree of pathogenicity and is measured by the number of organisms required to cause disease

- The **infectious dose** of an organism required to cause disease varies among the pathogenic bacteria.
- e.g. *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 about 100,000 organisms.

- **Parasitism:** is a life style that has been adapted by many types of living organisms.
- **The term parasitic:** describe any relationship in which two organisms live together in an intimate association.

- The term **parasite** is used with several meanings:

- **In medical terminology:** parasites include intestinal worms and organisms causing malaria, Kala azar or amoebic dysentery, whereas bacteria and viruses do not find mention as parasites.
- **In true sense:** it includes all organisms living in or on the bodies of other organisms and obtaining feed and shelter. Thus parasites include: Bacteria, Viruses, Fungi, Protozoa, Helminthes, and arthropods

- **Symbiotic include**:
- **Mutualism:** is an association in which both members of associated organisms get benefit from this relationship
- **Commensalism:** association in which the symbiont get benefit and the host not harmed
- **Parasitism**: association where the symbiont get benefit while the host is harmed to a lesser or greater degree

Infecting agents: organisms parasites the host eg. Bacteria, viruses, fungi, protozoa, helminthes etc.

Infection: is a term applied to the establishment, growth and multiplication of microorganism in the host for a period of time

Infectious Diseases: People get infectious diseases when microorganisms overpower the host defenses

- The two critical determinants in overpowering the host are:

1. The number of the organisms
2. The virulence of the organisms

Asymptomatic infections when a person acquires an organism but no infectious disease occurs because the host defenses were successful

Types of Bacterial Infections

Bacteria cause disease by two major mechanisms:

1. Toxin production
2. Invasion and inflammation

- Toxins are of two types' exotoxins and endotoxins.
- **Exotoxins** are polypeptides released by the cell, whereas **endotoxins** are lipopolysaccharides which are part of the cell wall. Endotoxins occur only in Gram-negative bacteria and cause fever, shock, and other generalized symptoms

- Many infections are communicable i.e. spread from one host to other. For example;

1. Tuberculosis is communicable disease that can spread from person- to- person via airborne droplets produced by coughing
2. Botulism is not a communicable disease, the exotoxin produced by the bacteria in the contaminated food affects only those eating that food

Contagious diseases are those diseases which are highly communicable

Epidemic infection if it occurs much more frequently than usual

Pandemic infection if it has worldwide distribution

Endemic infection is constantly present at a low level in a specific population

Subclinical or **inapparent infections** are those that result in overt symptoms and can be detected only by the rise in antibody titer or by isolating the organism

Stages of Bacterial Pathogenesis

- Most bacterial infections are acquired from an external source and some infections are caused by members of the normal flora
- The sequence of the stage 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), during steps 3,4 and 5
7. Progression or resolution of the disease

Determinants of Bacterial Pathogenesis

1. Transmission

- The mode of transmission of many infectious diseases is human- to- human, but may also transmitted from soil, water, and animals
- Organisms can also be transmitted by sexual contact, urine, skin contact, blood transfusions, contaminated needles, or biting insects

Transmission

- Pathogens exit the infected patient mostly form the respiratory and gastrointestinal tracts, therefore, transmission to the new host usually occurs via

1. airborne respiratory droplets or
2. fecal contamination of food or water

Vertical transmission

- Bacteria, viruses and other microbes can be transmitted from mother to her child by this process
- The mode by which organisms are transmitted by vertical transmission is:

1. Across the placenta
2. Within the birth canal during birth
3. Via breast milk

Horizontal transmission

- Is person- to- person transmission that is **not** from mother to her child

2. Adherence to Cell Surfaces

- Certain bacteria have specialized structures such as pili whereas other organisms produce substances like capsule or glycocalyx that allow them to adhere to the surface of human cells thereby enhancing their ability to cause disease

3. Invasion, Inflammation, and Intracellular Survival

- Several enzymes secreted by invasive bacteria play a role in pathogenesis, among them are:

1. Collagenase and hyaluronidase
2. Coagulase
3. Immunoglobulin A (IgA) protease
4. Leukocidins

Invasion, Inflammation, and Intracellular Survival

- Bacteria can cause two types of inflammation **pyogenic** and **granulomatous**
- In pyogenic (pus-producing) inflammation, neutrophils are the predominant cells
- In granulomatous inflammation, macrophages and T cells predominate.

Table 1: Important modes of transmission

Mode of Transmission	Clinical Example	Comment
1. Human to human		
A. Direct contact	Gonorrhea	Sexual contact or passage through birth canal
B. No direct contact	Dysentery	Fecal- oral
C. Trans placental	Congenital syphilis	Bacteria cross the placenta and infect the fetus
2. Nonhuman to human		
A. Soil source	Tetanus	Spores in soil enter wound in skin
B. Water source	Legionnaire's disease	Bacteria in water aerosol inhaled into lungs
C. Animal source		
1. Directly	Cat- scratch fever	Bacteria enter in cat scratch
2. Via insect vector	Lyme disease	Bacteria enter in tick bite
3. Via animal excreta	E.coli (HUS)	Bacteria in cattle feces are ingested in undercooked beef burger

4. Toxin Production

- There are two types of toxins produced by certain bacteria, exotoxins and endotoxins
- **Exotoxins**
- Produced by several Gram-positive and Gram-negative bacteria and are secreted by the bacteria.
- They are polypeptides whose genes are frequently located on plasmids or lysogenic bacteria viruses (bacteriophages).

Toxin Production

- Some important exotoxins encoded by bacteriophage DNA are diphtheria toxin, cholera toxin, and botulism toxin
- When exotoxins treated with formaldehyde (or acid or heat) the exotoxin polypepdides are converted into **toxoids,** which are used in protective vaccines because they retain their antigenicity but have lost their toxicity.

Endotoxins

- These are parts of the cell walls of both Gram-negative rods and cocci
- They are lipopolysaccharides (LPS) and the enzyme that produce the LPS are encoded by genes on the bacterial chromosome.
- The toxicity of endotoxins is lower than that for exotoxins
- They produce the same generalized effects of fever and shock
- No toxoids have been produced from endotoxins and they are not used as antigens in any vaccine

Typical Stages of an Infectious Disease

A typical acute infectious disease has 4 stages:

1. The **incubation period**, which is the time between the acquisition of the organism (or toxin) and the beginning of symptoms (this time varies from hours to days to weeks, depending on the organism)
2. The **prodrome period,** during which nonspecific symptoms such as fever, malaise, and loss of appetite occur

Typical Stages of an Infectious Disease

3. The specific **illness period,** during which the overt characteristic signs and symptoms of the disease occur
4. The **recovery period,** during which the illness abates and the patient return to the healthy state

- After the recovery period, some patients become chronic carriers of the organism and may shad them while remaining clinically well.
- Others may develop a **latent infection**, which can recur either in the same form as the primary infection or manifesting different sings and symptoms

- **Subclinical infections** when the individual remains asymptomatic although infected with the organism.
- In subclinical infections and after the recovery period is over, the presence of antibodies is often used to determine that an infection has occurred

Pathogenic properties of microbes

- **Pathogen;** is microorganism able to infect the host and produce the disease. On this basis, bacteria isolated from patients can be divided into 3 groups:

1. ***Frank pathogens:*** considered to be the probable agents of disease
2. ***Opportunistic pathogens:*** are those isolated from compromised patients
3. ***Nonpathogenic:*** rarely or never cause disease

Table 5-1 Microbial Pathogenicity attributes

1. Factors mediating adhesion
   - Adhesions
2. Antiphagocytic factors
   - Capsule
   - M-protein
   - Cytotoxin
3. Survival within phagocytes
   - Interference with oxidative burst
   - Prevention of fusion and degranulation
   - Resistance to lysosomal enzymes
   - Escape from phagosomes

4. Siderophore and iron acquisition
5. Enzymes and toxins
   - Enzymes
   - Endotoxins
   - Exotoxins
   - Genetic mechanisms
   - R-factors

Generalized infections

- **Bacteraemia, septicaemia** and **pyaemia** are some of the important manifestations which are mediated through blood
- **1-_Bacteraemia:** is the circulation of bacteria in the blood. It may be:
- **Transient**: occur frequently even in healthy individuals, while chewing, brushing of teeth or staining at passing stools. The circulating bacteria in this condition are usually commensal of oral or intestinal tracts and are quickly mopped up by phagocytes, thus initiation of infection is prevented

Generalized infections

Bacteraemia of long duration: occurs with pathogenic organisms such as *Salmonella typhi* and *Brucella* and is essential for disease initiation

2- Septicaemia: Bacteria circulate and multiply in the blood, form toxic products and cause high swinging type of fever. This is due to both endotoxin producing bacteria as well as exotoxin producing organisms

Table 5.2. Organisms producing septicaemia

	Exotoxic	***Endotoxic***
1	*Corynebacterium diphtheriae*	*Salmonella*
2	*Clostridium tetani*	*Shigella*
3	*Clostridium perfringens*	*Escherichia coli*

3- Pyaemia: pyogenic bacteria produce septicaemia with multiple abscesses in internal organs such as spleen, liver, lung, heart, and kidneys

Examples include:

Pyelonephritis due to → *Streptococcus pyogenes*
Lung abscesses due to → *Klebsiella spp., Pneumococci, Staphylococcus aureus*
Pyocarditis
Pyopneumothorax
Liver abscesses

Multiple abscesses in the body are produced by *Mycobactrium tuberculosis*

	Term	Characteristic of infection	Examples
Duration	Acute disease	Symptoms develop rapidly and that runs its course quickly	Measles, cold
	Chronic disease	Symptoms develop slowly and disease is slow to disappear	T.B, leprosy
	Subacute disease	Symptoms intermediate between acute and chronic	gingivitis
	Latent disease	Symptoms appear and/or reappear long after infection	Herpes-simples

Locations	Local infection	Infection contained in a small region of the body	Boils, bladder infection
	Focal infection	Infection in a confined region from which pathogens travel to other regions of the body	Abscessed tooth or infected sinuses
	Systemic infection	Infection in which the pathogen is spread throughout the body, often by traveling through blood or lymph	Typhoid fever

Generalized infections	Septicemia	Presence and multiplication of pathogens in blood	Due to endo- and exo-toxins
	Bacteremia	Presence but not multiplication of bacteria in blood	Transit e.g. chewing, brushing teeth
	Viremia	Presence but not multiplication of viruses in blood	
	Toxemia	Presence of toxins in blood	
	Septicemia	Presence of metabolic products of saprophytes in blood	fungi

Other attributes	Primary infection	Infection in a previously healthy person	Common cold
	Secondary infection	Infection that immediately follows a primary infection	Middle-ear infections
	Superinfection	Secondary infection that is usually caused by an agent resistant to the treatment for the primary infection	Pseudomembraneous colitis, vaginal candidiasis
	Mixed infection	Infection caused by two or more pathogens	Dental caries, periodontal disease
	Inapparent (subclinical) infection	Infection that fails to produce full set of signs and symptoms	Carriers of hepatitis-B virus

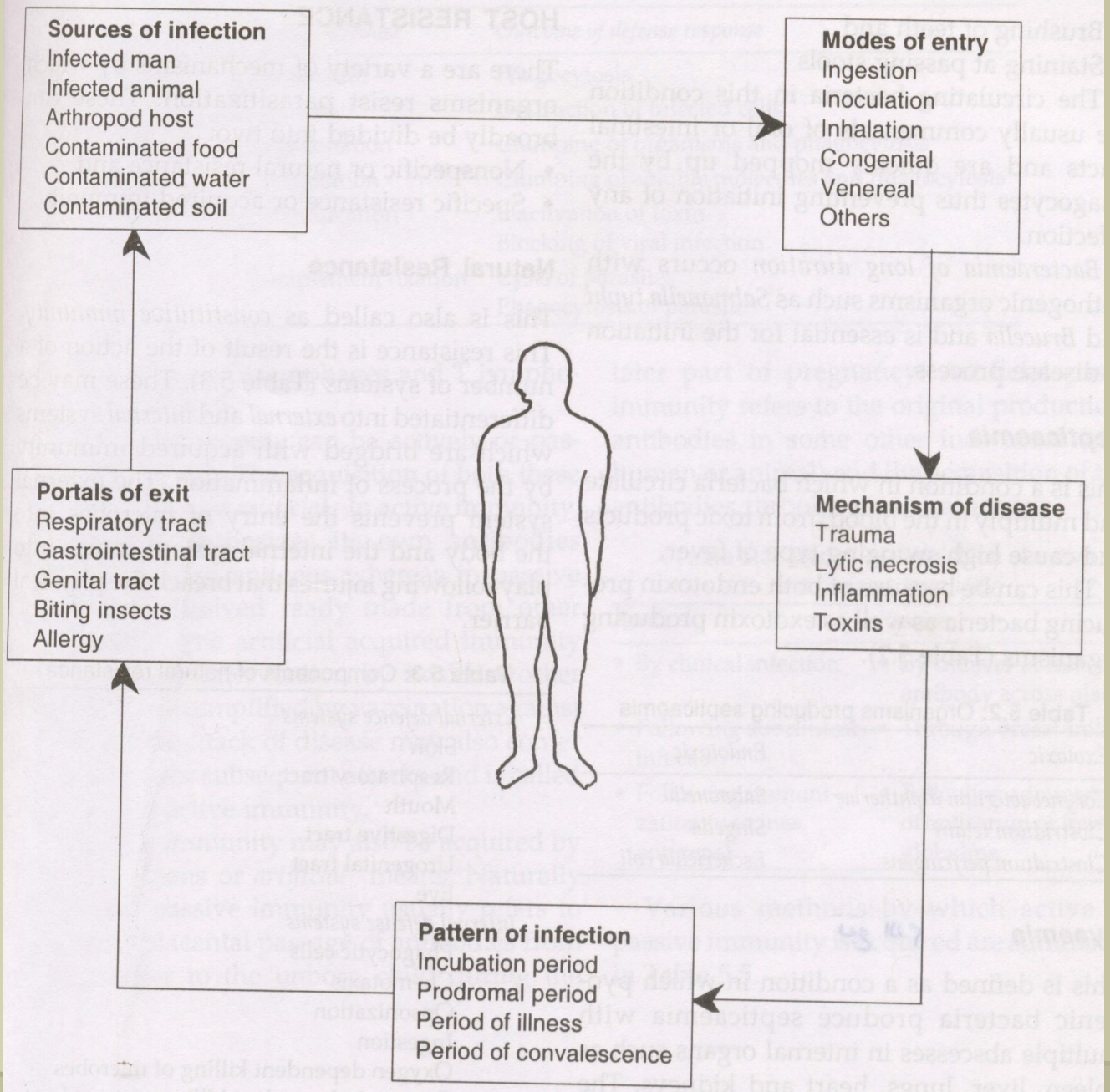

Fig. 5.3: Dynamics of infection

Table 5.5 Modes of acquisition of active and passive immunity

Active	*Passive*
By clinical infection	By transfer of maternal antibody across placenta
Following subclinical infection	Through breast-milk
Following immunization (vaccines, antigens)	Following administration of antiserum or immunoglobulins

Table 7–8. Main features of exotoxins and endotoxins.

	Comparison of Properties	
Property	**Exotoxin**	**Endotoxin**
Source	Certain species of some gram-positive and gram-negative bacteria	Cell wall of most gram-negative bacteria
Secreted from cell	Yes	No
Chemistry	Polypeptide	Lipopolysaccharide
Location of genes	Plasmid or bacteriophage	Bacterial chromosome
Toxicity	High (fatal dose on the order of 1 µg)	Low (fatal dose on the order of hundreds of micrograms)
Clinical effects	Various effects (see text)	Fever, shock
Mode of action	Various modes (see text)	Includes TNF and interleukin-1
Antigenicity	Induces high-titer antibodies called antitoxins	Poorly antigenic
Vaccines	Toxoids used as vaccines	No toxoids formed and no vaccine available
Heat stability	Destroyed rapidly at 60 °C (except staphylococcal enterotoxin)	Stable at 100°C for 1 hour
Typical diseases	Tetanus, botulism, diphtheria	Meningococcemia, sepsis by gram-negative

TNF = tumor necrosis factor.

Table 7–9. Important bacterial exotoxins.

Bacterium	Disease	Mode of Action	Toxoid Vaccine
ram-positive rods			
Corynebacterium diphtheriae	Diphtheria	Inactivates EF-2 by ADP-ribosylation	Yes
Clostridium tetani	Tetanus	Blocks release of the inhibitory neurotransmitter glycine by proteolytic cleavage of releasing proteins	Yes
Clostridium botulinum	Botulism	Blocks release of acetylcholine by proteolytic cleavage of releasing proteins	Yes[1]
Clostridium difficile	Pseudomembranous colitis	Exotoxin B is cytotoxic to enterocytes by disaggregating actin filaments	No
Clostridium perfringens	Gas gangrene	Alpha toxin is a lecithinase. Enterotoxin is a superantigen	No
Bacillus anthracis	Anthrax	One of the toxins is an adenylate cyclase	No
ram-positive cocci			
Staphylococcus aureus	1. Toxic shock syndrome	Is a superantigen; binds to class II MHC protein and T-cell receptor; induces IL-1 and IL-2	No
	2. Food poisoning	Is a superantigen acting locally in the gastrointestinal tract	No
	3. Scalded skin syndrome	Is a protease that cleaves desmoglein in desmosomes	No
Streptococcus pyogenes	Scarlet fever	Is a superantigen; action similar to toxic shock syndrome toxin of *S. aureus*	No
ram-negative rods			
Escherichia coli	1. Watery diarrhea	Labile toxin stimulates adenylate cyclase by ADP-ribosylation; stable toxin stimulates guanylate cyclase.	No
	2. Bloody diarrhea	Verotoxin is cytotoxic to enterocytes by degrading 28S ribosomal RNA	No
Vibrio cholerae	Cholera	Stimulates adenylate cyclase by ADP-ribosylation	No
Bordetella pertussis	Whooping cough	Stimulates adenylate cyclase by ADP-ribosylation; inhibits chemokine receptor	Yes[2]

[1] For high-risk individuals only.
[2] The acellular vaccine contains pertussis toxoid and four other proteins.

Signs & symptoms	Probable nature of tissue damage
1- Incubation period	
None ***2- Prodromal phase***	None
Local redness and swelling Headache General aches and pains ***3- Invasive phase***	Pathogen has damaged tissue at site of invasion and caused release of chemicals that dilate blood vessels (redness)and allowed fluid from blood to enter tissue (swelling)
	Chemicals from tissue injury dilate blood vessels in the brain
	Chemicals from tissue injury stimulate pain receptors in joints and muscles
Cough	Mucosal cells of respiratory tract have been damaged by pathogens; excess mucous is released, and neural centers in the brain elicit coughing to remove mucous
Sore throat	Lymphatic tissue of the pharynx is swollen and inflamed by substances released by pathogens & leukocytes
Fever	Leukocytes release pyrogens that reset the body's thermostat and cause temperature to rise
Swollen lymph nodes	Leukocytes release other substances that stimulate cell division and fluid accumulation in lymph nodes; some pathogens multiply in lymph nodes

Skin rashes	Leukocytes release substances that damage capillaries and allow small hemorrhages; some pathogens invade skin cells and cause pox, vesicles, and other skin lesions
Nasal congestion	Nasal mucosal cells have been damaged by pathogens (usually viruses) that release fluids and increase mucous secretions
Pain at specific sites(earache, local pain at wound site)	Substances from pathogens or leukocytes have stimulated pain receptors; messages are relayed to the brain, where they are interpreted as pain
Nausea	Toxins from pathogens have stimulated neural centers; the stimuli is interpreted as nausea
Vomiting	Toxins in food have stimulated the brain's vomiting center; vomiting help body to get rid of toxins
Diarrhea	Toxins in food cause fluid to enter the digestive tract; some pathogens directly injure the intestinal epithelium; both toxins and pathogens stimulate peristalsis; frequent watery stools result
4- Acme	
All signs and symptoms are at peak intensity	Full development of all sings and symptoms
5- Decline phase	
signs and symptoms subside	Host defense mechanisms (and treatment, if applicable) have contributed to overcoming the pathogen
6- Convalescence period	
Patient regains strength	Tissue repair occurs; substances caused signs and symptoms are no longer released